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ORIGINAL INVESTIGATION

Effects of MDMA on sociability and neural response to social threat and social reward

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Abstract
Rationale ±3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") reportedly produces unique subjective effects, including increased sociability, feelings of closeness with others, and reduced interpersonal defensiveness. Despite their apparent importance in recreational and potential psychotherapeutic use of MDMA, the defining characteristics and neurobiological mechanisms of these interpersonal effects are poorly understood.
Materials and methods We investigated acute effects of MDMA on self-reported sociability and neuronal activation in response to socially threatening (angry and fearful faces) and socially rewarding (happy faces) stimuli. Assessment of social threat response focused on amygdala activation, whereas assessment of social reward focused on ventral striatum activation. Healthy volunteers (N=9) reporting past ecstasy use completed three experimental sessions, receiving MDMA (0.75 and 1.5 mg/kg) and placebo (PBO) under double-blind conditions. During peak drug effects, participants underwent functional magnetic resonance imaging while viewing standardized images depicting emotional facial expressions including angry, fearful, happy, and neutral expressions. They also completed standardized self-report measures of sociability.
Results MDMA (1.5 mg/kg) increased self-reported sociability compared to MDMA (0.75 mg/kg) and PBO. MDMA (1.5 mg/kg) attenuated left amygdala response to angry facial expressions compared to PBO, but MDMA did not affect amygdala reactivity to fearful expressions. MDMA (0.75 mg/kg) enhanced ventral striatum response to happy expressions relative to PBO.
Conclusions These data present the first evidence that MDMA may increase sociability in humans both by diminishing responses to threatening stimuli and enhancing responses to rewarding social signals.

Keywords MDMA · Ecstasy · Social reward · Social threat · Sociability

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Introduction

±3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is reported to have a unique subjective profile, including "empathogenic" effects such as increased sociability and decreased defensiveness (Parrott 2007). These properties are cited by users as a motivator to use ecstasy (Sumnall et al. 2006), and they may also underpin the purported effectiveness of MDMA as an adjunct to psychotherapy. Advocates for psychotherapeutic MDMA use argue that the drug increases psychological openness to the therapeutic process (Parrott 2007).

Despite generating widespread interest, the purported empathogenic effects of MDMA are poorly understood. Nevertheless, there is some evidence that MDMA induces social behavior in animals and increases sociability ratings in humans. In rats, moderate MDMA doses increase social

interaction (Morley et al. 2005; Thompson et al. 2007). Notably, MDMA increases rats' tendency to lie adjacent to each other, which is thought to indicate sociability (Morley et al. 2005; Thompson et al. 2007). These behavioral changes involve release of oxytocin (OT), a neuropeptide implicated in attachment and pair bonding, with OT receptor antagonism attenuating MDMA's prosocial effects in rodents (Thompson et al. 2007). In humans, MDMA doses ranging from 1 to 2 mg/kg increase self-reported extroversion (e.g., Liechti et al. 2000; Vollenweider et al. 1999), friendliness (Tancer and Johanson 2003, 2007), sociability (Tancer and Johanson 2003), talkativeness (Tancer and Johanson 2003, 2007), and closeness to others (Kolbrich et al. 2008), although some studies have failed to observe these effects (Harris et al. 2002; Johanson et al. 2006; Liechti and Vollenweider 2000).

Previous imaging studies suggest possible brain mechanisms for MDMA's social effects. Studies using functional magnetic resonance imaging (fMRI) to measure blood oxygenated level dependent (BOLD) signal, an indirect indicator of neural activation, show the amygdala to be particularly important in socioemotional processing, especially processing of threat-related social information (Whalen et al. 1998; Zald 2003). In normal individuals, exposure to threat-related social signals such as fearful and angry facial expressions increases amygdala activity (Whalen et al. 1998; Zald 2003); this effect is heightened in individuals with social anxiety (Phan et al. 2006). Administration of Δ^9-tetrahydrocannabinoid (THC), the main psychoactive constituent of cannabis, reduces amygdala response to social signals of threat, an action that may underlie anxiolytic effects of THC (Phan et al. 2008). OT administration also reduces amygdala activation in response to threatening social stimuli (Kirsch et al. 2005), and patients with Williams–Beuren syndrome, characterized by hypersociability, demonstrate attenuated amygdala responses to social threat (Meyer-Lindenberg et al. 2005). Thus, to the extent that MDMA increases sociability, it may be expected to reduce amygdala responses to threat-related social signals.

MDMA might also increase sociability by enhancing the rewarding value of positive social interactions. Positive social stimuli act as a natural reward; rodents demonstrate conditioned preferences for places previously paired with a social partner (Douglas et al. 2004; Thiele et al. 2008), and in humans, positive social signs such as smiling faces activate reward circuitry (Tsukiura and Cabeza 2008). The ventral striatum (VS) is central to reward processing (Knutson and Cooper 2005) and is activated by a range of rewarding stimuli including drugs of abuse (Gilman et al. 2008). Increased salience of rewarding social stimuli, reflected in enhanced VS activation in response to positive social cues, would be expected to lead to increased social approach behavior and, hence, sociability.

This study employed fMRI after acute MDMA administration to assess possible mechanisms for the effects of MDMA on sociability in humans. Initially, we investigated whether controlled laboratory administration of MDMA enhances self-reported sociability. We then aimed to assess whether MDMA alters neural processing of threatening and rewarding social stimuli, focusing on amygdala and VS, respectively. We hypothesized that (a) MDMA would increase self-reported sociability; (b) MDMA would decrease amygdala reactivity in response to threatening (angry and fearful) facial expressions; and (c) MDMA would enhance VS responses to rewarding (happy) facial expressions.

Materials and methods

Participants

Recruitment used online advertisements and word of mouth. Nine healthy, right-handed volunteers (18–29 years) reporting ecstasy use at least twice participated. Exclusion was based on lifetime psychotic or bipolar disorder, past year other Axis 1 psychiatric disorder (DSM-IV, APA 1994); medical/neurological illness assessed with medical exam, electrocardiogram, and clinical interview; body mass index outside healthy range (18–30); prior adverse ecstasy response; and MRI counter indication. All participants provided written informed consent and were fully debriefed at completion, as approved by University of Chicago Institutional Review Board and in accordance with the Declaration of Helsinki.

Protocol

We employed a three-session, within-participants, double-blind design. Participants received MDMA (0.75 and 1.5 mg/kg) in ascending order with randomized placebo (PBO); sessions were scheduled ≥6 days apart. Participants abstained from cannabis for 7 days, alcohol for 24 h, and all other recreational drugs for 48 h prior to sessions. Compliance was verified with urine (Rapid Check 9 Panel Multi-Drug Screen, Craig Medical, Vista, CA), saliva (Oratect III, Branan Medical Corporation, Irvine, CA), and Breathalyzer (Alco-sensor III, Intoximeters, St. Louis, MO) screens. Female participants provided a negative pregnancy test at each session (Aimstrip, Craig Medical, Vista, CA). Participants did not eat for 2 h before sessions.

Drug sessions commenced at noon. After baseline measurements including cardiovascular and subjective measures, participants ingested an opaque gelatin capsule (size 00) containing either MDMA (0.75 or 1.5 mg/kg) with lactose or PBO (lactose). Doses in this low-to-moderate

range have been safely administered to humans previously (Dumont and Verkes 2006). Doses as low as 0.5 mg/kg produce significant, although modest, increases in euphoria (Harris et al. 2002), whereas our moderate dose (1.5 mg/kg) is within the recreational dose range (see Cole et al. 2002) and produces robust subjective effects (see Dumont and Verkes 2006). After capsule ingestion, participants remained in the hospital for at least 4.5 h, during which they underwent regular cardiovascular checks and completed subjective questionnaires in a comfortable laboratory environment. Approximately 45 min after capsule administration, participants were escorted to the Brain Research Imaging Center within the hospital where they underwent imaging. Participants then returned to the study room where they remained until session completion.

Subjective measures included a Drug Effects Questionnaire (DEQ; Johanson and Uhlenhuth 1980), a seven-item visual analog scale (VAS; Folstein and Luria 1973), and the profile of mood states (POMS; McNair and Droppleman 1971). The DEQ requires participants to rate on a visual analog scale the extent to which they (1) feel any drug effect (from "none at all" to "a lot"); (2) like the drug effect; (3) feel high; and (4) would like more drug. The VAS comprised the following: stimulated, anxious, sedated, down, elated, sociable, and nauseated. Participants rated whether each adjective described how they were feeling (from "not at all" to "extremely"). The POMS is a 72-item adjective checklist rated on a five-point Likert Scale. The POMS yields eight subscores, including a friendliness scale. DEQ and VAS were administered at 0, 30, 60, 135, 210, and 240 min post-capsule with cardiovascular measurements. POMS was administered at 0, 60, and 240 min, with the middle time coinciding with onset of peak drug effect (Cami et al. 2000). Based on hypotheses, subjective outcome measures were (1) VAS sociability and (2) POMS friendliness. We also report DEQ feel drug scores to confirm nonspecific subjective MDMA effects.

fMRI data collection commenced approximately 85 min after capsule administration (PBO=80.8±6.6 min; 0.75 mg/kg MDMA=82.1±12.6 min; 1.5 mg/kg MDMA=91.4±10.5 min) to coincide with peak drug effects (Cami et al. 2000). Participants underwent a facial emotion recognition (ER) task, employing stimuli from the Ekman and Friesen (1976) series. These stimuli have recruited amygdala in previous pharmacological fMRI studies (e.g., Anderson et al. 2007). There were four ER runs per session, each including six blocks of faces (happy, neutral, angry, fearful, disgusted, and sad, each presented in a separate block; see Fig. 1; based on emotion- and region-specific hypotheses, disgusted and sad face block data were not employed in these analyses). Using a button box with their right hand, participants rated whether stimuli showed an unpleasant, neutral, or pleasant expression. A block of radios was also presented; responses to radio stimuli were not utilized in these analyses. Each run contained novel stimuli and presentation order of emotions was pseudo-randomized across runs. Face blocks were interleaved with equal length fixation blocks; for fixation, participants rated the shading of each screen. Each run consisted of fourteen 20-s blocks; six emotional faces, one radio, and seven fixation blocks. Total task time (four runs) was 18 min and 40 s.

Participants also performed a motor–visual task to enable examination of MDMA's effects on brain response to non-emotional stimuli. This task involved alternating 20-s blocks during which participants saw a flashing checkerboard while pressing a single button every second or a gray fixation screen while remaining still. Participants viewed six checkerboard and eight gray blocks over two runs, with a total task time of 4 min and 40 s.

Imaging: acquisition and analyses

Imaging data were collected with a 3T GE magnetic resonance scanner. BOLD functional images were collected from 30 axial, 5-mm-thick slices using T2*-sensitive gradient echo reverse spiral acquisition sequences (repetition, 2,000 ms; echo, 25 ms; 64×64 matrix; 24 cm field of view; flip angle, 77). Functional runs were followed by a high-resolution, T1-weighted volumetric anatomical scan for anatomical localization.

Data from three Ekman and three motor–visual runs were excluded for excessive movement (>3 mm displacement or >3° rotation in any one direction). All other data met stability criteria with minimum motion correction. Data were analyzed using SPM2 (Welcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm); a similar approach is described in Phan et al. (2008). Images were spatially realigned to correct for head motion, warped to an EPI template in Montreal Neurologic Institute (MNI) space, resampled to 2-mm^3 voxels, and smoothed with an 8-mm^3 kernel. The general linear model was applied to the time series, convolved with the canonical hemodynamic response function (Friston et al. 1995) with a 128-s high-pass filter. Condition effects were modeled with box-car regressors representing the occurrence of each block type, and effects were estimated at each voxel for each participant. Individual contrast maps (statistical parametric maps) were then analyzed at the second level in a random effects statistical model (Holmes and Friston 1998). We assessed for significant differences in amygdala activation (anger versus neutral and fear versus neutral) and in VS (happy versus neutral) between drug conditions using repeated-measures analyses of variance (ANOVAs). First, we conducted whole-brain ANOVA to examine main effects of drug on emotion-related brain reactivity in the a priori regions of interest (ROIs); we set a whole-brain, voxel-wise significance threshold of $p<0.005$ uncorrected. Second, we followed up

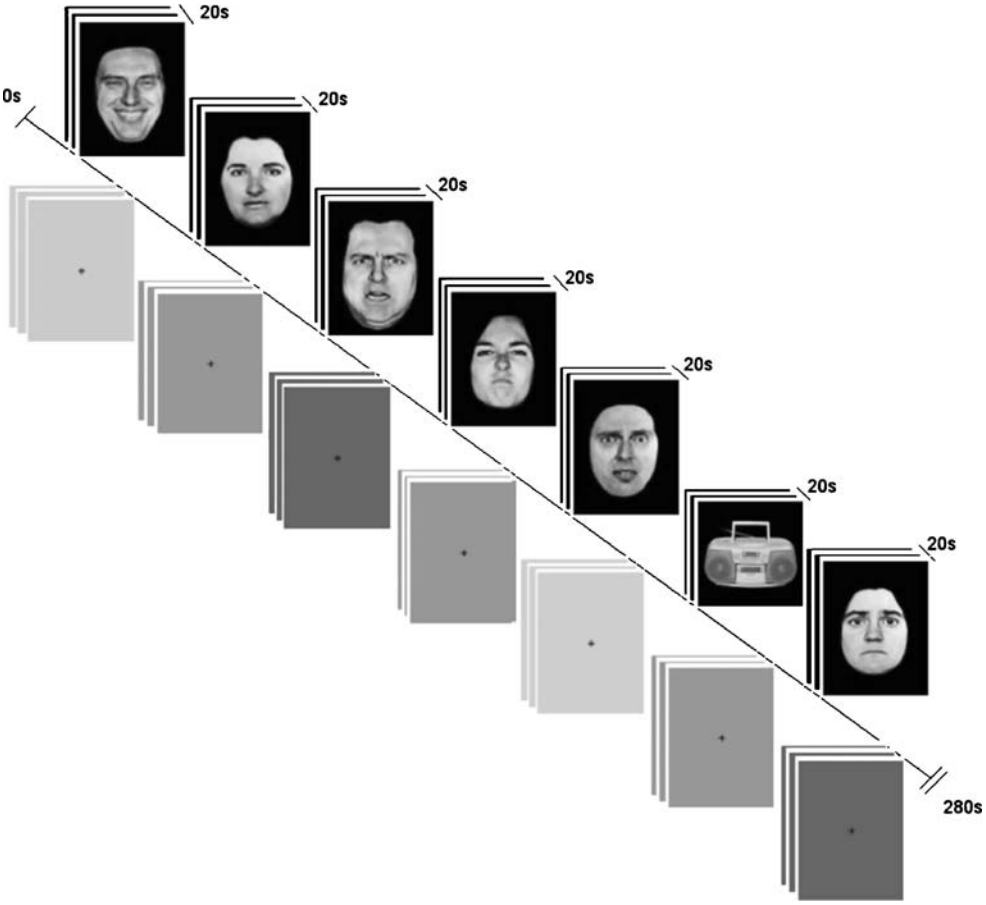

Fig. 1 Schematic of emotional recognition stimuli employed during fMRI

significant main effects with paired *t* tests based on our directionally specific hypotheses, with the same whole-brain, voxel-wise significance threshold of $p<0.005$ uncorrected. Third, we examined if these activation clusters reached significance after correction for multiple comparisons across a small volume (small volume correction (SVC)) using anatomically based volumes/ROIs. These statistical thresholds have recently been applied to fMRI studies of amygdala-striatum function (Del-Ben et al. 2005; Hariri et al. 2002; McBride et al. 2006). Fourth, we clarified the direction and extent of activation changes by extracting BOLD signal responses (parameter estimates, β weights) from 10-mm diameter spheres around peak activations from amygdala (for anger and fear) and VS (for happy). Extracted estimates were entered into repeated-measures ANOVA, followed by paired *t* tests as necessary (significance set at $p<0.05$).

The amygdala ROI was defined by a 10-mm diameter sphere around MNI coordinates (±24, −2, −24), based on our prior fMRI study employing emotional faces (Fitzgerald et al. 2006). VS ROI was defined by a 10-mm diameter sphere surrounding MNI coordinates (±6, 10, −6) based on previous research on reward-related VS activation (Schott et al. 2008). To assess effects of MDMA on regions other than amygdala and VS, we analyzed activation of primary visual (V1) and motor cortex (M1) during the motor–visual task (checkboard versus gray). M1 and V1 were defined anatomically by atlas (Walter et al. 2003); significance for ANOVAs and follow-up tests was set liberally at $p<0.005$, uncorrected across ROIs.

In addition, for generation of novel hypotheses for future research, we assessed effects of MDMA on whole-brain activation in response to each emotion contrast (anger > neutral, fear > neutral, happy > neutral) and to the motor–visual task (motor–visual > rest). For these exploratory analyses, repeated-measures ANOVAs were used to assess for significant main effects of drug (across PBO, MDMA 0.75 mg/kg, and MDMA 1.5 mg/kg) on each of the four contrasts (anger > neutral, fear > neutral, happy > neutral, motor–visual > rest). Activations were thresholded at $p<0.001$, uncorrected, with a minimum cluster size of 80 mm^3.

Cardiovascular, subjective, and behavioral data analyses

For cardiovascular measures and DEQ feel drug scores, peak change from pre-capsule measures were analyzed using repeated-measures ANOVAs, followed by paired *t* tests as necessary. For subjective sociability, two-way repeated-measures ANOVAs assessed for interactions between drug and time on change from baseline scores. Two-way ANOVAs investigated main effects of drug, and interactions

between drug and facial emotion type, on accuracy and reaction time for the ER task. Significant main effects were followed-up with paired *t* tests. Interactions were followed-up with simple main effects with effects of drug examined at each time or emotion; *t* tests assessed significant simple main effects as required. Alpha was set at $p<0.05$ for initial ANOVAs. An adjusted alpha level of $p<0.01$ was employed for post hoc analyses.

Results

Participants' mean age (±SD) was 24.0 (3.2). Two of nine participants were female and six identified as Caucasian. Lifetime ecstasy use ranged from two to 300 occasions. In the month before the study, five participants reported daily cigarette use, five reported using cannabis at least once, and eight used alcohol. All participants reported cannabis use, eight had used stimulants (e.g., cocaine), and seven reported hallucinogen use (e.g., psilocybin) in their lifetime (see Tables 1 and 2).

MDMA increased peak systolic and diastolic blood pressure (BP) and heart rate (Table 3). Systolic BP was higher after MDMA (both doses) compared to PBO and after MDMA (1.5 mg/kg) compared to MDMA (0.75 mg/kg). Diastolic BP only increased after MDMA (1.5 mg/kg) compared to PBO, whereas HR increased on MDMA (both doses) compared to PBO, with no difference between the two active conditions. MDMA increased peak DEQ ratings of feeling any drug effect (DEQ feel drug; see Table 3). Feel drug ratings were higher on MDMA (both doses) compared to PBO and in the MDMA (1.5 mg/kg) condition compared to MDMA (0.75 mg/kg). There were no serious adverse effects of MDMA.

MDMA significantly increased VAS ratings of sociability (interaction of drug versus time), with a very large effect size ($\acute{\eta}p^2=0.28$). Simple main effects analyses of drug condition at individual time points revealed that MDMA (1.5 mg/kg) increased ratings at 135 min relative to MDMA (0.75 mg/kg) and marginally increased ratings compared to PBO (see Table 3; Fig. 2).

A similar pattern of results was found for POMS friendliness (see Table 3; Fig. 2), although the effect did not reach significance. However, the effect size of the main effect of drug was large ($\acute{\eta}p^2>0.23$); thus, the absence of a significant effect may be due to the sample size.

MDMA did not affect accuracy of emotion recognition or reaction time, and there was no interactive effect of drug by emotion on accuracy or reaction time.

fMRI analyses showed that MDMA attenuated amygdala activation to angry, but not fearful, faces. Repeated-measures ANOVA revealed a difference in left amygdala activation to angry versus neutral faces [peak MNI coordinates (−20, −2, −24); $F(2,16)=9.64$, $p<0.005$]. *t* tests showed that left amygdala activation to angry versus neutral faces was greater on PBO than MDMA (1.5 mg/kg: $t(8)=4.41$, $p<0.005$). After small volume correction for multiple comparisons, this finding was significant at $p=0.052$. Analyses of extracted BOLD signal responses from spheres about peak activation for left amygdala also revealed an overall effect of drug ($F(2,16)=7.24$, $p<0.01$), with amygdala activation (angry versus neutral) lower on MDMA (1.5 mg/kg) than both PBO ($t(8)=3.34$, $p<0.05$) and MDMA (0.75 mg/kg; $t(8)=2.44$, $p<0.05$; Fig. 3). There was no effect of drug on amygdala reactivity to fear versus neutral faces.

MDMA enhanced VS activation to happy faces. There was a significant effect of drug on right VS activation in response to happy versus neutral faces [peak MNI coordinates (6, 8, −10); $F(2,16)=9.75$, $p<0.005$]. *t* tests indicated that VS activation to happy versus neutral faces was greater on MDMA (0.75 mg/kg) than PBO ($t(8)=6.13$, $p<0.001$). After SVC, this finding was significant at $p<0.05$. While not reaching significance, there was also a trend for VS activation to happy versus neutral faces to be greater on MDMA (1.5 mg/kg) than PBO ($t(8)=2.72$, $p<0.05$); this trend did not survive SVC. Analyses of BOLD signal responses extracted from spheres about peak activation for

Table 1 Participants' ecstasy use and recent drug use

	Mean	SD	Range
Past month cigarettes/day[a]	10.20	5.93	5–20
Past month alcohol units/week[a]	7.88	5.62	1–18
Past month THC days used[a]	6.60	4.56	3–14
Ecstasy use—lifetime occasions	63.89	94.92	2–300
Ecstasy use—age of first use	17.44	1.94	15–20
Ecstasy use–months since use	10.22	9.15	0.5–24

Ecstasy use in past year: yes, $n=4$; no, $n=5$

[a] Includes only participants reporting use of the substance in month prior to participation

Table 2 Participants' lifetime drug use

Lifetime occasions of use	Never *N*	1–10 *N*	11–50 *N*	51–100 *N*	100+ *N*
THC	0	0	1	1	7
Stimulants[a]	1	3	3	0	2
Hallucinogens[b]	2	2	2	1	2
Opiates[c]	1	5	2	0	1
Tranquillizers[d]	4	4	1	0	0

[a] e.g. amphetamine, cocaine

[b] e.g. lysergic acid diethylamide, psilocybin

[c] e.g. heroin, opium, and misused prescription opiates

[d] e.g. diazepam, clonazepam

Table 3 Effects of MDMA on cardiovascular, subjective, and behavioral measures

Measure	Placebo (PBO) Mean (SD)	0.75mg/kg MDMA (LOW) Mean (SD)	1.5mg/kg MDMA (MOD) Mean (SD)	ANOVA *F* (df)	PBO vs. LOW *t* (df)	PBO vs. MOD *t* (df)	LOW vs. MOD *t* (df)
Systolic BP (mmHg)[a]	4.8 (19.0)	34.8 (13.5)	48.1 (11.6)	41.9* (2,16)	5.9* (8)	7.5* (8)	3.9* (8)
Diastolic BP (mmHg)[a]	3.6 (13.9)	15.8 (13.4)	26.0 (5.1)	8.0* (2,16)	2.2 (8)	4.0* (8)	1.8 (8)
Heart rate (beats/minute)[a]	−5.3 (11.0)	19.7 (16.2)	35.3 (19.9)	21.9* (2,16)	4.1* (8)	5.8* (8)	2.9 (8)
DEQ feel drug[a]	14.5 (5.0)	57.1 (4.6)	91.8 (4.0)	98.6* (2,16)	7.1* (8)	16.1* (8)	6.1* (8)
VAS sociability—drug vs. time	–	–	–	3.1* (8,64)	–	–	–
VAS sociability 135 min[b]	−6.3 (17.7)	−9.5 (13.5)	19.7 (24.7)	7.3* (2,16)	0.5 (8)	2.5 (8) p=0.04	3.8* (8)
POMS friendliness—drug vs. time	–	–	–	1.3 (2,16)	–	–	–
ER accuracy[c]	0.89 (0.04)	0.91 (0.01)	0.86 (0.02)	0.9 (2,16)			
ER accuracy—drug vs. emotion type	–	–	–	1.2 (10,80)			
ER RT[d]	1,345.7 (45.6)	1,168.9 (79.5)	1,292.3 (115.5)	3.1 (2,16)	–	–	–
ER RT—drug vs. emotion type	–	–	–	0.6 (10,80)	–	–	–

BP blood pressure, *DEQ* drug effects questionnaire, *VAS* visual analog scale, *POMS* profile of mood states, *ER* emotional recognition, *RT* reaction time

*p=<0.05 (p<0.01 for posthoc tests)

[a] Peak change from pre-drug baseline

[b] Change from pre-drug baseline

[c] Marginal means of accuracy scores by drug across all emotional facial expressions, presented with standard error

[d] Marginal means of reaction time scores (in microseconds) across all emotional facial expressions, presented with standard error

VS happy versus neutral faces also indicated an overall drug effect (F(2,16)=8.41, p<0.005), with VS activation (happy versus neutral faces) greater in both MDMA conditions than PBO (0.75 mg/kg: t(8)=5.51, p<0.005; 1.5 mg/kg: t(8)=2.44, p<0.05; Fig. 4).

In the motor–visual task, MDMA decreased activation in V1 and M1. In V1, MDMA (1.5 mg/kg) decreased activation relative to PBO ((6, −82, 6), t(8)=3.81, p<0.005, (12, −92, 16), t(8)=3.72, p<0.005). In M1, MDMA (1.5 mg/kg) also reduced activation compared to PBO ((10, −12, 76), t(8)=5.82, p<0.005, (−12, −28, 74), t(8)=4.77, p<0.005, (66, −6, 14), t(8)=3.80, p<0.005, (16, −36, 70), t(8)=3.54, p<0.005). Effects of drug on emotional face activation contrasts (anger > neutral, fear > neutral, happy > neutral) and the motor–visual contrast (motor–visual > rest) outside the a priori ROIs are presented in Table 4.

Discussion

MDMA attenuated amygdala reactivity to angry, but not fearful, faces, while enhancing ventral striatum response to

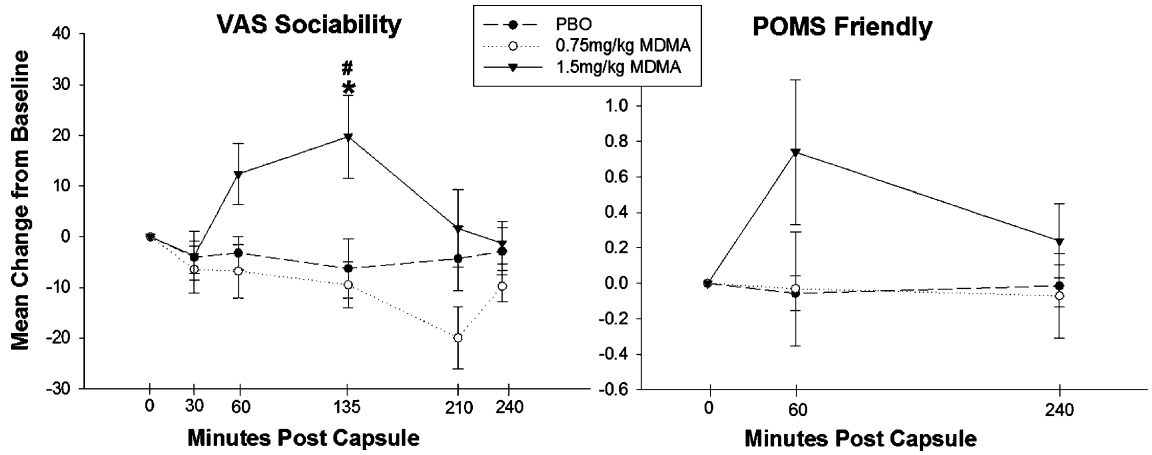

Fig. 2 MDMA effects on self-reported sociability. *Left* Visual analog scale sociability. *Right* Profile of mood states friendliness. Data are mean change from pre-drug baseline (±SEM) as a function of minutes post-capsule. *Asterisk* denotes difference from MDMA (0.75 mg/kg; p<0.01); # denotes marginal difference from PBO (p=0.04)

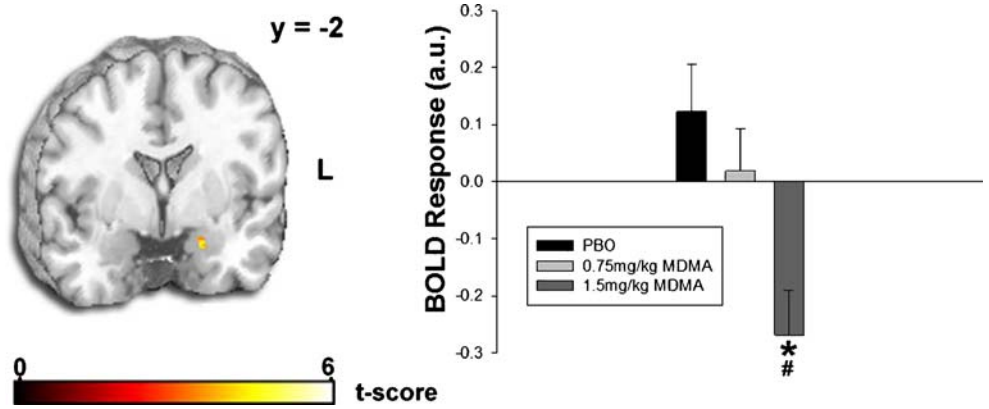

Fig. 3 MDMA effects on amygdala activation. *Left* Statistical *t* map overlaid on a canonical brain rendering (MNI coronal *y* plane=−2) showing greater left amygdala reactivity to angry versus neutral faces in the PBO relative to the MDMA (1.5 mg/kg) condition (PBO > MDMA). Cluster size is 280 mm^3 (35 contiguous voxels). Statistical *t* score is shown at the bottom of the brain rendering. *L* left. *Right* Left amygdala BOLD response (β weight in arbitrary units) angry versus neutral faces across drug conditions. *Asterisk* denotes difference from PBO ($p<0.05$); # denotes difference from MDMA (0.75 mg/kg; $p<0.05$)

happy faces. As expected, MDMA also increased subjective sociability at 1.5 mg/kg. These findings suggest that MDMA alters processing of emotionally salient social information in at least two ways, by reducing responses to threat and by enhancing responses to reward.

Converging lines of evidence in humans and nonhumans suggest that MDMA increases sociability. Controlled MDMA administration to humans increases subjective ratings of sociability (Johanson et al. 2006; Tancer and Johanson 2003, 2007; Vollenweider et al. 1999), and recreational users describe feeling sociable after ecstasy (Sumnall et al. 2006). In rodents, MDMA produces a unique pattern of adjacent lying behavior that is interpreted as sociability (Morley et al. 2005; Thompson et al. 2007). Our finding that MDMA (1.5 mg/kg) increases self-reported sociability is consistent with these reports.

Here, we investigated neural mechanisms that may mediate this increase in sociability, by studying neural responses to emotional stimuli. We found that MDMA both dampened neuronal responses to threat-related social stimuli and increased responses to positive social images, suggesting that these processes may contribute to the drug's prosocial effects. The findings regarding threat-related stimuli are consistent with other imaging studies investigating responses to socioemotional material. Two other drugs that purportedly decrease social anxiety, THC (Phan et al. 2008) and alcohol (Gilman et al. 2008), also attenuate limbic responses to social threat (Gilman et al. 2008; Phan et al. 2008). Individuals with social anxiety, who typically avoid social interactions, have heightened amygdala response to threat signals (Phan et al. 2006); whereas those genetically predisposed towards exaggerated sociability have dampened amygdala reactivity to social threat (Meyer-Lindenberg et al. 2005). OT administration attenuates limbic threat response (Kirsch et al. 2005) and increases behavioral indicators of trust (Kosfeld et al. 2005). Together, these previous findings

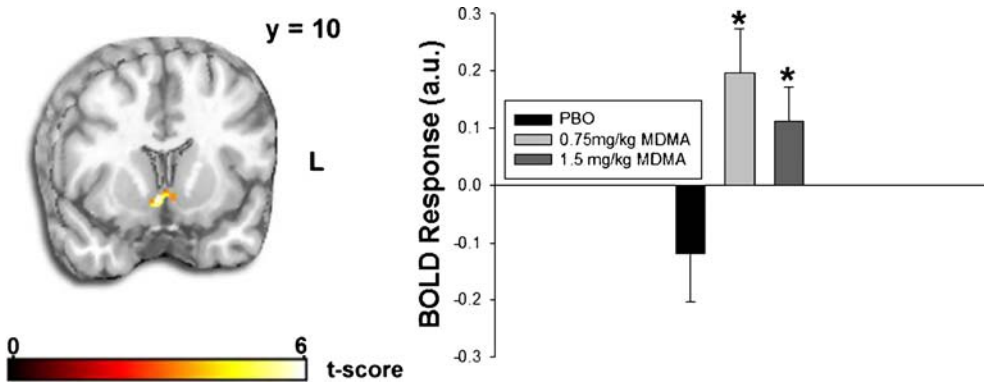

Fig. 4 MDMA effects on ventral striatum activation. *Left* Statistical *t* map overlaid on a canonical brain rendering (MNI coronal *y* plane= 10) showing greater ventral striatum reactivity to happy versus neutral faces in the MDMA (0.75 mg/kg) relative to the PBO condition (MDMA > PBO). Cluster size is 1,520 mm^3 (190 contiguous voxels). Statistical *t* score is shown at the bottom of the brain rendering. *L* Left. *Right* Ventral striatum BOLD response (β weight in arbitrary units) happy versus neutral faces across drug conditions. *Asterisks* denote difference from PBO ($p<0.05$)

Table 4 ANOVA-derived main effect of drug on brain response to emotional faces

Contrast	Region	Laterality	Size (mm^3)	*Z* score	MNI coordinates		
					x	*y*	*z*
Angry > neutral	Middle frontal gyrus	R	536	4.33	32	36	22
		R	136	3.94	36	38	2
		R	272	3.54	30	50	−10
		L	152	3.39	−40	56	2
	Caudate	L	384	4.11	−20	−14	24
	Precuneus	L	312	4.03	−12	−54	52
		R	280	3.37	18	−50	50
	Precentral gyrus	R	456	4.02	14	−22	78
		R	104	3.42	28	−10	56
	Postcentral gyrus	R	280	3.98	12	−34	82
	Superior frontal gyrus	R	344	3.94	18	8	56
	Middle temporal gyrus	L	784	3.74	−34	−66	14
		R	184	3.54	42	−58	20
	Supplementary motor area	L	848	3.73	−16	−14	60
		R	104	3.48	4	2	72
	Mid cingulate	R	400	3.72	18	−20	38
		L	88	3.45	−10	−10	28
	Cerebellum	L	168	3.72	−8	−72	−30
	Putamen	R	144	3.39	24	8	6
	Insula	L	96	3.35	−28	20	6
	Amygdala	**L**	**80**	**2.91**	**−20**	**−2**	**−24**
Fearful > neutral	Superior parietal gyrus	R	200	3.60	18	−80	50
Happy > neutral	Supramarginal gyrus	R	152	3.60	74	−20	16
	Ventral striatum	**R**	**240**	**2.93**	**6**	**8**	**−10**
Motor–visual > rest	Parahippocampal gyrus	R	224	4.28	16	−18	−28
	Inferior occipital gyrus	R	200	4.03	40	−84	−16
	Angular gyrus	R	80	3.56	52	−76	34
	Postcentral gyrus	R	136	3.49	74	−2	18

Significant activations across whole-brain search are presented at $p<0.001$, minimum cluster size of 10 voxels (80 mm^3). Activations shown in bold are within a priori ROIs, thresholded at $p<0.005$

suggest that dampened neural response to social threat leads to greater sociability. Our findings regarding increased responses to positive social stimuli are relatively novel, because there is little existing evidence regarding effects of drugs on social reward. However, the finding is consistent with a large body of evidence that activation of dopaminergic reward circuitry is critically important in human socioaffiliative behavior (Skuse and Gallagher, 2008), supporting the hypothesis that enhanced social reward processing would also lead to heightened sociability.

The effects of MDMA were dose-dependent on some, but not all, measures. As has been reported previously (see Dumont and Verkes 2006), the drug increased subjective sociability only at a higher dose. Similarly, MDMA attenuated amygdala response to angry faces only at the higher dose. Of note, however, was the apparent dissociation between self-report and VS recruitment in response to happy facial expressions. At the lower dose, MDMA enhanced neural response to happy faces without changing subjective sociability ratings. It is possible that brain responses to social stimuli are more sensitive indicators of prosocial effects, and that higher doses may be needed for individuals to report feeling more sociable. Moreover, it is not known whether the subjective experience of feeling social is essential for individuals to actually behave more sociably. Further research is required to clarify relationships between behavioral, subjective, and neural dimensions of MDMA's effects, and to better characterize active doses of MDMA in terms of sociability.

Neurobiological substrates of MDMA's unusual effects are poorly understood (Thompson et al. 2007). However, there is some evidence that they may be mediated through effects on both oxytocin and dopaminergic (DA) neurocircuitry. OT plays a key role in modulating attachment and affiliation, and OT antagonism attenuates the prosocial effects of MDMA in rodents (Thompson et al. 2007). Ecstasy self-administration in humans is also associated with increased plasma OT levels (Wolff et al. 2006). It has been suggested that the effects of

OT on social behavior may involve interactions between OT systems and DA reward circuitry (Skuse and Gallagher, 2008). This possibility has not been directly assessed in relation to MDMA. However, a recent study found that in rodents, MDMA administration in a social context produced greater neural activation than MDMA in isolation. Regions preferentially activated included some high in OT receptors and implicated in social behavior, as well as regions involved in the mesolimbic DA system, known to subserve reward (Thompson et al. 2009). Thus, it may be hypothesized that MDMA's reinforcing effects involve enhancement of the rewarding value of social stimuli through interactions between OT and DA circuits (Thompson et al. 2009). Other studies reporting interactions between social reward and cocaine reward in rats (Thiele et al. 2008) suggest that interactions between OT and DA may be involved more broadly in addictive behaviors (McGregor et al. 2008).

It is also likely that MDMA's well-described effects on serotonergic (5-HT) signaling play a role in alterations to social processing and behavior. MDMA's acute pharmacodynamic actions include carrier-mediated release of 5-HT from presynaptic vesicles and monoamine oxidase inhibition, resulting in sudden increases in extracellular 5-HT levels (for review, see Green et al. 2003). A substantial body of literature implicates 5-HT neurotransmission in social processing and behavior (e.g. Del-Ben et al. 2008; Young and Leyton 2002). Selective 5-HT manipulations alter identification (Del-Ben et al. 2008) and neural processing of emotional faces (Harmer et al. 2006), as well as affiliative behavior (Tse and Bond 2002). It is unclear to what extent these effects would be expected to overlap with those of MDMA, given that MDMA also affects a range of other systems (see Green et al. 2003). Future research, perhaps employing pretreatment with selective 5-HT agents, is needed to clarify the role of 5-HT in social effects of MDMA in humans. Individual and interactive effects of 5-HT, OT, and DA signaling will provide a rich source for future investigations of MDMA and the neural circuitry underlying social behavior and addiction.

Although these findings suggest that MDMA's apparently specific effects relate to altered social threat and reward processing, effects of drugs of abuse in general on processing of salient material are poorly understood. It may be that other drugs also exert some of their effects by altering threat and reward processing; indeed, both cannabinoids (Phan et al. 2008) and alcohol (Gilman et al. 2008) appear to attenuate social threat responding. To our knowledge, no other drug has been found to increase subjective sociability while both attenuating responses to social threat and increasing social reward responding. However, further research is required to better assess whether other drugs also affect processing of socioemotionally salient material.

The present findings should be regarded as preliminary; there are a number of limitations remaining to be addressed. The sample was small; these findings require replication in a larger sample. Due to the sample size, we restricted analyses to two a priori identified brain regions; larger samples would facilitate detailed examination of whole brain. Furthermore, MDMA may have actions on cerebral blood flow that affected either global or regionally specific BOLD signal. Indeed, a previous study employing [$H_2{}^{15}O$] positron emission tomography to assess effects of MDMA on regional cerebral blood flow (rCBF) in humans found the drug reduced rCBF in left amygdala, independent of task (Gamma et al. 2000). Thus, although our interpretation of these findings is supported by their emotion-specific nature, potentially confounding acute effects of MDMA on cerebrovasculature cannot be ruled out. We observed decreased activation with MDMA in both primary visual and motor cortex during a simple motorvisual task, also indicating a need for caution due to the possibility of generalized activation decreases arising from MDMA. However, a global decrease in activation would not give rise to the present finding of increased VS activation to happy versus neutral faces on MDMA. Moreover, decreased visual cortex activation might be expected in the context of decreased amygdala response, given functional connections between the two in processing socially relevant material (Skuse and Gallagher 2008).

For ethical reasons, all participants had prior ecstasy exposure. There was substantial variability in degree and recency of exposure. This may have affected results, as it is possible that heavy ecstasy use causes long-term alterations to serotonergic neurotransmission (McCann et al. 2000; see also Bedi and Redman 2008 for discussion of methodological issues). Moreover, due to involvement of serotonin in vasoconstriction (Cohen et al. 1996), it is possible that prior or recent MDMA exposure might have affected BOLD responses. To assess this possibility, we examined correlations between extracted BOLD response, lifetime ecstasy use and time since most recent use. There were no correlations between ecstasy use variables and extracted BOLD signals, suggesting past ecstasy use did not affect results. This may have been because the majority of participants had used MDMA less than 50 times, and were not current users at the time of participation.

For safety reasons, MDMA doses were administered in ascending order, which may have influenced outcomes. In addition, we allowed 6 days between sessions; preclinical findings suggest that in non-human primates serotonin depletion may persist for up to 2 weeks after single doses (Ricaurte et al. 1988) or repeated oral doses (Mechan et al. 2005). Thus, it is possible that a longer period between sessions was required to ensure the absence of carry-over effects. However, although the minimum period between sessions was 6 days, sessions were an average of 10.72

(±7.15) days apart. The doses we employed were substantially less than those used in the primate studies. In addition, assessment of subjective and cardiovascular measures and extracted BOLD signal responses revealed no effect of session order, suggesting that the partial randomization protocol and length of time between sessions did not affect outcomes.

Finally, although the fMRI protocol was designed to coincide with peak drug effects, we did not obtain blood plasma measurements ensuring that imaging data collection coincided with peak plasma MDMA levels. Subjective effects support the timing of the imaging protocol. However, future studies could valuably measure plasma MDMA levels to confirm that imaging data collection coincided with peak plasma MDMA levels. Moreover, assessment of plasma MDMA levels may cast light on the dose-dependency of the sociability-altering effects of MDMA.

Such limitations notwithstanding, these data provide the first evidence that the unusual subjective profile of MDMA may be related to alterations in neural processing of social signals of threat and reward. This possibility has important implications in terms of recreational use and abuse of ecstasy, and potential use of MDMA as a psychotherapeutic agent.

This experiment complied with the current laws of the country in which it was performed (USA).

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