Supporting Information

Titel: Common and dissociable effects of oxytocin and lorazepam on the neurocircuitry of fear

Authors: Ann-Kathrin Kreuder, Dirk Scheele, Johannes Schultz, Juergen Hennig, Nina Marsh, Torge Dellert, Ulrich Ettinger, Alexandra Philipsen, Mari Babasiz, Angela Herscheid, Laura Remmersmann, Ruediger Stirnberg, Tony Stöcker, and René Hurlemann

Corresponding Author: René Hurlemann, E-mail: renehurlemann@icloud.com

www.pnas.org/cgi/doi/10.1073/pnas.1920147117

SI Methods

Ethics and Enrollment

The study was approved by the local ethics committee of the Medical Faculty of the University of Bonn, Germany. It was registered in the ClinicalTrials.gov database (Identifier: NCT03829839) provided by the US National Institutes of Health. All participants gave written informed consent and the study was conducted in accordance with the latest revision of the Helsinki Declaration. Participants were recruited from the local population by means of online advertisement and public postings. After completion of the study, participants received monetary compensation. The random allocation sequences for both study subtrials were generated by A.K., while D.S. 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.

Screening Session

Study enrollment was preceded by a detailed screening session to ensure that subjects were free of any current or past physical or psychiatric illness as assessed by medical history and the Mini-International Neuropsychiatric Interview (MINI) (1). To further characterize the study sample, we assessed trait anxiety and depressive symptoms using the State-Trait Anxiety Inventory (STAI) (2) and the Beck Depression Inventory (3). Autistic-like traits were measured via the Autism Spectrum Quotient questionnaire (4). Treatment groups did not differ in the abovementioned questionnaire data (all *P*s > .11; cf. **Supplemental Table S1**). All subjects were naive to prescription-strength psychoactive medication and to the purpose of the study. Contraindications for MRI scanning were additional exclusion criteria.

The participants were asked to maintain their regular sleeping and waking times and to abstain from caffeine and alcohol intake on the day of the experiment. This was verified via a questionnaire administered at the beginning of the testing session.

Experimental Design and Procedure

A recent kinetic study observed decreased amygdala responses to fearful faces between 15 and 100 min after intranasal administration of oxytocin (OXT) (5). According to this pharmacodynamic profile and given a task duration of about 15 min, we started the fMRI measurement for subjects in the OXT trial

(subtrial A) 30 min after nasal spray administration. Orally administered lorazepam (LZP) is rapidly absorbed and a peak plateau of plasma lorazepam concentrations has been found between 60 and 120 min after ingestion (6). Thus, in the LZP trial (subtrial B) the fMRI task started 90 min after the treatment.

To examine potential changes in endogenous OXT levels, two plasma samples of each subject were collected. One was taken before the administration of the treatment (pre) and another sample immediately after the fMRI task (post) (cf. **SI Results**). Additionally, subjects' state anxiety level was assessed by a computer-based Visual Analogue Mood Scale (7, 8) prior to the treatment administration (pre fMRI) and immediately after the fMRI (post fMRI).

Acquisition of fMRI Data

A 7-Tesla whole-body MRI research system (Siemens Healthineers, Erlangen, Germany) with a 32 channel head array coil (32Rx/1Tx, Nova Medical, Wilmington, MA) was used to obtain T2*-weighted echoplanar imaged (EPI) with blood-oxygen-level-dependent contrast. A segmented 3D-EPI sequence (9) was employed to achieve rapid whole brain coverage at 1.7 mm isotropic resolution (imaging parameters: TR = 1900 ms, TE = 22 ms, FOV = 204 mm x 204 mm x 149.6 mm, water excitation (10) , nominal flip angle = 13°, TA = 9:09 min, GRAPPA parallel imaging acceleration factor R = 2 x 2, 48 x 48 autocalibration lines). The subjects' cardiac and respiratory cycle phases were recorded synchronously with the EPI scans using the vendor-provided respiration belt fastened around the upper abdomen and plethysmograph placed on the left forefinger.

To enable offline distortion correction of the functional images based on B0-field inhomogeneity, a field mapping sequence was included in the scanning protocol (imaging parameters: TR = 400 ms, TE 1 = 5.19 ms, TE 2 = 7.65 ms, FOV = 204 mm x 204 mm, slice thickness = 3.2 mm, distance factor = 25%, nominal flip angle = 60°, TA = 0:54 min, 37 sagittal slices).

In addition, high-resolution anatomical whole brain images were acquired on the same 7T MRI using a custom T1-weighted 3D MPRAGE sequence at 0.6 mm isotropic resolution (imaging parameters: TR = 2500 ms, TE = 2.91 ms, FOV: 256 mm x 217.6 mm x 153.6 mm, nominal flip angle = 7°, TA = 6:47 min, R = 2 x 1, 48 x 1 autocalibration lines). To homogenize the main magnetic field, up to 2nd order spherical harmonics shim settings were automatically calculated and applied for each scan based on a whole head

shim scan acquired at the beginning of each imaging session. The total measurement time for each subject in the 7-Tesla scanner was proximately 60 min.

Analysis of fMRI Data

Functional MRI data were preprocessed and analyzed using SPM12 software (Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (The MathWorks Inc., Natick, MA). 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. To correct for signal distortion based on B0-field inhomogeneity, the images were unwarped by applying the voxel displacement map (VDM file) to the EPI time series (Realign & Unwarp).

For normalization, a two-step procedure was applied. Normalization parameters were first determined using the co-registered individual T1 image as the source and the multi subject T1-template integrated in SPM12. This step included by default tissue segmentation using tissue probability maps. Next, normalization parameters were applied to normalize the functional images. Finally, these images were presented in standard anatomical Montreal Neurological Institute (MNI) space and resampled at 2 x 2 x 2 mm^3 voxel size. The normalized images were spatially smoothed using a 2-mm FWHM Gaussian kernel. Raw time series were detrended by the application of a high-pass filter (cut-off period, 128 sec).

On the first level, we computed the following contrasts for each subject: [fearful > neutral]; [happy > neutral] and [all faces > house]. Unspecific, domain-general effects of OXT and LZP (i.e., the main effect of treatment) were analyzed by comparing all conditions with the low-level baseline ([OXT > PLC], [OXT < PLC], [LZP > PLC] and [LZP < PLC]). Additionally, to control for physiologically induced signal artifacts (11), we calculated RETROICOR (retrospective artifact correction) regressors using a 3^{rd} order Fourier expansion for the respiratory and the cardiac phase (12) and RVHRCOR (corrections for respiratory volume and heart rate variations) regressors (13) based on the respiration belt and plethysmograph data. Thus,

fourteen nuisance regressors for physiological noise correction and six movement regressors were included in the GLM. In addition, the response button presses were entered as regressors of no interest.

To examine possible effects on the processing of happy versus neutral faces and of faces versus houses, we conducted two additional full-factorial designs: a 3 x 2 full-factorial analysis of variance (ANOVA) with “treatment” (OXT, LZP, PLC) as a between-subjects factor and “emotion category” (happy, neutral) as a within-subjects factor and a 3 x 2 full-factorial ANOVA with “treatment” (OXT, LZP, PLC) as a between-subjects factor and “stimulus category” (all faces, houses) as a within-subjects factor.

A generalized psychophysiological interactions (gPPIs) analysis (14) was used to examine the effects of OXT and LZP on intra- and extra-amygdalar functional connectivity during emotional face processing. In contrast to the standard PPIs implementation in SPM, a gPPI analysis allows modeling of more than two task conditions in the same PPI by spanning the entire experimental space to improve model fit, specificity to true-negative and sensitivity to true-positive findings. Hemodynamic deconvolution was performed on the extracted time series to remove the effects of canonical hemodynamic response function (HRF). The resulting time series were multiplied by the psychological variables and reconvolved with the HRF to obtain the gPPIs interaction terms. The gPPI analysis for each subject was performed on the first level and included regressors for [fearful], [happy], [neutral] and [house].

Power Calculation

The main aim of the current study was to compare the anxiolytic effects of LZP and OXT on amygdala reactivity. Thus, based on the effect size obtained in our recent OXT dose-response study (5), we used G*Power 3 (15) to conduct an *a priori* power analysis for the project. For the effects of OXT (24 IU and a latency of 45 min) on amygdala responses to high intensity fearful faces, we observed an effect size of dz = 0.56 in a within-subjects design (conversion to Cohen’s d for between-subjects designs: $d = (2*dz)/\sqrt{(2/(1-r))}$ with r = 0.03 is d = 0.78). To detect an OXT effect of this size (with $\alpha = 0.05$ and power = 0.75), we needed to test at least 48 participants in a between-subjects design. Assuming a drop-out rate of 5 %, at least 25 healthy men were tested in each treatment condition (i.e., oxytocin treatment: $n \geq 25$; placebo treatment: $n \geq 25$). Given that this power calculation revealed a necessary sample size of at least 25 subjects and that a previous study observed significant amygdala effects of 1 mg LZP with a sample size

of 15 subjects (cross-over) (16), we aimed to replicate a LZP-dependent reduction of fear-related amygdala activity with 25 subjects in all treatment conditions.

Hormonal Assessment

Plasma samples were collected with commercial sampling devices (Vacuette, Greiner Bio-One International, Austria) containing EDTA and aprotinin. Vacuettes were immediately centrifuged at 3250 rpm for 10 min, and aliquoted samples were stored at -80°C until assayed. OXT concentrations were extracted and quantified using a highly sensitive and specific radioimmunoassay (RIAgnosis, Munich, Germany) (17). The limit of detection was 0.1-0.5 pg, 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.

SI Results

Missing Values

Eight plasma samples are missing due to problems in sample assessment or analysis. MRI data from three subjects had to be excluded due to excessive head movements (> 3 mm/° movement in any direction as assessed by SPM's realignment procedure).

Behavioral Results

The effects of OXT and LZP on the subjects' hit rate in the fMRI paradigm

In an additional analysis we tested whether the administration of OXT or LZP affected the subjects' correct responses in the emotional face matching paradigm. For this purpose, we conducted a mixed ANOVA with "treatment" (OXT, LZP, PLC) as between-subjects factor, "stimulus category" (fearful, happy, neutral, house) as within-subjects factor and the percentage of correct responses (hit rate) as dependent variable. We found no significant main effect of stimulus category ($F_{(3,345)} = 0.67$, $P = .570$, $\eta_P^2 = 0.01$), no significant main effect of treatment ($F_{(2,115)} = 2.16$, $P = .120$, $\eta_P^2 = 0.04$) and no significant interaction of stimulus category x treatment ($F_{(6,345)} = 0.98$, $P = .438$, $\eta_P^2 = 0.02$). All participants showed high hit rates for fearful faces (mean correct responses in % ± SD = 97.91 ± 8.92), happy faces (97.74 ± 5.86), neutral faces (97.46 ± 7.79) and houses (98.19 ± 5.28).

The effects of OXT and LZP on state anxiety level

Additionally, we examined whether OXT and LZP modulate the subjects' state anxiety level as assessed by a computer-based Visual Analogue Mood Scale (7, 8) prior to the treatment administration (pre fMRI) and immediately after the fMRI (post fMRI). The mixed ANOVA with the within-subjects factor "time" (pre fMRI, post fMRI), the between-subjects factor "treatment" (OXT, LZP, PLC) and the "state anxiety level" as dependent variable revealed a significant main effect of time ($F_{(1, 113)} = 6.15$, $P = .015$, $\eta_P^2 = 0.05$). The subjects' state anxiety was significantly higher before (54.53 ± 46.62) than after the fMRI (43.91 ± 36.06). We found neither a significant main effect of treatment ($F_{(2, 113)} = 0.09$, $P = .919$, $\eta_P^2 < 0.01$) nor a significant interaction between treatment and time ($F_{(2, 113)} = 1.01$, $P = .366$, $\eta_P^2 = 0.02$) indicating that the administration of OXT or LZP did not affect the subjects' state anxiety level. This is in line with former

studies reporting that the effects of anti-anxiety agents are limited to reducing emotion induced by threat (18, 19). Indeed, a previous study using the threat-potentiated startle paradigm reported a specific effect of LZP (2 mg) for the threat-induced increase in self-rated anxiety, but no effect on baseline ratings (20). Moreover, our previous studies did not reveal significant effects of intranasal OXT on baseline anxiety or mood ratings (21, 22), but found an OXT-dependent effect on the stress-induced increase in self-rated concern (23).

A correlation analysis in the PLC group between the pre fMRI state anxiety level and the reaction times to fearful, happy and neutral faces showed no significant correlations (all *P*s ≥ .05).

Plasma OXT concentrations in the treatment groups

Furthermore, we compared the plasma OXT concentrations at baseline and after the fMRI paradigm between the treatment groups. The mixed-effects ANOVA with "treatment" (OXT, LZP, PLC) as between-subjects factor and "time point of plasma OXT concentration measurement" (Pre, Post) as within-subjects factor yielded significant main effects of treatment ($F_{(2,107)}$ = 208.34, P < .001, η_P^2 = 0.80), of time point ($F_{(1,107)}$ = 307.56, P < .001, η_P^2 = 0.74) and a significant interaction of treatment x time point ($F_{(2,107)}$ = 254.51, P < .001, η_P^2 = 0.83). The plasma OXT concentrations at baseline did not differ significantly between the OXT and PLC groups (OXT: 1.78 ± 0.19 pg/ml; PLC: 1.77 ± 0.23 pg/ml ml; $t_{(81)}$ = -0.62, P_{corr} > .99, d = -0.15), the OXT and the LZP groups (OXT: 1.78 ± 0.19 pg/ml; LZP: 1.85 ± 0.25 pg/ml ml; $t_{(55)}$ = -1.06, P_{corr} = .888, d = -0.28) or the LZP and PLC groups (LZP: 1.85 ± 0.25 pg/ml; PLC: 1.77 ± 0.23 pg/ml ml; $t_{(84)}$= -1.76, P_{corr} = .246, d = -0.40). However, following the fMRI paradigm, the plasma OXT level was significantly higher under OXT than under PLC (OXT: 7.48 ± 2.31 pg/ml; PLC: 1.83 ± 0.25 pg/ml ml; $t_{(79)}$ = 17.97, P_{corr} < .001, d = 4.28) and LZP (OXT: 7.48 ± 2.31 pg/ml; LZP: 1.94 ± 0.29 pg/ml; $t_{(54)}$ = 13.00, P_{corr} < .001, d = 3.48). The plasma OXT level after the fMRI paradigm did not differ significantly between the LZP and the PLC groups (LZP: 1.94 ± 0.29 pg/ml; PLC: 1.83 ± 0.25 pg/ml ml; $t_{(83)}$ = 1.75, P_{corr} = .255, d = 0.40). Post-hoc paired t-tests revealed a significant increase in the plasma OXT concentration after the paradigm only in the OXT group (pre: 1.78 ± 0.19 pg/ml; post: 7.48 ± 2.31 pg/ml; $t_{(26)}$ = 12.91, P_{corr} < .001, d = 2.82,).

Finally, we examined possible correlations between the baseline plasma OXT levels and the reaction times to fearful, happy and neutral faces in the PLC, in the LZP and in the OXT group. These analyses

yielded no significant correlations in the PLC and the LZP group (all Ps ≥ .05). In the OXT group, we found significant positive correlations between baseline plasma OXT levels and the reaction time to fearful faces ($r_{(27)}$ = 0.43, P = .024) and to neutral faces ($r_{(27)}$ = 0.52, P = .005).

fMRI Results and Functional Connectivity

LZP-dependent effects on amygdalar-frontal functional connectivity

Considering an involvement of GABA-ergic transmission within the medial prefrontal cortex (mPFC) in the top-down modulation of the amygdala (24, 25), we tested whether LZP modulates the functional coupling between the bilateral cmA, as seed regions, and the mPFC in response to fear-related stimuli. Using an ROI-based approach, these additional analyses did not reveal significant effects of LZP on the functional connectivity between the cmA and the mPFC in response to fearful compared to neutral faces (all Ps ≥ 0.05).

The modulatory effects of OXT and LZP on faces versus houses processing

To examine whether OXT and LZP influence the general neural processing of faces versus houses stimuli, we conducted a supplementary full-factorial ANOVA with “treatment” (OXT, LZP, PLC) as between-subjects factor and “stimulus category” (all faces, houses) as within-subjects factor. On the whole brain level, participants in the PLC group showed increased neural response to all faces versus houses in the right fusiform gyrus (Montreal Neurological Institute (MNI) peak coordinates: x, y, z: 39, -49, -17; k_e= 455, $t_{(224)}$ = 7.47, P_{FWE} < .001), right lingual gyrus (22, -97, -14; k_e= 69, $t_{(224)}$ = 7.29, P_{FWE} = .002), right middle temporal gyrus (41, -46, 19; k_e= 1473, $t_{(224)}$ = 6.27, P_{FWE} < .001) and left inferior temporal gyrus (-41, -51, -19; k_e= 194, $t_{(224)}$ = 5.79, P_{FWE} = .008). The region-of-interest (ROI)-analysis revealed elevated neural activity in response to all faces compared to houses in the bilateral cmA (left cmA -21, -8, -12; $t_{(224)}$ = 5.87, P_{FWE} < .001; right cmA: 18, -7, -14; $t_{(224)}$ = 4.69, P_{FWE} < .001; 18, -3, -16; $t_{(224)}$ = 4.48, P_{FWE} = .01) and the bilateral superficial amygdala (sfA; left sfA: -16, -5, -17; $t_{(224)}$ = 2.99, P_{FWE} = .048; right sfA: 18, -5, -16; $t_{(224)}$ = 3.89, P_{FWE} = .004) in the PLC group. Moreover, we found a trend-to-significant increased neural activity in response to all faces relative to houses in the right blA (30, -3, -24; $t_{(224)}$ = 3.51, P_{FWE} = .057) in the LZP group compared to the PLC group. However, we observed no significant effects of OXT compared

to PLC on the neural processing of all faces relative to houses on whole brain level and in the amygdala subregions.

In addition, a direct comparison of the OXT and LZP effects on the neural response to faces versus houses showed that OXT increased activation in the left cmA (-22, -10, -10; $t_{(224)} = 3.70$, $P_{FWE} = .008$) and the right sfA (15, -8, -16; $t_{(224)} = 3.12$, $P_{FWE} = .044$) relative to LZP, whereas LZP significantly increased the neural activity in the right superior parietal gyrus compared to OXT (18, -66, 51; $k_e = 58$, $t_{(224)} = 5.09$, $P_{FWE} = .007$).

The modulatory effects of OXT and LZP on the processing of happy versus neutral faces

Following an exploratory approach, an additional full-factorial ANOVA with "treatment" (OXT, LZP, PLC) as between-subjects factor and "emotion category" (happy, neutral) as within-subjects factor was performed. In the PLC group, we found a trend towards significantly increased neural response to happy versus neutral faces in the left cmA (-24, -7, -14; $t_{(224)} = 2.88$, $P_{FWE} = .084$). On the whole brain level, the administration of LZP versus PLC attenuated the neural response to happy versus neutral faces in the right supramarginal gyrus (42, -41, 41; $k_e = 58$, $t_{(224)} = 4.39$, $P_{FWE} = .006$). Furthermore, LZP significantly increased neural response to happy relative to neutral faces in the right sfA (15, -5, -16; $t_{(224)} = 3.44$, $P_{FWE} = .019$) compared to OXT. In an additional functional connectivity analysis, we tested whether the administration of OXT or LZP changed the functional interplay between the cmA and any regions in the whole brain compared to PLC during happy face processing. Intranasal OXT significantly increased the connectivity between the right cmA (seed region) and the left blA (-22, -1, -19; $t_{(224)} = 4.04$, $P_{FWE} = .005$) compared to PLC and decreased the functional interplay between the left cmA (seed region) and the right inferior occipital gyrus (32, -86, -2; $k_e = 59$, $t_{(224)} = 5.09$, $P_{FWE} = .002$). Direct comparisons of the OXT and LZP effects on the functional connectivity during the processing of fearful versus neutral faces, happy versus neutral faces and faces versus houses did not reveal significant results.

Domain-general effects of OXT and LZP

We examined potential unspecific, domain-general effects of OXT and LZP (main effect of treatment) by comparing all conditions with the low-level baseline ([OXT vs. PLC], [LZP vs. PLC]). This supplementary

analysis revealed increased activity in the left precentral gyrus (-29, -7, 46; k_e= 79, $t_{(112)}$ = 4.81, P_{FWE} < .001; -41, -1, 30; k_e= 55, $t_{(112)}$ = 4.72, P_{FWE} = .003) and the left sfA (-16, -5, -21; $t_{(112)}$ = 3.28, P_{FWE} = .028) under LZP compared to PLC.

Further moderation effects

In an additional correlation analysis, we tested whether changes in centromedial amygdala (cmA) activity and extra- and intra-amygdalar functional connectivity while processing fearful versus neutral faces were related to changes in state anxiety (pre fMRI MINUS post fMRI). These analyses revealed no significant correlations in any treatment group (OXT, LZP, PLC; all *P*s ≥ 0.05). Furthermore, we examined a potential association between trait anxiety and neural activity in the cmA as well as the intra- and extra-amygdalar functional connectivity in response to fearful versus neutral faces. We found no significant correlations in the OXT, LZP or PLC group (all Ps ≥ 0.05). In addition, we used the PROCESS macro (26) implemented in IBM SPSS to test whether the effects of OXT and LZP on cmA activity and on intra- and extra-amygdala connectivity were moderated by trait anxiety. These moderation analyses showed no significant moderation effects (all *P*s ≥ 0.05). Additionally, we examined if the OXT effects on cmA activity to fearful compared to neutral faces were moderated by the subjects' body mass index, age or level of autistic-like traits. These analyses revealed no significant moderation effects (all *P*s ≥ 0.05).

An analysis of the correlation between the neural response to fearful relative to neutral faces and the baseline plasma OXT concentration in the PLC group was conducted. On the whole brain level, we found a significant negative correlation between the baseline plasma OXT concentration and the neural response to fearful versus neutral faces in the bilateral supramarginal gyrus (58, -29, 29; k_e= 300, $t_{(52)}$ = 5.71, P_{FWE} < .001; -63, -29, 32; k_e= 67, $t_{(52)}$ = 4.55, P_{FWE} = 0.001), bilateral middle cingulate (15, -35, 44; k_e= 80, $t_{(52),}$ = 4.39, P_{FWE} < .001; -4, 4, 42; k_e= 70 $t_{(52)}$ = 5.17, P_{FWE} = .001), bilateral supplementary motor area (12, 0, 64; k_e= 45, $t_{(52)}$ = 4.12, P_{FWE} = .020; -14, -3, 64; k_e= 57, $t_{(52)}$ = 4.99, P_{FWE} = 0.004), superior (-60, -34, 20; k_e= 46, $t_{(52)}$ = 5.16, P_{FWE} = .018) and middle temporal gyrus (47, -63, 15; k_e= 136, $t_{(52)}$ = 5.25, P_{FWE} < .001), right insula (37, 7, 5; k_e= 105, $t_{(52)}$ = 5.82, P_{FWE} < .001),right superior parietal gyrus (17, -52, 61; k_e= 121, $t_{(52)}$ = 4.48, P_{FWE} < .001) and right putamen (37, -20, -4; k_e= 75, $t_{(52)}$ = 4.28, P_{FWE} = .001). The

neural response to fearful versus neutral faces in the amygdala subregions (*a priori* defined ROIs) did not correlate significantly with the baseline plasma OXT level in the PLC group (all *P*s > .05).

Finally, we tested a potential correlation between the neural responses to fearful relative to neutral faces and changes in plasma OXT concentration (post minus pre) in the OXT-group. This analysis revealed in the OXT group no significant correlation on the whole brain level or in the *a priori* defined ROIs (all *P*s > .05).

Supplemental Tables

Supplemental Table S1. Demographics and Psychometric Questionnaire Data

	LZP group (n=32) Mean (± SD)	OXT group (n = 27) Mean (± SD)	PLC group (n = 59) Mean (± SD)	*F*	*P*
Age (years)	24.41(± 3.71)	26.67 (± 4.33)	25.90 (± 4.52)	2.22	.114
Education (years)	17.06 (± 2.45)	16.56 (± 3.38)	17.19 (± 3.20)	0.40	.671
AQ [a]	14.66 (± 6.28)	16.04 (± 5.36)	14.10 (± 5.20)	1.13	.327
BDI [b]	1.41 (± 1.74)	1.96 (± 2.23)	1.68 (± 2.02)	0.57	.568
STAI trait [c]	30.66 (± 7.63)	29.56 (± 5.75)	29.76 (± 5.56)	0.29	.751

Notes. Autistic-like traits were assessed by the [a] AQ (Autism Spectrum Quotient) and depressive symptoms were assessed by the [b] BDI (Beck's Depression Scale, Version II). Trait anxiety symptoms were measured by the [c] STAI (State Trait Anxiety inventory). Abbreviations: LZP, lorazepam; OXT, oxytocin; PLC, placebo.

Supplemental Table S2. Whole Brain Activation Table for GLM Analysis under Placebo (PLC; Fearful vs. Neutral)

Region	Right/left	Cluster size (voxels)	t-score	MNI coordinates		
				x	y	z
PLC: Fearful > Neutral						
Hippocampus	L	22	4.51	-24	-12	-14
Cerebellum	R	28	4.45	24	-49	-46
Cerebellum	R		3.39	27	-56	-43
Posterior Cingulate *	R	93	4.34	3	-47	27
Posterior Cingulate	L		3.99	-5	-47	27
Precuneus	L		3.75	-5	-46	37
Cerebellum	R	16	4.21	20	-85	-39
Caudate	R	13	4.18	20	21	3
Middle temporal gyrus *	R	42	4.17	52	-41	8
Middle temporal gyrus	R		3.81	56	-35	1
Middle temporal gyrus	L	20	4.13	-51	-44	3
Posterior cingulate	R	11	4.11	7	-52	30
Superior temporal pole	L	13	4.08	-50	22	-24
Middle temporal pole	L		3.62	-43	19	-27
Cerebellum	R	10	3.98	27	-83	-31
Cerebellum	R		3.92	18	-85	-29
Angular gyrus	L	21	3.89	-41	-58	25
Anterior cingulate	L	11	3.74	-9	46	7
Precuneus	L	27	3.73	-9	-56	34
Precuneus	L		3.55	-9	-51	42

Notes. For this whole brain analysis, a height threshold of $P < .001$ (uncorrected) and a cluster extent of $k_e = 10$ voxels were used. *cluster level $P_{FWE} < .05$. Abbreviations: PLC, placebo.

Supporting References

1. D. V. Sheehan *et al.*, The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry* **59 Suppl 20**, 22-33;quiz 34-57 (1998).
2. C. D. Spielberger, R. L. Gorsuch, R. E. Lushene, *Manual for the State-Trait Anxiety Inventory* (Consulting Psychologists Press, Palo, Alto, CA, 1970).
3. B. M. Hautzinger M, Worall H, Keller F, *Beck-Depressions-Inventar (BDI)* (Huber, Bern, 1995).
4. S. Baron-Cohen, S. Wheelwright, R. Skinner, J. Martin, E. Clubley, The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Devl Disord* **31**, 5-17 (2001).
5. F. B. Spengler *et al.*, Kinetics and Dose Dependency of Intranasal Oxytocin Effects on Amygdala Reactivity. *Biol Psychiatry* **82**, 885-894 (2017).
6. U. E. Busto *et al.*, A comparative pharmacokinetic and dynamic evaluation of alprazolam sustained-release, bromazepam, and lorazepam. *J Clin Psychopharmacol* **20**, 628-635 (2000).
7. H. Norris, The action of sedatives on brain stem oculomotor systems in man. *Neuropharmacology* **10**, 181-191 (1971).
8. A. W. Zuardi, R. A. Cosme, F. G. Graeff, F. S. Guimaraes, Effects of ipsapirone and cannabidiol on human experimental anxiety. *J Psychopharmacol* **7**, 82-88 (1993).
9. B. A. Poser, P. J. Koopmans, T. Witzel, L. L. Wald, M. Barth, Three dimensional echo-planar imaging at 7 Tesla. *Neuroimage* **51**, 261-266 (2010).
10. R. Stirnberg, D. Brenner, T. Stocker, N. J. Shah, Rapid fat suppression for three-dimensional echo planar imaging with minimized specific absorption rate. *Magn Res Med* **76**, 1517-1523 (2016).
11. R. Sladky *et al.*, High-resolution functional MRI of the human amygdala at 7 T. *Eur J Radiol* **82**, 728-733 (2013).
12. G. H. Glover, T. Q. Li, D. Ress, Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magn Res Med* **44**, 162-167 (2000).
13. C. Chang, J. P. Cunningham, G. H. Glover, Influence of heart rate on the BOLD signal: the cardiac response function. *Neuroimage* **44**, 857-869 (2009).

14. D. G. McLaren, M. L. Ries, G. Xu, S. C. Johnson, A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *Neuroimage* **61**, 1277-1286 (2012).

15. F. Faul, E. Erdfelder, A. G. Lang, A. Buchner, G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* **39**, 175-191 (2007).

16. M. P. Paulus, J. S. Feinstein, G. Castillo, A. N. Simmons, M. B. Stein, Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. *Arch Gen Psychiatry* **62**, 282-288 (2005).

17. S. M. Kagerbauer *et al.*, Plasma oxytocin and vasopressin do not predict neuropeptide concentrations in human cerebrospinal fluid. *J Neuroendocrinol* **25**, 668-673 (2013).

18. A. M. Perkins *et al.*, Effects of Lorazepam and citalopram on human defensive reactions: ethopharmacological differentiation of fear and anxiety. *J Neurosci* **29**, 12617-12624 (2009).

19. A. M. Perkins *et al.*, A dose of ruthlessness: interpersonal moral judgment is hardened by the anti-anxiety drug lorazepam. *J Exp Psychol Genl* **142**, 612-620 (2013).

20. S. J. Graham *et al.*, Effects of lorazepam on fear-potentiated startle responses in man. *J Psychopharmacol* **19**, 249-258 (2005).

21. A. K. Kreuder *et al*., Oxytocin enhances the pain-relieving effects of social support in romantic couples. *Hum Brain Mapp* **40**, 242-251 (2019).

22. A. Maier *et al.*, Oxytocin reduces a chemosensory-induced stress bias in social perception. *Neuropsychopharmacology* **44,** 281-288 (2018).

23. M. Eckstein *et al.*, Oxytocin facilitates the sensation of social stress. *Hum Brain Mapp* **35**, 4741-4750 (2014).

24. S. Delli Pizzi *et al.*, Functional and neurochemical interactions within the amygdala-medial prefrontal cortex circuit and their relevance to emotional processing. *Brain Struct Funct* **222**, 1267-1279 (2017).

25. I. Akirav, M. Maroun, The role of the medial prefrontal cortex-amygdala circuit in stress effects on the extinction of fear. *Neural Plast* **2007**, 30873 (2007).

24. A. F. Hayes, *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach.* (The Guilford Press, New York, NY, 2013), vol. 51, pp. 335-337.