

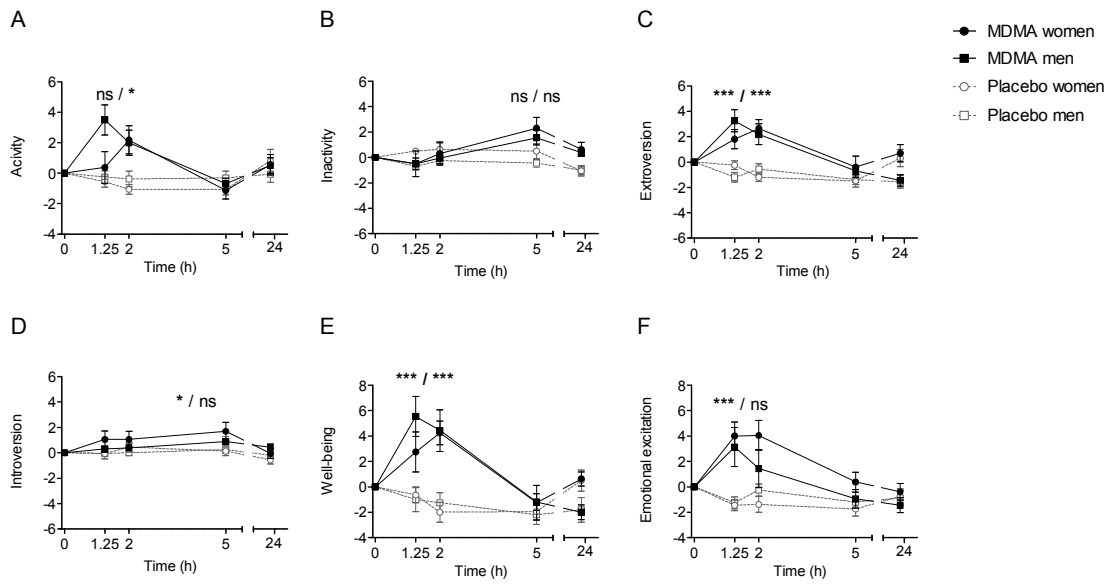
### **Immunoassays used to measure plasma hormone concentrations.**

Oxytocin concentrations were determined by R. Landgraf, Munich (Neumann *et al.*, 2013). Copeptin was determined according to (Morgenthaler *et al.*, 2006; Simmler *et al.*, 2011). Cortisol concentrations were determined by an automated immunoassay (Immulite 2000 Cortisol<sup>®</sup>, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). The limit of detection was 5.5 nmol/L. The intra-assay coefficient of variation was 5.3% and the inter-assay coefficient of variation was 7.2%. Prolactin concentrations were determined by an immunoassay (Cobas<sup>®</sup>, Roche Diagnostics, Basel, Switzerland) using a modular analytics E170 analyzer. Sensitivity was 1mU/L. The intra-assay coefficient of variation was 1.7% and the inter-assay coefficient of variation was 1.4%. Testosterone was determined using an electro-chemiluminescence immunoassay (Cobas<sup>®</sup>, Roche Diagnostics, Basel, Switzerland). Sensitivity was 0.4 nmol/L. The intra-assay coefficient of variation and the inter-assay coefficient of variation were both <5%.

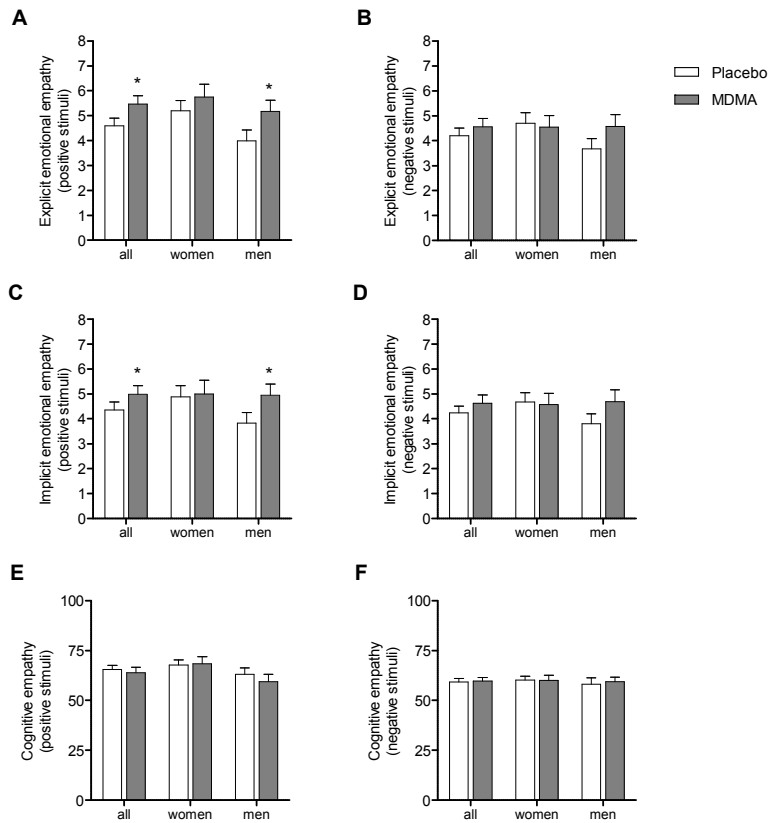
Table S1. Mean ± SEM values and statistics for subjective, empathic, social, emotional, and endocrine effects of MDMA (N=32)

		all		women		men		MDMA (all)		MDMA		sex		MDMA × sex	
		Placebo	MDMA	Placebo	MDMA	Placebo	MDMA	$F_{(1,31)}$	$p$	$F_{(1,31)}$	$p$	$F_{(1,31)}$	$p$	$F_{(1,31)}$	$p$
<b>Visual Analog Scale (VAS)</b>															
Happy	$\Delta E_{max}$	3.7 ± 1.6	37.4 ± 2.7***	0.0 ± 0.0	42.5 ± 2.7***	7.3 ± 2.9	32.4 ± 4.5***	120.59	< 0.001	157.52	< 0.001	0.19	0.668	10.49	0.003
Close to others	$\Delta E_{max}$	2.6 ± 1.6	28.6 ± 3.2***	0.3 ± 0.3	31.7 ± 4.0***	4.9 ± 3.2	25.6 ± 4.9***	67.52	< 0.001	72.01	< 0.001	0.04	0.851	3.06	0.090
Open	$\Delta E_{max}$	1.8 ± 0.7	31.7 ± 3.3***	0.7 ± 0.5	31.8 ± 4.1***	2.9 ± 1.2	31.6 ± 5.1***	80.77	< 0.001	78.18	< 0.001	0.02	0.896	0.01	0.940
<b>Adjective Mood Rating Scale (AMRS)</b>															
Activity	$\Delta E_{max}$	0.09 ± 0.30	2.88 ± 0.67***	-0.19 ± 0.39	2.19 ± 0.91*	0.38 ± 0.48	3.56 ± 0.97**	24.48	< 0.001	24.10	< 0.001	1.25	0.272	0.51	0.479
Inactivity	$\Delta E_{max}$	0.72 ± 0.34	2.28 ± 0.49**	1.56 ± 0.54	2.75 ± 0.82	-0.13 ± 0.23	1.81 ± 0.56	7.72	0.009	7.58	0.010	4.85	0.035	0.44	0.514
Extroversion	$\Delta E_{max}$	-0.19 ± 0.26	3.41 ± 0.58***	-0.13 ± 0.29	3.31 ± 0.83***	-0.25 ± 0.42	3.50 ± 0.84***	40.58	< 0.001	39.37	< 0.001	0.00	0.965	0.07	0.787
Introversion	$\Delta E_{max}$	0.59 ± 0.26	2.09 ± 0.39**	0.75 ± 0.44	2.81 ± 0.65*	0.44 ± 0.27	1.38 ± 0.39	10.05	0.003	10.19	0.003	3.86	0.059	1.43	0.241
Well-being	$\Delta E_{max}$	-0.06 ± 0.49	5.81 ± 0.87***	-0.19 ± 0.64	5.63 ± 1.03***	0.06 ± 0.77	6.00 ± 1.43***	36.99	< 0.001	35.81	< 0.001	0.09	0.767	0.00	0.950
Emotional excitation	$\Delta E_{max}$	-0.66 ± 0.37	4.56 ± 0.91***	-1.06 ± 0.57	5.75 ± 1.04***	-0.25 ± 0.48	3.38 ± 1.47	28.46	< 0.001	30.12	< 0.001	0.62	0.438	2.81	0.104
Anxiety	$\Delta E_{max}$	0.19 ± 0.20	0.44 ± 0.20	0.06 ± 0.23	0.69 ± 0.34	0.31 ± 0.34	0.19 ± 0.21	0.78	0.390	0.80	0.380	0.19	0.670	1.79	0.191
Dreaminess	$\Delta E_{max}$	0.31 ± 0.24	3.72 ± 0.60***	0.69 ± 0.44	4.06 ± 0.62	-0.06 ± 0.19	3.38 ± 1.05**	25.48	< 0.001	24.66	< 0.001	1.34	0.256	0.00	0.964
<b>Multifaceted Empathy Test (MET)</b>															
<i>Explicit emotional empathy</i>															
All stimuli	rating	4.40 ± 0.29	5.01 ± 0.30**	4.96 ± 0.37	5.15 ± 0.41	3.84 ± 0.41	4.87 ± 0.44*	6.05	0.019	6.45	0.017	1.85	0.184	3.03	0.092
Positive stimuli	rating	4.60 ± 0.31	5.46 ± 0.35**	5.21 ± 0.40	5.75 ± 0.53	3.99 ± 0.44	5.17 ± 0.46*	8.60	0.006	8.65	0.006	2.38	0.133	1.17	0.288
Negative stimuli	rating	4.20 ± 0.31	4.57 ± 0.33	4.71 ± 0.42	4.55 ± 0.46	3.68 ± 0.41	4.58 ± 0.48	1.90	0.178	2.10	0.158	0.77	0.388	4.15	0.051
<i>Implicit emotional empathy</i>															
All stimuli	rating	4.30 ± 0.29	4.81 ± 0.32*	4.78 ± 0.39	4.79 ± 0.47	3.82 ± 0.40	4.82 ± 0.44*	4.29	0.047	4.80	0.036	0.69	0.412	4.68	0.039
Positive stimuli	rating	4.36 ± 0.32	4.98 ± 0.35*	4.89 ± 0.45	5.00 ± 0.56	3.83 ± 0.43	4.95 ± 0.45*	5.02	0.032	5.49	0.026	0.80	0.377	3.86	0.059
Negative stimuli	rating	4.24 ± 0.28	4.63 ± 0.33	4.68 ± 0.37	4.57 ± 0.46	3.81 ± 0.40	4.69 ± 0.48	2.14	0.154	2.33	0.138	0.44	0.512	3.79	0.061
<i>Cognitive empathy</i>															
All stimuli	% correct	62.3 ± 1.5	61.9 ± 1.6	64.1 ± 1.7	64.2 ± 2.2	60.6 ± 2.6	59.5 ± 0.3	0.13	0.717	0.13	0.721	2.05	0.163	0.23	0.634
Positive stimuli	% correct	65.5 ± 2.1	63.9 ± 2.7	67.8 ± 2.6	68.4 ± 3.6	63.1 ± 3.2	59.4 ± 3.7	0.57	0.455	0.11	0.58	0.454	1.13	0.296	
Negative stimuli	% correct	59.2 ± 1.8	59.7 ± 1.8	60.3 ± 1.9	60.0 ± 2.6	58.1 ± 3.2	59.4 ± 2.5	0.05	0.822	0.05	0.824	0.23	0.638	0.14	0.711
<b>Social Value Orientation (SVO) test</b>															
	angle (°)	31.75 ± 2.73	36.83 ± 1.68*	36.83 ± 1.59	36.60 ± 1.87	26.66 ± 4.94	37.06 ± 2.86**	4.42	0.044	5.061	0.032	1.63	0.211	5.52	0.026
	IA index	0.48 ± 0.07	0.36 ± 0.06	0.44 ± 0.08	0.34 ± 0.09	0.54 ± 0.12	0.42 ± 0.08	3.39 <sup>a</sup>	0.079	3.23 <sup>a</sup>	0.088	1.63 <sup>a</sup>	0.217	0.02 <sup>a</sup>	0.904
<b>Facial Emotion Recognition Task (FERT)</b>															
<i>Accuracy</i>															
All emotions	% correct	75.3 ± 2.4	66.2 ± 2.4***	79.6 ± 1.8	66.7 ± 2.0***	71.0 ± 4.3	65.8 ± 4.5	28.63	< 0.001	33.28	< 0.001	1.10	0.302	6.04	0.020
Happy	% correct	94.5 ± 2.2	93.5 ± 2.9	98.4 ± 1.1	96.9 ± 1.3	90.6 ± 4.0	90.1 ± 5.7	0.27	0.607	0.26	0.613	2.46	0.128	0.07	0.800
Fearful	% correct	55.5 ± 4.6	39.3 ± 4.0***	62.0 ± 5.3	35.9 ± 6.0***	49.0 ± 7.2	42.7 ± 5.3	14.90	< 0.001	17.60	< 0.001	0.17	0.682	6.61	0.015
Angry	% correct	85.2 ± 3.0	72.7 ± 4.1***	91.2 ± 1.6	76.6 ± 4.5**	79.2 ± 5.4	68.8 ± 6.9	18.60	< 0.001	18.31	< 0.001	2.37	0.134	0.51	0.481
Sad	% correct	83.1 ± 3.0	78.4 ± 2.9	88.5 ± 2.1	75.5 ± 3.2**	77.6 ± 5.3	81.3 ± 4.9	2.34	0.136	2.98	0.095	0.27	0.608	9.42	0.005
Disgust	% correct	64.8 ± 3.5	54.7 ± 4.6*	64.6 ± 5.5	53.5 ± 6.5	65.1 ± 4.6	55.7 ± 6.6	5.81	0.022	5.63	0.024	0.03	0.856	0.03	0.855
Surprise	% correct	68.8 ± 3.5	58.9 ± 3.6**	72.9 ± 4.3	61.5 ± 4.8	64.6 ± 5.5	56.3 ± 5.3	9.79	0.004	9.55	0.004	1.16	0.291	0.24	0.629
<i>Stopping threshold</i>															
All emotions	% intensity	51.6 ± 2.3	40.0 ± 1.9	51.2 ± 3.0	55.6 ± 3.3	52.1 ± 3.5	51.9 ± 3.3	1.19	0.284	1.20	0.282	0.11	0.740	1.38	0.250
Happy	% intensity	39.7 ± 2.2	64.4 ± 3.1	38.5 ± 2.9	40.1 ± 2.8	40.9 ± 3.4	39.9 ± 2.6	0.02	0.883	0.02	0.884	0.09	0.767	0.38	0.541
Fearful	% intensity	57.3 ± 3.2	56.3 ± 2.6*	59.2 ± 4.0	67.0 ± 4.4	55.4 ± 5.1	61.6 ± 4.5	4.92	0.032	5.01	0.033	0.09	0.772	0.61	0.442
Angry	% intensity	56.6 ± 2.4	57.7 ± 2.5	54.7 ± 3.4	57.4 ± 3.8	57.6 ± 3.7	55.1 ± 3.9	0.21	0.653	0.18	0.672	0.02	0.878	0.45	0.510
Sad	% intensity	56.6 ± 2.4	52.5 ± 2.6	56.2 ± 3.0	59.3 ± 3.8	57.0 ± 3.9	56.1 ± 3.9	0.19	0.666	0.19	0.668	0.08	0.784	0.59	0.449
Disgust	% intensity	49.5 ± 2.0	52.7 ± 3.2	49.8 ± 2.7	55.1 ± 3.3	49.2 ± 2.9	50.1 ± 4.0	0.97	0.332	1.00	0.325	0.60	0.445	0.52	0.476
Surprise	% intensity	50.5 ± 2.9	53.8 ± 2.3	48.7 ± 4.0	55.5 ± 4.4	52.4 ± 4.3	49.9 ± 4.8	0.77	0.388	0.84	0.367	0.03	0.861	3.89	0.058
<b>Hormones</b>															
Oxytocin (pg/ml)	$\Delta E_{max}$	12.2 ± 8.0	66.0 ± 14.9***	13.36 ± 15.39	54.7 ± 18.3*	11.10 ± 5.11	77.36 ± 23.67**	19.84	< 0.001	19.31	< 0.001	2.12	0.156	0.16	0.691
Copeptin (pg/ml)	$\Delta E_{max}$	-1.1 ± 0.3	1.6 ± 1.1	-0.5 ± 0.4	1.2 ± 0.6	-1.8 ± 0.4	2.3 ± 2.1	1.10	0.303	1.22	0.278	0.71	0.407	1.88	0.180
Cortisol (nmol/L)	$\Delta E_{max}$	-198.8 ± 24.4	187.2 ± 21.1***	-208.0 ± 41.0	155.8 ± 20.5***	-189.5 ± 27.6	218.7 ± 35.8***	98.70	< 0.001	95.88	< 0.001	0.12	0.736	0.11	0.738
Prolactin (mU/L)	$\Delta E_{max}$	-177.8 ± 26.6	402.6 ± 68.7***	-222.6 ± 50.0	495.3 ± 108.4***	-133.1 ± 15.4	310.0 ± 81.4***	127.8	< 0.001	126.21	< 0.001	0.07	0.794	0.61	0.440
Testosterone (nmol/L) only men	$\Delta E_{max}$	-2.74 ± 0.50	-0.94 ± 0.92					2.62 <sup>b</sup>	0.127						
Testosterone (nmol/L) only women	$\Delta E_{max}$	-0.11 ± 0.05	-0.04 ± 0.03					1.62 <sup>b</sup>	0.222						

<sup>a</sup> $p < 0.05$ , <sup>\*\*</sup> $p < 0.01$ , <sup>\*\*\*</sup> $p < 0.001$ . MDMA main effect for all subjects or *post hoc* test for male or female subjects compared with placebo. IA, inequality-aversion; <sup>a</sup> $F_{(1,29)}$ ; <sup>b</sup> $F_{(1,15)}$

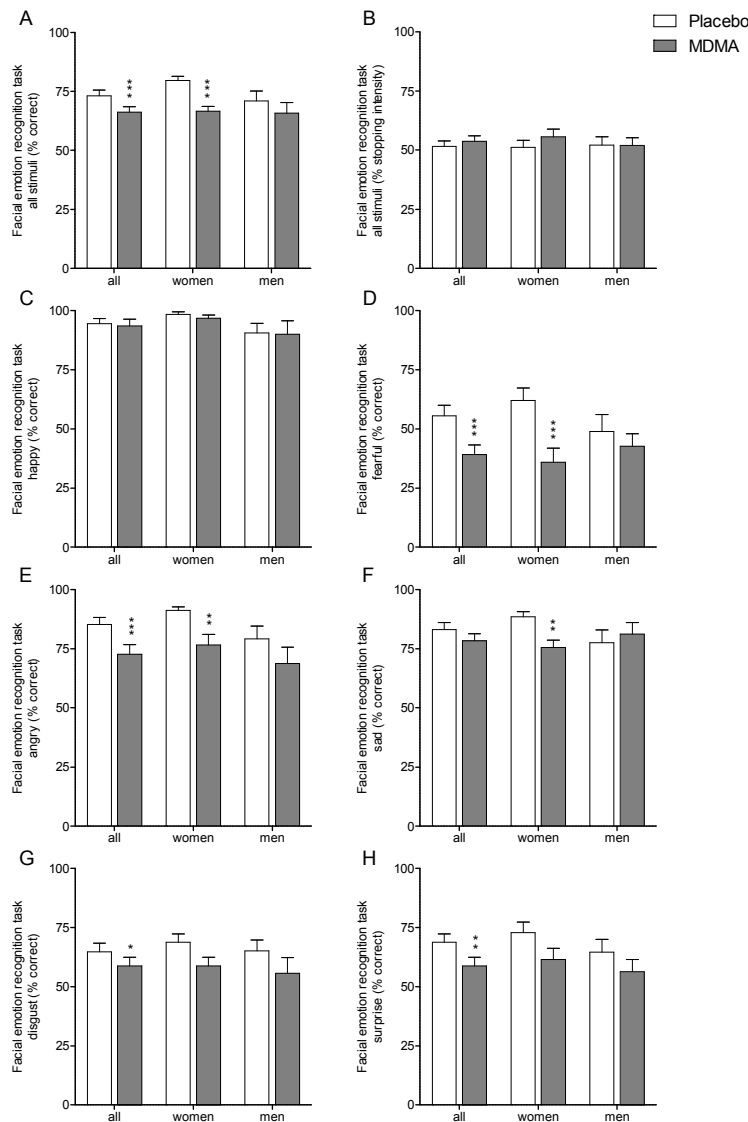


**Figure S1.** Subjective effects of MDMA measured using the adjective mood rating scale (AMRS). The data are expressed as mean  $\pm$  SEM score changes from predrug baseline. \* $p < 0.05$ , \*\*\* $p < 0.001$ , significant differences ( $E_{max}$ ) from placebo in women/men. ns=not significant.



**Figure S2.** Effect of MDMA on (A,B) explicit and (C,D) implicit emotional empathy and (E,F) cognitive empathy according to emotional valence of the stimuli as assessed using the Multifaceted Empathy Test (MET). The significant MDMA-induced increases in explicit and implicit empathy observed for all stimuli (positive and negative stimuli combined as shown in Figure 2A,B in the article) are due to significant increases for (A,C) positive but not for (B,D) negative stimuli. In addition, effects of MDMA on emotional empathy were more pronounced in men. MDMA had no effect on cognitive empathy. The data are expressed as mean  $\pm$  SEM in 32 subjects. \* $p < 0.05$ , significant difference from placebo.

**Facial affect recognition.** Facial affect recognition was tested using a dynamic FERT (Domes *et al.*, 2008). Pictures of the six basic emotions (i.e., fear, sadness, disgust, happiness, anger, and surprise) were chosen from the NimStim set of facial expressions (Tottenham *et al.*, 2009) and morphed by 1% steps of intensity from 0% (neutral) to 100% of intensity of a specific emotion using Winmorph 2.0. Three female and three male faces were chosen, resulting in 36 sets of faces (6 emotions  $\times$  6 faces) with 100 pictures each. Each picture was presented for 80ms, beginning with 0% intensity and increasing up to 100% in 1% steps. The participants were instructed to press a stop button as soon as they recognized a specific emotion. After pressing the stop button, the picture disappeared, and the participants had to indicate the correct emotion out of six emotions. The 36 trials in one block were presented in a randomized order and presented twice, resulting in 72 trials. As dependent variables, the emotional intensity at which the trial was stopped for correct answers was recorded. The emotion recognition accuracy was then assessed, defined as the percentage of correctly identified emotions (Domes *et al.*, 2008).



**Figure S3.** Effect of MDMA on affect identification accuracy in the Facial Emotion Recognition Task (FERT). (A) MDMA significantly reduced recognition accuracy for all subjects due to a significant effect in women but not in men. (D,E) MDMA primarily reduced the recognition accuracy of negative emotions, especially in women. The data are expressed as mean  $\pm$  SEM in 32 subjects. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , significant difference from placebo.

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