Review

The effects of MDMA on socio-emotional processing: Does MDMA differ from other stimulants?

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Abstract

±3,4-Methylenedioxymethamphetamine (MDMA) is a popular recreational drug that enhances sociability and feelings of closeness with others. These "prosocial" effects appear to motivate the recreational use of MDMA and may also form the basis of its potential as an adjunct to psychotherapy. However, the extent to which MDMA differs from prototypic stimulant drugs, such as dextroamphetamine, methamphetamine, and methylphenidate, in either its behavioral effects or mechanisms of action, is not fully known. The purpose of this review is to evaluate human laboratory findings of the social effects of MDMA compared to other stimulants, ranging from simple subjective ratings of sociability to more complex elements of social processing and behavior. We also review the neurochemical mechanisms by which these drugs may impact sociability. Together, the findings reviewed here lay the groundwork for better understanding the socially enhancing effects of MDMA that distinguish it from other stimulant drugs, especially as these effects relate to the reinforcing and potentially therapeutic effects of the drug.

Keywords

MDMA, social behavior, stimulants, amphetamines, emotion

Introduction

Psychostimulant drugs produce feelings of euphoria and stimulation, as well as increasing confidence and enhancing social interaction. One stimulant drug in particular, ±3,4-methylenedioxymethamphetamine (MDMA, "ecstasy," "molly"), is known for its unusual prosocial and "empathogenic" subjective effects, and for its potential use as an adjunct to psychotherapy. In the 1970s, MDMA was used to facilitate self-awareness and empathy during psychotherapy (Downing, 1986; Greer and Tolbert, 1986; Grinspoon and Bakalar, 1986; Shulgin, 1986). Even after the drug became illegal in the USA in 1985, recreational use of MDMA increased steadily, especially in a dance-music culture that was arguably influenced by the drug's unusual effects (Reynolds, 1998). In the mid-1980s, based on the structure–activity relationships of MDMA-like molecules, Nichols (1986) proposed that the psychosocial effects of MDMA represented a novel pharmacological class, which he named "entactogens" to capture its apparently unique sensory and emotional effects. Data from rodent drug-discrimination paradigms (reviewed in Glennon, 1999; Nichols and Oberlender, 1989) suggested that MDMA was clearly distinguishable from hallucinogens, but shared many pharmacological, discriminative, and behavioral effects with prototypic amphetamine-like stimulants. Finally, in the 1990s, researchers began to conduct controlled studies to measure the psychosocial effects of MDMA in humans and to compare these to the effects of other stimulants.

This review complements a recent paper by Kamilar-Britt and Bedi (2015) who comprehensively reviewed empirical studies of the psychosocial effects of MDMA. Here, we extend that overview by focusing on the contrasts between MDMA and prototypic stimulant drugs. Kamilar-Britt and Bedi (2015) concluded, based on about 30 published studies, that MDMA has "prosocial" effects and that it dampens reactivity to negative emotional stimuli. Here, we extend that analysis to examine possible differences between MDMA and prototypic stimulant drugs in order to identify which subjective and behavioral effects are unique to MDMA, and how the mechanism of action of the drug may explain these effects. One of the apparently distinctive effects of MDMA is that it enhances sociability and interpersonal closeness (M ter Bogt and Engels, 2005; Peters and Kok, 2009; Sumnall et al., 2006), which may contribute to both recreational use and potential therapeutic use. Inducing a state of sociability and interpersonal closeness may allow psychotherapy patients to explore negative emotions and cognitions, such as traumatic memories related to post-traumatic stress disorder (Mithoefer et al., 2011, 2013; Oehen et al., 2013). Interestingly, classic stimulant drugs also produce prosocial effects and were historically also proposed as adjuncts to psychotherapy (Moon, 2009;

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Rasmussen, 2008). Thus, although MDMA purportedly has distinctive effects, the empirical basis for this has not been examined closely.

Here, we review these drugs' effects on self-report ratings, behavioral tasks, and social interactions in placebo-controlled, double-blind studies in human volunteers. We also review preclinical and clinical studies investigating the potential neurochemical mechanisms of the observed prosocial effects. Our goal is to determine the extent to which the effects of MDMA are distinct from approved and widely studied drugs such as amphetamine. Unfortunately, because relatively few studies have examined the effects of classic stimulant drugs on socio-emotional processing, less is known about these effects, relative to MDMA. Few studies have directly compared the two. Another challenge is determining doses that are comparable for each drug. Throughout this review, we have made an effort to note and discuss the comparability of doses of MDMA compared to other stimulants, when appropriate. The aim of this review is to improve the understanding of the nature and mechanisms of how MDMA and other stimulants produce their psychosocial effects and how these effects contribute to both recreational use and potential therapeutic value.

Methods

Relevant articles for this review were selected via two methods. First, PubMed and Google Scholar searches were conducted using a combination of search terms, including "human," "MDMA," "psychostimulants," "stimulants," "social," "emotion," "methamphetamine," "methylphenidate," "*d*-amphetamine," and "mechanism." Second, additional articles were selected from the reference lists of the articles obtained from the searches if they (1) included a sample of healthy human volunteers and (2) assessed the acute effects of drugs on some aspect of socio-emotional function, including subjective, behavioral, physiological, and neural outcomes. The results are summarized in Table 1.

Self-report effects

Much of our knowledge about the effects of MDMA and other psychostimulants comes from self-reports of users; either retrospective reports from recreational users or reports obtained during controlled administration in laboratory studies. These self-report measures provide some of the primary evidence for the prosocial effects of the drugs. Early evidence about MDMA, based on MDMA users' recall of their experiences in naturalistic settings, consistently suggests that this drug produces powerful prosocial effects. Siegel (1986) found that 68% of users reported "enhanced communication, empathy, or understanding." Peroutka et al. (1988) surveyed university students who had used MDMA, and found the most common effect reported was a heightened sense of "closeness" with others. There are, to our knowledge, no corresponding naturalistic studies of social effects of other stimulants such as methamphetamine. However, there are quite a number of placebo-controlled laboratory-based studies confirming that both MDMA and other stimulants increase feelings of sociability. MDMA dose-dependently increases ratings of sociability, euphoria, and positive mood (Dumont and Verkes, 2006; Kamilar-Britt and Bedi, 2015). MDMA at doses of 1.0–1.5 mg/kg, but not lower doses, produces feelings of friendliness and sociability (e.g. Bedi et al., 2009, 2010; Harris et al., 2002). Similarly, modest oral doses (10–20 mg) of prototypic stimulants such as dextroamphetamine (*d*-amphetamine) and methamphetamine enhance self-reported positive mood and increase self-reports of feeling "social," "stimulated," "friendly," and "talkative" (Kirkpatrick et al., 2012; Tancer and Johanson, 2003). However, several subjective effects appear to be unique to MDMA, including increases in feelings of "closeness," "trust," and "openness" (Schmid et al., 2014), suggesting that the drug may have distinctive effects on intimate interaction. Interestingly, a recent study showed that lysergic acid diethylamide (LSD; 200 μg), which, like MDMA, has important serotonergic activity, increased ratings of trust, openness, and closeness to others (Schmid et al., 2015a). This similarity suggests that the unique effects of MDMA among stimulants on these feelings of connection may be related to its effects on serotonin. Although these findings are suggestive of qualitative differences in subjective interpersonal feelings between MDMA and other stimulants, one caution is that researchers have not specifically sought to test for these effects with prototypic stimulants, leaving the possibility that they may exist.

One psychological process whereby a drug might increase feelings of sociability is by decreasing social anxiety. For example, MDMA may increase feelings of social connectedness by dampening anxiety in social settings. However, evidence that the prosocial effects of MDMA are secondary to a general anxiolytic effect is mixed. In fact, MDMA sometimes produces modest *increases* in anxiety (e.g. Kirkpatrick et al., 2014b), and participants report feeling impaired in some aspects of social or cognitive functioning. It is possible that MDMA specifically dampens social anxiety versus other forms of anxiety. In support of this idea, Baggott et al. (2016) reported MDMA (1.5 mg/kg) *decreased* social anxiety (measured with the Brief Fear of Negative Evaluation) while also *increasing* visual analog scores for general anxiety. There is little evidence that other stimulant drugs, such as amphetamine, decrease anxiety, and indeed they can increase anxiety (Angrist and Gershon, 1970; Ellinwood et al., 1973; Kirkpatrick et al., 2012; Wardle et al., 2012). Notably, although few studies have examined the effects of classic stimulant drugs specifically on social anxiety, we recently reported that *d*-amphetamine does not decrease social anxiety induced by a standardized public-speaking task (Childs et al., 2016). Whether either MDMA or other stimulants have selective effects on other forms of social anxiety remains to be determined.

Another psychological process by which MDMA may produce its effects is by increasing feelings of "authenticity." Authenticity is a construct with roots in humanistic psychology, which refers to the feeling of being connected to one's inner being rather than to external demands (Maslow, 1968; Rogers, 1961). It is associated with lessened defensiveness and feeling that one is able to be oneself. Using the Authenticity Index (Kernis and Goldman, 2006; Lakey et al., 2008; Wood et al., 2008), Baggott et al. (2016) recently reported that MDMA increases feelings of authenticity, including related feelings such as self-regard and self-acceptance. These findings are consistent with a recent naturalistic self-report study indicating that illicit ecstasy preparations increase self-compassion (Kamboj et al., 2015). To our knowledge, these dimensions of authenticity have not been studied with typical stimulant drugs, although it has

Table 1. Results of human laboratory studies investigating the socio-emotional effects of MDMA and other stimulant drugs.

Measure	Study	*N*	MDMA	Effect	Other stimulant	Effect
Mood states						
Friendly (POMS or VAS)	Bedi et al., 2009	9	1.5 mg/kg	↑	—	—
	Tancer and Johanson, 2003	12	1 mg/kg	NE	10 mg *d*-amph	NE
			2 mg/kg	↑	20 mg *d*-amph	↑
	Van Wel et al., 2012	17	75 mg	↑	—	—
	Harris et al., 2002	8	1.5 mg/kg	↑	—	—
	Bedi et al., 2010	21	0.75 mg/kg	NE	—	—
			1.5 mg/kg	↑		
	Johanson et al., 2006	8	1.0 mg/kg	↑	20 mg *d*-amph	↑
			1.5 mg/kg	↑		
Social (VAS)	Tancer and Johanson, 2003	12	1 mg/kg	NE	10 mg *d*-amph	NE
			2 mg/kg	↑	20 mg *d*-amph	↑
	Kirkpatrick et al., 2012	11	100 mg	↑	20 mg meth	↑
					40 mg meth	↑
	Bedi et al., 2010	21	0.75 mg/kg	NE	20 mg meth	↑
			1.5 mg/kg	NE		
Talkative (VAS)	Tancer and Johanson, 2003	12	1 mg/kg	NE	10 mg *d*-amph	NE
			2 mg/kg	↑	20 mg *d*-amph	↑
	Kirkpatrick et al., 2012	11	100 mg	↑	20 mg meth	—
					40 mg meth	↑
Ratings of emotional images (IAPS)						
Positive ratings for images with social content only	Wardle et al., 2014	101	0.75 mg/kg	NE	—	—
			1.5 mg/kg	↑		
Positive ratings of images with and without social content	Wardle and de Wit, 2012	36	—	—	10 mg *d*-amph	NE
					20mg *d*-amph	↑
Emotional empathy (MET)						
For both positive and negative situations	Hysek et al., 2014a	32	125 mg	↑	—	—
	Kuypers et al., 2014	30	75 mg	↑	—	—
For positive situations only	Schmid et al., 2014	30	75 mg	↑	40 mg methylphenidate	NE
Emotion recognition (FERT, RMET, DEIT)						
Recognition: all emotions	Wardle et al., 2012	36	—	—	10 mg *d*-amph	NE
					20 mg *d*-amph	↑
Recognition: anger	Wardle et al., 2014	36	0.75 mg/kg; 1.5 mg/kg	NE	—	—
				↓		
Recognition: sadness	Schmid et al., 2014	30	75 mg	↓	40 mg methylphenidate	NE
Recognition: anger and fear	Kirkpatrick et al., 2014b	65	0.75 mg/kg 1.5 mg/kg	NE	—	—
				↓		
Recognition: fear	Bedi et al., 2010	21	0.75 mg/kg	NE	20 mg meth	NE
			1.5 mg/kg	↓		

(Continued)

Table 1. (Continued)

Measure	Study	*N*	MDMA	Effect	Other stimulant	Effect
Recognition: negative emotions	Hysek et al. 2014a	32	125 mg MDMA	↓	—	—
	Hysek et al., 2014b	16	125 mg MDMA	↓	60 mg methylphenidate	↑
Psychophysiological responses						
Positive responses to happy faces	Wardle and De Wit, 2014	36	0.75 mg/kg	NE	—	—
			1.5 mg/kg	↑		
Positive responses to positive stimuli	Wardle et al., 2012	36	—	—	10 mg *d*-amph	NE
					20 mg *d*-amph	↑
Amygdala responses to negative faces	Bedi et al., 2010	9	1.5 mg/kg	↓	—	—
	Hariri et al., 2002	12	—	—	0.25 mg/kg	↑
Ratings of erotic images	Schmid et al., 2015b	30	75 mg	NE	40 mg methylphenidate	↑
Speech						
Quantity	Marrone et al., 2010	11	100 mg	NE	20 mg meth	↑
					40 mg meth	↑
	Ward et al., 1997	6	—	—	5 mg *d*-amph	--
					10 mg *d*-amph	↑
	Griffiths et al., 1977	7	—	—	5–30 mg *d*-amph	↑
	Wardle et al., 2012	36	—	—	10 mg *d*-amph	NE
					20mg *d*-amph	↑
Fluency	Marrone et al., 2010	11	100 mg	↓	20 mg meth	↑
					40 mg meth	↑
Content	Baggott et al. 2016		1.5 mg	↑	—	—
Social words						
	Bedi et al., 2014		0.75 mg/kg	NE	20 mg meth	NE
			1.5 mg/kg	↑		
Effects of social interactions on drug responses						
Subjective effects	Kirkpatrick et al., 2015	32	0.5 mg/kg 1.0 mg/kg	NE	—	—
				↑		
	de Wit et al., 1997	42	—	—	10 mg *d*-amph	NE
					20 mg *d*-amph	NE
Physiological effects (heart rate, blood pressure)	de Wit et al., 1997	42	—	—	10 mg *d*-amph	NE
					20 mg *d*-amph	↑
	Zacny et al., 1992	8	—	—	20 mg *d*-amph	NE
	Kirkpatrick et al., 2015	32	0.5 mg/kg; 1.0 mg/kg	NE	—	—
				↑		

MDMA: ±3,4-methylenedioxymethamphetamine; ↑: increase; ↓: decrease; NE: no effect; VAS: Visual Analogue Scale; POMS: Profile of Mood States; MET: Multifaceted Empathy Test; FERT: Facial Emotion Recognition Test; RMET: Reading the Mind in the Eyes Test; *d*-amph: *d*-amphetamine; meth: methamphetamine.

been reported that positive mood can increase feelings of authenticity (Lenton et al., 2013). It therefore remains to be determined whether MDMA affects this feeling state in a way that differs from typical stimulants.

Social perception

Another way of assessing "prosocial" effects of drugs is to measure how the drug affects the perception or processing of social stimuli. Several studies have investigated the acute effects of MDMA and other simulants on aspects of social perception. These studies, summarized here, suggest that both MDMA and other stimulants alter the ways in which individuals respond to social and sexual visual stimuli, as well as the degree to which they recognize emotions in the faces of others (i.e. "cognitive empathy"). Other studies have investigated the effect of MDMA on the experience of social rejection.

Responses to social images and empathy

Several studies have examined the effects of both MDMA and other stimulants on ratings of positivity or negativity of images depicting social or nonsocial scenes. Some of these studies addressed the hypothesis that MDMA produces its prosocial effects by increasing positive responses to positive social stimuli, and dampening negative responses to negative social stimuli. Wardle et al. (2014) measured MDMA (0.75 mg/kg, 1.5 mg/kg) effects on ratings of positive and negative, social and nonsocial images from the International Affective Picture System (IAPS). MDMA *increased* how positively participants rated positive social images (i.e. those depicting people), but *decreased* how positively they rated positive images without social content. The drug did not alter ratings of negative or neutral images, whether social or non-social. In contrast, *d*-amphetamine (10 mg, 20 mg) enhanced positive emotional responses in general, but its effects were not specific to stimuli with social content (Wardle and De Wit, 2012). This provides some evidence that MDMA may selectively alter how people process social, compared to nonsocial, rewards.

The effects of MDMA and other stimulants on social perception have also been studied using measures of empathy. Empathy has been defined as either "empathic concern," that is, an individual's emotional response to the emotional state of another (Dziobek et al., 2008), or a more cognitive measure, that is, the ability to detect emotions in others. Empathic concern has been assessed using the Multifaceted Empathy Test in which participants view images of emotionally charged situations, and report how much they "feel for" each person depicted (explicit emotional empathy), and how "aroused" they feel (implicit emotional empathy; Dziobeck et al., 2008). Hysek et al. (2014a) reported that MDMA (125 mg) modestly increased both explicit ("feel for") and implicit ("aroused") emotional empathy for positive situations, especially in men. Schmid et al. (2014) replicated these findings at a lower dose (75 mg), and Kuypers et al. (2014) found that MDMA increased emotional empathy for both positive and negative emotional situations. Of the few of studies that compared the effects of MDMA to a classic stimulant, Schmid et al. (2014) reported that methylphenidate (40 mg) did not increase ratings of emotional empathy for positive situations. Thus, while there have been slight inconsistencies across studies, MDMA appears to increase emotional empathy, especially for positive situations, and these effects have not been reported for other stimulant drugs. Inconsistencies across studies may be related to variations in the drug use histories of the participants; Kuypers et al. (2014) recruited poly-drug MDMA users, while the other two studies recruited subjects with light drug-use histories, most of whom were MDMA-naïve. Although Kirkpatrick et al. (2014a) reported that the drug use history has little effect on subjective responses to MDMA, it remains possible that prior drug use has subtle effects on responses to MDMA.

Other studies have examined the effects of drugs on the cognitive component of empathy, which involves inferring the mental states of others. This is usually measured by asking participants to identify the emotion expressed in images of faces, such as the Reading the Mind in the Eyes Task (Baron-Cohen et al., 2001) or the Facial Emotion Recognition Task (Bedi et al., 2010). Facial expressions are potent social cues that signal how others are feeling, and thus may guide appropriate social responses. Changes in detection of emotions could affect social behavior by increasing sensitivity to positive expressions or blunting responses to negative expressions (for a review, see Miller et al., 2015). The findings from the studies with MDMA are mixed, but tend to show that MDMA acts differentially on identification of positive and negative expressions. In some cases, MDMA enhanced identification of positive emotions and reduced identification of negative emotions, whereas in other studies, MDMA selectively reduced responses to negative emotional expressions without altering responses to positive faces (Bedi et al., 2010; Hysek et al., 2014b; Kirkpatrick et al., 2014b; Schmid et al., 2014; Wardle et al., 2014). In contrast, *d*-amphetamine (20 mg) enhanced the ability to identify both positive and negative emotional expressions on the emotion identification task (Wardle et al., 2012), and methylphenidate (60 mg) enhanced the ability to identify negative emotional expressions (Hysek et al., 2014b). These findings suggest that prototypical stimulant drugs such as *d*-amphetamine may act in a non-selective way, or even a negative way, to enhance emotion identification, while MDMA tends to bias emotion identification in a positive direction. Some of these conclusions are tempered by concerns about possible response biases with different emotional expressions. Happiness, for example, is easier to identify in many stimulus sets, and it may be the case that MDMA selectively impairs identification of the more difficult to identify expressions first.

Responses to emotional stimuli can also be measured using physiological or neural assessments. Facial electromyography (EMG), for example, assesses subtle facial movements indicative of positive and negative emotional responses, arguably at a lower threshold than self-report measures (Dimberg, 1990). Wardle and De Wit (2014) found that 1.5 mg/kg (approx. 105 mg) MDMA increased positive EMG responses to happy faces. In a functional magnetic resonance imaging, Bedi et al. (2010) reported MDMA (1.5 mg/kg) attenuated amygdala activity during presentation of angry faces, and enhanced ventral striatum activity during presentation of happy faces. The ventral striatum is activated during reward anticipation of both social and nonsocial reward (Haber and Knutson, 2010), and the amygdala is involved in the processing of threat-related information (Whalen et al., 1998; Zald, 2003). In contrast to the effect of MDMA, Wardle et al. (2012) found that amphetamine *magnified* EMG responses to negative

emotional stimuli, and Hariri et al. (2002) showed that amphetamine potentiated amygdala responses to fearful and angry faces. Thus, by these measures, there are clear differences between classic stimulants and MDMA. Interestingly, the serotonergic hallucinogen psilocybin (0.16 mg/kg) appears to have similar effects on amygdala reactivity as MDMA, dampening responses to negative emotional faces (Kraehenmann et al., 2015). Taken together, these findings indicate that MDMA has distinctive effects on emotional processing compared with amphetamine at the neural level. These findings help to explain why MDMA reduces social anxiety (i.e. by reducing responses to negative or threatening social stimuli and increasing responses to positive stimuli), and may also lend support for the idea that these effects are partly a result of the drug's serotonergic activity.

In addition to emotional responses to social stimuli, one study investigated the effects of both MDMA (75 mg) and methylphenidate (40 mg) on arousal responses to sexual stimuli (Schmid et al., 2015b). In this study, subjects viewed and rated explicit erotic images, and pressed a button to increase image presentation time. Interestingly, methylphenidate increased arousal ratings and increased the average time participants chose to spend viewing implicit erotic images, whereas MDMA did not affect either of these measures. These findings suggest that classic stimulants, but *not* MDMA, increase desire for sexual contact. This is consistent with a rodent study showing that MDMA produced a transient disruption in male copulatory behavior (Dornan et al., 1991), and with user reports emphasizing increased emotional closeness and openness to sexual activity rather than sexual desire per se (Buffum and Moser, 1986; McElrath, 2005; Zemishlany et al., 2001).

Social rejection

Responses to social cues can also be assessed using actual positive and negative social experiences. One potent social experience is exclusion or rejection by others, as modeled in the computerized virtual ball-tossing game called Cyberball. Frye et al. (2014) used Cyberball to measure the effects of MDMA on perceptions of social rejection and acceptance. In the game, players are first "accepted" and then "rejected" by other "players" (i.e. the participant either receives many throws or very few throws from the other, computer-controlled players; Williams and Jarvis, 2006). Participants then rate their emotions during the game and estimate the number of throws received. Rejection in the game reliably increases negative mood and reduces self-esteem (Zadro et al., 2004). Frye et al. (2014) reported that MDMA (0.75 and 1.5 mg/kg) reduced the effects of simulated social rejection on mood and self-esteem, and that the higher dose (1.5 mg/kg) also increased the estimated number of throws subjects received during the rejection condition. Thus, MDMA not only affected mood, but also arguably altered their objectively estimated level of rejection. An interesting secondary observation in this study was that because in the placebo condition participants tended to underestimate the number of throws they received when rejected, MDMA appeared to improve subjects' accuracy of the number of throws they received. This observation is consistent with the possibility that MDMA may also decrease the distortion of negative self-relevant facts, a phenomenon common in depression. The dampening of social rejection may also contribute to the psychotherapeutic benefits of MDMA by allowing patients to speak freely and openly about their issues. To our knowledge, no studies have yet examined the effects of an acute dose of amphetamine on the social rejection task.

Overall, these findings suggest that MDMA attenuates response to negative emotional stimuli and negative social experiences. The extent to which these effects differ from prototypic stimulant drugs has not been fully studied. Decreased responsiveness to negative stimuli would not only make a drug attractive to users who seek to enhance social experiences, but also, in the case of MDMA, may also help patients feel safer and more accepted in psychotherapy.

Social behavior

Speech

The psychosocial effects of MDMA and other stimulants have also been assessed by analyzing spontaneous speech production and content. Speech is a crucial component of human social interaction, and drugs can alter many aspects of speech, including self-reports of feeling talkative, speech quantity, production, fluency, and content (Higgins and Stitzer, 1989; Marrone et al., 2010; Stitzer et al., 1978). Both MDMA and other stimulants such as *d*-amphetamine (Wardle et al., 2012) increase self-ratings of talkativeness, although the drugs' effects on actual speech vary. Both *d*-amphetamine (Griffiths et al., 1977; Strakowski et al., 1996; Ward et al., 1997; Wardle et al., 2012) and methamphetamine (Marrone et al., 2010) increase speech quantity as well as speech fluency (i.e. decreasing the number of silent pauses or "um/uh's" during speaking; Barch and Carter, 2005; Marrone et al., 2010). However, MDMA does not affect speech production (Bedi et al., 2014), and may *decrease* verbal fluency (Marrone et al., 2010). Drugs may also affect the degree of synchronization between speakers, and it has been reported that both *d*-amphetamine and the hallucinogen LSD enhance synchronization of speech between a therapist and patient (Natale et al., 1979). Whether MDMA produces this effect remains to be determined.

Other studies have investigated the effects of drugs on speech *content*, providing an indication of mental and emotional states during intoxication. In these studies, participants received a drug and were asked to speak freely about a close personal relationship, for instance a close friend or family member, with a research assistant. Speeches were then analyzed for preselected content categories, such as words pertaining to emotion, social interaction, and cognition. Relative to placebo, MDMA (1.5 mg/kg) increased the use of sexual, social, and emotional words (Baggott et al., 2016) and the use of positive emotion words (Wardle and De Wit, 2014). In a study comparing MDMA and methamphetamine, Bedi et al. (2014) reported that speech following 1.5 mg/kg of MDMA had greater semantic proximity to concepts of "friend, support, intimacy, and rapport," and 0.75 mg/kg had greater proximity to empathy. By contrast, methamphetamine (20 mg) did not increase the social content of speech. Thus, while both MDMA and prototypic stimulant drugs affect speech, their effects appear to be different, perhaps reflecting the different character of their social effects.

Taken together, the evidence reviewed here suggests that stimulant drugs alter speech in ways that are consistent with their effects on social behaviors. Methamphetamin*e* and *d*-amphetamine increased talkativeness and speech fluency, whereas MDMA

appears to increase the emotional and social content of speech. These findings lend support to the idea that MDMA preferentially affects intimate social interaction and emotional openness rather than nonspecifically increasing speech output. Analysis of speech is a promising approach to identify the social processes by which drugs work.

Trust and reciprocity

The effect of MDMA on ratings of "trust" and "closeness to others" (Greer and Tolbert, 1986; Schmid et al., 2014), and its effect on trust decisions, reciprocity, and resource allocation, appear to be unique. MDMA (125 mg) increased prosocial behavior on the Social Value Orientation Task in which participants allocate resources between themselves and others (Hysek et al., 2014a). In a naturalistic study querying users in their normal drug-taking environments, Stewart et al. (2014) found that self-reported illicit ecstasy use (the presence of MDMA was not confirmed) was associated with increased ratings of trustworthiness of faces and more prosocial decisions on three cooperative behavior tasks. These results are complicated, however, by the lack of information about the other drugs that participants had used, the doses, subjects' expectancies, and the psychosocial context in which they were assessed. In another laboratory-based study, Kirkpatrick et al. (2015) used the Welfare Trade-Off Task (Delton and Robertson, 2012) to show that MDMA (1.0 mg/kg; approx. 75 mg) increased participants' willingness to allocate money toward a friend (but not to a stranger) rather than themselves. Interestingly, this differential effect coincides with a report that the neuropeptide oxytocin (discussed below) selectively enhances trust among individual members of a social in-group (Van IJzendoorn and Bakermans-Kranenburg, 2012). Because MDMA potently increases oxytocin, it is tempting to speculate that the effects on MDMA on responses to friends versus strangers are mediated by its effects on oxytocin. However, in other studies, MDMA did not affect resource allocation of trust in the Trust Game, or reciprocity in a ball-tossing game (Kuypers et al., 2014; Schmid et al., 2014). In summary, there is some evidence that MDMA increases trust and generosity, as measured by resource allocation tasks. To our knowledge, these measures have not been studied with classic stimulant drugs, and future studies should include a prototypical stimulant control condition to be able to tease apart the MDMA-specific effects.

Social interactions

A final behavioral process that has been used to investigate the pro-social effects of drugs is the study of in-person social interaction. Drugs are typically used in social settings, and users of both MDMA and other stimulant drugs report using these drugs to enhance social experiences (Sumnall et al., 2006). The relationship between social interactions and drug taking can be reciprocal: drugs can enrich social interactions and, in turn, the presence of others may heighten the rewarding effects of the drug. To examine the interactive effects of drugs and interpersonal relations, several studies have tested MDMA on perceptions of others, and how the presence of others affects responses to the drug.

MDMA can alter perceptions of others during an actual social interaction (Baggott et al., 2016; Bedi et al., 2014; Wardle and De Wit, 2014). Typically in these studies, participants perform a brief speech task with a research assistant and subsequently rate their interaction with the research assistant. In one study (Wardle and De Wit, 2014), MDMA (1.5 mg/kg) modestly increased the degree to which participants felt the research assistant understood and was interested in them. Interestingly, this effect is distinguishable from reports that the drug increased empathy for others. Here, MDMA increased perceptions of empathy *from* others. This appears consistent with the report by Baggott et al. (2016) that MDMA increased the comfort participants felt when describing autobiographical memories to a researcher. Increased feelings of being understood and accepted by real others provides additional evidence for the drug's benefits in strengthening therapist–patient alliances in psychotherapy settings (Bouso et al., 2008; Johansen and Krebs, 2009; Mithoefer et al., 2011).

Kirkpatrick et al. (2015) examined the effect of MDMA (0.5 and 1.0 mg/kg) in participants who were tested under either social conditions, with another person, or isolated conditions. Participants were tested under three conditions: alone in a room, with a research assistant present, or with another participant who received the same drug. Participants who received MDMA in the presence of another participant showed the greatest increases in physiological responses to the drug (i.e. heart rate) and greater subjective responses of feeling and liking the drug. These effects are consistent with findings that social context can heighten effects of other drugs, including alcohol and benzodiazepines (e.g. De Wit and Griffiths, 1991; Kirkpatrick and De Wit, 2013). But the findings also suggest that the type of social context matters in affecting acute responses to the drug; that is, the presence of another drug user facilitates responses, whereas the presence of a research assistant does not. Together, these two studies suggest that MDMA not only enhances social situations, but also that its effects are stronger when taken in the presence of others. This may explain why MDMA is so commonly used in social settings. Two studies with similar designs have investigated the effects of social settings on responses to *d*-amphetamine. In one study (De Wit et al., 1997), *d*-amphetamine (10 mg, 20 mg) produced greater physiological responses (heart rate and body temperature) when subjects were tested with other participants compared with alone, although this was not found in an earlier study (Zacny et al., 1992). Notably, unlike with MDMA, social conditions did not alter the subjective effects of amphetamine in either study. This suggests that social settings enhance the subjective effects of MDMA but not other stimulants.

Mechanisms

Classic stimulant drugs such as amphetamine, methamphetamine, and methylphenidate are thought to exert their psychoactive effects primarily by inducing the release of dopamine and norepinephrine, and, to a lesser extent, serotonin (Fleckenstein et al., 2007; Rothman et al., 2001; Sitte and Freissmuth, 2015; Sulzer et al., 2005). In contrast, MDMA preferentially increases serotonin and norepinephrine release (Rothman et al., 2001; Rudnick and Wall, 1992) and induces dopamine release indirectly as a consequence of serotonergic release (Gudelsky and Nash, 1996; Koch and Galloway, 1997). MDMA directly inhibits dopamine reuptake (Verrico et al., 2007). In a recent review, Liechti (2015) hypothesized that this high ratio of serotonergic to dopaminergic effects is key for producing MDMA-like effects, and that similar drugs with a lower ratio produce more familiar, prototypic stimulant effects. One study showed that specifically

blocking $5HT_{2A}$ signaling reduced the positive mood-inducing effects of MDMA without affecting negative mood, which is particularly interesting in light of some of the drug's similar effects to serotonergic hallucinogens such as LSD and psilocybin (Van Wel et al., 2012). While less studied, MDMA also induces acetylcholine release (Fischer et al., 2000; Nair and Gudelsky, 2006) and has low micromolar affinity for histamine H1 and muscarinic M1 and M2 receptors (Battaglia et al., 1988).

The exact mechanisms by which MDMA produces its unusual prosocial effects are not known, and the drug's complex pharmacology makes this difficult to determine. Studies with humans indicate that both serotonergic and noradrenergic mechanisms are likely important for self-reported social effects. Studies with both rodents and humans suggest that some of the drug's effects are related to release of oxytocin and vasopressin, two structurally related neuropeptides that are known to regulate social recognition and affiliation, anxiety, and aggression (Anacker and Beery, 2013; Carter et al., 2008; Dumont et al., 2010; Insel, 2010).

MDMA-induced oxytocin release appears secondary to the drug's serotonergic effects. Released serotonin stimulates $5\text{-}HT_{1A}$ receptors on hypothalamic oxytocin-containing neurons (Hunt et al., 2011; Thompson et al., 2007), inducing release of oxytocin into peripheral blood. Several studies have confirmed that MDMA also elevates peripheral oxytocin in humans (Dumont et al., 2009; Hysek et al., 2012a; Kirkpatrick et al., 2014b; Wolff et al., 2006). One study reported a correlation between peak oxytocin levels after MDMA and self-reported social effects (Dumont et al., 2009), although this correlation has yet to be replicated (Hysek et al., 2012a; Kirkpatrick et al., 2014b). Another recent study showed that genetic differences in the oxytocin receptor gene (*OXTR*) may affect feelings of sociability in response to MDMA (Bershad et al., 2016); that is, individuals homozygous for the A allele at rs53576 did not report enhanced sociability on 1.5 mg/kg of MDMA, unlike G allele carriers. Importantly, methamphetamine does not appear to induce the release of oxytocin (Bershad et al., 2015), lending weight to the possibility that differing oxytocinergic effects may contribute to differential social effects of MDMA and prototypic stimulants.

The downstream mechanisms by which oxytocin contributes to MDMA's effects may also include vasopressin. Exogenous administration of both oxytocin and vasopressin can produce prosocial behavior, an effect that is blocked by a V_{1A} vasopressin receptor antagonist but not an oxytocin antagonist (Ramos et al., 2013). This suggests oxytocin in high concentrations may significantly stimulate vasopressin receptors (Li et al., 2008), and raises the possibility that MDMA-induced vasopressin release may contribute to prosocial effects of the drug. MDMA and its metabolites induce vasopressin release from isolated rat hypothalamus (Fallon et al., 2002) and may elevate serum vasopressin (or the co-released copeptin) in humans (e.g. Henry et al., 1998; Simmler et al., 2011). However, V_{1A} vasopressin receptor antagonism with SR49059 only partially blocked the prosocial effects of MDMA in rodents (Ramos et al., 2013), supporting a limited role for this pathway.

Several studies with humans have examined effects of drugs that attenuate serotonin or oxytocin function on social effects of MDMA. The $5\text{-}HT_{1A}$ antagonist pindolol, which would be expected to reduce oxytocin release, had little effect on responses to MDMA (Hasler et al., 2009). However, this lack of effect may have been due to insufficient receptor occupancy or lack of sensitive "prosocial" measures. Similarly, while pretreatment with a selective serotonin reuptake inhibitor (SSRI) attenuates self-reported effects of MDMA in humans, it is unclear to what extent SSRIs attenuate the social effects of the drug. Liechti et al. (2000) found that citalopram attenuated MDMA effects on self-reported ratings of self-confidence and extraversion but did not decrease ratings of emotional sensitivity and excitability. Farré et al. (2007) reported that paroxetine attenuated MDMA effects on both social and nonspecific measures of euphoria (i.e. very happy, good mood, more positive view about things). Tancer and Johanson (2007) found that fluoxetine did not change MDMA effects on self-report ratings of talkative and friendly. In sum, serotonin release likely contributes to some of the self-reported social effects of MDMA in humans, but the extent to which non-serotonergic mechanisms contribute is not fully known.

Noradrenergic mechanisms appear particularly likely to be involved in the effects of MDMA (Hysek et al., 2012b). Duloxetine, which inhibits release of both serotonin and norepinephrine, reduced global effects of MDMA and euphoria as well as the visual analog items Closeness, Openness, and Talkativeness. Duloxetine also showed a nonsignificant trend effect on the Reading the Mind in the Eyes Task, suggesting a possible attenuation of MDMA effects on empathy. Further, reboxetine, which inhibits MDMA-induced norepinephrine but not serotonin release, reduced "closeness," but not the other social visual analog items (Hysek et al., 2011). Overall, this suggests both norepinephrine and serotonin release contribute to the social effects of MDMA in humans, although it is not clear how these mechanisms and effects relate to those of classic stimulant drugs.

Conclusions and further directions

Taken together, it appears that MDMA produces distinctive effects that are distinguishable from prototypic stimulants across several social domains, including appraisal of social stimuli and naturalistic social interactions. The evidence reviewed here suggests that compared with typical stimulants, MDMA has both shared and distinctive effects on social processing and social behavior. Prototypic stimulants increases self-reported feelings of friendliness, increase some aspects of verbal behavior, increase positive responses to stimuli (regardless of social or emotional content), and increase sexual arousal. MDMA more specifically increases self-reported feelings of trust and generosity, increases responses to social and emotionally valenced stimuli, increases empathy, and increases the social and emotional themes in spontaneous speech. However, relatively few studies have directly compared MDMA to other stimulants. Because MDMA has generated research interest as a "prosocial" drug and an empathogen, more studies have examined these effects with MDMA than for typical stimulants. Thus, the full constellation of social effects that are truly unique to MDMA remains to be determined. Direct comparisons across drugs will also help to determine the neural substrates for the social psychological processes, including social versus nonsocial reward processes.

Most of the studies included in this review are highly controlled laboratory-based investigations into emotion processing. Such studies, while providing insight into basic mechanisms of social processing, may not directly represent more real-world drug-use situations. Beyond the artificiality of the laboratory setting, the paradigms used to investigate drug effects on emotion processing come with their own limitations. Self-report ratings, for example, provide a critical index of the psychological effects of MDMA and prototypic stimulants by providing a rich profile of both the qualitative and quantitative features of the drugs. Arguably, these

drug-induced subjective states form the basis for an individual's future decisions about drug use, either recreational or therapeutic. On the other hand, self-report measures also have limitations. Currently, the effects that researchers can detect are limited by the descriptors of mood and social effects that are provided to them, and by the participants' ability to report them accurately. Therefore, there is also an important role for behavioral and physiological measures to quantify the prosocial effects of MDMA.

A final consideration is the potential role of these prosocial MDMA effects in psychotherapy. MDMA may strengthen the patient-therapist relationship and alter processing of both external and internally generated emotional stimuli. MDMA may also affect other processes, such as memory or memory reconsolidation. Carhart-Harris et al. (2014) showed that participants rated positive memories as more vivid, emotionally intense, and positive following the administration of MDMA (100 mg) compared with placebo. Indeed, it has been suggested that psychotherapy can be viewed as the activation of negative emotional memories within a positively valenced therapeutic context, resulting in reconsolidated of memories in a new, more positive form (Lane et al., 2014). These interesting psychological processes, and their distinctness from those that occur under the influence of prototypical stimulant drugs, remain to be studied under carefully controlled conditions.

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