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The Prosocial Effects of 3,4-methylenedioxymethamphetamine (MDMA): Controlled Studies in Humans and Laboratory Animals

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Abstract

Users of \pm 3,4-Methylenedioxymethamphetamine (MDMA; ‘ecstasy’) report prosocial effects such as sociability and empathy. Supporting these apparently unique social effects, data from controlled laboratory studies indicate that MDMA alters social feelings, information processing, and behavior in humans, and social behavior in rodents. Here, we review this growing body of evidence. In rodents, MDMA increases passive prosocial behavior (adjacent lying) and social reward while decreasing aggression, effects that may involve serotonin 1A receptor mediated oxytocin release interacting with vasopressin receptor 1A. In humans, MDMA increases plasma oxytocin and produces feelings of social affiliation. It decreases identification of negative facial expressions (cognitive empathy) and blunts responses to social rejection, while enhancing responses to others’ positive emotions (emotional empathy) and increasing social approach. Thus, consistent with drug folklore, laboratory administration of MDMA robustly alters social processing in humans and increases social approach in humans and animals. Effects are consistent with increased sociability, with mixed evidence about enhanced empathy. These neurobiologically-complex prosocial effects likely motivate recreational ecstasy use.

Keywords

MDMA; ecstasy; molly; sociability; prosocial; social reward; social threat; empathy

1. Introduction

\pm 3,4-methylenedioxymethamphetamine (MDMA) is the main psychoactive substance in the street drug known as ecstasy (in pill form) or, in the more recently emerging powder form, ‘molly’ (Duterte et al., 2009; Kahn et al., 2012). In 2012, ecstasy was estimated to be the 3rd most commonly used recreational drug among adults between the ages of 18 and 25 in the

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Disclosures

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US (SAMHSA, 2013). Although use appeared to be declining in the early 2000s, there are indications of a re-emergence in popularity of this drug, with an estimated 869,000 first time users in the US in 2012 (SAMHSA, 2013). In addition to recreational use, MDMA is under investigation as a potential adjunct to psychotherapy for conditions such as Post Traumatic Stress Disorder (PTSD; Mithoefer et al., 2011; Mithoefer et al., 2013).

Although many recreational drugs are believed to alter social experiences (e.g. ‘beer goggles’, whereby alcohol is said to make potential romantic partners appear more attractive; Attwood et al., 2012), MDMA is, in popular culture, the prototypical social drug. Reflecting the belief that MDMA enhances empathy, classifying it under a novel drug class, ‘empathogens’, has been proposed (see Hysek et al., 2014a; Nichols et al., 1993). Language associated with MDMA use, such as the ‘love drug’ (Holland, 2001) and ‘cuddle puddle’ (a group of people cuddling while under the influence of ecstasy; Leneghan, 2013) further reflects popular perceptions of the drug’s apparent prosocial effects. Critically, these effects appear to motivate recreational ecstasy use (Morgan et al., 2013; Sumnall et al., 2006), suggesting that they contribute to the reinforcing properties of MDMA. Moreover, putative socio-emotional effects are argued to underlie the rationale for adjunctive MDMA use in psychotherapy (Johansen and Krebs, 2009; Oehen et al., 2013). Scientifically characterizing these effects is, thus, an important component of understanding both motivations for recreational MDMA use and possible mechanisms of any therapeutic effects. Research on prosocial effects of MDMA and their neurobiological substrates may also reciprocally inform understanding of the neurobiology of social behavior.

Over the past decade a rich body of research has emerged documenting alterations to social behavior in animals, as well as social feelings, information processing, and behavior in humans after controlled administration of MDMA. Here, we provide a systematic overview of these studies. Our aim is to elucidate the nature of identified social changes as well as their potential neurobiological mechanisms. We discuss implications of these findings in relation to recreational ecstasy/molly use and possible psychotherapeutic effects. Finally, we discuss important questions yet to be studied.

2. Methods

Collection of relevant articles was carried out using a multi-step search method. First, the databases PubMed, PsycINFO, and HighWire were periodically searched from October 2013 until June 2015 using a combination of the following keywords: “Human”, “animal”, “MDMA” “administration”, “social”, “subjective”, “acute”, “ecstasy”, and “mood”. Once all keyword combinations were exhausted, reference sections of the collected articles were manually searched for additional relevant publications that were not initially identified. Studies were included if they: 1) Employed controlled laboratory administration to study the acute effects of MDMA; and 2) Included assessments of social mood states, social processing or social behavior. Studies that examined long-term effects of recreational ecstasy use (in humans) or effects of chronic MDMA administration (in animals) were excluded.

A total of 49 articles were selected for review based on our inclusion criteria. We categorized findings as follows: 1) Effects of MDMA on social behavior in animals; 2) Effects of MDMA on social processing and behavior in humans; and 3) Mechanisms of MDMA's prosocial effects in animals and humans.

3. Effects of MDMA on Social Behavior in Laboratory Animals

MDMA acutely facilitates prosocial behaviors in several rodent species, most frequently assessed with the social interaction test (which measures behavior during brief exposures to unfamiliar conspecifics). Morley and McGregor (2000) reported that in comparison to placebo, MDMA (5 mg/kg) increased the amount of time that Wistar rats engaged in adjacent lying, a form of social behavior in which animals lie next to each other in close physical contact sometimes accompanied by body repositioning to maintain immediate physical proximity (Ando et al., 2006). Similar responses have been documented in different rodent species after MDMA, with increased adjacent lying being the most common apparently prosocial behavior observed (Ando et al., 2006; Morley et al., 2005; Procopio-Souza et al., 2011; Ramos et al., 2015; Ramos et al., 2013; Thompson et al., 2007). Adjacent lying in rodents has been elicited using MDMA doses from 5 mg/kg (Morley et al., 2005; Morley and McGregor, 2000; Ramos et al., 2013; Thompson et al., 2007) to 15 mg/kg (Ando et al., 2006). Increased peaceful following (non-aggressive pursuit of a conspecific), social investigation/approach, and overall social interaction have also been noted in rodents following doses of MDMA ranging from 2.5 to 10 mg/kg (Daza-Losada et al., 2009; Morley et al., 2005; Morley and McGregor, 2000; Procopio-Souza et al., 2011; Thompson et al., 2007; Thompson et al., 2008; Thompson et al., 2009).

Other MDMA-induced behavioral changes in rodents include decreased rearing (Ando et al., 2006; Morley et al., 2005; Ramos et al., 2013; Thompson et al., 2007; Thompson et al., 2009), anogenital sniffing (Morley et al., 2005; Procopio-Souza et al., 2011; Ramos et al., 2013; Thompson et al., 2007; Thompson et al., 2009), and partner grooming (Homberg et al., 2007). Rodents use anogenital sniffing to identify conspecifics (Ramos et al., 2013), while rearing can be considered a form of risk assessment (Blanchard and Blanchard, 1989). Thus, decreases in these behaviors may signify an MDMA-induced enhancement in social comfort with unfamiliar conspecifics (see Ramos et al., 2013). Supporting this view, doses of MDMA that reduced levels of anogenital sniffing in rodents also increased adjacent lying (Morley et al., 2005; Procopio-Souza et al., 2011; Ramos et al., 2013), social approach behavior (Morley et al., 2005; Procopio-Souza et al., 2011), and peaceful following (Procopio-Souza et al., 2011). Similarly, MDMA-induced decreases in rearing are frequently accompanied by increased adjacent lying (Ando et al., 2006; Morley et al., 2005; Ramos et al., 2013). In all but one study (Ando et al., 2006), decreased rearing and sniffing occurred with either no change or increases in locomotor activity, suggesting that these effects were not due to sedation.

MDMA may heighten prosocial behaviors in rodents by enhancing the rewarding value of social interaction. In a recent investigation, Ramos et al. (2015) used a social reward-conditioned place preference model (social-CPP; Thiele et al., 2008) to assess the rewarding effects of MDMA when administered under social and non-social conditions. Habituation

and conditioning phases were similar to traditional conditioned place preference models, however, for social-CPP conditioning phases, rats received MDMA (5 mg/kg) paired with a sex- and weight-matched conspecific that had received the same drug treatment. Another group of rats received the same dose of MDMA in the presence of a tennis ball, to assess for object-CPP produced by the combination of MDMA and a tactile, but non-social stimulus. MDMA (5 mg/kg) did not produce a CPP in the absence of the social or tactile stimuli. However, rats given MDMA under social conditions exhibited greater preference for the test environment that contained the drug and social pairing compared to the vehicle/object pairing. The same dose of MDMA administered to rats in the non-social tactile condition produced a preference for the test environment that contained the tennis ball over vehicle/social-paired settings, although this effect was less pronounced than the MDMA/social place preference. Thus, MDMA appears to intensify social and to a lesser degree tactile reward, potentially contributing to the drug's prosocial effects.

MDMA (1-20 mg/kg) has also been shown to reduce aggression in rodents and fish (Capurro et al., 1997; Kirilly et al., 2006; Maldonado and Navarro, 2001; Miczek and Haney, 1994; Morley and McGregor, 2000; Navarro and Maldonado, 1999). Morley and McGregor (2000) found that MDMA (1.25, 2.5, and 5 mg/kg) decreased the frequency and duration of agonistic encounters (kicking, biting, boxing, and aggressive grooming) relative to placebo in rats meeting for the first time, while only the higher dose (5 mg/kg) increased adjacent lying. In an earlier study, MDMA (1 and 5 mg/kg) dissolved in saline and injected into pairs of electrical fish inhibited the aggressive behaviors normally observed in this species during novel social encounters, as indicated by prolonged first-bite latency and decreased frequency of combative bites (Capurro et al., 1997). Notably, agonistic behaviors were often replaced by parallel swimming characterized by a head-to-head formation and reduced competitiveness for spatial position. In some instances, fish appeared to 'rest' together in close proximity, possibly akin to rodent adjacent lying. Although the higher MDMA dose (5 mg/kg) attenuated spontaneous motor activity, lower doses reduced agonistic displays without decreasing locomotion, again suggesting that the observed reductions in aggression were not explained by decreased locomotion alone (Capurro et al., 1997).

Other studies have also documented reduced aggression after MDMA, however these changes were not consistently associated with heightened prosocial behavior and may have resulted from severe intoxication or increased social anxiety. For instance, Navarro and Maldonado (1999) found that mice subjected to extended social isolation in the isolation-induced aggression model spent less time threatening (aggressively grooming and tail rattling) and attacking unfamiliar conspecific opponents following MDMA (5, 10, 15 and 20 mg/kg). However, while these doses reduced aggressive behavior they also potentiated social anxiety-like behavior (avoidance, defense, and submission postures) and reduced social investigation compared to placebo. Analogous findings were reported in a more recent study involving similar doses (8 and 15 mg/kg; Maldonado and Navarro, 2001). Additionally, MDMA (15 mg/kg) reduced overall aggression but also decreased social exploration compared to placebo in adult male Agouti rats (Kirilly et al., 2006). A subsequent investigation (Homberg et al., 2007) revealed that, in comparison to placebo, MDMA (0.5, 2, and 5 mg/kg) administered to peri-adolescent male Wistar rats dose-

independently decreased the frequency of pinning, pouncing, and boxing, commonly viewed as aggressive behaviors, although the authors note that these can be playful social behaviors in younger rats. Furthermore, 2 and 5 mg/kg doses reduced social exploration, friendly following, and grooming relative to placebo, suggesting that MDMA increased social inhibition in these peri-adolescent male rats (Homberg et al., 2007).

Potentially contributing to these somewhat contradictory findings, recent evidence suggests that individual differences in trait aggressiveness can moderate MDMA's effects on aggression and prosociality. Machalova et al. (2012) administered MDMA (2.5, 10, 30 mg/kg) to adult male mice allocated to timid or aggressive groups based on behavior in a baseline interaction. Mice subsequently underwent testing involving short dyadic exposures to non-aggressive conspecifics following drug administration. In aggressive mice, all MDMA doses decreased the duration of agonistic acts and increased defense postures. Higher doses increased the frequency of alert postures (10, 30 mg/kg) and escape attempts (30 mg/kg). Aggressive mice also displayed greater amounts of social sniffing after 2.5 mg/kg MDMA and friendly following was increased after 2.5 and 10 mg/kg MDMA doses relative to placebo. Conversely, MDMA intensified trait timidity in timid mice, as indicated by increased alert postures (10 and 30 mg/kg) and escape behaviors (30 mg/kg), with no effect on aggression and a decrease in social sniffing (2.5, 10, and 30 mg/kg) and friendly following (10 and 30 mg/kg). This suggests that MDMA may decrease aggression and increase both timidity and prosocial behaviors in rodents with high-trait aggressiveness, while increasing timidity and reducing prosocial behavior in low-aggressive mice.

Although MDMA has been found to promote certain prosocial behaviors, some studies have documented inhibitory or anxiety-like social effects. Accounts of decreased rodent social investigation following MDMA administration have been noted, though infrequently (8 and 15 mg/kg; Daza-Losada et al., 2009; Maldonado and Navarro, 2001; Navarro et al., 2004). Bhattacharya et al. (1998) report that, similar to the known anxiogenic yohimbine, MDMA (5 and 10 mg/kg) reduced total social interaction in male Foster rats as measured by the social interaction task. However, individual social behaviors (e.g. grooming, laying etc.) were not reported in this study, making interpretation difficult. More recently, MDMA (1, 8 and 15 mg/kg) decreased social investigation and heightened avoidance/flee responses (8, 15 mg/kg) without decreasing locomotor activity or aggression in mice (Navarro et al., 2004), suggesting clear social anxiety-like effects. Higher doses of MDMA (20 mg/kg) produced social inhibition relative to placebo in mice while lower doses (5 mg/kg) conversely increased social exploration (Daza-Losada et al., 2009), suggesting dose-dependent effects.

In summary, MDMA increases certain prosocial behaviors in rodents, namely adjacent lying and friendly following, enhances social reward, and decreases markers of rodent and fish aggression. Conversely, under some conditions MDMA appears to potentiate social anxiety-like behaviors in rodents, although these effects have been less frequently reported. Although MDMA's effects on social behavior are complex and appear to depend on the developmental stage, species, trait factors, dose, testing environment, and the specific behavior measured, findings are thus broadly consistent with a prosocial effect profile of MDMA in laboratory animals.

4. Effects of MDMA on Social Feelings, Processing, and Behavior in Humans

MDMA has now been administered to healthy humans in numerous controlled laboratory studies resulting in over 80 published reports with, to our knowledge, no unexpected drug-related serious adverse events. Here, we only include studies involving randomized, placebo-controlled, blinded drug administration. The studies reviewed tested for prosocial effects of MDMA in volunteers with a range of prior exposure to ecstasy (e.g. Bedi et al., 2014; Bedi et al., 2010; Bedi et al., 2009; Frye et al., 2014; Kirkpatrick et al., 2014a; Kirkpatrick et al., 2014b), as well as in primarily ecstasy naïve samples (e.g. Hysek et al., 2012a; Hysek et al., 2014a; Hysek et al., 2012c). Despite preclinical evidence that the acute prosocial effects of MDMA may be altered by prior MDMA exposure (Thompson et al., 2008), there is, as yet, no evidence showing differential effects of MDMA in humans due to previous drug use. Thus, we have not grouped studies based on whether participants were experienced users or MDMA naïve.

Consistent with prosocial effects reported by recreational users, controlled laboratory administration of moderate doses of MDMA (0.5-2.0 mg/kg) relative to placebo increased self-report ratings of a broad range of socially-relevant mood states (see Table 1). After MDMA, participants endorsed feeling 'loving' (Bedi et al., 2010; Frye et al., 2014; Kirkpatrick and de Wit, 2014; Kirkpatrick et al., 2014a; Kirkpatrick et al., 2014b; Wardle and de Wit, 2014; Wardle et al., 2014), 'talkative' (Hysek et al., 2012a; Hysek et al., 2012c; Tancer and Johanson, 2007; Tancer and Johanson, 2003), 'extroverted' (Gamma et al., 2000; Hysek et al., 2013; Hysek et al., 2014a; Hysek et al., 2011; Hysek et al., 2012c; Liechti et al., 2000b), 'sociable' (Bedi et al., 2009; Kirkpatrick et al., 2014a; Kirkpatrick et al., 2014b; Tancer and Johanson, 2003), 'self-confident' (Gamma et al., 2000; Harris et al., 2002; Hysek et al., 2013; Kirkpatrick and de Wit, 2014; Kirkpatrick et al., 2014b), 'friendly' (Johanson et al., 2006; Kirkpatrick et al., 2014a; Kirkpatrick et al., 2014b; Kuypers et al., 2013; Kuypers et al., 2011; Tancer and Johanson, 2007; Tancer and Johanson, 2003; van Wel et al., 2012), 'playful' (Bedi et al., 2010; Kirkpatrick et al., 2014a; Kirkpatrick et al., 2014b), 'open' (Hysek et al., 2012a; Hysek et al., 2012c; Schmid et al., 2014), 'trusting' (Schmid et al., 2014), 'close to other people' (Hysek et al., 2012a; Hysek et al., 2012b; Hysek et al., 2014a; Hysek et al., 2011; Kolbrich et al., 2008; Schmid et al., 2014) and 'emotionally concerned' (Kuypers et al., 2014).

While these effects have primarily been documented under non-social testing conditions, some evidence suggests an effect of social setting. In a recent study (Kirkpatrick and de Wit, 2014), MDMA (1.0 mg/kg only) increased feelings of confidence only in subjects who, during experimental testing, were accompanied by one or two other participants also under the influence of MDMA, with no effect of accompaniment by a research assistant who was not given the drug. Thus, MDMA's subjective prosocial effects may be enhanced if the drug is administered in the presence of others with similar levels of MDMA intoxication. Further highlighting the possible significance of social setting, increased ratings of loneliness have been noted (Bedi et al., 2010; Kirkpatrick et al., 2014b) following MDMA (0.75 mg/kg or 1.5 mg/kg) administered to individual participants, possibly reflecting enhanced affiliative

motivation combined with comparatively isolated testing conditions. However, the MDMA-induced increases in subjective prosociality noted above have occurred in environments with limited opportunities for social interaction (e.g. relatively isolated laboratory settings) and even in the confined environment of a Magnetic Resonance Imaging (MRI) scanner (Bedi et al., 2009). Thus, although social stimuli may enhance the subjective prosocial effects of MDMA, these effects do not appear wholly dependent on a facilitating social environment.

Whereas drug effects on mood and mental state are commonly assessed with self-report measures (e.g. Visual Analogue Scales; Bedi et al., 2009; Kirkpatrick et al., 2014b; Wardle et al., 2014), in a recent study we used computer science methods to investigate the semantic structure of free speech using Latent Semantic Analyses (LSA) as a ‘window into the mind’ after MDMA (0.75, 1.5 mg/kg; Bedi et al., 2014). This method of measuring MDMA-induced mood changes also revealed apparently prosocial drug effects, with free speech after MDMA (1.5 mg/kg) showing greater LSA semantic proximity to concepts such as ‘friend’ and ‘support’ as well as ‘empathy’ (0.75 mg/kg) compared to speech on placebo. Speech analysis was also used by Wardle and de Wit (2014) to assess the effects of MDMA using a version of the Interpersonal Perception task (Janowsky, 2003). Participants talked to a trained interviewer about an important person in their life following MDMA (0.75, 1.5 mg/kg) or placebo. Speech was recorded and later analyzed for changes in emotional content using word-counting and dictionary categorization software. Relative to placebo, MDMA (0.75 & 1.5 mg/kg) increased the percentage of positive, but not negative, emotion words used during free speech, although it is somewhat unclear whether this reflects a specifically social effect or more generalized positive mood. A similarly modified version of the Interpersonal Perception task was used by Baggott et al. (2015) to determine if MDMA alters the prevalence of social and emotional words used during free speech. MDMA (1.5 mg/kg) increased the use of words relating to sexual and social content relative to placebo, while also increasing the use of words pertaining to death. Self-report ratings of “loving”, “social”, “friendly”, and “confident” after MDMA accurately predicted increased use of social words, suggesting that MDMA’s effects on speech reflect underlying alterations to social mood states. Importantly, “want more drug” ratings predicted greater use of words with social content, suggesting that prosocial mood effects may be associated with the abuse liability of MDMA. Thus, findings to date using both subjective (self-report) and objective (quantitative speech analysis) indices of mood alterations suggest that MDMA robustly generates prosocial feelings and mental states in humans in controlled laboratory settings.

Despite this substantial evidence of increased social feelings after MDMA, data on alterations to social information processing and behavior in humans have only recently begun to emerge (see Tables 2 and 3). Most relevant studies have focused on the effects of MDMA on social processing (e.g. Bedi et al., 2009; Frye et al., 2014; Hysek et al., 2012a; Wardle et al., 2014), defined here as the cognitive, affective, and neurobiological processes underlying interpersonal behavior. Components of social processing can be assessed with a wide range of behavioral tasks, however one common approach is to measure accuracy of affect recognition from pictures of facial expressions (facial emotion recognition; FER). The capacity to accurately detect others’ facial emotions is a critical aspect of social cognition (Ekman, 2003) and correlates with self-reported interpersonal problems (Kornreich et al., 2002) and social dysfunction (Phillips et al., 2003). FER is thought to represent a component

of empathy known as ‘cognitive empathy’ (Blair, 2005). In this conceptualization, empathy is dependent on both the capacity to decode others’ emotional and mental states from facial, verbal, and behavioral cues (cognitive empathy), and the spontaneous experience of emotional responses that are consistent with the affective states expressed by others (emotional empathy; Blair, 2005).

Several studies have investigated the effects of MDMA on cognitive empathy, specifically FER performance. In the first such study, we found that MDMA (1.5 mg/kg only) preferentially reduced recognition of fearful faces relative to placebo (Bedi et al., 2010). A subsequent study, which employed a dynamic FER task (Hysek et al., 2014a), revealed that MDMA (125 mg) decreased accurate identification of fearful, sad, angry, disgusted, and surprised, but not happy, facial expressions compared to placebo. However, the drug also reduced overall FER performance, suggesting a more generalized effect (Hysek et al., 2014a). In addition, reductions in identification of fearful, sad, and angry faces after MDMA compared to placebo were only observed in females, suggesting possible sex-dependent effects. These authors reported similar findings in another study (Hysek et al., 2014b), namely that MDMA (125 mg) reduced identification of sad, angry, and fearful faces relative to placebo. Accurate identification of fearful and angry faces was also decreased in another recent study after MDMA (1.5 mg/kg only; Kirkpatrick et al., 2014b). The authors reported that MDMA (1.5 mg/kg) lowered accuracy ratings for all four emotions tested but these effects did not reach statistical significance for sadness or happiness recognition, also suggesting generalized rather than emotionally specific effects on FER (Kirkpatrick et al., 2014b). In a further investigation, MDMA (75 mg) increased misclassifications of both positive and negative facial emotions as neutral, with no effect on overall recognition accuracy (Schmid et al., 2014). Alterations to FER following MDMA (0.75, 1.5 mg/kg) were further assessed using a dynamic emotion recognition task, in which participants were asked to identify facial emotions from videos as quickly and accurately as possible (Wardle and de Wit, 2014). Consistent with decreased negative social processing, MDMA (1.5 mg/kg only) slowed accurate identification of anger. Together, findings indicate that MDMA reduces the overall capacity to accurately decode facial emotional expressions, with more prominent reductions in recognition of threat-related emotions, such as anger and fear, and no clear effects on identification of happy faces.

A particularly important facial feature for emotion recognition is the eye region, which communicates subtle yet important emotional cues (Adolphs, 2008). Three studies investigated the effects of MDMA on emotion recognition from pictures of the eye region using the Reading the Mind in the Eyes Test (RMET), which was designed to assess social cognition in individuals with autism (Baron-Cohen et al., 2001). In the first such study (Bedi et al., 2010), MDMA (0.75 & 1.5 mg/kg) had no effect on overall RMET performance compared to placebo, which is consistent with findings from the more recent investigations, which used MDMA doses of 75 mg (Kuypers et al., 2014) and 125 mg (Hysek et al., 2012a). Based on the potential for differential effects of MDMA as a function of stimuli valence, Hysek et al. (2012a) also examined recognition accuracy for positive and negative emotions separately, finding that MDMA (125 mg) *increased* correct identification of positive emotions but impaired recognition of negative emotions from pictures of the eye region.

An earlier pharmacology-MRI study (Bedi et al., 2009) suggests a potential neural mechanism for such valence-dependent effects of MDMA. In this study, MDMA (0.75 and 1.5 mg/kg) increased ventral striatum activation in response to happy versus neutral faces, whereas higher doses (1.5 mg/kg only) reduced amygdala activation compared to placebo in response to angry versus neutral faces, suggesting that the drug may blunt social threat responding and enhance processing of socially rewarding stimuli (Bedi et al., 2009). However, further research is required to confirm such effects given the small sample size of this preliminary within-subjects study (N=9).

The ability to decode emotional cues from behaviors other than facial expressions, such as vocal intonation or prosody, is also critical for social interaction. One prior study examined the effects of MDMA (0.75, 1.5 mg/kg) on recognition of emotions from voices, however no effects of MDMA were observed on this measure compared to placebo (Bedi et al., 2010). To our knowledge, the effects of MDMA on other dimensions of emotion recognition, such as affect decoding from body postures or gestures, have yet to be explored.

A broader assessment of MDMA's effects on cognitive and emotional empathy was undertaken by Hysek et al. (2014a) employing the multifaceted empathy test (MET). This task requires participants to infer others' mental states from pictures depicting an emotionally charged situation (cognitive empathy) as well as to rate their own affective state (i.e. feelings of concern and arousal levels), while viewing the images (emotional empathy). MDMA (125 mg) did not affect cognitive empathy but increased overall emotional empathy ratings, an effect apparently driven by enhanced affective responses to positive rather than negative emotional situations. Schmid et al. (2014) reported similar findings using the MET, namely that MDMA (75 mg) increased emotional empathy for positive, but not negative, stimuli compared to placebo. MDMA's effects on inference of others' mental state (another dimension of cognitive empathy) was assessed by asking volunteers to infer the intentions and emotions of actors in a 15-minute video depicting a social scenario. Consistent with reports by Hysek et al. (2014a), MDMA (75 mg) did not alter overall cognitive empathy on this measure. Kuypers et al. (2014) also employed the MET and similarly noted that MDMA (75 mg) increased overall emotional, but not cognitive, empathy, although no valence specific effects were noted.

The balance of evidence thus suggests that MDMA may dampen cognitive empathy, in particular lowering awareness of others' negative facial emotional expressions, with limited support for the notion that MDMA increases accurate identification of positive emotions in others. Conversely, MDMA appears to enhance emotional empathy, increasing affective responses such as concern and arousal in response to others' emotions, particularly their positive emotions. An interesting question arises from these findings: if cognitive empathy is blunted by MDMA, it seems plausible that emotional responses to others' affective states (i.e. emotional empathy) may be based on a cognitive 'misread' of those emotional states. To our knowledge, this possibility has not yet been assessed.

Although most existing research has focused on measures of cognitive or emotional empathy, a small number of studies assessed MDMA's effects on other dimensions of social processing. For instance, Kirkpatrick et al. (2014b) investigated the effects of MDMA (0.75,

1.5 mg/kg) on social evaluation, specifically on ratings of others' facial attractiveness, friendliness, and trustworthiness. No drug effects were reported on these measures. However, Kirkpatrick & de Wit (2014) revealed contrary findings using a more naturalistic social evaluation task: participants rated the attractiveness of others after being randomly assigned to one of three social conditions. In the first condition, participants were tested in isolation, and were asked to rate the attractiveness of a research assistant who spent minimal time in the test room (solitary condition). In the second and third conditions, participants spent the majority of testing accompanied by a research assistant or with one or two other participants who were administered the same dose level of MDMA or placebo, and rated the attractiveness of either the research assistant or the other participants with whom they spent the session. Compared to placebo, MDMA (1.0 mg/kg only) increased the tendency to rate others as more socially and physically attractive across all three social conditions, suggesting no effect of social setting on MDMA-induced alterations to this dimension of social evaluation.

Only one study to date assessed the effects of MDMA (75 mg) on subjective and objective responses to sexual imagery (Schmid et al., 2015). In this investigation, participants viewed a series of erotic pictures and provided subjective arousal ratings. As a behavioral measure of motivation to view these stimuli, they could rapidly press a button box to extend the presentation time of preferred images. MDMA did not alter subjective arousal ratings in response to images with implicit (people in suggestive erotic poses) or explicit (pornographic) sexual content. MDMA (75 mg) did, however, increase button presses in response to implicit, but not explicit, sexual imagery compared to placebo.

Frye *et al.* (2014) studied the impact of MDMA on subjective mood and social evaluation in response to simulated social rejection and acceptance. Participants were administered MDMA (0.75, 1.5 mg/kg) before playing Cyberball (a virtual ball toss game in which participants play catch with two computer controlled characters whose toss behavior is experimentally manipulated to induce the experience of social acceptance or rejection). To simulate social acceptance, participants received ball tosses $63 \pm 3\%$ of the time, whereas in the rejection condition they only received the ball in $30 \pm 3\%$ of tosses. As expected, simulated social rejection decreased mood and self-esteem under placebo. MDMA (0.75 & 1.5 mg/kg) attenuated these negative feelings after rejection trials, indicating a blunting of the otherwise potent effects of this manipulation. MDMA-induced 'loving' feelings were unaffected by social rejection. Moreover, MDMA (1.5 mg/kg only) caused participants to inaccurately inflate their perception of the number of tosses they received during the rejection but not acceptance trials, suggesting that MDMA not only blunted emotional responding to rejection, it reduced *awareness* of the rejection. These results suggest that MDMA's prosocial effects may stem partially from dampened processing of social rejection, extending findings of decreased identification and neural processing of negative social stimuli (Bedi et al., 2010; Bedi et al., 2009; Hysek et al., 2012a; Kirkpatrick et al., 2014b). However, a more recent investigation (Kuypers et al., 2014) used an adapted version of CyberBall and found no effect of a lower dose of MDMA (75 mg) on subjects' toss behavior or subjective ratings of 'trust' and 'preference' in regards to the other computer

players after social rejection or inclusion trials. These conflicting findings suggest that blunting effects of MDMA on processing of social rejection may only occur at higher doses.

In addition to blunting responses to social rejection, there is some evidence that MDMA may enhance social reward. Wardle et al. (2014) reported that MDMA (1.5 mg/kg only) increased positivity ratings for positive social, but not nonsocial, imagery. A lower dose (0.75 mg/kg) decreased positivity ratings for positive non-social imagery, suggesting a preferential effect whereby MDMA increases perceptions of positivity for social scenes but devalues non-social stimuli.

Tasks involving hypothetical social scenarios have been used in recent studies to assess the effects of MDMA on preference for cooperative behaviors and trust (Hysek et al., 2014a; Kirkpatrick et al., 2015; Kuypers et al., 2014; Schmid et al., 2014) as well as moral-decision making (Schmid et al., 2014). Hysek et al. (2014a) used a behavioral economic task to measure the impact of MDMA on economic decisions that maximize resource gain for both oneself and another person (joint gain maximization), and minimize differences in resource distribution between oneself and another (inequality aversion). Participants believed that their choices would determine the amount of real money that would be allocated to other study volunteers. Prosociality in this measure is defined as preference for maximizing total allocation of resources for the self and others and reducing inequality between the two (Murphy and Ackermann, 2014). MDMA (125 mg) increased preference for equal distribution of funds (joint gain maximization) relative to placebo, though only in men. MDMA also reduced inequality aversion in those with prosocial tendencies. In contrast, a lower dose of MDMA (75 mg) had no effect on this measure in a more recent study (Schmid et al., 2014), suggesting dose-dependent effects of MDMA on fairness preferences and cooperative behavior. Kirkpatrick et al. (2015) also reported dose-dependent effects of MDMA on preference for prosocial resource allocation. In this study, participants were asked how they would hypothetically distribute a sum of money between themselves and a friend or a stranger if the only two allocation options were to (1) give the other person (friend or stranger) the total sum and receive nothing in return or (2) give nothing to the other person and receive a smaller portion of the sum. For every hypothetical exchange, the amount of money that the participant could receive was experimentally varied in order to determine the point at which the participant was willing to trade off their well-being for the welfare of another (welfare trade-off ratio; WTR). Generosity in this measure is defined as a higher WTR. Compared to placebo, MDMA (1.0 mg/kg only) increased preference for economic generosity (heightened WTR) towards a friend, whereas generosity towards a stranger was only greater following lower doses (0.5 mg/kg only) and only in women. Kuypers et al. (2014) investigated the effects of MDMA (75 mg) on reciprocity and trust using a hypothetical economic decision-making task in which preference for trustful and cooperative behaviors regarding resource distribution determined the amount of actual money to be shared between a subject and another co-participant. No drug effects were reported on this measure. Lastly, Schmid et al. (2014) examined the effects of MDMA (75 mg) on moral decision-making by asking participants how they would react to hypothetical scenarios involving avoidable or inevitable harm to others (Moral-Judgment task). Again, no effects of MDMA were observed. In combination, results suggest that MDMA does increase

cooperative behavior, but that these effects depend on dose, sex, and the familiarity of the social partner.

Despite substantial evidence of prosocial feelings and social processing alterations broadly consistent with increased social approach behavior after MDMA, only one study (Kirkpatrick et al., 2014b) has investigated the effects of MDMA (0.75 and 1.5 mg/kg) on preferences to socialize, a direct indicator of social approach and reinforcement. Participants were asked to rate their desire to socialize with an unfamiliar person (a research confederate) versus remaining alone in their laboratory room. They were informed that these ratings, combined with an element of chance, would determine which activity (i.e. socializing versus remaining alone) they ultimately undertook later in the session (Kirkpatrick et al., 2014b). Consistent with increased social reinforcement, MDMA (1.5 mg/kg only) preferentially increased self-reported willingness to socialize with others relative to placebo, an effect accompanied by heightened feelings of friendliness.

Whereas recent studies have examined prosocial effects of MDMA using simulated social scenarios, two investigations explored the drug's effects on social behavior during actual social interactions (Kirkpatrick and de Wit, 2014; Wardle and de Wit, 2014). In the first study, participants completed the Interpersonal Perception Task (speech task described above) after receiving placebo or MDMA (0.75, 1.5 mg/kg). In addition to speech assessments (described above), physiological markers of prosociality (facial muscle movements) during viewing of facial affect stimuli were collected and subjects rated the interviewer's level of empathy and regard following the interaction. MDMA (1.5 mg/kg) decreased corrugator muscle activity (frown response) to happy relative to negative faces, and increased zygomatic activity (smile response) to happy relative to negative faces, reflecting increased prosocial responses to positive, but not negative, facial expressions. MDMA (1.5 mg/kg) also increased perceptions of interviewer empathy relative to placebo (Wardle and de Wit, 2014).

In the second investigation (Kirkpatrick and de Wit, 2014), social behavior was assessed after participants received MDMA (0.5, 1.0 mg/kg) under one of three social conditions (described above; alone, with a research assistant, or with other participants). Social interactions (talking or playing games) and non-social activities (sleeping, watching a movie, or reading) were video recorded for subsequent analysis. Participants who spent sessions in the company of other participants engaged in more social interaction after MDMA (0.5 & 1.0 mg/kg) relative to placebo, while those in the company of a research assistant showed more social interaction after low doses only (0.5 mg/kg). Moreover, participants in the company of a research assistant exhibited *lower* social interaction after high MDMA doses (1.0 mg/kg) compared to the low dose, suggesting that interactions between dose and social setting can either enhance or diminish MDMA's propensity to promote prosocial behavior.

Thus, although the studies reviewed herein involved varying doses of MDMA administered to diverse samples, MDMA consistently and robustly increased prosocial feelings relative to placebo. Despite the notion that MDMA might represent a novel pharmacological class of 'empathogens' (see Hysek et al., 2014a; Nichols et al., 1993), data regarding empathy

suggest that MDMA may *impair* recognition and processing of negative, but not positive, emotional states from social stimuli, including pictures of faces and eyes. Some data suggests that MDMA could enhance emotional responding to positive but not negative affective states in others (i.e. emotional empathy). Data are more consistent with regards to sociability: acute doses of MDMA appear to decrease the awareness of simulated social rejection and its negative emotional impact, increase physiological markers of prosociality, and heighten perceptions of others' level of empathy and attractiveness, all changes that are consistent with enhanced sociability. These prosocial effects may be due to decreased neural processing of negative social information and enhanced processing of socially rewarding stimuli, although to date little research has addressed neural mechanisms of the social effects of MDMA in humans. MDMA also produced alterations to social behavior, increasing social interaction in subjects when accompanied by other intoxicated study participants. Together, these findings indicate that the prosocial effects of MDMA in humans are highly replicable in terms of subjective states, but more nuanced when measures of social processing and behavior are employed. Overall findings, however, are consistent with a prosocial profile of this drug in humans.

5. Pharmacological mechanisms of MDMA's prosocial effects in humans and animals

The pharmacological mechanisms underlying the non-social acute effects of MDMA have been the subject of substantial research. Although the pharmacodynamic effects of MDMA are complex, non-social psychoactive effects in humans appear to be mediated primarily by transporter-mediated release of serotonin, norepinephrine, and dopamine (Hysek et al., 2012b; Liechti et al., 2000a; Liechti et al., 2000b; Liechti and Vollenweider, 2000, 2001). Recent studies have investigated the role of changes in serotonin and norepinephrine signaling on the prosocial effects of MDMA, examining both objective (Reading the Mind in the Eyes) and subjective (self-reported mood state) indices (Hysek et al., 2012c). Pretreatment with duloxetine (a serotonin-norepinephrine reuptake inhibitor) blunted the subjective prosocial effects of MDMA (125 mg) relative to placebo, as indicated by decreased ratings of "closeness", "open", and "talkative" (Hysek et al., 2012c). Pretreatment with the selective norepinephrine transporter inhibitor reboxetine only inhibited MDMA-induced increases in ratings of "any drug effect" and "closeness" (Hysek et al., 2011), while clonidine (a sympatholytic α_2 -adrenergic receptor agonist) had no effect on subjective MDMA responses compared to placebo (Hysek et al., 2012b). All three pretreatments failed to attenuate the valence-dependent effects of MDMA on RMET performance. Pretreatment with citalopram (a serotonin reuptake inhibitor) diminished ratings of "extroversion" and "self-confidence" produced by MDMA (1.5 mg/kg; Liechti et al., 2000a) while ketanserin (a 5-HT₂ receptor antagonist) attenuated MDMA-induced increases in "friendliness" ratings (75 mg; van Wel et al., 2012). These findings suggest that MDMA elicits heightened prosocial feelings primarily via serotonergic mechanisms, with some effect of noradrenergic transmission. In support of this view, serotonin reuptake inhibitors have themselves been shown to alter social processing, diminishing the perception of negative emotions in others (Harmer et al., 2004; Hinkelman et al., 2010).

MDMA increases plasma concentrations of the neuropeptide oxytocin in rodents (Ramos et al., 2013; Thompson et al., 2007) and humans (Dumont et al., 2009; Hysek et al., 2012a; Hysek et al., 2014a; Kirkpatrick et al., 2014a; Kuypers et al., 2014; Schmid et al., 2014), an effect mediated by interaction with serotonin 1A receptors in rats (Thompson et al., 2007). Oxytocin is thought to regulate numerous social behaviors in humans and animals (Bartz et al., 2011b; Baumgartner et al., 2008; Bos et al., 2012; Dumont et al., 2009; Kirkpatrick et al., 2014a; Lee et al., 2009). Although some evidence suggests that the social effects of oxytocin in humans may be more complex than previously thought (Bartz et al., 2011a; Ebert et al., 2013; Shamay-Tsoory et al., 2009), intranasal oxytocin administration produces many behavioral effects that are similar to those elicited by MDMA, including reduced amygdala activity in response to negative emotional stimuli (Kirsch et al., 2005), increased generosity (Zak et al., 2007), feelings of sociability and friendliness (Kirkpatrick et al., 2014b), decreased responses to others' negative emotional states (Di Simplicio et al., 2009) and increased reaction time for negative facial emotion identification (Di Simplicio et al., 2009). It has thus been proposed that MDMA's prosocial effects may be partially mediated by oxytocin release (McGregor et al., 2008).

Providing some support for this view, Dumont et al. (2009) found that MDMA-induced increases in subjective amicability and gregariousness were positively correlated with plasma oxytocin concentrations. However, several recent investigations provide contrary findings, reporting no relationship between plasma oxytocin levels and prosocial feelings after MDMA from both fixed (125 mg; Hysek et al., 2012a; Hysek et al., 2014a) and weight-based doses (0.75, 1.5 mg/kg; Kirkpatrick et al., 2014a). Recent studies also examined associations between plasma oxytocin concentrations and objective indices of social processing following MDMA. In two studies (Hysek et al., 2012a; Hysek et al., 2014a), increased plasma oxytocin due to MDMA (125 mg) was not correlated with alterations in emotion recognition. Similarly, Schmid et al. (2014) reported that plasma oxytocin and social cognitive effects (i.e. facial emotion recognition, cognitive and emotional empathy and social decision-making) were not correlated following MDMA (75 mg) treatment. Lastly, heightened levels of plasma oxytocin following MDMA (75 mg) were not correlated with MDMA-induced increases in emotional empathy (Kuypers et al., 2014).

Three studies (Kirkpatrick et al., 2014a; Kirkpatrick et al., 2014b; Kuypers et al., 2014) have directly compared the effects of intranasal oxytocin and MDMA on measures of prosociality in humans. In two of these investigations, oxytocin had no effect on prosocial feelings (20, 40 IU; Kirkpatrick et al., 2014a; 16, 40 IU; Kuypers et al., 2014). Kuypers et al. (2014) also reported that oxytocin (16, 40 IU) did not alter emotional or cognitive empathy, emotion recognition from pictures of the eyes, or objective and subjective measures of trust and reciprocity. However, Kirkpatrick et al. (2014b) found that both doses of oxytocin (20 & 40 IU) increased self-reported friendliness while only the lower dose (20 IU) heightened self-reported sociability. In addition, ratings of 'insightful' following oxytocin (20 IU) and MDMA (0.75, 1.5 mg/kg) were positively correlated, as were ratings of 'playful' after oxytocin (20 IU) and MDMA (1.5 mg/kg). Despite the fact that both drugs increased subjective sociability, oxytocin did not enhance preference for social interaction, whereas MDMA did. Differential effects were also observed on an emotional identification task

(Kirkpatrick et al., 2014b), in which oxytocin (40 IU) increased accurate recognition of sad facial expressions, while MDMA (1.5 mg/kg) impaired identification of fearful and angry faces. Thus, in humans the extent to which oxytocin release following MDMA administration is involved in MDMA's prosocial effects remains somewhat unclear. Understanding the role of oxytocin in these effects has been hampered by difficulties estimating central oxytocin concentrations from peripheral measurements (Landgraf and Neumann, 2004) and the absence of studies using an oxytocin antagonist to directly assess oxytocinergic mediation of MDMA's prosocial effects.

Oxytocinergic mechanisms have been more comprehensively assessed in relation to MDMA-induced prosocial behavior in rodents (Ramos et al., 2013; Thompson et al., 2007). MDMA (5 mg/kg or 10 mg/kg) activated neural regions involved in oxytocin production (Hargreaves et al., 2007; Hunt et al., 2011) and increased plasma oxytocin levels in rats (Ramos et al., 2013; Thompson et al., 2007). Pre-treatment with tocinoic acid (20 mg/kg; an oxytocin receptor antagonist) attenuated the prosocial effects of MDMA (5 mg/kg) while the 5-HT_{1A} antagonist WAY 100,635 (1 mg/kg i.p.) blunted both plasma oxytocin elevations and adjacent lying produced by MDMA (Thompson et al., 2007). In an earlier study (Morley et al., 2005), MDMA-induced increases in rodent prosocial behavior were similarly prevented by the same dose of WAY 100,635 as well as the 5-HT_{2B/2C} receptor antagonist, SB 206553 (2mg/kg), suggesting that the prosocial effects of MDMA in rodents may be mediated by oxytocin release via interactions with 5-HT_{1a} and 5-HT_{2b/2c} receptors.

Consistent with reports that administration of oxytocin and MDMA produce some similar behavioral effects in humans, peripheral administration of both oxytocin (0.5 mg/kg) and vasopressin (0.01 mg/kg) elicit MDMA-like prosocial effects in rats, namely increased adjacent lying (Ramos et al., 2013). Of note, administration of an oxytocin antagonist (C25; 5 mg/kg, IP) that is more selective than tocinoic acid failed to prevent heightened adjacent lying due to oxytocin administration (Ramos et al., 2013). Conversely, administration of the vasopressin receptor 1A (V1AR) antagonist SR49059 (1 mg/kg, IP) attenuated increases in adjacent lying elicited by MDMA (5 mg/kg), oxytocin (0.5 mg/kg), and vasopressin (0.01 mg/kg). These findings suggest a common mechanism, mediated by V1AR, for the prosocial behavioral effects of MDMA, oxytocin, and vasopressin; the authors suggest that the earlier findings with tocinoic acid (Thompson et al., 2007) may have been due to the non-specific nature of this oxytocin antagonist, which also blocks vasopressin receptors. The hypothesis that the prosocial effects of MDMA, oxytocin, and vasopressin share a common mechanism is supported by the observation that low doses of MDMA (2.5 mg/kg), oxytocin (0.25 mg/kg), and vasopressin (0.0025 mg/kg), which do not produce adjacent laying when administered alone, have an additive effect when co-administered (Ramos et al., 2013).

6. Prosocial Effects of MDMA: Implications and Outstanding Questions

Although numerous questions remain, the literature reviewed above indicates that MDMA produces robust alterations in social behavior in animals, and in social feelings, processing, and behavior in humans. These changes are broadly consistent with enhanced sociability facilitating social approach behavior due to MDMA. Evidence with regard to empathy is less consistent, suggesting that although MDMA may produce *feelings* of closeness and

empathy, it may actually degrade some empathic capacities, specifically the ability to decode negative or threatening emotional expressions in others. Although such changes could facilitate social approach (blunting sensitivity to others' negative emotional states), they are not entirely consistent with the notion of MDMA as an 'empathogen'.

The broadly prosocial effects of MDMA are frequently cited by recreational users as a motivator for use of this drug. Thus, from a public health perspective, understanding these acute prosocial effects may prove important. To date no research has directly assessed the role of drug-induced prosocial states in the reinforcing effects of MDMA. One study examined, on a preliminary basis, MDMA's prosocial subjective and objective effects as predictors of self-reported desire to take the drug again, finding limited evidence for such a relationship (Wardle and de Wit, 2014). A more conclusive assessment of the role of prosocial effects in MDMA's reinforcing properties would require pharmacological blockade of prosocial effects, combined with assessment of self-administration of MDMA, in animals or humans. Such research could be a valuable future direction.

Characterizing prosocial effects of MDMA may also prove useful from the perspective of treating problematic ecstasy use. Although most ecstasy users appear to decrease or stop use as part of a natural trajectory (Smirnov et al., 2013; Verheyden et al., 2003), some users do endorse criteria for ecstasy use disorders (Degenhardt et al., 2010; McKetin et al., 2014; Uosukainen et al., 2015) or develop compulsive patterns of use (Bruno et al., 2009; Degenhardt et al., 2010) and a small subset seek treatment for ecstasy use (Degenhardt et al., 2010; SAMHSA, 2014). The extent to which prosocial effects motivate these less instrumental patterns of use remains unclear. Nevertheless, taking into account these unique potential motivating factors may facilitate treatment for those individuals who do seek treatment for use of this drug.

Findings about the prosocial effects of MDMA in humans generate intriguing questions about what constitutes ideally calibrated social processing for different social contexts. For example, fine grained awareness of transient threatening facial expressions in others' may be highly adaptive in interpersonally threatening situations. Conversely, blunting such awareness could remove interpersonal barriers and facilitate social closeness in contexts such as dance parties. Thus, alterations such as decreased awareness of threat-related emotions in others may be positive in some environments while being dangerous in situations in which objective threats exist. Similarly, whereas decreased awareness of subtle cues about social rejection may decrease social inhibitions and facilitate social bonding, such changes could also lead to 'misreading' of some social situations.

In the context of therapeutic use, MDMA could enhance perceptions of the therapists' empathic awareness, potentially strengthening the therapeutic alliance. However, it is unclear whether these effects, which have been demonstrated in the context of short interviews in laboratory studies in healthy volunteers (Wardle and de Wit, 2014), also occur in clinical settings. MDMA's blunting effect on recognition of negative emotions in others might also be beneficial in therapy for trauma-related conditions, which can be associated with hyper-vigilance for negative or threat-related stimuli, but again it remains unclear whether the changes observed in healthy volunteers would occur in clinical populations.

Moreover, even if these changes do generalize to adjunctive use of MDMA in therapy, it remains unknown whether the prosocial effects of MDMA mediate its putative efficacy as an adjunct to psychotherapy (Mithoefer et al., 2011; Mithoefer et al., 2013). Identifying both the mechanisms of MDMA's prosocial effects and the active components of MDMA-assisted psychotherapy will be important future research directions, potentially leading to use of other, more targeted pharmacological adjuncts to psychotherapy.

Several basic science questions remain about the prosocial effects of MDMA. Existing studies have not revealed the pharmacological mechanisms of these effects in humans; future research could valuably assess the effects of 5-HT_{2A} antagonism on MDMA's prosocial effects, given recent findings in rodents (Ramos et al., 2013). Another area requiring further research is the extent to which social environments facilitate the prosocial effects of MDMA, and reciprocal influences of MDMA effects on social group formation (e.g. see Sayette et al., 2012). Such effects could be important in psychotherapeutic contexts. The extent to which there are sex differences or menstrual cycle effects on the prosocial effects of MDMA is also poorly understood. There are indications that sex differences may occur: for instance, MDMA-related increases in emotional empathy for others' positive emotions were found to be driven by effects in males (Hysek et al., 2014a). Males, however, had lower baseline levels of emotional empathy than did females, thus differential effects in males and females may result from individual differences in baseline social processing. To date, no studies have focused on individual differences in prosocial responses to MDMA. Finally, one important oversight of most existing studies in humans is a lack of measures of non-social cognition: thus, the extent to which alterations to social processing are related to more generalized cognitive and motivational changes remains poorly understood.

Remaining questions notwithstanding, the past decade has seen the emergence of a rich body of controlled studies investigating the prosocial effects of MDMA in laboratory animals and humans. As reviewed above, this evidence indicates that MDMA alters social behavior and cognitive motivational processing in a manner broadly consistent with the notion that this drug has unusual sociability-enhancing effects in humans and other animals.

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Table 1

Acute Effects of MDMA on Social Mood States

Study	N	Age*	Ecstasy Use**	MDMA Dose	Tasks/ Measures	Results
Bedi et al (2009)	9	24.0 (±3.2)	63.9 (±94.9)	0.75, 1.5 mg/kg	VAS POMS	1.5 mg/kg ↑ VAS Sociable
Bedi et al (2010)	21	24.4 (±4.9)	15 (±23.1)	0.75, 1.5 mg/kg	VAS POMS	1.5 mg/kg ↑ VAS Loving, VAS Playful, POMS Friendly 0.75 mg/kg ↑ VAS Lonely
Dumont et al (2009)	15	21.1 (±1.7)	110.5 (±175.3)	100 mg	BLMRS	↑ BLMRS Gregarious, BLMRS Amicable Positive correlation between Gregarious and Amicable and plasma oxytocin levels
Frye et al (2014)	36	24.6 (±4.7)	4-40 ^d	0.75, 1.5 mg/kg	VAS	0.75, 1.5 mg/kg ↑ VAS Loving
Gamma et al (2000)	16	26.0 (±2.5)	MDMA naïve	1.7 mg/kg	OAV EWL	↑ EWL, Self-confidence, EWL Extroversion
Harris et al (2002)	8	24-39 ^d	5-200 ^d	0.5, 1.5 mg/kg	VAS	1.5 mg/kg ↑ VAS Confident
Hysek et al (2011)	16	25.7 (±5.5)	5 ^b	125 mg	VAS 5D-ASC AMRS STAI	↑ VAS Closeness to others, AMRS Extroversion
Hysek et al (2012a)	48	26.0 (±5.0)	5 ^c	125 mg	VAS ARCI	↑ VAS Open, VAS Closeness to others, VAS Talkative
Hysek et al (2012b)	16	25.4 (±4.9)	5 ^d	125 mg	VAS 5D-ASC AMRS STAI	↑ VAS Open, VAS Closeness to others
Hysek et al (2012c)	16	26.1 (±6.0)	MDMA naïve	125 mg	VAS AMRS 5D-ASC	↑ VAS Open, VAS Closeness to others, VAS Talkative, AMRS Extroversion
Hysek et al (2013)	16	25.8 (±3.3)	5 ^e	125 mg	AMRS VAS 5D-ASC	↑ AMRS Extroversion, AMRS Self-confidence
Hysek et al (2014a)	32	25.0 (±3.0)	5 ^f	125 mg	VAS AMRS	↑ VAS Open, VAS Close to others, AMRS Extroversion
Hysek et al (2014b)	16	24.8 (±2.6)	5 ^g	125 mg	VAS AMRS ARCI 5D-ASC	↑ VAS Close to others, AMRS Extroversion

Study	N	Age*	Ecstasy Use**	MDMA Dose	Tasks/ Measures	Results
Johanson et al (2006)	8	25.0 ^h	20.0 ^h	1.0, 1.5 mg/kg	VAS ARCI POMS	1.0 and 1.5 mg/kg ↑ VAS Friendly
Kirkpatrick et al (2014a)	14	25.4 (±3.7)	13.5 (±12.0)	0.75, 1.5 mg/kg	VAS	1.5 mg/kg ↑ VAS Friendly, VAS Loving, VAS Sociable
Kirkpatrick et al (2014b)	65	Group 1: 24.1 (±4.1) Group 2: 23.1 (±3.5)	Group 1: 13.5 (±10.6) Group 2: 18.1 (±12.0)	0.75, 1.5 mg/kg	VAS	0.75 and 1.5 mg/kg ↑ VAS Friendly, VAS Loving, VAS Playful, VAS Sociable 1.5 mg/kg ↑ VAS Lonely
Kirkpatrick and de Wit (2014)	32	SOL: 24.7 (±2.7) RAP: 25.7 (±4.8) OPP: 24.5 (±3.3)	SOL: 14.5 (±22.2) RAP: 18.4 (±13.1) OPP: 20.9 (±21.5)	0.5, 1.0 mg/kg	VAS	SOL: 1.0 mg/kg ↑ VAS Insightful RAP: 1.0 mg/kg ↑ VAS Insightful, VAS Loving OPP: 0.5 and 1.0 mg/kg ↑ VAS Insightful; 1.0 mg/kg ↑ VAS Loving
Kolbrich et al (2008)	8	21.1 (±0.8)	^j	1.0, 1.6 mg/kg	VAS	1.6 mg/kg ↑ VAS Closeness to others
Kuypers et al (2011)	14	23.4 (±3.0)	65.8 (±134.5)	75 mg	POMS	↑ POMS Friendliness
Kuypers et al (2013)	17	21.0 (±1.2)	18.0 (33.0)	75 mg	POMS	↑ POMS Friendliness
Liechti et al (2000a)	16	27.4 (±4.4)	Data not presented; 13 MDMA naive	1.5 mg/kg	AMRS 5D-ASC ASC	↑ AMRS Extroversion, AMRS Self-confidence
Liechti et al (2000b)	14	26.0 ^h	Data not presented; 12 MDMA naive	1.5 mg/kg	AMRS STAI OAV	↑ AMRS Extroversion, AMRS Self-confidence
Schmid et al (2014)	30	24.0 (±4.2)	^k	75 mg	5D-ASC VAS AMRS	↑ VAS Openness, VAS Trust, VAS Close to others
Tancer and Johanson (2003)	12	22.3 ^h	14.5 ^h	1.0, 2.0 mg/kg	VAS ARCI POMS	2.0 mg/kg ↑ VAS friendly, VAS Social, VAS Talkative
Tancer and Johanson (2007)	8	23.9 ^h	28.6 ^h	1.5 mg/kg	VAS ARCI POMS	↑ VAS Talkative, VAS Friendly
Van wel et al (2012)	17	22.8 (±2.8)	72.4 ^h	75 mg	POMS	↑ POMS Friendliness
Wardle et al (2014)	101	24.1 (±4.2)	13.3 (±10.5)	0.75, 1.5 mg/kg	VAS	0.75 and 1.5 mg/kg ↑ VAS Playful, VAS Loving
Wardle and de Wit (2014)	36	24.6 (±4.7)	10.2 (±8.2)	0.75, 1.5 mg/kg	VAS POMS	0.75 and 1.5 mg/kg ↑ VAS Loving

↑ = drug increased measure relative to placebo; MDMA = 3,4-methylenedioxymethamphetamine; VAS = Visual Analogue Scales; POMS = Profile of Mood States; BLMRS = Bond and Lader Mood Rating Scale; OAV = Altered States of Consciousness Questionnaire; EWL = Mood Rating Scale; 5D-ASC = 5 Dimensions of Altered States of Consciousness Rating Scale; AMRS = Adjective Mood Ratings

Scale; STAI = State-Trait Anxiety Inventory; ARCI = Addiction Research Center Inventory; SOL = solitary condition; RAP = research assistant present during drug sessions; OPP = other participant present during drug sessions; IRI = Interpersonal Reactivity Index; ASC = Altered States of Consciousness scale;

* Mean (\pm S.D.);

** Mean (\pm S.D.), except where otherwise noted;

^a Means and SD not reported, therefore the range is presented;

^b Participants had used illicit drugs 5 times. Thirteen participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 3 participants who reported previous MDMA/ecstasy use;

^c Participants had used illicit drugs 5 times. Forty-four participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 4 participants who reported previous MDMA/ecstasy use;

^d Participants had used illicit drugs 5 times. Sixteen participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 2 participants who reported previous MDMA/ecstasy use;

^e Participants had used illicit drugs 5 times. Thirteen participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 3 participants who reported previous MDMA/ecstasy use;

^f Participants had used illicit drugs 5 times. Twenty-two participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 10 participants who reported previous MDMA/ecstasy use;

^g Participants had used illicit drugs 5 times. Ten participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 6 participants who reported previous MDMA/ecstasy use;

^h SD not presented;

ⁱ All participants received MDMA (0.75, 1.5 mg/kg) and placebo, in addition the total N was divided into 2 groups. Group 1 completed a final session in which they were administered 20 IU intranasal oxytocin, whereas Group 2 received 40 IU oxytocin as their 4th condition;

^j Participants had used ecstasy/MDMA at least five times, lifetime use data are not presented;

^k Participants had used illicit drugs 5 times. Twenty-two participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 8 participants who reported previous MDMA/ecstasy use.

Table 2

Acute Effects of MDMA on Processing and Evaluation of Positive Social Material

Study	N	Age* (±SE)	Ecstasy Use** (±SE)	MDMA Dose (mg/kg)	Tasks/Measures	Hypothesized Component Process	Results
Bedi et al (2009)	9	24.0 (±3.2)	63.9 (±94.9)	0.75, 1.5 mg/kg	FERT	Social cognition Social reward processing	0.75 mg/kg ↑ ventral striatum BOLD response to happy versus neutral faces ↑ accurate recognition for positive emotions
Hysek et al (2012a)	48	26.0 (±5.0)	5 ^a	125 mg	RMET	Social cognition	↑ emotional empathy (positive stimuli) ↑ prosocial decision-making
Hysek et al (2014a)	32	25.0 (±3.0)	5 ^b	125 mg	FERT MET SVO	Social cognition Emotional/cognitive empathy Altruistic decision-making	1.5 mg/kg ↑ AQ scores in SOL, RAP, OPP RAP: 0.5 mg/kg ↑ social interaction OPP: 0.5, 1.0 mg/kg ↑ social interaction
Kirkpatrick et al (2014b)	65	Group 1: 24.1 (±4.1) Group 2: 18.1 (±3.5)	Group 1: 13.5 (±10.6) Group 2: 23.1 (±12.0)	0.75, 1.5 mg/kg	mFER SET SCT	Social cognition Social evaluation Social motivation	1.0 mg/kg ↑ prosocial decision-making/ prosocial resource allocation
Kirkpatrick and de Wit (2014)	32	SOL: 24.7 (±2.7) RAP: 25.7 (±4.8) OPP: 24.5 (±3.3)	SOL: 14.5 (±22.2) RAP: 18.4 (±13.1) OPP: 20.9 (±21.5)	0.5, 1.0 mg/kg	AQ PRQ SIQ	Social evaluation Social behavior	↑ overall emotional empathy (including for positive stimuli)
Kirkpatrick et al (2015)	32	24.9 (±3.7)	17.0 (±19.3)	0.5, 1.0 mg/kg	WTT	Altruistic decision-making	↑ emotional empathy (positive stimuli)
Kuypers et al (2014)	20	21.6 (±2.5)	11.0 (±9.0)	75 mg	MET RMET Trust game Cyberball	Social cognition Emotional/cognitive empathy Social evaluation Response to social rejection/ acceptance	↑ emotional empathy (positive stimuli)
Schmid et al (2014)	30	24.0 (±4.2)	5 ^d	75 mg	FERT MET MASC SVO MIT	Social cognition Emotional/cognitive empathy Altruistic decision-making Moral Judgment	↑ responses to prolong viewing of implicit sexual imagery
Schmid et al (2015)	30	24.0 (±4.2)	5 ^e	75 mg	SAT ART CAT	Response to sexual stimuli Social evaluation	1.5 mg/kg ↑ zygomatic (smile) response to happy vs. negative faces 1.5 mg/kg ↓ corrugator (frown) response to
Wardle and de Wit (2014)	36	24.6 (±4.7)	10.2 (±8.2)	0.75, 1.5 mg/kg	DEIT IPT	Social cognition Social reward processing Social evaluation	

Study	N	Age* (±S.D.)	Ecstasy Use** (±S.D.)	MDMA Dose	Tasks/Measures	Hypothesized Component Process	Results
Wardle et al (2014)	101	24.1 (±4.2)	13.3 (±10.5)	0.75, 1.5 mg/kg	Image Rating Task	Social behavior Social motivation	happy vs. negative faces 0.75, 1.5 mg/kg ↑ % positive emotion words used 1.5 mg/kg ↑ ratings of others' empathy 1.5 mg/kg ↑ positivity ratings for positive social images 0.75 mg/kg ↓ positivity ratings for positive non-social images

↑= drug increased function relative to placebo; ↓= drug decreased function relative to placebo; MDMA = 3,4-methylenedioxymethamphetamine; RMET = Reading the Mind in the Eyes Test; FERT = Facial Emotion Recognition Task; BOLD = Blood Oxygen Level Dependent; MET = Multifaceted Empathy Test; SVO = Social Value Orientation Test; MASC = Movie for the Assessment of Social Cognition; MIT = Moral Judgment Task; mFER = morphed Facial Emotion Recognition task; SET = Social Evaluation Task; SCT = Social Choice Task; WTT= Welfare Trade-off Task; IRO = Interpersonal Reactivity Index; DEIT = Dynamic Emotional Identification Task; IPT = Interpersonal Perception Task (modified); SOL = solitary condition; RAP = research assistant present during drug sessions; OPP = other participant present during drug sessions; AQ = Interpersonal Attraction Questionnaire; PRQ = Perceived Responsiveness Questionnaire (self and other); SIQ = Social Interaction Questionnaire; SAT = Sexual Arousal Task; ART = Arousal Rating Task; CAT = Couples Appraisal Task;

* Mean (±S.D.);

** Mean (±S.D.), except where otherwise noted;

^a Participants had used illicit drugs 5 times. Forty-four participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 4 participants reporting previous MDMA/ecstasy use;

^b Participants had used illicit drugs 5 times. Twenty-two participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 10 participants reporting previous MDMA/ecstasy use;

^c All participants received MDMA (0.75, 1.5 mg/kg) and placebo, in addition the total N was divided into 2 groups. Group 1 completed a final session in which they were administered 20 IU intranasal oxytocin, whereas Group 2 received 40 IU oxytocin as their 4th condition;

^d Participants had used illicit drugs 5 times. Twenty-two participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 8 participants reporting previous MDMA/ecstasy use;

^e Participants had used illicit drugs 5 times. Twenty-two were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 8 participants who reported MDMA/ecstasy use.

Table 3

Acute Drug Effects on Processing and Evaluation of Negative Social Material

Study	N	Age*	Ecstasy Use**	MDMA Dose	Tasks/Measures	Hypothesized Component Process	Results
Bedi et al (2009)	9	24.0 (±3.2)	63.9 (±94.9)	0.75, 1.5 mg/kg	FERT	Social cognition Social threat processing	1.5 mg/kg ↓ amygdala BOLD response to angry versus neutral faces
Bedi et al (2010)	21	24.4 (±4.9)	15 (±23.1)	0.75, 1.5 mg/kg	FERT RMET DANVA-Prosody	Social cognition	1.5 mg/kg ↓ accurate identification of fearful faces ↑ misclassification of facial emotions (including negative emotions) as neutral
Frye et al (2014)	36	24.6 (±4.7)	4-40 ^a	0.75, 1.5 mg/kg	Cyberball	Response to social rejection/acceptance	1.5 mg/kg ↓ awareness of social rejection cues 1.5 mg/kg ↓ negative mood responses to social rejection
Hysek et al (2012a)	48	26.0 (±5.0)	5 ^b	125 mg	RMET	Social cognition	↓ accurate identification of negative emotions
Hysek et al (2014a)	32	25.0 (±3.0)	5 ^c	125 mg	FERT MET	Social cognition Emotional/cognitive empathy	↓ accurate identification of fearful, sad, angry, and disgusted faces
Hysek et al (2014b)	16	24.8 (±2.6)	5 ^d	125 mg	FERT	Social cognition	↓ accurate identification of sad, angry, and fearful faces
Kirkpatrick et al (2014b)	65	Group 1: 24.1 (±4.1) Group 2: 23.1 (±3.5)	Group 1: 13.5 (±10.6) Group 2: 18.1 (±12.0)	0.75, 1.5 mg/kg	mFER	Social cognition	1.5 mg/kg ↓ accurate identification of angry and fearful faces
Kuypers et al (2014)	20	21.6 (±2.5)	11.0 (±9.0)	75 mg	MET RMET Cyberball	Social cognition Response to social rejection/acceptance	↑ overall emotional empathy (including for negative stimuli)
Schmid et al (2014)	30	24.0 (±4.2)	5 ^f	75 mg	FERT MET MASC MJT	Social cognition Emotional/cognitive empathy Theory of mind Moral Judgment	↑ misclassification of facial emotions (including negative emotions) as neutral
Wardle and de Wit (2014)	36	24.6 (±4.7)	10.2 (±8.2)	0.75, 1.5 mg/kg	DEIT IPT	Social cognition Social threat processing Social evaluation Social behavior	1.5 mg/kg ↑ threshold to accurately identify anger

↑ = drug increased function relative to placebo; ↓ = drug decreased function relative to placebo; MDMA = 3,4-methylenedioxymethamphetamine; FERT = Facial Emotion Recognition Task; BOLD = Blood Oxygen Level Dependent; MET = Multifaceted Empathy Test; SVO = Social Value Orientation test; mFER = morphed Facial Emotion Recognition task; RMET = Reading the Mind in the Eyes Test; MASC = Movie for the Assessment of Social Cognition; MJT = Moral Judgment Task; DANVA = Diagnostic Analysis of Nonverbal Accuracy; DEIT = Dynamic Emotional Identification Task; IPT = Interpersonal Perception Task (modified);

* Mean (\pm S.D.);

** Mean (\pm S.D.), except where otherwise noted;

^a Means and SD not reported, therefore the range is presented;

^b Participants had used illicit drugs 5 times. Forty-four participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 4 participants reporting previous MDMA/ecstasy use;

^c Participants had used illicit drugs 5 times. Twenty-two participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 10 participants reporting previous MDMA/ecstasy use;

^d Participants had used illicit drugs 5 times. Ten participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 6 participants reporting previous MDMA/ecstasy use;

^e All participants received MDMA (0.75, 1.5 mg/kg) and placebo, in addition the total N was divided into 2 groups. Group 1 completed a final session in which they were administered 20 IU intranasal oxytocin, whereas Group 2 received 40 IU oxytocin as their 4th condition;

^f Participants had used illicit drugs 5 times. Twenty-two participants were MDMA naïve; data for lifetime MDMA use (mean and SD) are not presented for the 8 participants reporting previous MDMA/ecstasy use.