

Acute effects of MDMA on trust, cooperative behaviour and empathy: a double-blind, placebo-controlled experiment

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Supplementary Materials

Methods

Participants

Medical screening involved routine blood tests, electrocardiogram, heart rate, blood pressure and brief neurological exam. The Mini International Neuropsychiatric Interview version 5 (MINI-5) was performed by an experienced psychiatrist to assess mental health. Additional exclusion criteria included a diagnosis of a psychiatric (ICD-10 or DSM-IV Axis I) requiring current psychological or pharmacological treatment, neurological or endocrine illnesses, a history of drug or alcohol dependence, having a Body Mass Index below 19 or above 24 and being a non-native English speaker. Participants with nicotine dependence were not excluded. Ethnicity was not recorded.

Assessments

Empathic Stories Task

This task aimed to assess emotional empathy by assessing participants' emotional reactions in response to stories with different emotional themes. Participants were given 6 different stories to read on each visit day. There were 2 "happy" themed stories, 2 "angry" themed stories, 2 "sad" themed stories. Stories were a one paragraph description of a situation. For

27 example, a “happy” story described a family reunion at an airport, a “sad” story described a
28 family being in a car accident where one of the children died, an “angry” story described
29 someone missing a flight due to train cancellations.

30 Participants were asked to rate how “good” (any positive emotion– for example happy,
31 pleased, hopeful, cheerful) or “bad” (any negative emotion– for example unhappy, scared,
32 angry, melancholic) the stories made them feel. These ratings relate to “implicit” emotional
33 empathy – that is, amount of emotional arousal in response to stimuli (Mehrabian and
34 Epstein, 1972; Dziobek et al., 2008). Participants were asked to rate their personal, “gut-
35 feeling” reaction by picking a self-assessment manikin (SAM) best corresponding to the
36 positivity or negativity of their emotion on a scale of 1 (most positive) to 9 (most negative).
37 Self-assessment manikins have been found to be a good way of assessing emotional response
38 (Bradley and Lang, 1994). This score of 1-9 was analysed as the dependent variable.

39 See Figure S1 for an example of the self-assessment Manikin scale used in the study.

40

41 **Trust investment (Berg et al., 1995)**

42 Participants made a total of 20 decisions. Participants were told they had £500, which they
43 could choose to invest in 20 different entrepreneurs, played by a computer. They were told
44 all entrepreneurs were highly skilled, but not all were trustworthy. Participants were told
45 they might be able to triple their original investment if they chose wisely, or that they may
46 lose all their money if not. Participants could choose to not send any money and therefore
47 keep their £500. They were shown the face of the individual running the business and asked
48 to choose an amount that they wished to invest. Faces the participants were shown were
49 computer generated with neutral expressions. Participants were told their goal was to
50 maximise the amount of money they would keep. Participants were not given any feedback

51 on the outcome of each investment until the end of the task. Participants were told they
52 would be paid the amount of money remaining after one randomly chosen trial, divided by
53 100. This was added to the standard reimbursement they received for taking part. The
54 'entrepreneurs' responses were pre-determined.

55

56 **Cooperative behaviour games:**

57 Participants were told they were playing these games with all the other participants in the
58 study. These tasks were done on paper. The tasks were organised as 'one-shot' games.
59 Participants were told that one of their responses would be chosen at random and this would
60 be paid to them in addition to their standard reimbursement for taking part.

61 **Dictator Game** (Hoffman et al., 1996): Every participant played the role of the
62 'dictator' at both of their sessions, with another study participant (unknown to them) being
63 affected by their decision. Participants completed one trial at each session. Both parties
64 would receive the amount that the 'dictator' chose.

65 **Ultimatum Game** (Thaler, 1988; Guth and Tietz, 1990): For both roles, participants
66 were told that their response to this game from one of their sessions would be randomly
67 paired with another participants' and they would both receive the result of that decision.
68 Every participant completed one trial as the proposer and one trial as the decider.

69 The following tasks have been shown to be sensitive to recreational MDMA: Trustworthy
70 Face Rating, Dictator Game, Ultimatum Game (Stewart et al., 2014) and MDMA: Ultimatum
71 Game (Gabay et al., 2019).

72 A task similar to our Trust Investment Task (Trust Game) used by Kosfeld et al. (2005) was
73 sensitive to the effects of oxytocin. Their study did not include pictures of faces.

74 Participants were not trained on the tasks described in this report.

75 Results

76 Demographics

77 Table S1 reports participants' lifetime drug history. Data were missing for four participants,
78 so we analysed 21 participants' data.

79 Task Results

80 See Table S2 for full task results.

81

82 Table S3 lists full statistics for all Mood & Symptom VAS analyses.

83 Subacute Mood & Symptom VAS and BDI

84 Table S4 lists all subacute Mood & Symptom VAS and questionnaire analyses.

85

86 Tasks results

87 **Empathic Stories Task**

88 The significant main effect of story Emotion reflected that 'Happy' stories led participants to
89 feel more positive than 'Angry' stories ($t_{20}=-9.011$, $p<0.001$, mean difference=-3.262, 95%
90 CI: -4.207 to -2.317), and 'Sad' stories led to more negative feelings than both 'Happy'
91 ($t_{20}=10.174$, $p<0.001$, mean difference=4.619, 95% CI: 3.432 to 5.806) and 'Angry' stories
92 ($t_{20}=5.702$, $p<0.001$, mean difference=1.357, 95% CI: 0.735 to 1.979).

93 **Trustworthiness ratings of faces**

94 14 received MDMA at first visit, placebo at second visit; 10 received placebo at first visit,
95 MDMA at second visit. After adding drug order, a significant Drug by Face Gender by Order
96 interaction emerged ($F_{1,22}=4.797$, $p=0.039$, $\eta_p^2=0.179$). Female faces were rated as more
97 trustworthy than male faces under MDMA ($t_{13}=2.21$, $p=0.025$, 95% CI: 0.041 to 0.547), but
98 only for participants who received MDMA at their first visit. See Figure S2 for representation
99 of this effect.

100 **Trust Investment Task**

101 13 received MDMA at first visit, placebo at second visit; eight received placebo at first visit,
102 MDMA at second visit. After adding Order as an additional factor, we found a significant
103 interaction between Drug and Order ($F_{1,19}=11.923$, $p=0.003$, $\eta_p^2=0.386$). Exploration of the
104 drug by order interaction showed that when participants received MDMA first they invested
105 more money under the placebo condition than the MDMA condition, ($t_{12}= 3.73$, $p=0.001$,
106 mean difference=1594.538, 95% CI: 700.225 to 2488.851). When participants received

107 placebo first, there was no significant difference in the amount of money invested between
108 conditions ($t_7=-1.461$, $p=0.160$, mean difference=-795.875, 95% CI: -1935.905 to 344.155).
109 We also assessed an effect of Session Day. There was no interaction between Session Day and
110 Order ($F_{1,19}=1.331$, $p=0.263$, $\eta_p^2=0.065$), however there was a main effect of Session Day
111 ($F_{1,19}=11.923$, $p=0.003$, $\eta_p^2=0.386$) reflecting a higher amount invested at the second session
112 than the first session ($t_{20}=3.453$, $p=0.003$, mean difference=1195.207, 95% CI: 470.730 to
113 1919.683).

114 Correlations

115 We found no significant correlations between plasma MDMA levels and task performance.
116 We note a negative correlation between emotional ratings on “Sad” stories and plasma
117 MDMA levels at two hours, which was significant at trend level ($r=-0.550$, $p=0.015$). This
118 correlation reflects a less negative emotional response to stories with a “Sad” valence as
119 plasma MDMA levels increased. Please see Table S5-S8 for full results.

120

121 [Supplementary discussion](#)

122 We found a significant order effect on our Trust Investment task, which could suggest that
123 the effects of MDMA carryover to later testing sessions. This may have relevance for the
124 psychotherapeutic application of MDMA, whereby drug-assisted sessions are integrated over
125 subsequent drug-free psychotherapy sessions (Mithoefer et al., 2016). However, in a separate
126 analysis, there was a significant effect of Session Day: participants were more trusting with
127 their financial allocations at their second session. This offers an alternative explanation to our
128 Drug by Order interaction; participants may be simply more willing to invest on their second
129 visit. This may be related to familiarity, which is recognised as an important component of
130 economic decision making and may also affect trust (Cao et al., 2011). However, we cannot
131 determine what caused this effect from our data- a study where drug order is experimentally
132 manipulated would be necessary. Particularly as no previous laboratory MDMA studies have
133 found order effects on these tasks, any interpretation of these results must remain tentative.

134

135 In the Public Good Game, our participants donated close to the maximum under placebo, and
136 over £1 more than the control participants in the Stewart et al (2014) study. Our ability to
137 detect an effect of MDMA may have therefore been limited. It is interesting to explore our
138 results for the Ultimatum Game in more detail. In the 'Decider' condition, our participants
139 were willing to accept 37% of the total stake under placebo, 34% of the total stake under
140 MDMA. Brandts and Charness (2011) argue that the method we used elicits less punishment
141 than the 'direct-response' method used by Gabay et al. (2018). Our results would align with
142 this, given that offers of below 40% of the total stake are not considered 'fair' (Gabay et al.,

143 2014). Interestingly, the participants in Gabay et al. (2018) made lower proposals (48.2% of
144 the total stake in the placebo condition in vs 62.5% of the total stake in our placebo condition;
145 55.7% in the MDMA condition vs 69.5% in our MDMA condition). Again, this may have limited
146 our ability to detect an effect of MDMA increasing generosity or reducing punishment.

147

148 We found a trend for a negative correlation between plasma MDMA levels at two hours and
149 empathic response ratings on the “Sad” stories. Given that we found no effect of drug on this
150 task, we cannot draw any firm conclusions from this trend result. However, it is interesting to
151 see a correlation between a biological measure and a psychological effect that has been
152 previously noted – that MDMA reduces the impact of negative stimuli (Carhart-Harris et al.,
153 2014; Frye et al., 2014). This would merit further study.

154 **Further limitations**

155 We used a novel task for our measure of empathy, as opposed to a more validated method
156 such as the Multifaceted Empathy Test. Thus, our task may have lacked sensitivity to detect
157 an effect of MDMA. As we had limited power, we were also not able to assess the impact of
158 sex differences, which have been noted as relevant in MDMA research (Allott and Redman,
159 2007).

Table S1 Recent and lifetime drug history

	Min	Max	Median	Interquartile range (IQR)	N
Recent drug use					
Alcohol (weekly units)	0	35	13	3-19	21
Cigarettes (daily number)	0	3	0	0-1	21
Cigarettes (days since last use)	0.75	2920	2	551.83	9
Cannabis (days since last use)	2	8760	90	1455	19
Lifetime drug use (number of times)					
MDMA	1	200	10	3-45	21
Cannabis	0	1000	150	20-500	21
LSD	0	500	1	0-5.5	21
Psilocybin	0	100	1	0-10	21
Ketamine	0	200	1	0-17.5	21
Mephedrone	0	30	0	0-4	21
Amphetamine	0	150	0	0-35	21
Cocaine	0	200	4	0-20	21

Table S2 Task results with mean values (standard deviation) reported.

Empathic Stories Task emotional response rating	MDMA	Placebo	JZS Bayes Factor
"Happy" story	2.786 (1.347)	2.857 (1.296)	5.821
"Sad" story	7.476 (1.308)	7.405 (1.633)	5.898
"Angry" story	5.786 (1.210)	6.381 (0.773)	1.101
Trustworthy Face Rating			
Female Face	4.071 (0.450)	3.923 (0.525)	1.837
Male Face	3.927 (0.585)	3.890 (0.690)	5.768
Trust Investment Task (amount invested out of £10000)			
	4740.095 (2413.100)	5424.000 (2429.796)	1.780

	Baseline 0 hour	2 hours post	4 hours post	Baseline 0 hour	2 hours post	4 hours post	Drug	Time	Drug x Time	Drug x Time x Order	Time 0 (MDMA vs placebo)	Time 2 (MDMA vs placebo)	Time 4 (MDMA vs placebo)	MDMA (Time 0 vs 2), Time 0 vs 4	Placebo (Time 0 vs 2, time 0 vs 4)
General drug effects															
Euphoria	1.250 (2.023)	6.750 (2.653)	2.200 (2.353)	1.550 (2.481)	1.050 (1.820)	0.500 (1.192)	F_{1,19}=39.594 p<0.001 η_p^2 =0.676	F_{2,38}=29.128 p<0.001 η_p^2 =0.605	F_{2,38}=44.519 p<0.001 η_p^2 =0.701	F _{2,36} =1.012 p=0.373 η_p^2 =0.053	t ₁₉ =-0.645 p=0.527	t₁₉=9.194 p<0.001	t₁₉=3.448 p=0.003	t₁₉=-8.197 p<0.001 ; t ₁₉ =- 1.900 p=0.218	t ₁₉ =1.190 p=0.745; t ₁₉ =2.303 p=0.098
Drug effect	0.250 (1.118)	6.500 (2.838)	3.100 (3.059)	0.250 (1.118)	0.600 (1.698)	0.400 (1.273)	F_{1,19}=57.031 p<0.001 η_p^2 =0.750	F_{2,38}=43.406 p<0.001 η_p^2 =0.696	F_{2,38}=43.125 p<0.001 η_p^2 =0.694	F _{2,36} =1.431 p=0.252 η_p^2 =0.074	Identical ratings at time 0 for MDMA/placebo	t₁₉=9.035 p<0.001	t₁₉=4.212 p<0.001	t₁₉=-9.585 p<0.001 ; t ₁₉ =- 4.222, p=0.001	t ₁₉ =-1.159 p=0.780; t ₁₉ =- 1.000 p=0.990
Jaw clenching	0.750 (1.803)	4.750 (3.291)	2.950 (3.137)	1.550 (2.523)	1.200 (2.191)	0.750 (1.410)	F_{1,19}=23.339 p<0.001 η_p^2 =0.551	F_{2,38}=17.933 p<0.001 η_p^2 =0.486	F_{2,38}=14.812 p<0.001 η_p^2 =0.438	F _{2,36} =1.821 p=0.176 η_p^2 =0.092	t ₁₉ =-1.670, p=0.111	t₁₉=5.007 p<0.001	t₁₉=4.104, p=0.001	t₁₉=-5.540, p<0.001 ; t ₁₉ =- 3.443, p=0.008	t ₁₉ =1.129 p=0.819; t ₁₉ =1.848, p=0.241
Energy	6.300 (2.130)	6.950 (2.964)	6.300 (2.386)	6.350 (1.814)	5.900 (2.049)	5.600 (2.458)	F _{1,19} =3.228 p=0.088 η_p^2 =0.145	F _{2,38} =0.601 p=0.553 η_p^2 =0.031	F _{2,38} =.677 p=0.514 η_p^2 =0.034	F _{2,36} =1.262 p=0.295 η_p^2 =0.066					
Prosocial effects															
Trusting of others	2.000 (1.947)	2.150 (2.346)	1.850 (1.954)	1.550 (1.761)	1.750 (1.773)	1.750 (1.916)	F _{1,19} =0.679 p=0.420 η_p^2 =0.035	F _{2,38} =0.266 p=0.768 η_p^2 =0.014	F _{2,38} =0.211 p=0.811 η_p^2 =0.011	F _{2,36} = 0.344 p=0.711 η_p^2 =0.019					
Empathy	5.53 (2.195)	6.630 (2.733)	5.950 (2.297)	5.050 (2.121)	5.110 (2.447)	5.00 (2.333)	F _{1,19} =10.073 p= 0.005 η_p^2 =0.359	F _{1,410,25,384} =2.20 2 p=0.143 η_p^2 =0.109	F _{2,36} =1.792 p=0.181 η_p^2 =0.091	F _{1,799,30,590} =0.21 3 p=0.787 η_p^2 =0.012					
Friendly	1.700 (2.273)	1.050 (2.188)	1.500 (2.626)	1.750 (2.197)	2.050 (2.417)	1.750 (2.173)	F _{1,19} =0.944 p=0.343 η_p^2 =0.047	F _{2,38} =0.260 p=0.752 η_p^2 =0.014	F _{1,349,25,629} =2.073 p=0.158 η_p^2 =0.098	F _{1,375,24,756} = 1.238 p=0.293 η_p^2 =0.064					
Closeness to others	4.900 (2.049)	6.400 (2.909)	5.350 (2.601)	4.250 (2.447)	4.600 (2.722)	5.300 (2.227)	F _{1,19} =6.013 p=0.024 η_p^2 =0.240	F _{2,38} =3.719 p=0.033 η_p^2 =0.164	F_{2,38}=8.010 p=0.001 η_p^2 =0.297	F _{2,36} =2.056 p=0.143 η_p^2 =0.103	t₁₉=2.218 p=0.039	t₁₉=3.636 p=0.002	t ₁₉ =0.108 p=0.915	t₁₉=-2.941 p=0.025 ; t ₁₉ =- 1.014 p=0.971	t ₁₉ =-0.837 p=1.00; t ₁₉ =-2.365 p=0.087
Amicable	2.400 (2.798)	1.800 (2.949)	1.900 (2.532)	1.800 (2.093)	1.900 (2.245)	1.955 (2.139)	F _{1,19} =.167 p=0.687 η_p^2 =0.009	F _{2,38} =0.387 p=0.682 η_p^2 =0.020	F _{1,338,25,414} =0.666 p=0.464 η_p^2 =0.034	F _{1,324,23,829} =0.38 2 p=0.601 η_p^2 =0.021					
Want to be with others	5.550 (1.791)	7.050 (2.328)	6.450 (2.012)	5.550 (1.820)	5.600 (1.536)	5.40 (1.984)	F _{1,19} =4.046 p=0.059 η_p^2 =0.176	F _{2,38} =3.460 p=0.042 η_p^2 =0.154	F _{1,310,24,894} =2.660 p=0.107 η_p^2 =0.123	F _{1,278,23,003} =0.291 p=0.651 η_p^2 =0.016					
Compassionate	3.320 (2.583)	2.160 (2.968)	2.740 (2.746)	3.420 (2.610)	3.260 (2.579)	3.840 (2.522)	F _{1,16} =8.041 p=0.011 η_p^2 =0.309	F _{2,38} =3.767 p=0.033 η_p^2 =0.173	F _{2,36} =2.295 p=0.115 η_p^2 =0.113	F _{2,34} =0.624, p=0.542, η_p^2 =0.035					

Table S3 Subjective Effects- Acute – mean (standard deviation) self-ratings VAS 0-10 of MDMA and placebo groups at pre-drug 0 hour, 2 hour post-drug, 4 hour post-drug and test statistics (F and t) for RM-ANOVA and post-hoc pairwise comparisons (Bonferroni-corrected). When required, F tests were Greenhouse-Geisser corrected. The α for the F test was Bonferroni corrected by dividing by 11 to give $\alpha=0.0045$. Significant results are highlighted in **bold**.

	MDMA		Placebo		F ($\alpha = 0.01$)					t	JZS Bayes Factor
	Baseline 0 hour	3 days post-drug	Baseline 0 hour	3 days post-drug	Drug	Day	Drug x Day	Drug x Day x Order	Baseline vs Day 3		
Happy – sad (n=17)	2.240 (2.251)	2.240 (1.522)	2.060 (1.784)	2.120 (2.088)	$F_{1,16}=0.282$ $p=0.603$ $\eta_p^2 = 0.017$	$F_{1,16}=0.011$ $p=0.919$ $\eta_p^2 = 0.001$	$F_{1,16}=0.008$ $p=0.930$ $\eta_p^2 = 0.001$	$F_{1,15}=0.011$ $p=0.919$ $\eta_p^2 = 0.001$			5.443
Calm – anxious (n=17)	3.000 (2.208)	1.940 (1.435)	2.710 (1.993)	1.880 (1.900)	$F_{1,16}=0.269$ $p=0.611$ $\eta_p^2 = 0.017$	$F_{1,16}=11.506$ $p=0.004$ $\eta_p^2 = 0.418$	$F_{1,16}=0.119$ $p=0.735$ $\eta_p^2 = 0.007$	$F_{1,15}=1.031$ $p=0.326$ $\eta_p^2 = 0.064$	$t_{16}=3.397$ $p=0.004$		1.110
Trusting of others - Distrusting of others (n=16)	1.940 (2.048)	2.130 (1.746)	1.880 (1.928)	2.370 (1.668)	$F_{1,15}=0.064$ $p=0.804$ $\eta_p^2 = 0.004$	$F_{1,15}=1.076$ $p=0.316$ $\eta_p^2 = 0.067$	$F_{1,15}=0.311$ $p=0.585$ $\eta_p^2 = 0.020$	$F_{1,14}=0.063$, $p=0.806$, $\eta_p^2 = 0.004$			4.992
Want to be alone - Want to be with others (n=16)	5.690 (1.493)	5.810 (1.721)	5.250 (0.775)	5.750 (1.238)	$F_{1,15}=0.732$ $p=0.406$ $\eta_p^2 = 0.047$	$F_{1,15}=0.940$ $p=0.348$ $\eta_p^2 = 0.059$	$F_{1,15}=0.368$ $p=0.553$ $\eta_p^2 = 0.024$	$F_{1,14}=0.776$ $p=0.393$ $\eta_p^2 = 0.052$			5.161
No empathy – extreme empathy (n=16)	5.500 (1.592)	5.440 (1.931)	5.310 (1.662)	5.310 (1.991)	$F_{1,15}=0.701$ $p=0.416$ $\eta_p^2 = 0.045$	$F_{1,15}=0.007$ $p=0.935$ $\eta_p^2 = 0.000$	$F_{1,15}=0.011$, $p=0.917$ $\eta_p^2 = 0.001$	$F_{1,14}=5.939$ $p=0.029$ $\eta_p^2 = 0.298$			5.241
BDI (n=15)	2.130 (3.114)	1.270 (2.344)	1.330 (1.877)	1.400 (2.473)	$F_{1,14}=0.459$ $p=0.509$, $\eta_p^2 = 0.032$	$F_{1,14}=0.599$, $p=0.452$, $\eta_p^2 = 0.041$	$F_{1,14}=0.876$, $p=0.365$, $\eta_p^2 = 0.059$	$F_{1,13}=0.100$ $p=0.756$ $\eta_p^2 = 0.008$			3.096

Table S4 - Subacute effects, comparison of pre-drug baseline on acute days vs 3 days post drug. JZS Bayes Factor are calculated from t-statistic comparing pre-MDMA and 3 days post-MDMA results. The α for the F test was Bonferroni corrected to 0.01.

Table S5 Correlations between plasma MDMA levels and Task results. $\alpha = 0.005$

		Trust Investment Task	Public Good Game	Dictator Game	Ultimatum Game		Trustworthiness rating		Empathic stories task		
					Proposer	Decider	Male faces	Female faces	Happy	Sad	Angry
Plasma MDMA levels (2 hours post-drug)	Pearson <i>r</i>	-0.116	-0.305	-0.015	0.014	0.226	-0.339	-0.381	0.280	-0.550	-0.221
	<i>p</i>	0.616	0.190	0.950	0.953	0.339	0.123	0.080	0.245	0.015	0.364

Table S6 Correlations between plasma MDMA levels and Mood & Symptom VAS results. $\alpha = 0.01$

		Euphoria	Jaw clenching	Feel drug effect	Closeness to others
Plasma MDMA levels (2 hours post-drug)	Pearson <i>r</i>	-0.161	0.334	-0.029	-0.109
	<i>p</i>	0.497	0.150	0.902	0.646

Table S7 Correlations between VAS measured 'Trust' at 2 hours post-drug and task-measured trust. $\alpha = 0.008$

Trusting VAS	Trustworthiness rating		Trust investment
	Male faces	Female faces	
Pearson <i>r</i>	-0.478	-0.322	-0.029
<i>p</i>	0.028	0.154	0.904

Table S8 Correlations between VAS measured 'Empathy' at 2 hours post-drug and task-measured empathy. $\alpha = 0.008$

Empathy VAS	Empathic stories task		
	Happy	Angry	Sad
Pearson <i>r</i>	0.255	0.020	0.162
<i>p</i>	0.264	0.932	0.483

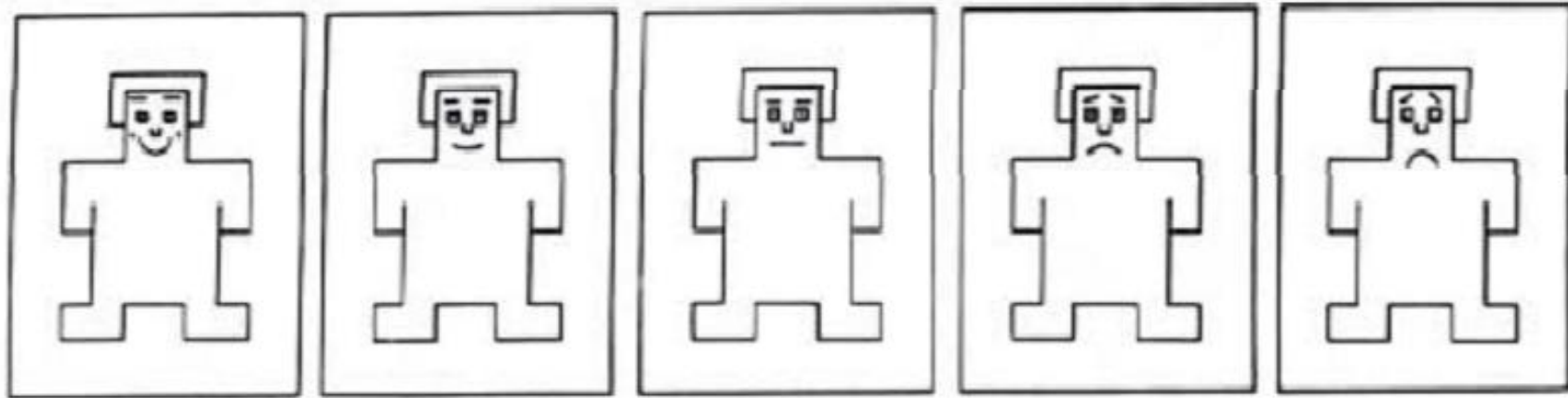


Figure S1 Self-assessment Manikin - participants could choose 1 - 9, including space between specific manikins, to correspond to the positivity or negativity of the emotion they felt in response to the task. Figure adapted from Bradley & Lang 1994.

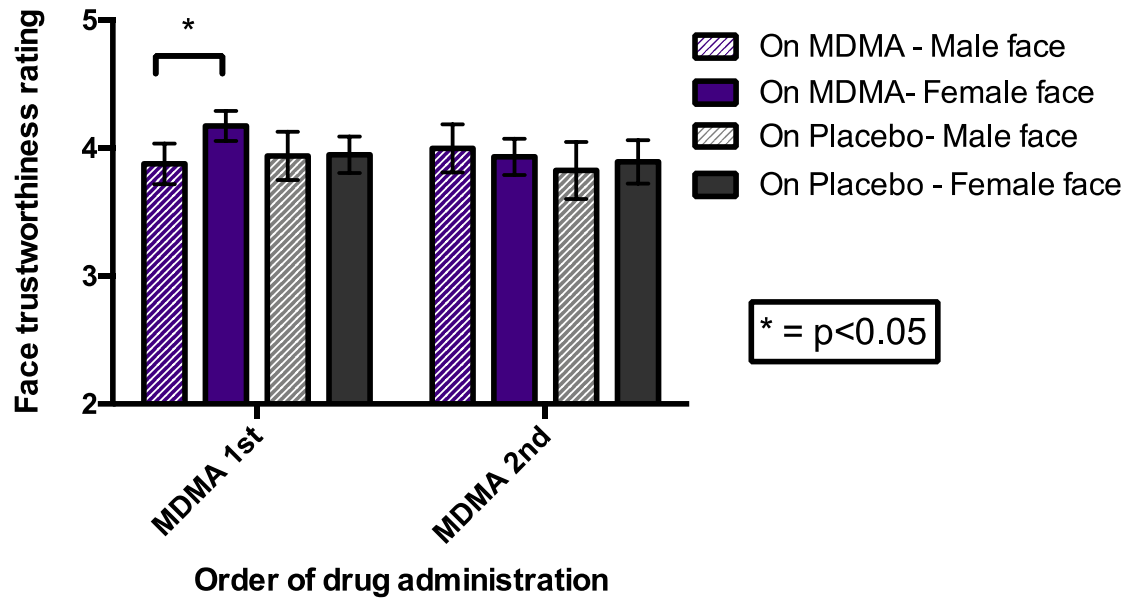


Figure S1 Face trustworthiness ratings are affected by session order. Participants rate female faces highest post-MDMA, but only when this is their first session within the study. $*=p<0.05$

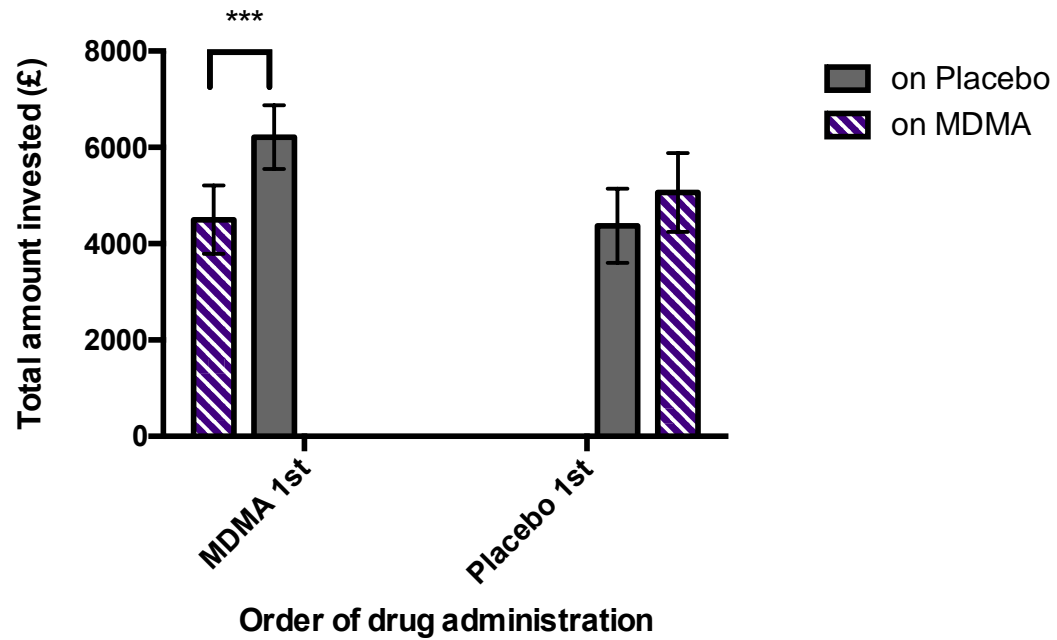


Figure S3. Trust Investment (a trust-related behaviour) is affected by drug order, with participants investing more money post-placebo when they had received MDMA at their previous session.

This can alternatively be explained by an overall greater investment on the second visit compared to the first visit. ***= $p=0.001$

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