

Oxytocin facilitates protective responses to aversive social stimuli in males

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The neuropeptide oxytocin (OXT) can enhance the impact of positive social cues but may reduce that of negative ones by inhibiting amygdala activation, although it is unclear whether the latter causes blunted emotional and mnemonic responses. In two independent double-blind placebo-controlled experiments, each involving over 70 healthy male subjects, we investigated whether OXT affects modulation of startle reactivity by aversive social stimuli as well as subsequent memory for them. Intranasal OXT potentiated acoustic startle responses to negative stimuli, without affecting behavioral valence or arousal judgments, and biased subsequent memory toward negative rather than neutral items. A functional MRI analysis of this mnemonic effect revealed that, whereas OXT inhibited amygdala responses to negative stimuli, it facilitated left insula responses for subsequently remembered items and increased functional coupling between the left amygdala, left anterior insula, and left inferior frontal gyrus. Our results therefore show that OXT can potentiate the protective and mnemonic impact of aversive social information despite reducing amygdala activity, and suggest that the insula may play a role in emotional modulation of memory.

emotion | functional imaging | psychophysiology | cognition

Current concepts of the neuromodulatory role of the peptide hormone oxytocin (OXT) in human cognition and behavior emphasize its prosocial effects. Ample evidence for this view comes from a plethora of behavioral experiments in healthy subjects (1), which have demonstrated beneficial effects of a single intranasal dose (24–48 IU) of OXT across a wide range of cognitive tasks, probing, for example, interpersonal trust and cooperation (2, 3; see also ref. 4), generosity (5), social recognition (6–8) and related memory (9–11), social reinforcement learning and emotional empathy (12), and social judgments (13–15).

This prosocial perspective on OXT is challenged, however, by evidence that OXT also enhances envy and schadenfreude (gloating) (16), ethno-centrism (including prejudice, xenophobia, and racial bias) (4), and outgroup derogation (17). Moreover, OXT hinders trust and cooperation when social information about interaction partners is lacking (18). Furthermore, OXT appears to negatively bias recollections of maternal care and closeness and to diminish trust and cooperation in insecurely or anxiously attached individuals (19, 20).

In an attempt to reconcile this controversial evidence, it has been proposed that the social effects of OXT could be mediated by reduced anxiety or by an increased perceptual salience of social cues (21). The anxiolytic action of OXT has been confirmed by showing reduced amygdala responses to aversive social stimuli in healthy people (22–25; but see also refs. 26 and 27), and subjects with social phobia (28). It is compatible with decreased endocrine and subjective responses to social stress (29), as well as reduced negative cognitive self-appraisal in individuals scoring high in trait-anxiety (30). In contrast, the social salience hypothesis has gained substantial support from studies demonstrating increased eye contact (31) and improved mind-reading from facial expressions (32) as a result of OXT treatment. Whether these mechanisms

quintessentially yield positive or negative social outcomes may vary depending on contextual or person-specific characteristics (21). An alternative view holds that emotional valence may be the key in guiding the social effects of OXT, with it facilitating social approach to positive cues and inhibiting social withdrawal from negative ones (33).

Against this empirical background we performed two experiments, using paradigms in the social-protective domain, to disentangle the valence-specific effects of OXT and to determine if anxiolytic, salience, or approach-enhancing mechanisms are most influential. Specifically, Exp. 1 examined the emotional modulation of the acoustic startle reflex (ASR) and we predicted that anxiolytic effects should lead to overall diminished ASR magnitudes and less pronounced potentiation of the ASR in the context of negative stimuli. On the other hand, the social-salience hypothesis would be compatible with facilitated emotional modulation both with negative and positive stimuli, whereas the social-approach/withdrawal hypothesis would predict differential modulation, with startle responses being reduced to negative (withdrawal) and increased to positive (approach) stimuli. Exp. 2 addressed the question of how OXT shapes the neural correlates of emotion perception and subsequent memory, thus enabling us to characterize the neuromodulatory influence of OXT on information of both immediate and future relevance. Decreased amygdala responses to negative stimuli and reduced memory for them should be a consequence of anxiolytic effects, whereas an increased salience of such stimuli could improve subsequent memory performance. On the other hand, if OXT enhances social approach behavior then one might predict either no effect—because negative stimuli would not normally promote approach behavior—or possibly make them less memorable because of weakening of the normal withdrawal response.

Results

Sample Characteristics. From 80 subjects enrolled in Exp. 1, 11 subjects [OXT, $n = 5$; PLC (placebo: sodium chloride solution), $n = 6$] were excluded from further analysis because of technical failures during data acquisition ($n = 4$), mood alterations ($n = 1$), or lack of distinct startle responses ($n = 6$). Consequently, subsequent analyses included data from 69 subjects (OXT, $n = 36$; PLC, $n = 33$). From the 73 subjects enrolled in Exp. 2, three were excluded from further analysis because of technical failures during data acquisition. Consequently, subsequent analyses were performed on the

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data obtained from 70 subjects (OXT, $n = 35$; PLC, $n = 35$). In both experiments, treatment groups showed no differences regarding demographics, pretreatment neuropsychological performance, attention, or anxiety (Tables S1 and S2).

Experiment 1. Emotion-modulated startle. A repeated-measures ANOVA with “group” (PLC, OXT) as between-subjects factor, “valence” (negative, neutral, or positive) as within-subjects factor, and “ASR magnitude” as dependent variable revealed a main effect of valence [$F_{(2, 134)} = 34.49$, $P < 0.01$, $\eta^2 = 0.34$] and an interaction effect of valence and group [$F_{(2, 134)} = 4.09$, $P = 0.02$, $\eta^2 = 0.06$]. Both groups showed a significant linear trend for valence (i.e., negative > neutral > positive), but a comparison of the effect sizes indicated that the emotional modulation in the OXT group [$F_{(1, 35)} = 84.10$, $P < 0.01$, $\eta^2 = 0.71$] was more than twice as large as in the PLC group [$F_{(1, 32)} = 13.78$, $P < 0.01$, $\eta^2 = 0.30$] (Fig. 1A). Post hoc Bonferroni-corrected two-sample t tests showed that the ASR magnitude in the OXT group was significantly larger than in the PLC group during the viewing of negative [$t_{(67)} = 2.92$, $P = 0.01$, $\eta^2 = 0.11$], but not neutral [$t_{(54,94)} = -1.54$, $P = 0.37$, $\eta^2 = 0.04$] or positive [$t_{(53,91)} = -1.04$, $P = 0.91$, $\eta^2 = 0.02$] pictures. The contrasts “negative minus neutral” [$t_{(57,77)} = 2.56$, $P = 0.01$, $\eta^2 = 0.09$] and “negative minus positive” [$t_{(59,97)} = 2.33$, $P = 0.02$, $\eta^2 = 0.08$] yielded significantly larger difference scores in the OXT group, but there was no OXT effect for the contrast “positive minus neutral” [$t_{(67)} = 0.31$, $P = 0.76$, $\eta^2 < 0.01$] (Fig. 1B). In summary, administration of OXT profoundly potentiated the emotional modulation of the ASR specifically for negative stimuli.

Emotion ratings. A repeated-measures ANOVA with “group” (PLC, OXT) as between-subjects factor, “valence” (negative, neutral, positive) as within-subjects factor, and “valence ratings” as dependent variable yielded a main effect of valence [$F_{(1,38, 92,46)} = 270.68$, $P < 0.01$, $\eta^2 = 0.80$], but no interaction effect [$F_{(1,38, 92,46)} = 0.22$, $P = 0.72$, $\eta^2 < 0.01$]. As expected, negative pictures were rated as more aversive than neutral ones and positive pictures as more pleasant than neutral ones (Table S3). For the arousal ratings, there was a main effect of valence [$F_{(2, 134)} = 302.18$, $P < 0.01$, $\eta^2 = 0.82$] but no interaction effect [$F_{(2, 134)} = 0.16$, $P = 0.85$, $\eta^2 < 0.01$]. Negative and positive pictures were therefore rated as equally more arousing than neutral ones in both groups (Table S3).

Baseline startle response. Raw startle response magnitudes from the interstimulus intervals were individually examined. At visual inspection, the overall startle magnitude seemed to be smaller in the OXT group (mean \pm SD, 31.0 ± 46.2 μ V) than in the PLC group (47.1 ± 40.4 μ V); however, an independent-samples t test revealed

no significant difference [$t_{(67)} = -1.54$, $P = 0.13$, $\eta^2 = 0.03$]. Similarly, the raw startle response magnitude in the neutral condition for the OXT group (25.9 ± 42.7 μ V) was not significantly different from that of the PLC group (40.8 ± 34.6 μ V) [$t_{(67)} = -1.6$, $P = 0.12$, $\eta^2 = 0.04$].

Experiment 2. Behavioral data. Two-sample t tests revealed no between-group differences in the overall number of subsequently remembered items nor in the numbers of subsequently remembered negative or neutral items (all P values > 0.20). Thus, OXT had no influence on memory capacity in general nor on a valence-specific effect. However, we observed a shift in the proportion of subsequently remembered negative to neutral items. Specifically, the OXT group showed a subsequent memory bias toward negative information at the cost of neutral information [remembered negative items minus remembered neutral items: OXT, 4.9 ± 2.8 ; PLC, -2.8 ± 3.0 ; $t_{(68)} = -2.98$, $P < 0.01$, $\eta^2 = 0.12$] (Fig. 2A and Table S4).

Whole-brain analysis of functional MRI data. The pooled sample showed greater activity in response to negative stimuli in left inferior occipital gyrus [$t_{(34)} = 8.87$, $P_{FWE} < 0.05$, Montreal Neurological Institute (MNI): $x = -44$, $y = -70$, $z = -6$] and right middle occipital gyrus [$t_{(34)} = 8.58$, $P_{FWE} < 0.05$, MNI: $x = 48$, $y = -80$, $z = 4$] (main effect of “valence”). In general, successful encoding was associated with greater responses in left fusiform gyrus [$t_{(34)} = 6.08$, $P_{FWE} < 0.05$, MNI: $x = -30$, $y = -48$, $z = -14$] (main effect of “subsequent memory”). Separate analyses for the PLC and OXT groups yielded no significant clusters of activation for these contrasts. Although there was no main effect of OXT treatment, we found a group \times subsequent memory interaction effect in the left anterior insula for negative but not for neutral stimuli [$t_{(68)} = 6.08$, $P_{FWE} < 0.05$, MNI: $x = -38$, $y = 22$, $z = 4$] (Fig. 2B and Table S5). Extraction of individual percent signal changes revealed that successful encoding of negative stimuli was associated with greater left anterior insula responses in the OXT group, an effect that was reversed in the PLC group (Fig. 2B). Combined masking confirmed that this interaction effect was independent of simple main effects.

Regions of interest analysis of functional MRI data. In line with previous findings (22–25; but see also refs. 26 and 27), amygdala activity was globally reduced as a result of OXT treatment (Table S5). This reduction was histoprobabilistically mapped to the superficial amygdala, reflecting the demonstrated importance of this amygdala subregion in social stimulus processing (34, 35).

Functional connectivity analysis of functional MRI data. Given that the amygdala has been identified as a key target of OXT effects in the

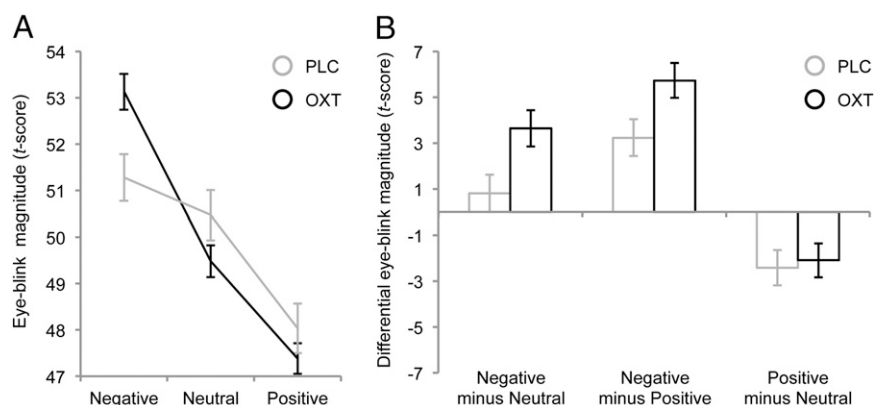


Fig. 1. Exp. 1 examined the effects of OXT relative to PLC on emotion-modulated startle reactivity. (A) Both groups showed a significant linear trend for valence (i.e., negative > neutral > positive), but the emotional modulation of eye-blink magnitudes in the OXT group was more than twice as large as in the PLC group. (B) The difference in eye-blink magnitude between negative and neutral as well as negative and positive conditions (but not between positive and neutral) was significantly larger in the OXT group than in the PLC group. Taken together, these results show that OXT profoundly potentiated the emotional modulation of the startle response specifically for negative stimuli. Error bars indicate the SEM.

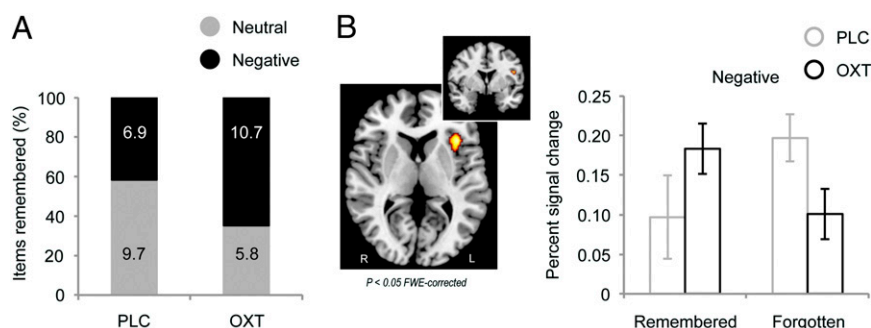


Fig. 2. Exp. 2 examined the effects of OXT relative to PLC on subsequent memory for emotional stimuli. (A) Both groups did not differ in their total amount of later remembered items (absolute numbers are given in the bars) in the surprise free-recall test 24 h postscan. However, OXT induced a shift in the relative proportion of later remembered items, evident in a recall bias toward aversive social information. (B) Successful encoding of negative stimuli was associated with larger left anterior insula responses (MNI: $x = -38, y = 22, z = 4$) in the OXT group, an effect that was reversed in the PLC group. Extraction of individual percent signal changes confirmed this pattern. For illustration purposes, results are displayed at uncorrected significance ($P < 0.001$) thresholds. Error bars indicate the SEM.

brain (22–27), we focused, in a first analysis, on potential effects of OXT treatment on functional connectivity of the amygdala using a generalized form of context-dependent psychophysiological interactions (gPPIs) analysis (36). Our results showed that OXT reduced functional coupling between the left amygdala and left anterior cingulate cortex (ACC) [$t_{(68)} = 4.35, P_{FWE} < 0.05$, MNI: $x = -4, y = 26, z = 14$] for all stimuli regardless of valence. For negative stimuli OXT decreased, whereas for neutral stimuli it increased functional coupling between the right amygdala and left insula [$t_{(68)} = 4.23, P_{FWE} < 0.05$, MNI: $x = -42, y = -2, z = 16$]. These profiles were confirmed by extraction of individual parameter estimates (Fig. 3A). In a second analysis, we addressed the question of whether the observed OXT effects in the left anterior insula also influenced functional coupling with interconnected brain regions. Our analysis showed that OXT increased functional coupling between left anterior insula and both left inferior frontal gyrus (IFG) [$t_{(68)} = 4.53, P_{FWE} < 0.05$, MNI: $x = -46, y = 0, z = 24$] and left basolateral amygdala (BLA) [$t_{(68)} = 3.46, P_{FWE} < 0.05$, MNI: $x = -30, y = -14, z = -11$] during successful encoding of negative stimuli. Extraction of individual parameter estimates confirmed these profiles in the OXT group, whereas the PLC group exhibited the reverse pattern (Fig. 3B). Given a signal distribution of 25% in the hippocampus and 75% in the BLA, histoprobabilistic mapping identified the BLA as the major projection area of OXT-related enhanced cross-talk between the left anterior insula and left amygdala during successful encoding of negative stimuli.

Discussion

Despite the reported anxiolytic effects of OXT, and extensive evidence from our study and others for its suppression of amygdala reactivity to fear signals (22–25; but see also refs. 26 and 27), our results show that the peptide enhances the impact of aversive social information. Specifically, OXT facilitated startle responses to negative stimuli and increased the number of subsequently remembered negative relative to neutral items. Furthermore, our findings suggest that OXT may be acting to promote this potentiated impact of aversive social stimuli by facilitating anterior insula responses to them and by modifying its functional connectivity with the IFG and amygdala. Importantly, despite OXT reducing superficial amygdala responses to negative stimuli, the latter still produced startle and subsequent memory-modulating effects. Histoprobabilistic mapping indeed identified the BLA as the major projection area of OXT-related enhanced cross-talk between the left anterior insula and left amygdala during successful encoding of negative stimuli, suggesting that OXT puts the BLA under neural control of the insula. By hijacking the modulatory functions of the BLA, the insula may become more influential in biasing emotional

and cognitive processing toward information gaining crucial behavioral relevance under conditions of enhanced OXT signaling.

Our original aim was to distinguish between three current hypotheses concerning the role of OXT in the human brain, namely as a facilitator of (i) prosocial behavior, (ii) social salience, and (iii) social approach/withdrawal. Our results show that OXT does not simply facilitate responses to positive social cues and reduce them to negative ones, because in both experiments we found evidence for enhanced emotional modulation by, and subsequent memory for, aversive social information. Instead, our data seem to support specific aspects of the social salience and social-approach/withdrawal hypotheses, although before considering which is most relevant, we need to first discuss the implications of our findings in greater detail.

Our result of an enhanced ASR modulation by aversive information following OXT treatment shows that the peptide is not producing an overall anxiolytic effect. Although we found a trend to significant decrease in ASR baseline after OXT application, which is in line with previous findings (22, 37), these anxiolytic actions are clearly not the most influential effects of OXT in our study. Indeed, we found no evidence that OXT affected either arousal or valence ratings for any of the stimuli used. OXT also had no effect on skin conductance (38) or facial electromyographic (EMG) responses during the actual presentation of emotional stimuli (see *SI Text*). Thus, OXT facilitation of ASR modulation by aversive pictures appeared to be independent of any physiological arousal or conscious arousal/valence ratings (39, 40). Although we cannot completely rule out a contribution of physiological arousal changes to the observed facilitating effects of OXT, it seems unlikely that altered conscious feelings of arousal were playing a substantial role.

In view of our findings from Exp. 1, those in Exp. 2 showing an OXT-induced bias toward remembering aversive rather than neutral social information are also unlikely to be a result of altered arousal or valence ratings. Although a number of studies demonstrating anxiolytic effects of OXT (29, 41) and suppression of amygdala reactivity to fear signals (22–25; but see also refs. 26 and 27) have suggested a potential amnesic effect for aversive stimuli, direct evidence for this has been limited. In humans, OXT reduced emotional ratings to aversively conditioned (25) and angry faces (14). Although it has been hypothesized that OXT promotes amnesia for pain, there is in fact no direct evidence for this (1). Thus, despite assumptions that OXT release might aid forgetting of negative emotional experiences, actual evidence in humans is lacking. Indeed, results from our study suggest rather that OXT can bias learning in favor of aversive compared with neutral social information in at least some contexts.

heightened caution.” The empathogenic actions of OXT would clearly facilitate approach behavior but the peptide may also increase preparedness for defense as opposed to flight. The attenuated responsivity of the superficial amygdala to aversive social stimuli may act to reduce the likelihood of flight behavior, whereas the increased insula response may reflect both increased empathy and approach behavior toward threatened and suffering individuals together with a heightened visceral reaction and increased feeling of uncertainty and risk.

Methods

A detailed synopsis of all experimental procedures is provided in the [SI Text](#).

Subjects. Detailed information on study participants is provided in the [SI Text](#). The present study was approved by the institutional review board of the Medical Faculty of the University of Bonn, registered as a controlled clinical trial ([ClinicalTrials.gov](#) Identifiers: NCT01606462 and NCT01607970), and carried out in compliance with the latest revision of the Declaration of Helsinki.

Drug Application. The two experiments underlying the present study followed a randomized, placebo-controlled, double-blind, between-group design; that is, subjects were randomly assigned to either intranasal administration of OXT (24 IU; Syntocinon-Spray, Novartis; three puffs per nostril, each with 4 IU OXT) or PLC (sodium chloride solution), 45 min after which the experimental tasks were carried out.

Exp. 1. Participants were exposed to acoustic startle probes presented either alone or paired with a color picture. The paradigm featured 20 negative, 20 neutral, and 20 positive pictures, presented for 5 s each, which were mostly selected from the International Affective Picture System (57). Similar to the procedure reported by Becker et al. (58), the startle stimulus consisted of a single 50-ms burst of white noise (100 dB) with nearly instantaneous rise and was delivered binaurally via headphones during 60% of the pictures (i.e., 12 from each category) at 2–4 s after picture onset. Facial EMG activity was recorded from two Ag/AgCl electrodes placed over the orbicularis oculi muscle below the left eye (59). Furthermore, electrodermal activity was measured, and facial EMG activity was also analyzed in trials without startle probe. After task completion, participants were administered the self-assessment manikin (57) to obtain behavioral pleasantness (valence) and arousal ratings for each picture on a scale ranging from 1 (minimum) to 9 (maximum).

Exp. 2. This experiment consisted of two phases, a functional MRI (fMRI)-scanned encoding phase under drug challenge conditions and a surprise free-recall test 24 h postscan. Critically, for analyzing the subsequent memory (difference due to memory) effect, behavioral responses during free-recall were

used to backsort encoding trials as either successful (i.e., subsequently remembered) or not. The fMRI paradigm incorporated 24 aversive and 24 neutral picture stimuli selected from the International Affective Picture System (57) and a verbal description (a noun semantically identical to the picture) (60). Each stimulus was presented four times. Stimuli were shown in a random order for 5 s each, followed by a fixation cross that was presented for 2.5–4.5 s and served as a low-level baseline. MRI data were acquired on a 1.5 Tesla MRI scanner and preprocessed using standard procedures. MRI data were analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom). In the first-level analysis the following conditions were modeled: “neutral: later remembered,” “neutral: later forgotten,” “aversive: later remembered,” and “aversive: later forgotten,” using a stick function convolved with a hemodynamic response function (61). To examine if OXT affected the differential neural responses for later-remembered versus forgotten items separately for the aversive and neutral condition, we contrasted the OXT group with the PLC group ($\text{OXT}^{\text{aversive: later remembered}} > \text{aversive: later forgotten} > \text{PLC}^{\text{aversive: later remembered}} > \text{aversive: later forgotten}$ and $\text{OXT}^{\text{neutral: later remembered}} > \text{neutral: later forgotten} > \text{PLC}^{\text{neutral: later remembered}} > \text{neutral: later forgotten}$). Furthermore, groups were compared using the contrasts “aversive items > neutral items” (main effect of “valence”); “all subsequently remembered items > all forgotten items” (main effect of “subsequent memory”); and “all items > low-level baseline” (main effect of “group”). Emotion-specific effects of OXT treatment were examined using the contrasts “negative items > low-level baseline” and “neutral items > low-level baseline.” To address OXT’s effects on functional connectivity a PPI analysis was carried out using a gPPI (36). Compared with the standard PPI implementation in SPM, gPPI analysis allows to model more than two task conditions in the same model by spanning the entire experimental space to improve model fit, specificity to true negative findings, and sensitivity to true positive findings (36). First, we examined potential modulatory effects of OXT on functional connectivity of the amygdala. For this aim, we extracted the mean time series for each subject from the left and right amygdala that were defined by using the Wake Forest University Pickatlas (61–63). Second, we examined whether the OXT effect on functional activation in the left anterior insula affected functional coupling of this region with interconnected areas. For this aim, mean time series were extracted from a 6-mm sphere centered at the maximum interaction effect found in the functional activation analysis (MNI: $x = -38$, $y = 22$, $z = 4$). In all analyses, groups were compared using two-sample t tests, and group means were tested using one sample t tests with thresholds of $P < 0.05$ family-wise error-corrected for multiple comparisons. Details on image acquisition, preprocessing and statistical analysis are reported in the [SI Text](#).

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