Supplemental Information

Hormonal contraceptives suppress oxytocin-induced brain reward responses to the partner's face

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Supplemental Experimental Procedures

1. Study subjects

All subjects completed a comprehensive neuropsychological test battery. Neuropsychological testing before study enrollment included the DST (digit-span test), derived from the revised Wechsler adult intelligence scale (Wechsler, 1997) to assess working memory performance, the LPS 4 ('Leistungspruefsystem Subtest 4') (Horn, 1983) to assess nonverbal reasoning IQ, and the MWT-B ('Mehrfach-Wortschatz-IntelligenztestTeil B') (Lehrl *et al.*, 1995) to assess verbal IQ based on lexical decisions. The participants were asked to maintain their regular bed and waking times and to abstain from caffeine and alcohol intake on the day of the experiment. To control for potentially confounding effects of oxytocin (OXT) on state anxiety and mood, all subjects completed the State-Trait Anxiety Inventory (STAI) (Spielberger *et al.*, 1970) and the Positive and Negative Affective Scale (PANAS) (Watson *et al.*, 1988) immediately before the OXT/placebo (PLC) administration and after the experimental task. Three repeated-measure analyses of variance (ANOVA) with 'measurement' (before and after the experiment) and 'treatment' (OXT and PLC) as within-subjects factors and 'state anxiety', 'positive affect', or 'negative affect' as dependent variables revealed no significant main or interaction effects (all *P*s > 0.05; cf. *Supplemental Table S4*). Thus, OXT did not influence subjective anxiety or mood ratings. After completing the task, subjects were debriefed and asked to guess whether they had received OXT or PLC. Neither in the OXT (correct estimates 40 %, $\chi^2_{(1)} = 1.6$, $P = 0.21$) nor in the PLC session (correct estimates 60 %, $\chi^2_{(1)} = 1.6$, $P = 0.21$) was the correct estimation of the received treatment significantly different from chance, indicating that the subjects were unaware of whether they had received OXT or PLC.
In the group with hormonal contraception (HC) use, eight participants took second generation oral contraceptives containing a combination of 0.02 – 0.03 mg ethinylestradiol and 0.10 – 0.15 mg levonorgestrel. Another eight subjects used third or fourth generation contraceptives containing 0.02 – 0.04 mg ethinylestradiol and 2 mg dienogest or 0.15 mg desogestrel or 2 mg cyproterone acetate. The remaining five women used intrauterine release systems (20 mcg/daily levonorgestrel or 0.12 mg etonogestrel and 0.02 mg ethinylestradiol). All participants used the HC for at least three months. Two subjects in the PLC session reported side effects (slight tachycardia (n = 1) and headache (n = 1)). The random allocation sequence (for the double-blind OXT/PLC treatment) was generated by D.S.. J.P.

enrolled all participants and assigned participants to the treatment based on the random allocation plan. All behavioral and fMRI data were collected in Bonn, Germany.

2. FMRI paradigm

An independent sample of 10 heterosexual healthy women (mean age ± S.D.: 27.2 ± 4.66) rated attractiveness of and the arousal induced by the partner, the familiar and unfamiliar persons, and the quality of the photographs on a visual analog scale (0 = minimum, 100 = maximum) prior to the first fMRI session. In total, the task lasted approximately 12 minutes. The familiar control was a non-related woman whom the participants had known on average for 7 months (min: 1 month; max: 21 months).

3. Behavioral task

Before the start of the experiment, the subjects were asked if they knew any of the control persons and ratings of familiar persons (except for the partner and the familiar woman) were discarded from further analysis (in total 44 ratings). In the screening session, all subjects completed the Passionate Love Scale (PLS) (Hatfield and Sprecher, 1986), which had a good internal consistency (Cronbach's α = 0.87). A scale of 1 (minimum) to 9 (maximum) was used for the PLS. Example items are "I want ___ to know me – my thoughts, my fears, and my hopes" or "Sometimes I can't control my thoughts; they are obsessively on ___". Furthermore, all subjects completed the "Marburg Attitude Scales towards Love Styles" (German abbreviation: MEIL), which is a German version of Love Styles developed by Lee (Lee, 1988). It contains three primary styles of loving: Eros, a romantic love style that is similar to passionate love and is characterized by a powerful attraction to the beloved individual; Ludus, which describes lovers who view love as a game and often have several partners simultaneously; and Storge, a slow developing, friendship-based love. These primary love styles can be combined to form secondary styles of love: Pragma (Storge and Ludus combined; pragmatic view of the relationship), Mania (Eros and Ludus combined; obsessive and possessive lover), and Agape (Storge and Eros combined; altruistic love style). In the German version, each love style is assessed with 10 items and each dimension has an adequate reliability (Eros α = 0.85, Ludus α = 0.76, Storge α = 0.79, Pragma α = 0.84, Mania α = 0.86, Agape α = 0.87). In the present sample, we observed the highest scores for Eros and the lowest scores for Ludus (cf. *Supplemental Table S3*).

4. Acquisition of fMRI data

A Siemens Trio MRI system (Siemens, Erlangen, Germany) operating at 3T was used to obtain T2*-weighted echoplanar (EPI) images with blood-oxygen-level-dependent contrast (TR = 2500 ms, TE = 30 ms, pixel size: 2 x 2 x 3 mm, slice thickness= 3.0 mm, distance factor = 10 %, FoV = 192 mm, flip angle = 90°, 37 axial slices). In addition, high-resolution anatomical images were acquired on the same scanner using a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1660 ms, TE = 2.54 ms, matrix size: 256 x 256, pixel size: 0.8 x 0.8 x 0.8 mm, slice thickness = 0.8 mm, FoV = 256 mm, flip angle = 9°, 208 sagittal slices).

5. Analysis of fMRI data

The first five volumes of each functional time series were discarded to allow for T1 equilibration. Images were corrected for head movement between scans by an affine registration. For realignment, a two-pass procedure was used by which images were initially realigned to the first image of the time-series and subsequently re-realigned to the mean of all images. For spatial normalization, the mean EPI image of each subject was normalized to the current Montreal Neurological Institute (MNI) template using the unified segmentation function in SPM8. This algorithm combines image registration, tissue classification, and bias correction within the same generative model. All images were thereby transformed into standard stereotaxic space and resampled at 3 x 3 x 3 mm voxel size. The normalized images were spatially smoothed using an 8 mm FWHM Gaussian kernel. Raw time series were detrended by the application of a high-pass filter (cut-off period 128 s). A two-level random effects approach based on the general linear model as implemented in SPM8 was used for statistical analyses.

Based on our previous study investigating the effects of OXT on pair-bonding in men (Scheele *et al.*, 2013), we used spheres (10 mm radius) as regions of interest (ROI) centered at the following coordinates: nucleus accumbens (NAcc; left: -10,4,-4; right: 10,4,-4) and ventral tegmental area (left: -2,-12,-8; right: 2,-12,-8). The Wake Forest University (WFU) Pickatlas (Version 3.0) was used to generate ROI masks and the threshold for significance was set at $P < 0.05$, family-wise error corrected for multiple comparisons based on the size of the ROI.

6. Hormonal assessment

Salivettes were immediately centrifuged at 4180 g for 2 min, and aliquoted samples were stored at -80°C until assayed. Saliva OXT was extracted and quantified using a highly sensitive and specific radioimmunoassay (RIAgnosis, Munich, Germany) (Kagerbauer *et al.*, 2013). The limit of detection was 0.1 - 0.5 pg per sample tube, depending on the age of the tracer. Intra-assay and inter-assay coefficients of variability were < 10 %. All samples to be compared were assayed in the same batch, i.e. under intra-assay conditions. The OXT assay samples were run in unicate; due to the low concentrations samples could not be divided in two aliquots. The sample volume assayed was 0.3 ml. One participant in the PLC session and three participants in the OXT session did not provide saliva samples for the baseline measurement. For all analyses of baseline OXT concentrations, the OXT measurements before the nasal spray administration in the OXT and PLC sessions were averaged.

Serum FSH, LH, and estradiol were analyzed by fully automated homogeneous sandwich chemiluminescent immunoassays based on the LOCI™ technology on a Dimension Vista™ System according to the manufacturer´s instructions (Siemens Healthcare Diagnostics, Eschborn, Germany). The detection limits of each assay were 0.2 IU/l for LH and FSH and 11 pg/ml for estradiol, respectively. The coefficients of variation for intra-assay and inter-assay precision were <1.8 % and <2.1 % for LH, <1.9 % and <2.2 % for FSH, and <5.5 % and <5.9 % for estradiol, respectively. Serum progesterone was determined by a fully automated solid-phase competitive chemiluminescent enzyme immunoassay on an Immulite™ 2000xpi System according to the manufacturer´s instructions (Siemens Healthcare Diagnostics). The detection limit of the assay was 0.1 ng/ml. The coefficients of variation for intra-assay and inter-assay precision were <4.2 % and <5.5 %. The cross-reactivity of all assays with other related compounds was minimal. Saliva testosterone was determined by a competitive enzyme immunoassay (ELISA) according to the manufacturer´s instructions (IBL International, Hamburg, Germany). The detection limit of the assay was 4.7 pg/ml. The coefficients of variation for intra-assay and inter-assay precision were <7.1 % and <7.7 %.

7. Statistical analysis

Demographical, neuropsychological, and behavioral data were analyzed using SPSS 22 (SPSS Inc., Chicago, IL, USA). Quantitative behavioral data were compared by a repeated-measures analysis of

variance (ANOVA). Pearson's product-moment correlation (r) and Spearman's rank correlation (r_{SP}) were used for correlation analysis. Eta-squared and Cohen's d were calculated as measures of effect size. The assumption of normality for all target variables was assessed separately for the OXT and PLC sessions using Kolmogorov-Smirnov tests. All target data were derived from normally distributed populations (all Ps > 0.05). The assumption of sphericity was assessed with Mauchly's test, and Greenhouse-Geisser's correction was applied for significant violations. Pearson's chi-squared tests were used for qualitative variables. All reported P-values are two-tailed, if not otherwise noted, and P-values of $P < 0.05$ were considered significant.

Supplemental Results

1. Behavioral Results

Before and 5 minutes after the nasal administration, we measured the body temperature, blood pressure (systolic and diastolic), and pulse of all participants. A repeated-measures ANOVA with treatment (OXT, PLC) and time (before, 5 minutes after nasal spray administration) as within-subject factors did not yield any significant main or interaction effects (all *P*s > 0.05) indicating that 24 IU of intranasal OXT had at least no immediate effects on these vital signs.

A repeated-measures ANOVA with the salivary OXT concentrations as the dependent variable and the within-subject factors 'treatment' (OXT, PLC) and 'time' (before the nasal spray administration, after the fMRI paradigm) yielded significant main effects of treatment ($F_{(1, 29)} = 51.12$, $P < 0.01$, $\eta^2 = 0.64$) and time ($F_{(1, 29)} = 64.01$, $P < 0.01$, $\eta^2 = 0.69$) as well as an interaction of treatment and time ($F_{(1, 29)} = 58.73$, $P < 0.01$, $\eta^2 = 0.67$). As expected, intranasal OXT significantly increased salivary OXT concentrations, but the presentation of partner stimuli did not significantly increase OXT concentrations in the PLC session (PLC session: after nasal spray mean ± SD = 2.44 ± 2.20 pg/ml; OXT session: after nasal spray = 14.43 ± 7.88 pg/ml).

A repeated-measures ANOVA with treatment (OXT, PLC) as within-subject factor, HC (HC, no HC) as between-subject variable, and the positive partner bias based on the comparison with the familiar person (i.e. absolute difference between attractiveness or arousal ratings of the partner and the familiar person) for attractiveness as dependent variable revealed a treatment effect ($F_{(1, 32)} = 5.04$, $P = 0.03$, $\eta^2 = 0.14$), but no further main or interaction effects. Nevertheless, an exploratory analysis with paired *t*-tests revealed that OXT enhanced this positive attractiveness bias in freely cycling women ($t_{(16)} = 2.46$, $P = 0.03$, $d = 0.33$), but not in women with HC ($t_{(16)} = 0.94$, $P = 0.36$, $d = 0.14$).The OXT effect on the arousal-based positive partner bias did not reach statistical significance, yet it was also more pronounced in freely cycling women ($t_{(15)} = 1.73$, $P = 0.11$, $d = 0.43$) than women with HC ($t_{(16)} = -0.03$, $P = 0.98$, $d = -0.004$).

In an exploratory analysis, we tested whether the OXT effect in women not using HC varied as a function of their menstrual cycle phase. Two repeated-measures ANOVAs with treatment (OXT, PLC) as within-subject factor, cycle phase (follicular phase, luteal phase) as between-subject variable, and the positive partner bias for attractiveness and arousal as dependent variables yielded no significant main or

interaction effects of cycle phase (all *P*s > 0.05). Furthermore, due to the small sample size we could not differentiate between different types (e.g. generations) of HC. However, a descriptive comparison of the OXT effect in women using oral HC and women using intrauterine release systems did not reveal a clear pattern of results. While the positive partner bias for attractiveness was in fact higher under OXT (53.47 ± 15.32) compared to PLC (48.33 ± 16.97) in women using intrauterine release systems, the direction of the arousal-based positive partner bias was reversed (OXT: 49.04 ± 38.91, PLC: 52.73 ± 19.64). For women using oral HC, there was no evidence for any OXT effect (positive partner bias attractiveness, OXT: 47.58 ± 14.42, PLC: 47.32 ± 11.48; positive partner bias arousal, OXT: 41.03 ± 15.44, PLC: 41.40 ± 16.22).

The OXT effect on the attractiveness-based positive partner bias did not correlate with the attractiveness rating of the partner under PLC (HC: r = -0.17, P = 0.52; no HC: r = -0.29, P = 0.27) or with the 'objective' attractiveness of the partner as indicated by attractiveness ratings by the other female participants (HC: r = 0.23, P = 0.37; no HC: r = -0.27, P = 0.30). Furthermore, the positive partner bias for both attractiveness and arousal ratings was comparable between women using and not using HC (all *P*s > 0.84).

2. fMRI results

The mean endogenous OXT concentrations positively correlated with the extracted parameter estimates for the partner-specific neural responses [$Partner_{PLC}$ > $Familiar_{PLC}$] in the left (peak MNI x, y, z: -24, 14, -8, r = 0.52, P < 0.01; r_{SP} = 0.52, P < 0.01) and right (30, 5, -11, r = 0.53, P < 0.01; r_{SP} = 0.48, P < 0.01) lentiform nucleus. A ROI-based approach revealed similar correlations between the extracted parameter estimates for the partner-specific neural responses [$Partner_{PLC}$ > $Familiar_{PLC}$] in the left (-9, 8, -2, r = 0.49, P < 0.01; r_{SP} = 0.45, P < 0.01) and right (15, 11, -5,1, -11, r = 0.54, P < 0.01; r_{SP} = 0.52, P < 0.01) NAcc.

Consistent with our previous data in men (Scheele *et al.*, 2013), we found no significant association between neural response in the NAcc and VTA and OXT-induced changes in attractiveness ratings. This lack of correlation could be related to the absence of behavioral ratings performed during the fMRI scan, but it is also conceivable that the behavioral and neural OXT effects in this study are independent of each other. Likewise, we observed no significant associations between the duration of HC

use and partner-specific OXT effects. However, the reliability of the duration judgments was not very high because several women could not remember when they exactly started using HC.

Furthermore, a comparison of the partner-specific OXT effect [($Partner_{OXT}$ > $Familiar_{OXT}$) > ($Partner_{PLC}$ > $Familiar_{PLC}$)] between women in the follicular or luteal phase of the menstrual cycle revealed no significant whole-brain or ROI-based differences.

Supplemental References

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Tables

Table S1. Demographics and neuropsychological performance

	HC group Mean (± SD)	No HC group Mean (± SD)	*t*	*P*
Age (years)	24.00 (3.36)	24.79 (3.19)	-0.76	0.45
Education (years)	16.18 (2.32)	16.37 (1.54)	-0.29	0.77
Weight (kg)	63.62 (7.80)	60.47 (7.44)	1.30	0.20
Height (cm)	168.43 (5.55)	167.05 (5.10)	0.81	0.42
LPS-4 [a]	26.50 (4.37)	29.78 (4.40)	-1.58	0.13
MWT-B [b]	23.33 (8.78)	25.76 (5.11)	-0.64	0.54
DST, forward [c]	9.37 (2.11)	8.68 (1.80)	1.08	0.29
DST, backwards [c]	8.47 (2.12)	8.21 (2.23)	0.37	0.71
Trait anxiety [d]	36.95 (9.07)	37.32 (7.36)	-0.14	0.89
BDI [e]	4.95 (5.31)	4.37 (3.55)	0.40	0.69

Notes. Nonverbal reasoning IQ was assessed by the [a] LPS (Leistungsprüfsystem) subtest 4 (maximum possible score 40). Verbal IQ based on lexical decisions was assessed by the [b] MWT-B (Mehrfachwahl-Wortschatz-Intelligenz-Test, Teil B) (maximum possible score 37), working memory performance was assessed using the [c] DST (Digit-Span Test) forward and backward (maximum possible score 14). Anxiety symptoms were assessed by the [d] State Trait Anxiety Inventory and depressive symptoms by the self-report [e] BDI (Beck Depression Inventory, Version II). Abbreviations: HC, hormonal contraception.

Table S2. Baseline measurement of endocrine factors

	HC group Mean (± SD)	No HC group Mean (± SD)	*t*	*P*
Baseline Oxytocin OXT (pg/ml) [1]	1.84 (2.03)	2.29 (3.12)	-0.53	0.60
Estradiol OXT (pg/ml) [1]	28.00 (20.26)	71.49 (52.51)	-3.22	<0.01
FSH OXT (U/l) [1]	3.84 (2.03)	5.09 (2.73)	-1.61	0.12
LH OXT (U/l) [1]	4.35 (4.62)	7.21 (6.93)	-1.50	0.14
Progesterone OXT (ng/ml) [1]	0.62 (0.44)	3.46 (4.35)	-2.68	0.02
Testosterone OXT (pg/ml) [1]	282.33 (410.65)	124.68 (293.66)	1.33	0.19
Baseline Oxytocin PLC (pg/ml) [1]	2.40 (2.45)	1.40 (1.51)	1.51	0.14
Estradiol PLC (pg/ml) [1]	43.30 (76.87)	109.51 (70.90)	-2.63	0.01
FSH PLC (U/l) [1]	3.18 (2.89)	4.16 (2.97)	-1.01	0.32
LH PLC (U/l) [1]	3.04 (2.77)	7.91 (10.73)	-1.96	0.06
Progesterone PLC (ng/ml) [1]	0.95 (0.92)	3.59 (4.56)	-2.28	0.04
Testosterone PLC (pg/ml) [1]	236.90 (327.06)	109.43 (141.63)	1.48	0.15

Notes. Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; OXT, oxytocin; PLC, placebo; [1]There were no significant differences in any measurements between the OXT and PLC sessions (all *P*s > 0.05).

Table S3. Relationship characteristics

Variable	HC group Mean (± SD)	No HC group Mean (± SD)	*t*	*P*
Relationship duration (months)	35.83 (32.68)	30.94 (22.23)	0.54	0.60
Age of partner (years)	26.81 (5.11)	27.37 (4.27)	-0.37	0.71
PLS [a]	7.14 (0.76)	6.73 (1.26)	1.25	0.22
Time (days) since the last time seen OXT[1]	0.89 (1.59)	2.00 (2.33)	-1.69	0.10
Time (days) since the last time seen PLC[1]	1.11 (2.05)	2.69 (3.91)	-1.45	0.16
Time (days) since the last intimate contact OXT[1]	3.16 (2.97)	6.67 (11.33)	-1.31	0.20
Time (days) since the last intimate contact PLC[1]	3.56 (3.03)	5.69 (3.81)	-1.82	0.08
Love style Eros [b]	7.42 (0.88)	6.83 (1.31)	1.66	0.11
Love style Ludus [b]	2.44 (1.13)	2.76 (1.33)	-0.81	0.43
Love style Storge [b]	6.06 (1.41)	5.40 (1.13)	1.60	0.12
Love style Pragma [b]	4.93 (1.02)	4.95 (1.90)	-0.03	0.98
Love style Mania [b]	5.15 (1.43)	4.32 (1.48)	1.73	0.09
Love style Agape [b]	7.04 (0.99)	6.32 (1.25)	1.95	0.06

Notes. Love in the relationship was measured with [a] the PLS (Passionate Love Scale) and different love styles were assessed using a German version of [b] Lee's Love Styles ("Marburger Einstellungs-Inventar für Liebesstile (MEIL)"). Abbreviations: HC, hormonal contraception; OXT, oxytocin; PLC, placebo; [1]There were no significant differences in any relationship measures between the OXT and PLC sessions (all *P*s > 0.13).

Table S4. State measurement of anxiety and mood

	OXT session Mean (± SD)	PLC session Mean (± SD)	*t*	*P*
STAI – pre [a]	32.65 (5.04)	32.73 (6.07)	-0.10	0.92
STAI – post [a]	32.80 (6.61)	31.25 (5.21)	1.29	0.21
PANAS – positive – pre [b]	30.75 (6.16)	30.18 (5.84)	0.61	0.54
PANAS – positive – post [b]	31.30 (10.56)	30.48 (6.94)	0.49	0.63
PANAS – negative – pre [b]	11.50 (2.69)	11.30 (1.54)	0.53	0.60
PANAS – negative – post [b]	11.58 (3.29)	10.70 (0.99)	1.88	0.09

Notes. State anxiety before and after the experiment was assessed using the [a]STAI = State Trait Anxiety Inventory. Mood before and after the experiment was assessed using the [b] PANAS = Positive and Negative Affect Schedule. Abbreviations: OXT, oxytocin; PLC, placebo.

Table S5. Areas showing significantly greater activations in response to the partner compared to the familiar control (women not using hormonal contraception)

Region	Right/left	Cluster size (voxels)	*t*	*MNI-coordinates*		
				x	*y*	*z*
OXT						
Caudate nucleus	L	555	4.78	-18	-16	22
Anterior cingulate cortex	L/R		4.30	0	32	28
Superior frontal gyrus	L		3.87	-18	47	1
Superior frontal gyrus	L	26	3.91	-3	56	37
Inferior frontal gyrus	R	112	3.87	51	38	13
Inferior occipital gyrus	L	201	3.72	-39	-67	-8
Fusiform gyrus	L		3.59	-45	-49	-20
Middle temporal gyrus	L		2.95	-60	-61	-2
Inferior frontal gyrus	L	30	3.69	-39	26	4
Cingulate gyrus	R		3.35	15	2	28
Superior frontal gyrus	L	18	3.61	-27	47	34
Inferior frontal gyrus	L	11	3.48	-36	26	-20
Middle occipital gyrus	L	29	3.30	-30	-70	25
Middle occipital gyrus	R	24	3.13	30	-58	25
Middle occipital gyrus	R		2.93	30	-70	25
Inferior frontal gyrus	R	13	2.97	33	29	4
Precuneus	R	15	2.99	18	-61	58
Precuneus	R		2.69	24	-61	52
PLC						
Superior frontal gyrus	R	57	3.97	21	41	7
Anterior cingulate cortex	R		3.74	18	32	7
Anterior cingulate cortex	L/R	23	3.26	0	32	7

Notes. The whole-brain analysis was thresholded at an uncorrected $P < 0.001$ with a cluster extent threshold of k = 10 voxels. Abbreviations: OXT, oxytocin; PLC, placebo.

Table S6. Areas showing significantly greater activations in response to the partner compared to the familiar control (women using hormonal contraception)

Region	Right/left	Cluster size (voxels)	*t*	*MNI-coordinates*		
				x	*y*	*z*
OXT						
Medial frontal gyrus	R	41	3.31	6	53	16
Medial frontal gyrus	L		2.80	-6	59	13
PLC						
Superior frontal gyrus	R	63	3.46	6	17	58
Superior frontal gyrus	L		2.94	-9	8	64
Superior frontal gyrus	R	21	3.17	12	50	43
Medial frontal gyrus	L	20	3.03	-3	53	19
Uncus	L	12	3.00	-18	-7	-11

Notes. The whole-brain analysis was thresholded at an uncorrected $P < 0.001$ with a cluster extent threshold of k = 10 voxels.
Abbreviations: OXT, oxytocin; PLC, placebo.