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Considering the context: Social factors in responses to drugs in humans

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Abstract

Background—Drugs are typically used in social settings. Here, we consider two factors that may contribute to this observation: i) the presence of other people may enhance the positive mood effects of a drug, and conversely, ii) drugs may enhance the value of social stimuli.

Methods—We review evidence from controlled laboratory studies with human volunteers, which investigated either of these interactions between social factors and responses to drugs. We examine the bi-directional effects of social stimuli and single doses of alcohol, stimulants, opioids and cannabis.

Results—All four classes of drugs interact with social contexts, but the nature of these interactions varies across drugs, and depends on whether the context is positive or negative.

Conclusions—Alcohol and stimulant drugs enhance the attractiveness of social stimuli and the desire to socialize, and social contexts, in turn, enhance these drugs' effects. In contrast, opioids and cannabis have subtler effects on social interactions and their effects are less influenced by the presence of others. Overall, there is stronger evidence that drugs enhance positive social contexts than that they dampen the negativity of unpleasant social settings. Controlled research is needed to understand the interactions between drugs of abuse and social contexts, to model and understand the determinants of drug use outside the laboratory.

I. Introduction

People typically use drugs in social settings. Alcohol and other drugs are most often used in the presence of friends and in positive social contexts such as bars and parties. Users report that alcohol and other drugs, such as MDMA, enhance the pleasure of socializing, either by making social interactions more enjoyable or by dampening subtle negative emotional states such as social anxiety (Miller et al., 2015; Sayette, 2017). The reverse relationship also occurs, that is, social contexts can influence responses to drugs. Even the simple presence of other people can influence the direct effects of alcohol and other drugs, presumably thereby increasing consumption (Dimoff & Sayette, 2017; Shiffman et al., 2002). Yet, despite these widely recognized interactions, most laboratory-based studies in both humans and animals have investigated drugs under socially isolated conditions, creating an important gap in our understanding of nonmedical drug use. Here, we review some of the evidence for the bidirectional interactions between acute effects of drugs and the social contexts in which they are used, based on human laboratory studies. We focus on four pharmacologically

distinct drug types: alcohol, MDMA and other stimulants, opioids and cannabis. For each drug type, we review evidence for two factors: i) the effects of the drug on social stimuli or social interactions, and ii) the effects of social context on responses to drugs. These factors are closely intertwined, and indeed in a naturalistic situation they are inseparable. Nevertheless, carefully designed experiments can disentangle some of the processes underlying these complex bidirectional interactions.

Interactions between drugs and social settings depend on the valence and emotional quality of the social context. Positive social settings, such as being with friends or acquaintances, are likely to increase the positive mood effects of drugs, whereas negative or stressful social settings, such as job interviews, may dampen the euphorigenic effects of drugs. Alternatively, some drugs may reduce anxiety induced by negative social settings, and these anxiolytic effects may make the drug more attractive to the user. It is likely that many naturalistic social settings contain a combination of positive and negative emotional stimuli (e.g., socializing with both friends and strangers), making it difficult to distinguish these factors in complex non-laboratory settings. In this review we will take into account the positivity or negativity of the social context, where possible, when reviewing the findings.

To limit the scope of this review, we do not address several other aspects of drug-context interactions. First, we do not examine the role of social context *after* dependence has developed. Instead, we focus on acute effects of drugs in individuals who are occasional users, or during early stages of drug use. Once an individual becomes dependent on a drug, different variables (e.g., tolerance, sensitization, conditioning, withdrawal) may come to control drug-seeking behaviors, and complicate the interactions of drugs and social setting. Interestingly, there is a common perception that ‘solitary’ drug use is symptomatic of problem drug use, although Fairbairn and Sayette (2014) point out that there is little empirical support for this idea. Second, this review does not address how *chronic* social isolation, feelings of exclusion, or social anxiety affect responses to drugs. Many preclinical studies have compared drug effects in animals housed under social vs isolated conditions (Bardo et al. 2001; Bozarth & Wise, 1989; Panksepp et al. 1978), and chronic social isolation is thought to increase drug use in humans (Clark & Sayette, 1993; Heilig et al 2016). However, chronic isolation is likely to cause many fundamental psychophysiological alterations, whose effects and interactions with drugs are beyond the scope of this review. Instead, we focus on interactions between drugs and the current social context. A final topic that is not addressed here is the role of psychosocial and interpersonal factors, such as peer pressure and modelling, which increase the consumption of drugs (Dimoff & Sayette, 2017; Quigley & Collins, 1999). Although there is an extensive literature indicating that observing others can influence use, here we focus instead on how drugs alter responses to social stimuli, and how immediate social contexts modify the direct pharmacological effects of drugs.

For each drug type, we first examine the effects of drugs on social stimuli and social interactions. Several methods have been used to assess the acute effects of drugs on social interactions in the laboratory. First, researchers obtain self-report measures describing feeling states, which may include reports of feeling sociable or a desire to interact with others. Second, researchers obtain objective indices of the quantity and the quality of social

behaviors. These measures might include talking (e.g., time spent talking, content of speech), time spent interacting or socializing with others, or coordinated social activities such as eye contact or smiling. Third, researchers also use specific tasks to determine how drugs change psychological processes that influence interpersonal interactions. For example, drugs may affect the ability to identify emotional expressions in others' faces, and either a decrease in the threshold for recognizing happy expressions, or an increase in the threshold for detecting negative emotions could enhance social interactions. Here we examine evidence using these measures to study effects of several different drug types.

For each drug we also consider how the social setting can influence the quality or magnitude of response to the drug. For example, emotionally positive and stimulating settings such as parties or bars can enhance the mood-altering effects of drugs. Less positive social settings, such as sterile hospital or laboratory environments, can dampen pleasurable effects of drugs. The effects of social (vs isolated) contexts on drug responses have been examined systematically for some drugs, but not for others. When available, we review findings from laboratory-based studies that examined the effects of social context on drug responses.

II Alcohol

Alcohol is typically used in social settings (Kairouz & Greenfield, 2007; Single & Wortley, 1993). This may be the result of many factors, including the effect of alcohol on responses to social stimuli (Aan het Rot et al. 2008), as well as the effect of social contexts on responses to alcohol or, most likely, a combination between these two factors. A few studies have examined these factors under controlled conditions to identify the underlying processes.

IIa Effects of alcohol on responses to social stimuli

Alcohol is widely believed to increase sociability and facilitate social interactions. It might exert these 'prosocial' effects by at least two processes: it may increase reactions to positive social stimuli, or decrease reactions to negative social stimuli, such as social anxiety, that inhibit interpersonal interactions. Laboratory studies provide some support for both of these processes, using both subjective (self-report) measures and objective indices. Subjective measures include ratings of feeling social or increased desire to socialize. Objective indices include changes in perception of other emotions or attractiveness in other individuals, increases in attention to social stimuli, and changes in time spent engaging in social activities.

Both common experience and controlled studies indicate that moderate doses of alcohol increase feelings of sociability. Indeed, increased sociability is a key component in two widely used alcohol rating scales, the Subjective Effects of Alcohol Scale (SEAS; Morean et al. 2013) and the Biphasic Alcohol Effects Scale (Martin et al. 1993). One factor of the SAES includes the adjectives 'talkative', 'lively', 'fun' and 'funny', and a key scale of the BAES includes 'elated, energized, excited, stimulated, talkative, up and vigorous'. These descriptors are all consistent with a prosocial subjective response to alcohol. Thus, one of the apparent direct pharmacological effects of alcohol is to increase the desire to socialize and the pleasure derived from socializing.

The effects of alcohol on social stimuli extends beyond self-reported experiences to more objective measures. Not surprisingly, the social facilitatory, referred to here as 'prosocial', effects of alcohol are especially pronounced when the drug is consumed in a comfortable social setting, such as in the presence of other non-threatening individuals (e.g., Dolder et al. 2017; Kirkpatrick et al. 2013). In social contexts, alcohol increases measures of social interaction (Sayette et al. 2012). In their comprehensive study investigating effects of alcohol on social interactions, Sayette et al found multimodal evidence that alcohol bolstered affective interpersonal responding (Fairbairn et al., 2015b; Sayette et al., 2012). They compared the effects of alcohol vs placebo or no-alcohol control beverages in 720 individuals, measuring self-report, facial expression, content-free speech and acoustical responses. Alcohol robustly increased self-reports of social bonding, amount of time people spent talking and interacting, and Duchenne (enjoyment) smiling, while simultaneously decreasing negative affect-related facial expressions. Alcohol also increased the likelihood that group members would "catch" each other's smiles, as in emotional contagion, especially among male participants (Fairbairn et al., 2015a). Further analyses from this dataset revealed that individuals high in extraversion experienced greater mood-enhancement from alcohol under social conditions (Fairbairn et al. 2015c). Alcohol also influences the perception of emotions in others: It reduced the threshold for detecting happy faces, while leaving expressions of anger, sadness and fear unaffected (Dolder et al. 2017). Interestingly, alcohol also increases participants' ratings of physical attractiveness of others in both laboratory-based and naturalistic settings (e.g., Parker et al, 2008; Attwood et al, 2012; Johnco et al, 2010; Lyvers et al, 2011). Conversely, participants also rate the physical attractiveness of other people who have consumed a low dose of alcohol (0.4 g/kg) higher than sober individuals (Van Den Abbeele et al, 2015). These findings with alcohol are notable in that increased perceived attractiveness of partners is thought to enhance social experiences (Snyder, Tanke, & Berscheid, 1977). Thus, all these objective indices support the common perception that alcohol enhances the positive aspects of social interaction.

Another way in which alcohol can affect social interactions is by reducing social anxiety. There is an extensive literature addressing the common belief that alcohol reduces social anxiety (Cappell & Herman, 1972; Sayette 2017). Anecdotally, many people report that they drink alcohol to reduce anxiety or social stress, and social tension reduction is a primary component on standardized questionnaires of drinking motives and expectancies (DeMartini & Carey, 2011; Kuntsche et al., 2006). Yet, across decades of laboratory research, this anxiolytic, or tension-reducing effect of alcohol has been difficult to document under controlled conditions. The reasons for this are not fully understood (Merrill et al. 2009; Sayette 2017; Tuliao et al. 2016). One factor may be the a-social context of laboratory alcohol studies. Whereas most participants in experimental studies of alcohol and emotion are moderate "social" drinkers who report rarely drinking alone, in the laboratory studies they typically are required to consume alcohol and perform stressful tasks while in isolation (see Fairbairn & Sayette, 2014). This fundamental change in the social context of alcohol administration may contribute to the failure to detect anxiolytic effects. Moreover, even studies that do include a social context often rely on a confederate (e.g., an attractive opposite-sex person with whom the participant must interact) to create the social context. A recent review concluded that alcohol was more likely to enhance emotional experiences

(including relieving stress) when participants underwent unscripted, spontaneously occurring emotional experiences rather than scripted experiences that relied on confederates (Fairbairn & Sayette, 2014). This is an important concern that applies not only to the validity of alcohol challenge studies but also to studies with other classes of drugs. Several researchers have begun to apply more nuanced theories of the effects of alcohol on emotion and cognition (e.g., Bradford et al., 2013), and to use advanced approaches to assessment (e.g., Bartholow et al., 2012). These new approaches will help to understand the specific conditions under which alcohol relieves anxiety (see Sayette, 2017).

IIb Effects of social settings on responses to alcohol

Not only does alcohol alter responses to social stimuli, but social stimuli or social contexts also change responses to alcohol. Controlled studies support the common observation that alcohol produces greater positive mood, and is liked more when it is consumed in a social, compared to an isolated setting (Doty & de Wit, 1995; Kirchner et al., 2006; Kirkpatrick & de Wit, 2013; Pliner & Cappell, 1974; Sayette et al 2012). Doty and de Wit (1995) compared the effects of 2–4 drinks of alcohol or placebo in healthy social drinkers who were tested under either a social condition with other participants, or an isolated condition. Participants in the social condition reported liking the effects of alcohol more and experienced more euphoria (see also Pliner & Cappell, 1974). In addition, when they were given the opportunity to consume one or the other beverage, subjects in the social condition were more likely to choose the alcohol-containing beverage. Using a similar design (but without a choice session), Kirkpatrick et al (2013) compared the effects of alcohol in pairs of subjects tested together or subjects tested individually. In this study, the researchers systematically varied the drug state of the partners in the social condition (alcohol or placebo), so that across four sessions, each subject received alcohol and placebo in the presence of an alcohol-treated or placebo-treated partner. As in the Doty and de Wit study, subjects in the social condition reported feeling more intoxicated than subjects in the isolated condition. Further, subjects in the social condition reported greater feelings of stimulation from alcohol when their partner also received alcohol. In a systematic study using event-contingent recordings in the natural setting, Aan het Rot et al (2008) found that use of alcohol in social settings is usually associated with enhanced mood states and increased perception of agreeableness in others, although it is not certain that these outcomes were a direct effect of alcohol. Taken together, these findings indicate that the presence of others can alter the behavioral responses to alcohol, even under double-blind, controlled conditions. We speculate that the presence of other individuals permits the full expression of the prosocial effects of the drug, so that the drug facilitates social interaction, and the social context enhances the effects of the drug.

We have reviewed the effects of social environments on the direct mood-altering effects of alcohol, but there is also an extensive literature on the influence of social factors on the amount of alcohol consumed. Although the focus of this review is on direct effects of drugs rather than consumption of drugs, it is clear that social settings influence consumption through a range of psychosocial processes such as modelling, peer pressure and desire to conform, in both positive or negative social contexts (Beck et al. 2011; Caudill & Marlatt 1975; Collins & Marlatt, 1981; Cooper et al. 1979; Larsen et al 2012; Quigley & Collins,

1999; Watson & Sobell 1982). For example, social modelling of heavier consumption increases drinking of other group members, and this effect is moderated by several variables, including the participant's drinking history (see Quigley and Collins, 1999). It is likely that modeling, perhaps by creating expectancies, can influence not only consumption but also the direct, intoxicating effect of alcohol.

III. Stimulants

IIIa Effects of stimulants on social stimuli

Single doses of prototypic stimulant drugs such as d-amphetamine, methamphetamine, or methylphenidate increase subjective feelings of sociability as well as objective indicators of prosocial effects (Bershad et al 2016). Stimulant drugs dose-dependently increase ratings of feeling 'talkative', 'sociable' and 'friendly', although higher doses can increase anxiety (Williamson et al. 1997). On behavioral measures, stimulants also increase affective responses to positive social stimuli. In one study, *d*-amphetamine (10mg, 20mg) enhanced positive emotional responses to affective visual images, including those with social content (Wardle & de Wit 2012) and in another study it enhanced the ability to identify emotional expressions in others (Wardle et al, 2012). Surprisingly, methylphenidate specifically improved the ability to identify negative emotional expressions (Hysek et al., 2014), although this study used a relatively high dose of methylphenidate (60 mg), which also produced some unpleasant effects. Another prosocial effect of drugs is sexual approach, which can be measured by assessing responses to implicit or explicit sexual images. Schmid et al (2015) found that methylphenidate increased arousal ratings and increased the average time participants chose to spend viewing implicit erotic images, suggesting an increased interest in sexual social encounters. Whether this effect is unique to methylphenidate or whether it also occurs with other typical stimulants remains to be determined.

Another indicator of the prosocial effect of stimulants is their capacity to increase speech, a key index of human social interaction. Stimulant drugs increase both self-reports of feeling talkative and objective indices of speech quantity, production, fluency, and content (Griffiths et al., 1977; Higgins & Stitzer, 1989; Marrone et al., 2010; Stitzer et al., 1978; Strakowski et al., 1996; Ward et al., 1997; Wardle et al., 2012). Remarkably, stimulant drugs increase talkativeness even when subjects are tested alone (Higgins & Stitzer, 1989).

To our knowledge, only one study has examined the effects of typical stimulant drugs in an apparently negative social setting. In a recent study, Childs et al (2016) found that d-amphetamine did not dampen anxiety in response to a standardized public speaking task, compared to a nonstress control in healthy volunteers. They found that amphetamine did not decrease the stress response; instead the drug increased ratings of how stressful the subjects judged the task to be, and extended the feelings of tension after the stress task.

'Designer' stimulants such as 3,4-methylenedioxymethamphetamine (MDMA) appear to produce unique prosocial effects that distinguish them from typical stimulants (Bershad et al., 2016). In addition to the increased feelings of sociability and friendliness observed with other stimulants, MDMA also increases reports of feeling 'loving' and 'playful' and feelings of trust and empathy (e.g., Bedi et al., 2009; Harris et al., 2002; Kirkpatrick et al., 2012;

Tancer and Johanson, 2003), although higher doses induce feelings of anxiety (Bedi et al., 2010; Hall et al., 1996; MDMA (0.75mg/kg, 1.5mg/kg). MDMA increased positive social images (i.e., depicting people; Wardle et al., 2014), whereas the effects of d-amphetamine were not specific to social images. On a measure of emotional 'empathy' MDMA appears to modestly increase response to emotional states of others (Hysek et al., 2013; Kuypers et al., 2014; Schmid et al. 2014) whereas methylphenidate does not (Schmidt et al., 2014). On measures of sensitivity to detecting emotions in others, MDMA enhanced identification of positive emotions and reduced identification of negative emotions (Bedi et al., 2010; Hysek et al., 2014; Kirkpatrick et al., 2014; Schmid et al., 2014; Wardle et al., 2014). Schmid et al (2015) reported that, unlike prototypic stimulants, MDMA did not increase responses to sexual stimuli, suggesting that the effects of MDMA are not specifically related to sexual attraction. This finding is consistent with reports from users that MDMA increases emotional closeness and openness to sexual activity but not sexual desire *per se* (Buffum & Moser, 1986; McElrath, 2005; Zemishlany et al., 2001). MDMA also changes the content of speech, increasing the use of sexual, social and emotional, especially positive emotional, words (Baggott et al., 2015; Wardle & de Wit 2014). In one study (Bedi et al., 2014), MDMA increased speech with semantic proximity to concepts of "friend, support, intimacy, and rapport", whereas methamphetamine (20 mg) did not increase the social content of speech. Marrone et al (2010) directly compared the effects of MDMA and methamphetamine on speech. Whereas methamphetamine increased quantity of speech, fluency, and self-ratings of talkativeness and alertness, MDMA decreased fluency and impaired the ability to concentrate. Although these differences between MDMA and other stimulants may depend on the doses used, they might also suggest intriguing and unique effects of the drugs on verbal, or social, interaction.

There is also evidence that MDMA enhances perceptions of others during an actual social interaction (Baggott et al., 2015; Bedi et al., 2014; Wardle & de Wit, 2014). For example, MDMA increases the degree to which individuals feel understood by others, and increases the comfort participants feel when describing autobiographical memories to a researcher. MDMA also increases self-report ratings of "trust" and "closeness to others" (Greer & Tolbert, 1986, Schmid *et al.* 2014), overt behavioral indices of these concepts, including trust decisions, reciprocity, and resource allocation (Kirkpatrick et al. 2015). In the context of the use of MDMA as an adjunct to psychotherapy, each of these processes may help to strengthen alliances between psychotherapist and client (Bouso et al., 2008; Johansen & Krebs, 2009; Mithoefer et al., 2011). Unfortunately, some of these psychosocial processes have only been studied with MDMA, and there are no data directly comparing its effects to the effects of prototypic stimulants. Differences between MDMA and other stimulants are discussed in greater detail by Bershad et al (2016).

MDMA has mixed effects on responses to negative social encounters. Baggott et al. (2015) reported that MDMA (1.5 mg/kg) *decreased* social anxiety on the Brief Fear of Negative Evaluation measure, while at the same time the drug also *increased* ratings of general anxiety. Like d-amphetamine, MDMA did not dampen anxiety in response to a standardized public speaking task (Bershad et al. 2016), but it did reduce feelings of exclusion or rejection elicited by the Cyberball task (Frye et al. 2014; Williams & Jarvis, 2006; Zadro et al., 2004). It is not clear how these different outcomes can be reconciled. In the public

speaking task, participants are faced with an evaluative examiner, and required to perform a speech task in real life, whereas in the Cyberball task, subjects experience computer images simulating inclusion in a game, followed by exclusion. It is likely that the speech task and the Cyberball exclusion task target different forms of social anxiety. The conditions under which MDMA dampens responses to different types of negative social experiences are not fully understood. Importantly, however, the dampening of feelings of social rejection may contribute to the psychotherapeutic benefits of MDMA by allowing patients to speak freely and openly about difficult issues.

The studies reviewed here support the idea that stimulant drugs, including MDMA, increase reactivity to affective stimuli in ways that could enhance social interactions. The drugs appear to facilitate social interaction both by decreasing the threshold for detecting positive emotions in others, and by increasing the threshold for detecting negative emotions. MDMA may have unique effects on some these measures, consistent with its widespread use in highly social situations (e.g. ‘raves’), and its ability to enhance psychotherapy. It is likely that higher doses would have markedly different, and perhaps adverse, effects on social interactions, but this is difficult to study ethically under experimental conditions. It is also possible that chronic use of stimulant drugs, or use in less safe environments, would produce a markedly different profile of effects on social function.

IIIb Effects of social factors on responses to stimulant drugs

As in the case of alcohol, there is some evidence that social context can influence responses to stimulant drugs. Early studies with laboratory animals indicate that stimulant drugs have greater physiological effects when animals are tested in aggregate, compared to individually (Chance et al. 1946). We have previously tested whether the presence of other individuals changes the direct mood-altering and physiological effects of oral d-amphetamine in healthy young adults. In one study (de Wit et al. 1997), healthy young adults were randomly assigned to a social condition in which they received oral *d*-amphetamine with 2 or 3 other participants or an isolated condition in which they were tested alone. Within the testing groups in the group condition, members of the groups received drug or placebo in a randomized order. Although the presence of others had no effect on the mood-altering effects of d-amphetamine, the drug produced a greater increase in body temperature and heart rate under social, compared to isolated, conditions (de Wit et al., 1997). Zacny et al (1992) similarly found no effect of social context on subjective responses to amphetamine.

Kirkpatrick & de Wit (2015) compared the effects of MDMA in social or isolated conditions, with different results. Healthy young adults received MDMA (0, 0.5 and 1.0 mg/kg) during four-hour laboratory sessions under one of three conditions: i) tested in a room alone, ii) tested in the presence of a research assistant, or iii) tested in the presence of another participant who received the same dose of the drug. When subjects were tested together with another drug-treated participant, the drug produced a greater increase in heart rate, as well as greater subjective reports of feeling the drug and liking the drug, compared to either those who received the drug alone or with a research assistant. Social conditions increased not only physiological responses but also subjective responses to the drug relative

to isolated conditions. Thus, a drug known for its prosocial effects produced more positive effects when experienced in a social setting.

Much remains to be determined about the interactions between social contexts and responses to stimulant drugs. Compared to responses to alcohol, fewer studies have been conducted. Outside the laboratory, users take doses of stimulants far higher than those used in laboratory studies, leaving dose-related questions unanswered. Outside the laboratory, the social contexts in which drugs are used are rarely either completely safe or highly threatening, but rather a mixture of positive and negative. These factors make it difficult to generalize from laboratory findings. From a mechanistic point of view there is evidence that stimulant drugs may act on brain circuits that overlap with circuits mediating social reward (Fareri & Delgado, 2014), and these interactions could influence drug use in a social setting. These topics are rich areas for future research: How do positive or negative social contexts influence responses to stimulant drugs, and how these drugs affect social interactions?

IV. Opioids

IVa. Effects of opioids on social stimuli

Despite an extensive literature on the role of the endogenous opioid system on social behavior in rodents (Trezza et al. 2014; Bardo, et al 2013; Eitan et al 2017), surprisingly little is known about the acute effects of opioid drugs on social function and perception of social stimuli in humans. This may be in part because of ethical constraints on studies with opioids in humans. A recent review of evidence from studies with humans that opioids facilitate social connection (Inagaki 2017) notes evidence that opioid antagonists such as naltrexone reduce the pleasurable effects that typically arise from social experiences. In one study (Depue & Morrone-Strupinsky, 2005) naltrexone reduced feelings of warmth and affection to an affiliative film clip and reduced tolerance to painful heat following the film clip in women high in trait affiliation. In another study (Schweiger et al., 2014) naltrexone reduced pleasant feelings (e.g., cozy, liked) in women after a trust game. Inagaki and colleagues (2015) showed that naltrexone reduced feelings of social connection that are induced by holding a warm object, and it reduced feelings of social connection to reading loving messages from close friends and family members (Inagaki et al., 2016). In other studies, naltrexone decreased positive facial mimicry to smiling strangers (Meier et al., 2016) and decreased the amount of money invested during an economic trust game in women (Schweiger et al., 2014), although it did not alter ratings of emotional pictures or responses to emotional faces (Wardle et al., 2016). In contrast to drugs that block endogenous opioids, there is some evidence that drugs that activate the endogenous opioid system have social-facilitatory, or pro-social effects. Morphine increased the amount of time subjects spent viewing pictures of attractive faces, increased attractiveness ratings of the most physically attractive pictures, and increased eye gaze toward the eye region of the face (Chelnokova et al., 2015, 2016). Buprenorphine, a mixed partial mu agonist and kappa antagonist, improved memory for the location of happy faces, but not fearful or angry faces (Syal et al., 2015), and the mu agonist remifentanil increased ratings of pleasantness of neutral social and nonsocial pictures (Gospic et al., 2007).

There is some evidence that opioid drugs dampen responses to negative stimuli (Bershad et al. 2015; 2016; 2017). Single doses of buprenorphine reduced both subjective and physiological responses to images with negative emotional content in healthy adults (Bershad et al 2016), and reduced the ability to recognize fearful faces (Ipser et al., 2013), especially in individuals with high baseline levels of depression and anxiety (Bershad et al. 2017). In addition, buprenorphine blocked the increase in cortisol induced by an acute social stress task (public speaking), and decreased participants' ratings of how threatening they found the task (Bershad et al. 2015). These findings are consistent with the idea that opioid drugs reduce perception of negative social stimuli. As noted above, opioid antagonists have effects on social processes that are opposite to those of opioid agonists (Inagaki, 2017; Rutgen et al. 2015; Wardle et al. 2016). Taken together, these studies suggest that drugs that increase opioid function increase feelings of social connection.

IVb. Effects of social context on mood responses to opioids

To our knowledge, few experimental studies have examined the converse relationship, i.e., the effect of social setting on either mood-altering of physiological responses to opioids. It is not known whether social setting affects mood responses to opioid drugs in healthy volunteers without histories of drug use. One early study examined social behavior in men with a recent history of heroin use (Babor et al. 1976), The men allowed to self-administer heroin in a residential laboratory for 8 days. The authors noted that while the first self-administered dose of heroin seemed to increase talking, continued use over days reduced talking and motivation for social affiliation. Over the 8 days, participants showed reduced social interaction and chose to remain alone more of the day. In view of the extensive preclinical literature on the role of endogenous opioids and social bonding, there are many questions about how social factors influence responses to single doses of opioids, and how these change with chronic administration. Systematic studies are needed to determine how social context affects acute responses to opioid drugs in nondependent users, and how the social effects of opioids change with chronic administration or after dependence has developed.

V. Cannabis

Va Effects of cannabis on social interaction

Cannabis has mixed effects on social behaviors, including both increases and decreases in talking or interacting socially. Most of the studies examining effects of cannabis on social interaction were conducted in the 1980's. Higgins & Stitzer (1986) assessed the effects of smoked cannabis on social conversation. They recorded speech quantity after paced smoking of 0, 1.01, 1.84, and 2.84% THC cannabis cigarettes, while participants engaged in conversation with partners who smoked placebo cigarettes. The active cannabis increased heart rate and feelings of 'high', but decreased speech quantity. As noted by the authors, this pattern of decreased speech suggests that cannabis is an exception to the general rule that drugs of abuse increase verbal interaction. Foltin et al (1987) examined social interaction in cannabis users who were tested in small groups in a residential laboratory. Subjects remained in private rooms doing 'work' activities, and were allowed to socialize with other participants from 4 pm to midnight each day. In this context, active cannabis (compared to

placebo) increased social and verbal interaction, although these effects were most apparent in groups that displayed high baseline levels of interaction (Rachlinski et al., 1989). Cannabis decreased verbal interactions in participants who exhibited greater baseline interpersonal distance. In one other study from the same laboratory, Foltin & Fischman (1988) examined the effect of cannabis on the amount of time that participants socialized with other subjects. Participants were allowed to smoke four 2.7% THC cannabis cigarettes or placebo each day. Active cannabis did not increase the amount of time subjects spent in the social area. The drug increased the amount of time that subjects engaged in the same activities, but it did not increase verbal behavior. With the dramatic increases in availability and use of cannabis it is likely that there will be a resurgence of interest in the effects of cannabis on social functioning.

One aspect of cannabis use that has received relatively little attention is its potential to reduce the aversive effects of negative social settings. Recent evidence indicates that the endogenous cannabinoid system plays a key role in the body's response to stress (Hill et al, 2018), and many cannabis users claim to use the drug for its calming effects. In one of few systematic studies investigating this idea, Childs et al (2017) recently reported biphasic dose effects of THC on responses to a standardized social stress procedure in healthy young adults who reported some occasional use of cannabis but were not daily or dependent users. A low dose of oral THC (7.5 mg) slightly decreased distress during the task and decreased post-task appraisals whereas a higher dose (15 mg) had the opposite effect, increasing feelings of tension and stress. The nature of the purported calming effects of cannabis are poorly understood, and likely depend on expectancies, dose, context, and drug use history of the user. In conclusion, even though cannabis is often used in social settings, it does not robustly increase components of social behavior or facilitate interactions, either by enhancing the positive aspects of social interactions or by decreasing negative social experiences.

Vb Effects of social settings on responses to cannabis

To our knowledge, few studies have systematically examined the effects of social settings on responses to cannabis. One study by Foltin et al (1994) found that some subjects smoked more cannabis in the presence of other participants, but this was not accompanied by an increase in positive mood effects. Six male cannabis smokers were allowed to self-administer cannabis cigarettes (0.0% or 2.3% THC) during a 12-day residential study. Each day was divided into 6.5-h solitary work and social-access periods, in mixed order (work first or social first). Three subjects smoked more cannabis during the social-access period, regardless of when it occurred, whereas the other three smoked more in the morning regardless of activity. However, the number of cannabis cigarettes smoked was unrelated to THC content, suggesting that intake was controlled more by expectancies than by pharmacological effects. Although active cannabis increased subjective reports of "High," "Liking," "Potency" and "Drug", these subjective reports were not related to context or predictive of drug self-administration. These findings illustrate the important point that consumption of a drug is not determined solely by the subjective feelings derived from a drug. It is likely that the mood-altering effects of cannabis do contribute to use of the drug,

but use is also controlled by numerous other factors including current work demands, expectancies, time of day and presence of other individuals.

VI. Conclusions

We have reviewed empirical evidence that all four types of drugs considered here, alcohol, stimulants, opioids and cannabis, can influence social processes. We conclude that the drugs' effects on social stimuli vary with both the drug and the nature of the social context. Alcohol and stimulant drugs enhance the perception of positive social stimuli and increase positive social interactions, whereas opioids and cannabis have subtler effects on these indices. Surprisingly, there is only limited empirical evidence that any of these drugs dampen responses to negative social stimuli, with the exception of the stimulant MDMA. MDMA appears to have unique facilitatory effects on psychosocial function, including increased feelings of trust and empathy, and a decreased sensitivity to negative emotions in others. Further research will help to understand the neurochemical mechanisms that underlie interactions between drugs and social stimuli. Notably, each of these drugs are known to act on neurotransmitter systems known to be involved in processing of both positive and negative experiences (dopamine, serotonin, endogenous opioids and endocannabinoids),

We also reviewed studies of how positive or negative social contexts influence the acute mood-altering or other effects of drugs. Among the four drugs reviewed, only alcohol was clearly more pleasureable in the presence of others. Whether this reflects an aspect of its pharmacology, or environmental factors such as habit, culture or expectancies, remains to be determined. It is surprising that stimulant drugs, which increased feelings of sociability and increased talking), were not more rewarding in a social context. How positive, or negative, social contexts alter the direct effects of drugs is an important and understudied subject.

These findings from laboratory studies support anecdotal evidence from naturalistic settings that there are bi-directional interactions between drugs and the social contexts in which they are used. Indeed, we would argue that it is not possible to understand fully why drugs are used, and perhaps abused, without knowing how and why they interact with social settings. Many questions remain to be addressed especially at different stages of drug use (see Dimoff & Sayette, 2017). For example, to what extent do social settings influence drug use among drug-dependent individuals, and how do social contexts affect the course of withdrawal and relapse? How do various social contexts (e.g., strangers vs. friends or romantic partners) differentially influence drug effects (see Fairbairn, 2017)? To what extent are the findings with humans consistent with data from studies with laboratory animals, where there is also strong evidence for social factors in self-administration (e.g., Robinson et al, 2017)? Finally, there are critical questions about the neurobiological mechanisms that underlie the context-drug interactions, including questions about overlapping neurobiological pathways supporting both psychosocial function and drug use. Advances in our understanding of these processes will help to develop approaches to protect individuals from excessive drug use, and to develop aids in treating addiction once it has developed.

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