

MDMA enhances early visual processing for salient socio-emotional stimuli.

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Abstract

3,4-methylenedioxymethamphetamine (MDMA) has long been used non-medically, and it is currently under investigation for its potential therapeutic benefits. Both uses may be related to its ability to enhance empathy, sociability, emotional processing and its anxiolytic effects. However, the neural mechanisms underlying these effects, and their specificity to MDMA compared to other stimulants, are not yet fully understood. Here, using electroencephalography (EEG), we investigated the effects of MDMA and a prototypic stimulant, methamphetamine (MA), on early visual processing of socio-emotional stimuli in an oddball emotional faces paradigm. Specifically, we examined whether MDMA or MA enhance the processing of facial expressions, compared to placebo, during the early stages of visual perception. MDMA enhanced an event-related component that is sensitive to detecting faces (N170), specifically for happy and angry expressions compared to neutral faces. MA did not affect this measure, and neither drug altered other components of the response to emotional faces. These findings provide novel insights into the neural mechanisms underlying the effects of MDMA on socio-emotional processing and may have implications for the therapeutic use of MDMA in the treatment of social anxiety and other psychiatric disorders.

MDMA enhances early visual processing for salient socio-emotional stimuli.

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Abstract .

3,4-methylenedioxymethamphetamine (MDMA) has long been used non-medically, and it is currently under investigation for its potential therapeutic benefits. Both uses may be related to its ability to enhance empathy, sociability, emotional processing and its anxiolytic effects. However, the neural mechanisms underlying these effects, and their specificity to MDMA compared to other stimulants, are not yet fully understood. Here, using electroencephalography (EEG), we investigated the effects of MDMA and a prototypic stimulant, methamphetamine (MA), on early visual processing of socio-emotional stimuli in an oddball emotional faces paradigm. Specifically, we examined whether MDMA or MA enhance the processing of facial expressions, compared to placebo, during the early stages of visual perception. MDMA enhanced an event-related component that is sensitive to detecting faces (N170), specifically for happy and angry expressions compared to

neutral faces. MA did not affect this measure, and neither drug altered other components of the response to emotional faces. These findings provide novel insights into the neural mechanisms underlying the effects of MDMA on socio-emotional processing and may have implications for the therapeutic use of MDMA in the treatment of social anxiety and other psychiatric disorders.

Key words: EEG, MDMA, Methamphetamine, Faces, Emotion

Introduction .

3,4-methylenedioxymethamphetamine (MDMA) is a stimulant-like drug with both nonmedical and potential medical uses. Like other stimulants, it increases dopaminergic and noradrenergic signaling, but its effects on serotonin receptors are greater than those of other stimulants (Gough, Slikker & Holson, 1991; Kalant., 2001; Luethi & Liechti., 2020). MDMA is used recreationally, apparently for its euphoric and empathogenic effects, and it is in Phase 3 trials as an adjunctive treatment, with psychotherapy, for post-traumatic stress disorder (PTSD, Mitchell et al., 2021). Despite the widespread use of the drug and its great promise as a therapeutic agent, the specific behavioral and neural effects of MDMA are not fully understood.

MDMA increases subjective and objective indices of sociability, social perception, and empathy (Kamilar-Britt & Bedi., 2015; Bershad et al 2016). It increases self-reported feelings of empathy, openness, and social connectedness, and decreases social anxiety and fear (Hysek et al., 2014; Borissova et al., 2020), effects that may enhance social interactions. On behavioral tasks, MDMA reduces sensitivity to negative emotions such as fear or anger (Bedi, Hyman & de Wit, 2010; Hysek et al., 2014), and reduces social anxiety in some populations (Danforth et al., 2018). It also increases generosity and increases the pleasantness of social touch (Kirkpatrick et al., 2015; Bershad et al., 2019). These laboratory findings complement users' reports that the drug produces prosocial and entactogenic effects (Peroutka et al, 1988). MDMA produces increased effects on measures of social and emotional function (Bershad et al., 2016; Holze et al., 2019; Nardou et al., 2019; Heifets et al., 2019). These unique effects may be related to actions of MDMA on serotonin and oxytocin, which are implicated in social behavior, stress, and social bonding in animal models (Thompson et al., 2009) and humans (Bedi et al., 2009; Bershad et al., 2016; Kuypers et al., 2018). However, these neurochemical and behavioral actions have not yet been related to the neural processes by which MDMA enhances responses to socioemotional stimuli in healthy human volunteers.

Event-related potentials (ERPs) provide a sensitive measure of neural reactivity to emotional stimuli. Images of emotional faces in an oddball task elicit three distinctive ERP components: N170, P300 and mismatch negativity (MMN). The N170 component is a negative waveform occurring approximately 170 milliseconds after stimulus onset, that is thought to reflect the processing of facial features and the structural encoding of faces (Bentin et al., 1996). It has been shown that emotion can enhance the peak of this ERP (Blau et al., 2007; Qui et al., 2017). The P300 component is a larger positive waveform that occurs approximately 300-500 milliseconds after stimulus onset. The P300 is thought to reflect attention allocation and cognitive processing (Carretié et al., 1997). Finally, the MMN component is a negative waveform that occurs approximately 200-300 milliseconds after stimulus onset and appears to respond to novel stimuli (Stefanics et al 2014). By examining these components in response to emotional stimuli after administration of MDMA or a comparison drug, we may be able to understand which neural processes mediate the drug's effects on responses to emotionally salient stimuli.

Here we conducted a double-blind study examining effects of MDMA and MA, compared to placebo, on EEG responses to emotional faces. We contrasted MDMA to a prototypic amphetamine, MA, which is thought to lack the strong prosocial effects of MDMA (Bershad et al, 2016). Healthy young adults received MDMA (100 mg), MA (20 mg) or placebo during three sessions. We measured electrophysiological responses to emotional and neutral faces using an emotional oddball task. We hypothesized that MDMA, but not MA, would enhance the N170 and P300 ERP components associated with socioemotional processing specifically for more salient stimuli.

Materials and Methods.

Design. The study used a double-blind, within-participant design in which healthy adults received MDMA (100mg), MA (20mg) and placebo (PLC) on three separate sessions. At the expected time of peak drug effect participants engaged in an oddball task during which we recorded EEG responses to positive, negative, and neutral faces. ERP components related to different aspects of emotional and cognitive processing were recorded. Participants also completed self-report measures of the drugs' effects.

Participants. Healthy men and women (N=25) aged 18-35 were recruited from the university and surrounding neighborhoods. Eligibility was determined first by online screening and then by clinical interview and physical examination. Inclusion criteria consisted of a minimum high school education, fluency in English, BMI 18-26, and good health. Exclusion criteria included use of prescription medications, history of cardiac disease or high blood pressure and previous negative experience with MDMA or hallucinogenic substances. Participants had to report between 4 and 40 previous experiences of MDMA to qualify for the study. Women who were not on oral contraceptives were tested only during the follicular phase (1-12 days from menstruation; White, Justice et al. 2002).

Procedure. Participants first attended an orientation to understand the procedures, provide informed consent and practice the tasks from the experimental sessions. They were instructed to abstain from drugs and alcohol for 24 hours before their sessions. They were told they would receive a *sedative* (e.g., Valium), *stimulant* (e.g., MDMA or amphetamine), or *placebo* drug in each session. The study was approved by the local institutional review board.

The three, four-hour drug sessions were conducted from 9am-1pm, separated by at least 4 days (M=7.5 days). Upon arrival at the laboratory, participants completed a breathalyzer and urine sample to test for recent drug use (CLIA waived Instant Drug Test Cup, San Diego, CA; amphetamine, cocaine, oxycodone, THC, PCP, MDMA, opiates, benzodiazepines, barbiturates, methadone, methamphetamine, buprenorphine), alcohol use (Alcosensor III, Intoximeters, St. Louis, MO) and pregnancy (in females; Aimstrip, Craig Medical, Vista, CA). They completed pre-capsule questionnaires and cardiovascular measures, measures that were repeated 60, 90, 180 and 240 minutes after the capsule. They ingested capsules containing dextrose (placebo), MA (20mg) or MDMA (100mg) under double blind conditions. Thirty minutes after taking the capsule participants' EEG electrodes were placed, and recording began about 60 minutes after the capsule. Resting state EEG was determined first, and this was followed by three tasks completed in randomized order. Here we report data on an emotional oddball task assessing responses to happy, angry, and neutral faces (Raz et al., 2014). The EEG measures were obtained from 60 to 150 min post-capsule. After the EEG electrodes were removed, participants rated the arousal and valence of the faces they viewed during the EEG task. Participants left the laboratory after the final measure, 240 min post capsule.

Drugs: MDMA in powdered form (100 mg; Organix Inc, MA) was placed in opaque size 00 capsules with lactose filler. MA tablets (5 mg, total dose 20 mg; Desoxyn, Lundbeck) were placed in an opaque size 00 capsule with dextrose filler, and placebo capsules contained only dextrose.

Self-Report Measures.

1. The *Drug Effects Questionnaire* (DEQ; Morean et al., 2013) The DEQ consists of 100 point visual analog scales (VAS) describing responses to the drug. Here we focused only on the questions "Do you like the effects that you are feeling now?" ("Not at all" (0) to "Very much" (100)) and "Would you like more of what you consumed, right now?" ("Not at all" (0) to "Very much" (100)).
2. *Visual Analogue Scales* (VAS) . The VAS consisted of 14 words describing drug-like experiences. Here we present data from the words "Sociable" and "Friendly". Participants rated on a 100-point scale how strongly they felt those feelings ('not at all' to 'extremely') at each of the five time points during each session.
3. The *Session End Questionnaire* (SEQ). The SEQ consists of questions relating to the drug received during the session. Participants indicated how pleasant they found the experience (from 'dislike' (0) to 'like very much' (100)) and what they thought they had received (i.e., Valium, Ketamine, Amphetamine, MDMA, LSD, Placebo).

EEG Measures.

Data collection and Processing. A 64 channel electro-geodesic net was used (Magstim, EGI). Electrodes were soaked in a saline solution then placed on the head using measurements from nasion to inion and mastoid to mastoid. EEG data was acquired continuously, amplified, and digitized using Netstation software, sampled online at 1024Hz. Offline EEG recordings were analyzed using EEGLab (Delorme & Makeig, 2004) it was first down sampled to 512Hz then high pass filtered (1 Hz), and low pass filtered (60 Hz, -12 dB/octave) to remove extraneous high and low frequency noise. Data were visually inspected for movement and electronic artifact. PICARD Independent Components Analysis (Ablin, Cardoso & Gramfort, 2017) were performed to correct for EEG artifacts including blinks, horizontal and vertical eye movements, muscle movement and EKG signal. Data were segmented from -200 to 1000ms and baseline corrected following stimulus presentation for each of the stimulus types.

Emotional Oddball Task (Raz et al., 2014). To assess the neural responses to emotional stimuli, participants completed an emotional oddball task. The task consisted of 300 stimulus presentations, of which 80% were cartoon faces, and 20% were human faces. The stimuli were presented in three blocks of 100 stimuli consisting of the frequent cartoon image interspersed with infrequent angry, happy, or neutral faces. Subjects were instructed to respond on the left key on a button box when they saw a human face and, on the right when they saw a cartoon face. ERPs were recorded during each stimulus presentation.

Behavioral Measure.

Face Ratings Task. Following the EEG session participants completed a ratings task in which they rated the 6 faces presented in the oddball task for valence and arousal. Valence and arousal were rated on a Likert scale from -4 (Very Negative/ Not at all) to +4 (Very Positive/Extremely). Participants were told to indicate how positive or negative they perceived each face (valence) and how strongly they felt that emotion (arousal) (Supplementary Figure 1).

Analysis.

1. Subjective and behavioral measures were assessed with analysis of variance using peak change score from baseline, using individual paired samples T-tests to measure the differences between Placebo vs MA and Placebo vs MDMA. Peak drug effects were calculated by subtracting the baseline values from the highest or lowest value during the session.
2. Faces Ratings Task (supplementary results). Participants rated the valence and arousal of each of the 6 faces seen in the emotional oddball task (male and female; angry, happy, neutral). These ratings were analyzed using two 3x2 (Emotion x MDMA (vs PLC); Emotion x MA (vs PLC)) ANOVAs.
3. Emotional Faces Oddball Task. The N170 was measured at electrode PO8, extracting the mean peak from 150-200ms post stimulus onset. The P300 was measured at electrode parietal (Pz) extracting the mean peak between 300-400ms. The MMN was measured using electrodes Fz between 240-350ms. For each of these peaks of interest, two 3 (Emotion) x 2 (Drug condition; Drug vs PLC) repeated measures ANOVAS were conducted. We also examined ERP responses to the frequent cartoon faces for MMN to compare frequent vs infrequent stimuli. Initial analyses (supplementary materials) revealed that responses to the (infrequent) human faces differed from markedly from responses to the (frequent) cartoon face on all three ERP measures. The final analyses were conducted only with the human faces, comparing MDMA and MA vs PLC separately.

Results .

Demographics. Participants were 17 men and 8 women, mean age of 27.4 years, most of whom had completed partial college (Table 1). Participants had previously taken MDMA a mean of 7.1 times. None of the subjects were cigarette smokers. Sixty-four percent of participants correctly identified Placebo, 20% MA and 52% MDMA, showing the effectiveness of the blinding (Supplementary Table 1).

Table 1 . Demographic information and nonmedical drug use (N=25).

Sex (number M/F)
 Age (mean and sem)
 BMI (mean and sem)
 Years in Education (mean and sem)
 Ethnicity (percent of sample)

Recent Drug Use (last 30 days)

Lifetime MDMA (uses)

Note. Drug use data are represented as Mean (SEM) of uses only for the participants who reported ever using the drug [N

Subjective Measures. MDMA increased ratings of Drug liking relative to PLC ($t(24)=-3.93$, $p=.001$) but MA did not differ from PLC ($t(24)=-2.00$, $p=.06$). Both MDMA and MA increased wanting more drug ratings compared to PLC (MDMA, $t(24)=-3.32$, $p=.003$; MA, $t(24)=-2.38$, $p=.03$). For VAS ratings, MDMA significantly increased feelings of friendliness compared to PLC ($t(23)=-2.06$, $p=.05$), as did MA ($t(23)=-2.15$, $p=.04$). In contrast, MA but not MDMA increased feelings of sociability ($t(24)=-2.14$, $p=.04$) (Figure 1).

[Figure 1 here]

Figure 1. Mean and sem for ratings of Liking, Wanting More, feelings of Friendly and Sociable for PLC (green), MA (blue) and MDMA (red) sessions. MDMA significantly increased ratings for liking drug effects, wanting more of the drug and how Friendly participants felt, compared to placebo, whereas MA significantly increased ratings of wanting more drug, Friendly and Sociable.

Session End Questionnaire. On the end of session questionnaire, 64% of participants correctly identified PLC, 20% of participants correctly identified MA as a stimulant, and 52% correctly identified MDMA (full breakdown in supplementary results). Subjects reported liking MDMA (mean=78.0) and MA (mean=71.2) more than PLC (mean=48.2).

Drug Effects on ERP peaks.

N170 – Face processing. (Figure 2). MDMA significantly increased N170 peak amplitude compared to PLC specifically for Happy (MDMA/PLC; $M=-2.27\mu V$ /M=-1.04 μV) and Angry (MDMA/PLC; $M=-2.09\mu V$ /M=-1.31 μV) faces (significant Drug x Emotion interaction, $F(2,86)=4.49$, $p=.01$, $\eta_p^2=.01$). Regardless of whether participants received MDMA or PLC, the N170 amplitude was also greater with Happy and Angry faces compared to Neutral faces (main effect of Emotion $F(2,88)=7.86$, $p=.001$, $\eta_p^2=.015$). MA did not affect the N170 peak amplitude, compared to PLC (no significant interaction between Drug and Emotion, $F(2,86)=0.31$, $p>.05$, $\eta_p^2=0.007$). In this MA vs PLC analysis, Emotion did not affect peak N170 amplitude here (no main effect of Emotion, $F(2,86)=1.21$, $p>.05$, $\eta_p^2=0.03$).

[Figure 2 here]

Figure 2 . N170 ERPs at electrode PO8 (shaded area) for Happy, Angry and Neutral faces. ERPs are shown for PLC (blue), MA (red) and MDMA (green) faces. MDMA significantly increased N170 peak amplitude in response to Happy and Angry faces, but not Neutral faces when compared with PLC.

P300 – Emotion processing. (Figure 3). MDMA did not affect the P300 peak amplitude compared to PLC (no significant interaction between Drug and Emotion ($F(2,86)=1.36$, $p>.05$, $\eta_p^2=0.05$) or main effect of

Drug, ($F(2,86) = 3.37, p = .07, \eta_p^2 = 0.07$). Similarly MA did not affect P300 (no significant interaction with Emotion ($F(2,88) = 2.20, p > .05, \eta_p^2 = 0.05$) or main effect of Drug ($F(2,86) = 0.14, p > .05, \eta_p^2 = 0.003$)). Emotion was not significantly related to P300 peak for either MDMA or MA vs PLC (MDMA: $F(2,86) = 2.02, p > .05, \eta_p^2 = 0.05$; MA: $F(2,86) = 0.72, p > .05, \eta_p^2 = 0.02$) (Figure 3).

[Figure 3 here]

Figure 3. ERPs at electrode Pz. Shaded area represents P300 peak amplitudes for Happy (top), Angry (bottom left) and Neutral (bottom right) Faces with ERPs shown for PLC (blue), MA (red) and MDMA (green) sessions. Neither MDMA nor MA affected the peak amplitude of P300 ERPs. There was also no effect of Emotion on the P300 response.

MMN – Novelty processing. (Figure 4). MDMA did not affect MMN amplitude compared to PLC (no interaction between Drug and Emotion ($F(3,129) = 0.91, p > .05, \eta_p^2 = 0.02$) and no main effect of Drug ($F(1,43) = 0.48, p > .05, \eta_p^2 = 0.01$)). MA also did not affect the MMN peak amplitude (no significant interaction ($F(3,129) = 0.51, p > .05, \eta_p^2 = 0.01$) and no main effect of Drug ($F(1,43) = 0.90, p > .05, \eta_p^2 = 0.02$)). The type of face shown, however, did affect peak amplitude in PLC and MDMA sessions ($F(3,129) = 39.00, p < .001, \eta_p^2 = 0.48$) with Human faces resulting in a significantly greater MMN than Cartoon faces (all $ps < .001$). This was expected because MMN signals novel/infrequent stimuli. Similarly, in the analysis of MA vs PLC face type significantly affected MMN amplitude whereas drug type did not ($F(3,129) = 37.14, p < .001, \eta_p^2 = 0.46$) again with Human faces resulting in a significantly greater MMN than the Cartoon face (all $ps < .001$) (Figure 4).

[Figure 4 here]

Figure 4. ERPs at electrode Fz. Shaded area represents MMN peak amplitudes for Happy (top), Angry (bottom left), Neutral (bottom right) and Cartoon (dashed) Faces with ERPs shown for PLC (blue), MA (red), MDMA (green) sessions. MDMA and MA did not affect the peak amplitude of MMN however MMN was present for human faces compared to cartoon faces. Furthermore, MMN was not affected by the emotion of the face shown.

Discussion .

The current study investigated the effects of two drugs, MDMA and MA, compared to placebo, on evoked potential responses to emotional stimuli in healthy adults. The two drugs produced their expected subjective effects. MDMA increased the N170 peak amplitude for happy and angry faces compared to neutral faces, but MA did not have this effect. The N170 is thought to reflect processing of facial features and is sensitive especially to emotional faces. Neither drug significantly altered P300 or MMN evoked potentials which are thought to reflect attention allocation and cognitive processing (P300) and responses to novelty (MMN).

Both MDMA and MA had expected effects on subjective and behavioral measures. Both MDMA and MA increased ratings of liking the drug effect and wanting more of the drug. Both drugs also increased feelings of friendliness whereas only MA increased feelings of sociability. The lack of effect of MDMA on sociability was surprising considering some previous reports (Kirkpatrick et al., 2014), and because MDMA is often described as a pro-social drug. It is known that social context can influence responses to MDMA (Kirkpatrick and de Wit., 2015), and so it is possible that the solitary laboratory environment in the present study prevented the drug from producing feelings of sociability. Although as expected, participants rated happy faces more positively than neutral faces, and angry faces more negatively than neutral faces, neither MDMA nor MA altered these ratings.

The main finding in this study was that MDMA, but not MA, enhanced the N170 amplitude in response to salient emotional faces. The drug increased N170 signals with happy and angry, but not neutral, faces. To our knowledge, the effects of MDMA and MA on N170 ERPs have not previously been examined. The N170 is thought to represent early structural encoding of face stimuli, especially faces expressing emotions (Bentin et al., 1996). Emotional states can enhance the peak of this ERP (Blau et al., 2007; Qui et al., 2017). Interestingly, the prosocial hormone oxytocin reportedly increases N170 responses to faces, especially

sad faces (Peltola et al., 2018). The finding that the pro-social drug MDMA, like oxytocin, increased N170 responses to emotional faces is consistent with the idea that the N170 signals early social approach/avoidance behaviors (Schlindler & Bublatzky., 2020). The present finding suggests that MDMA may affect early visual processing of socially salient stimuli, which then affects later processing functions (Hysek et al., 2014; Kirkpatrick et al., 2014; Wardle & de Wit., 2014; Bershad et al., 2016). MDMA has also been shown to increase the recall of positive and emotional memories but do not affect neutral ones, which is consistent with the idea that MDMA indeed enhances emotional processing (Doss et al., 2017). MA, which has less pronounced effects on social processes (Bershad et al., 2016), did not affect the N170. It is important to consider also that there is evidence to suggest that long term MDMA use may impact social functioning differently. For example, Wunderli and colleagues (2018) reported that long term MDMA users showed enhanced cognitive empathy but not emotional empathy. Comparatively Carlyle and colleagues (2019) showed that both cognitive and emotional empathy were enhanced in the MDMA users. These are important considerations for social functioning in long-term use of MDMA as a pharmaceutical.

Contrary to our expectations, neither MA nor MDMA affected the P300 peak amplitude. The P300 is thought to reflect attention allocation and cognitive processing, and thus might be expected to be greater with drugs that increase attention, or with more salient stimuli (emotional faces). In the present study, the P300 was not affected by either of the two drugs or by emotion (angry or happy compared to placebo), although we did find that the P300 was smaller with cartoon faces compared to human faces. This suggests that the P300 is sensitive to faces but not emotions, although the cartoon faces were also presented much more frequently than the human faces. The P300 is thought to reflect cognitive processing related to attention and orientation (Morgan et al., 2008; Mueller et al., 2017). The lack of effect of either MDMA or MA on P300 is somewhat surprising, considering that both drugs are considered stimulants, which are thought improve attention. Moreover, MDMA has been shown to increase visual attention to happy faces compared to other emotions (Bershad et al., 2019), but this effect was not detected here with related EEG measures. Thus, the effects of MDMA and MA attention likely vary, depending on the measures that are used to assess attention, as well as the doses and participants studied (Cami et al., 2000; Silber et al., 2006).

The MMN ERP was not affected by either MDMA or MA. Because the MMN is thought to signal a response to novel stimuli, this suggest that neither drug increased neural response to novelty. Our finding that the MMN ERP was greater with the infrequent human faces than frequent cartoon faces indicates that the measure was sensitive to this indicator of novelty. However, the finding that neither drug affected MMN suggests that they did not affect processing of novelty of the emotional faces. Although there is indirect evidence that stimulants increase salience of stimuli (Taylor and Robbins., 2007; Chaudhri et al., 2007), few other studies have examined effects of stimulants specifically on MMN amplitude. In one of few reports of drug effects on MMN, single doses of the selective serotonin uptake inhibitor escitalopram significantly increased MMN, without affecting P300 amplitude (Wienberg et al., 2010). Further research is needed to determine whether, or how, stimulant drugs affect this neural indicator of novelty.

The study had several limitations. The sample was homogeneous, limited to healthy men and women aged 18-35, who had previously used MDMA. Thus, the results may not be generalizable to a more heterogeneous population including those with greater or lesser drug use histories. While the sample size was within the typical size for studies involving EEG recordings, it is likely that more subtle effects would be detected with a larger sample. The study used only single doses of MDMA and MA, making it difficult to compare across drugs. That is, higher or lower doses of either drug likely produce different effects, and future studies with dose-responses are critical. MA is seven times more potent than MDMA at inhibiting noradrenaline transporters (Simmler et al., 2012), therefore it is important to consider that an extremely high dose of MDMA would be required to appropriately compare these drugs together, for this reason the drugs were compared separately compared to PLC. In future studies it would be beneficial to accurately match doses for their potency. Finally, the study was limited by the task that was used, and it is possible that the emotional faces oddball task is not optimal to detect the effects of these drugs. In future studies more complex studies of social behavior and motivation may parse the effects that MDMA is having on these processes.

The main finding in this study was that MDMA, but not MA, increased the N170 peak amplitude for angry and human faces, compared to neutral faces. This finding is consistent with evidence that the N170 is selective for faces and sensitive to emotion. The effect of MDMA on N170 is consistent with both the known function of this ERP, with evidence that MDMA affects responses to social stimuli. An interesting and important future direction is to clarify whether MDMA equally affects both positive and negative emotional stimuli, as the present data suggest. This would have implications for its use in therapeutic settings. The finding that MA did not have similar effects suggests MDMA differs from other stimulants in the processing of social stimuli, although this conclusion must await testing with a full range of doses.

CRedit

Connor Haggarty : Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Anya Bershad** : Conceptualization, Formal analysis, Project administration, Writing – review & editing. **Mahesh Kumar**:Data curation, Formal analysis, Investigation, Visualization **Royce Lee** : Conceptualization, Data curation, Formal analysis, Writing – review & editing **Harriet de Wit**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Data Availability – Data is available raw or processed on request to the corresponding author

Competing interests - HdW serves on the Board of Directors of PharmAla Biotech and has served as Scientific Advisor to Awaken Life Sciences, Gilgamesh Pharmaceuticals and Mind Foundation. These roles are unrelated to the research reported here. CJH, AKB, MK, and RL have no conflicts of interest to disclose.

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