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# Intranasal Oxytocin Administration Dampens Amygdala Reactivity towards Emotional Faces in Male and Female PTSD Patients

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## Abstract

Post-traumatic stress disorder (PTSD) is a disabling psychiatric disorder. As a substantial part of PTSD patients responds poorly to currently available psychotherapies, pharmacological interventions boosting treatment response are needed. Because of its anxiolytic and pro-social properties, the neuropeptide oxytocin (OT) has been proposed as promising strategy for treatment augmentation in PTSD. As a first step to investigate the therapeutic potential of OT in PTSD, we conducted a double-blind, placebo-controlled, cross-over functional MRI study examining OT administration effects (40 IU) on amygdala reactivity toward emotional faces in unmedicated male and female police officers with (*n*=37, 21 males) and without (*n*=40, 20 males) PTSD. Trauma-exposed controls were matched to PTSD patients based on age, sex, years of service and educational level. Under placebo, the expected valence-dependent amygdala reactivity (ie, greater activity toward fearful-angry faces compared with happy-neutral faces) was absent in PTSD patients. OT administration dampened amygdala reactivity toward all emotional faces in male and female PTSD patients, but enhanced amygdala reactivity in healthy male and female trauma-

exposed controls, independent of sex and stimulus valence. In PTSD patients, greater anxiety prior to scanning and amygdala reactivity during the placebo session were associated with greater reduction of amygdala reactivity after OT administration. Taken together, our results indicate presumably beneficial neurobiological effects of OT administration in male and female PTSD patients. Future studies should investigate OT administration in clinical settings to fully appreciate its therapeutic potential.

## INTRODUCTION

Post-traumatic stress disorder (PTSD) is a highly disabling psychiatric disorder, which develops in ~10% of trauma-exposed individuals (de Vries and Olff, 2009). PTSD has an estimated lifetime prevalence of ~8% in the general population (de Vries and Olff, 2009) and is characterized by symptoms of intrusions and avoidance, negative alterations in cognition and mood (eg, diminished interest in significant activities), and hyperarousal (American Psychiatric Association, 2013). Exposure-based therapy, aimed at reducing excessive fear by repeatedly exposing the patient to (*in vivo*) trauma reminders (Foa *et al*, 2009), is the treatment of choice for PTSD. Unfortunately, a third of patients responds poorly to currently available psychotherapies (Bradley *et al*, 2005), stressing the need for novel pharmacological interventions to enhance treatment response (ie, medication-enhanced psychotherapy (Dunlop *et al*, 2012)). One promising strategy to improve treatment efficacy in anxiety-related disorders is to target neurobiological correlates of fear and fear extinction (de Kleine *et al*, 2013), the underlying mechanism of exposure-based therapies (Rothbaum and Davis, 2003).

In PTSD, pharmacological agents aimed at dampening (excessive) fear responses and facilitating the therapeutic alliance seem especially appropriate. The prevailing neurocircuitry model of PTSD postulates amygdala hyperactivity and ventromedial prefrontal cortex (vmPFC) hypoactivity toward both trauma-related and non-trauma-related stimuli (Pitman *et al*, 2012). According to a meta-analysis of functional connectivity studies in PTSD, amygdala hyperactivity in PTSD patients was predominantly observed in response to negative, non-trauma-related stimuli (Hayes *et al*, 2012; Sripada *et al*, 2012). This may result in decreased prefrontal control over the fear response and hence excessive fear in PTSD patients (Rauch *et al*, 2006). Notably, greater amygdala reactivity during extinction learning in PTSD patients has been associated with impaired extinction recall the next day (Milad *et al*, 2009). In PTSD, greater amygdala reactivity to fearful faces (Bryant *et al*, 2008) and negative pictures (van Rooij *et al*, 2015) before treatment predicted worse treatment outcome. In addition, effective exposure therapy was associated with decreased amygdala and enhanced vmPFC activity toward emotional faces over the course of treatment (Felmingham *et al*, 2010).

As the neuropeptide oxytocin (OT) has both anxiolytic (Heinrichs *et al*, 2003) and pro-social (Olff, 2012) properties, OT has been suggested as a promising pharmacological agent to enhance treatment response in PTSD (Koch *et al*, 2014; Olff *et al*, 2010). OT has anxiolytic properties both at the neurobiological and behavioral level. Behaviorally, OT administration resulted in decreased subjective anxiety during a public speaking stressor in healthy individuals (de Oliveira *et al*, 2012) and increased (recall of) extinction learning in both rodents (Zoicas *et al*, 2014) and healthy males (Acheson *et al*, 2013). In addition, functional MRI (fMRI) studies have shown that OT administration dampened amygdala reactivity toward emotional stimuli in healthy males (Kirsch *et al*, 2005), males with generalized social anxiety disorder (GSAD; Labuschagne *et al*, 2010) and females with borderline personality disorder (BPD; Bertsch *et al*, 2013), although findings for females have been mixed (Domes *et al*, 2010). Furthermore, OT administration resulted in increased resting-state functional connectivity between the amygdala and vmPFC in healthy males (Sripada *et al*, 2013) and in patients with GSAD (Dodhia *et al*, 2014), possibly enhancing top–down control over the fear response.

As a first step to examine the therapeutic potential of OT in PTSD patients, we conducted an fMRI study investigating intranasal OT administration effects on amygdala reactivity towards emotional faces in trauma-exposed police officers with and without PTSD. We included a highly trauma-exposed control group to account for potential confounding effects of trauma exposure on neurobiology. Both male and female participants were included to investigate possible sex-differential effects of OT administration. For both PTSD patients and trauma-exposed controls, we hypothesized that OT would dampen amygdala reactivity. We expected that OT administration would have greater effects in PTSD patients than in trauma-exposed controls, as OT administration effects may be more beneficial in those who have something to gain regarding fear regulation (Labuschagne *et al*, 2010) or social functioning (Olff *et al*, 2013).

## MATERIALS AND METHODS

### Participants

Male ($n$=21) and female PTSD patients ($n$=16) were recruited via a psychotrauma diagnostic outpatient clinic for police personnel (Diemen, the Netherlands) and via advertisements on websites and in journals of the Dutch police. PTSD patients had to fulfill the DSM-IV diagnostic criteria for PTSD, with a score of $\geqslant$45 on the clinician-administered PTSD scale (CAPS) (Blake *et al*, 1995). PTSD patients were excluded if they met DSM-IV criteria for current psychotic disorder, substance-related disorder, severe personality disorder, severe major depressive disorder (MDD) (ie, involving high suicidal risk and/or psychotic symptoms) or current suicidal risk, according to

the Dutch version of the Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al*, 1998; van Vliet *et al*, 2000) or the Structured Clinical Interview for DSM-IV (First *et al*, 2012; van Groenestijn *et al*, 1999) (for patients recruited via the police outpatient clinic).

Trauma-exposed male ($n$=20) and female ($n$=20) police officers were recruited via advertisements on websites and in journals of the Dutch police force and were matched to PTSD patients based on age, sex, number of years of service, and educational level. Trauma-exposed controls had to be exposed to at least one potentially traumatic event according to the DSM-IV PTSD A1 criterion, with a CAPS score of <15 and no lifetime history of PTSD or MDD, or any current DSM-IV axis 1 disorder, according to the MINI.

All participants had to be between 18 and 65 years of age and eligible for MRI (ie, no metals, pacemakers or claustrophobia). Participants had no history of neurological disorders (ie, seizure history) or any severe or chronic systemic disease or unstable medical condition, including endocrinological disorders. In addition, participants did not use psychotropic medications and female participants could not be pregnant or breastfeeding. The study was conducted in accordance with the declaration of Helsinki and was approved by the Institutional Review Board of the Academic Medical Center in Amsterdam, the Netherlands. All participants received oral and written study information and provided written informed consent before participation. See the supplemental CONSORT flow diagram and checklist for details regarding recruitment and randomization.

## Experimental Procedure

This randomized, double-blind, placebo-controlled, cross-over study consisted of three appointments: one intake session (T0) and two fMRI sessions (T1 and T2). During the intake session, in-and exclusion criteria were checked with the MINI and CAPS diagnostic interviews. Between the intake sessions and first fMRI session (which were on average 21.25 (±17.96) days apart), participants filled out a questionnaire about demographical characteristics and trauma history. The number of different types of police-related traumatic events was assessed with the police life events checklist (Carlier and Gersons, 1992) and the number of different types of childhood traumatic events was assessed with the self-report version of the Early Trauma Inventory short form (Bremner *et al*, 2007). The two fMRI sessions were scheduled on average 11.5 (±9.90) days apart. Participants were asked to abstain from alcohol and drugs the day before scanning and from food, beverages, nicotine and exercise 2.5 h prior to scanning. At the beginning of each scanning session, state anxiety was measured with the State-Trait Anxiety Inventory (Spielberger, 1983). Hereafter, the participants self-administered intranasal placebo (saline, NaCl

0.9%, five puffs per nostril) or OT (40 IU Syntocinon, produced by Delpharm Huningue France, five puffs of 4 IU per nostril), under experimenter supervision. Medication order was counterbalanced between sessions. An anatomical scan was first acquired, followed by an emotional face-matching task, which began on average 44.68 (±3.74) minutes after intranasal spray application. This is in line with previous intranasal fMRI studies (Kirsch *et al*, 2005; Labuschagne *et al*, 2010), and coincides with the pharmacodynamic peak response of intranasal OT in healthy individuals (Paloyelis *et al*, 2014).

The emotional face-matching task (Hariri *et al*, 2002) consisted of three conditions: one visuomotor control condition (elliptical scrambled faces) and two emotional faces conditions. The first emotion condition consisted of fearful and angry faces and the second emotion condition consisted of happy and neutral faces. Four blocks of each emotion condition were presented, two with fearful-angry faces and two with happy-neutral faces. The duration of each emotion block was 30 s, consisting of six trials of 5 s. The emotion blocks were interleaved with visuomotor control blocks. In total, four visuomotor control blocks were presented, each with a duration of 25 s, consisting of five trials of 5 s. No inter-stimulus or inter-block interval was used, resulting in a total task duration of 220 s. Two versions of the task were counterbalanced between the fMRI sessions, one version starting with a fearful-angry emotion block and the other version starting with a happy-neutral emotion block. Each trial consisted of three stimuli, with a cue stimulus presented on top and two target stimuli presented below. Participants were instructed to match the orientation (control blocks) or the emotional expression (emotion blocks) of the cue stimulus with one of the target stimuli. We used face stimuli from the NimStim face stimuli set ( https://www.macbrain.org ), presented with Presentation software version 16.0 ( www.neurobs.com ). See Supplementary Figure S1 for sample stimuli and the task design.

## fMRI Acquisition

Images were acquired on a 3T Philips Achieva MR system (Philips Medical Systems, Best, the Netherlands) with a 32-channel head coil. A high-resolution anatomical scan was obtained with a FAST MPRage sequence (220 slices; voxel size=1 $mm^3$; repetition time=8.2 s; echo time=3.8 s; flip angle=8°). The functional scans were obtained using an echo planar sequence sensitive to the blood-oxygen-level-dependent contrast (110 volumes; voxel size=3 $mm^3$; TR=2 s, echo time=28 ms; flip angle=76°).

## Data Analysis

## Demographics

Differences between PTSD patients and trauma-exposed controls on demographical, clinical and trauma-related characteristics were tested with SPSS version 20.0 (IBM statistics, Armonk, NY, USA). Variables were first checked for outliers and normality, and log-transformed when necessary. Independent sample *t*-tests or repeated measures ANOVA's were used for continuous variables and $\chi^2$-tests for categorical variables. A *p*-value of<0.05 (two-tailed) was considered significant.

## fMRI Data-Analysis

fMRI images were analyzed using SPM8 (http://fil.ion.ucl.ac.uk/spm/software/spm8 ). Preprocessing included realignment, slice-time correction, co-registration to the anatomical scan, spatial normalization to the Montreal Neurological Institute (MNI) template, resampling to 2 $mm^3$ voxels and spatial smoothing with a 5 mm full-width half maximum Gaussian kernel to optimize amygdala spatial resolution. For each participant, the two emotional conditions were modeled as box-car regressors, convolved with a canonical hemodynamic response function. The six realignment parameters were included in the model to control for movement artifacts. To remove slow drifts of the signal, a high-pass filter (cutoff 1/200 Hz) was used and we removed temporal autocorrelation using the AR(1) process. Contrast images were obtained for the fearful-angry condition and the happy-neutral condition *versus* the visuomotor control condition. These images were subsequently entered into a second-level ANOVA with task condition (fearful-angry—happy-neutral) and medication (placebo—OT) as within-subjects factors and group (PTSD—controls) and sex (male—female) as between-subject factors. We included medication order as covariate in the model, controlling for possible confounding effects of administration order. To assess baseline differences between PTSD patients and trauma-exposed controls, a second model was estimated using only contrast images acquired after placebo application. Regions of interest (ROIs) of the left and right amygdala were anatomically defined using the Harvard–Oxford probabilistic atlas ( http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases , 50% probability. *p*-values were family-wise error corrected for multiple comparisons in the predefined amygdala ROIs using small volume correction. In the placebo model, all main effects and interaction effects were tested for each amygdala ROI. In the OT model, the main effect of medication and interaction effects with medication were addition tested for each amygdala ROI. $P_{FWE}$-values <0.05 for the omnibus *F*-tests were considered significant and are reported in MNI stereotactic coordinates. In case of significant interaction effects, *post hoc t*-tests were performed within the second-level models to test the direction of observed interaction effects. Four participants had to be excluded from the analyses, because of scanner artifacts (*n*=2) and significant signal dropout in the temporal cortex (*n*=2), leaving 37 trauma-exposed controls (18 males) and 36 PTSD patients (21 males) for analysis.

### Correlation Analysis

To investigate associations between (OT administration effects on) amygdala reactivity and clinical characteristics (ie, PTSD symptom severity and anxiety before scanning) in PTSD patients, we extracted contrast estimates from the peak coordinate of the OT administration effect in PTSD patients (peak voxel *xyz*=−30 −4 −24, 5 mm sphere). Partial correlation analyses between extracted contrast estimates and clinical characteristics in PTSD patients, controlling for medication order, were conducted in SPSS. In addition, a mediation analysis was conducted in Process (Hayes, 2013), an add-on in SPSS. One female PTSD patient was a significant outlier on left amygdala reactivity towards fearful-angry faces (Z>3.29) and had to be excluded, leaving 35 PTSD patients (21 males) for this analysis.

## RESULTS

### Demographics and Questionnaires

See Table 1 for participant characteristics. PTSD patients and trauma-exposed controls did not differ significantly in age, years of service, educational level and time between OT administration and task performance (Table 1; all $p>0.05$). In addition, female PTSD patients and female trauma-exposed controls did not differ significantly on hormonal contraceptive use ($x^2=0.690$, $p=0.708$). As expected, PTSD patients showed higher total CAPS scores and state anxiety prior to scanning compared with trauma-exposed controls (all $p<0.0001$). Male PTSD patients experienced more different types of early-life traumatic events compared with male trauma-exposed controls ($t(39)=-2.18$, $p=0.037$), whereas female trauma-exposed controls experienced more different types of work-related traumatic events compared with female PTSD patients ($t(34)=2.114$, $p=0.042$).

Table 1. Participant Characteristics.

| | PTSD patients (*n*=36) | | Healthy controls (*n*=40) | | |
|---|---|---|---|---|---|
| | **Males (*n*=21)** | **Females (*n*=16)** | **Males (*n*=20)** | **Females (*n*=20)** | **M** |
| Age, in years | 42.29 (9.83) | 37.56 (9.78) | 41.35 (10.62) | 38.65 (9.48) | t(39) *p*= |
| Years of service | 16.29 (10.82) | 14.53 (10.74) | 18.42 (10.05) | 18.60 (9.84) | t(39 *p*= |
| *Educational level* | | | | | |
| Low | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | $\chi^2$= |
| Middle | 14 (67%) | 15 (93%) | 16 (85%) | 17 (90%) | *p*= |
| High | 7 (33%) | 1 (7%) | 4 (15%) | 3 (10%) | |
| CAPS total score (PTSD symptom severity) | 68.05 (15.62) | 67.56 (11.83) | 4.7 (4.79) | 4.45 (4.66) | t(39)= *p*<( |
| *State anxiety (STAI)* | | | | | |
| Placebo session | 47.14 (9.52) | 47.37 (6.89) | 28.77 (4.12) | 30.66 (3.66) | t(39) *p*<( |
| Oxytocin session | 47.52 (10.32) | 48.32 (11.34) | 29.33 (2.58) | 30.80 (4.52) | t(39) *p*<( |
| *Current comorbidity* | | | | | |
| MDD | 4 (19%) | 4 (25%) | NA | NA | |
| Dysthymia | 2 (9.5%) | 1 (6.3%) | | | |

| | PTSD patients (*n*=36) | | Healthy controls (*n*=40) | | |
|---|---|---|---|---|---|
| | **Males (*n*=21)** | **Females (*n*=16)** | **Males (*n*=20)** | **Females (*n*=20)** | **M** |
| Panic disorder | 1 (4.8%) | — | | | |
| Specific phobia | 1 (4.8%) | — | | | |
| Police life events scale, number of different types of experiences | 22.50 (5.95) | 13.50 (4.49) | 20.45 (6.42) | 19.4 (7.27) | t(39) *p*= |
| Early trauma inventory, number of different types of experiences | 6.09 (4.55) | 5.25 (5.18) | 3.65 (2.35) | 4.25 (4.82) | **t(39) *p*=(** |
| *Hormonal contraceptive use* | | | | | |
| None | NA | 7 (44%) | NA | 8 (40%) | |
| Hormonal | | 8 (50%) | | 9 (45%) | |
| Menopause | | 1 (6%) | | 3 (15%) | |
| | T1 T2 | T1 T2 | T1 T2 | T1 T2 | Ses gr |
| Time medication | 44.44 (5.44) 45.61 (4.50) | 44.88 (4.15) 45.00 (3.83) | 44.20 (5.05) 45.02 (4.21) | 45.55 (7.82) 42.90 (5.13) | F( <0 |

| | PTSD patients (*n*=36) | | Healthy controls (*n*=40) | | |
|---|---|---|---|---|---|
| | **Males (*n*=21)** | **Females (*n*=16)** | **Males (*n*=20)** | **Females (*n*=20)** | **M** |
| task, in minutes | | | | | *p*= |

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Abbreviations: CAPS, Clinician-Administered PTSD Scale; ETI, early trauma inventory; MDD, major depressive disorder; PLES, police life events scale; STAI, State-Trait Anxiety Inventory (state-version, administered before intranasal spray administration). Mean (±SD) or *N* (percentage) of demographic variables are shown for male and female PTSD patients and trauma-exposed controls. Differences between PTSD patients and trauma-exposed controls were tested for males and females separately. Bold values indicate significant between-group differences ($P<0.05$).

[a]Significant at $p<0.05$ level (two-tailed).

[b]Main effect of session: $F(1,39)=0.656$, $p=0.423$; main effect of group: $F(1,39)=0.007$ $p=0.935$.

[c]Main effect of session: $F(1,34)=0.998$, $p=0.325$; main effect of group: $F(1,34)=0.261$, $p=0.613$.

## Amygdala Reactivity Under Placebo

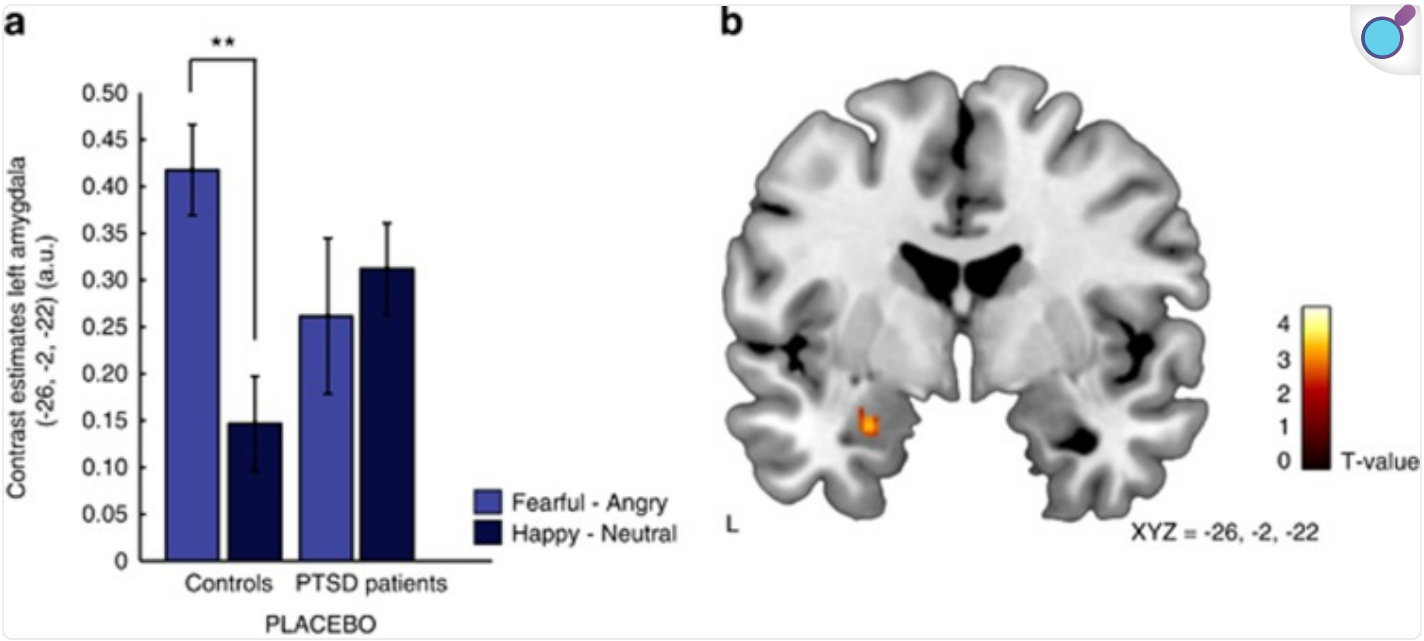
### Main effects

As expected, the emotional face-matching task reliably activated the bilateral amygdala ($P_{FWE}<0.05$, main effect of condition, collapsed across all participants and all emotional faces). In addition, a main effect of task condition was found in which the fearful-angry faces elicited more bilateral amygdala reactivity than happy-neutral faces ($P_{FWE}<0.001$). No other significant main effects were found for both the left and right amygdala (all $P_{FWE}>0.05$).

### Interaction effects

A positive group by task condition interaction effect was found for the left amygdala $P_{FWE}$=0.046), but not for the right amygdala ($P_{FWE}$=0.187) (see Figure 1; Table 2). *Post hoc t*-tests showed that left amygdala was significantly more activated in trauma-exposed controls in response to fearful-angry faces compared with happy-neutral faces ($P_{FWE}$<0.001). In PTSD patients, however, this valence-dependent amygdala reactivity was absent for the left amygdala ($P_{FWE}$=0.359). Right amygdala activity was significantly higher during fearful-angry compared with happy-neutral faces both in trauma-exposed controls ($P_{FWE}$<0.001) and PTSD patients ($P_{FWE}$=0.005). Direct *post hoc* comparison of amygdala reactivity toward fearful-angry faces and happy-neutral faces between PTSD patients and trauma-exposed controls revealed no significant differences (all $P_{FWE}$>0.05). No other significant interaction effects were found for both the left and right amygdala (all $P_{FWE}$>0.05).

Figure 1.




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Difference in amygdala reactivity between PTSD patients and trauma-exposed controls. (a) Mean contrast estimates (± standard errors) in arbitrary units (a.u.) of the left amygdala cluster (peak *xyz* =−26 −2 −22) during the processing of fearful-angry and happy-neutral faces (*versus* the visuomotor control condition) in PTSD patients and trauma-exposed controls (males and females combined). Under placebo, trauma-exposed controls showed differential activation toward fearful-angry faces compared with happy-neutral faces, whereas this effect was absent in PTSD patients. (b) Statistical map of the positive group by emotion interaction effect under placebo, overlaid on single-subject template using a statistical threshold of $p<0.01$ (uncorrected) (unmasked) for display purposes. **$p<0.001$.

Table 2. Significant Main and Interaction Effects in the Bilateral Amygdala.

| | Left amygdala | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Peak coordinate | | | *Z*-score | Cluster size | $P_{FWE}$ | Peak coordin | |
| | *X* | *Y* | *Z* | | | | *X* | *Y* |
| *Placebo model* | | | | | | | | |
| Main effect of task conditiona | −28 | −4 | −18 | 4.35 | 168 | 0.001 | 20 | −4 |
| Task × group | −26 | −2 | −22 | 3.15 | 47 | 0.046 | 28 | −10 |
| Controls: fearful-angry>happy-neutral | −28 | −2 | −18 | 5.05 | 189 | <0.001 | – | – |
| PTSD: fearful-angry>happy-neutral | −20 | −4 | −14 | 2.16 | 30 | 0.359 | – | – |
| *Oxytocin model* | | | | | | | | |
| Medication × group | −30 | −4 | −24 | 3.19 | 29 | 0.047 | 18 | −6 |
| Controls: oxytocin>placebo | −30 | 0 | −22 | 3.52 | 29 | 0.016 | – | – |
| PTSD: placebo>oxytocin | −30 | −2 | −24 | 3.26 | 20 | 0.034 | – | – |

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Significant main and interaction effects for the left and right amygdala region of interests (ROIs). Baseline differences between PTSD patients and controls, males and females and task conditions were tested within the placebo model. In addition, oxytocin (OT) administration effects were tested within the OT model. $P_{FWE}$-values <0.05 were considered significant. Peak voxel coordinates are given in MNI space.
[a]Main effect of task condition: fearful-angry faces elicited more amygdala activity compared with happy-neutral faces.

## OT Effects on Amygdala Reactivity

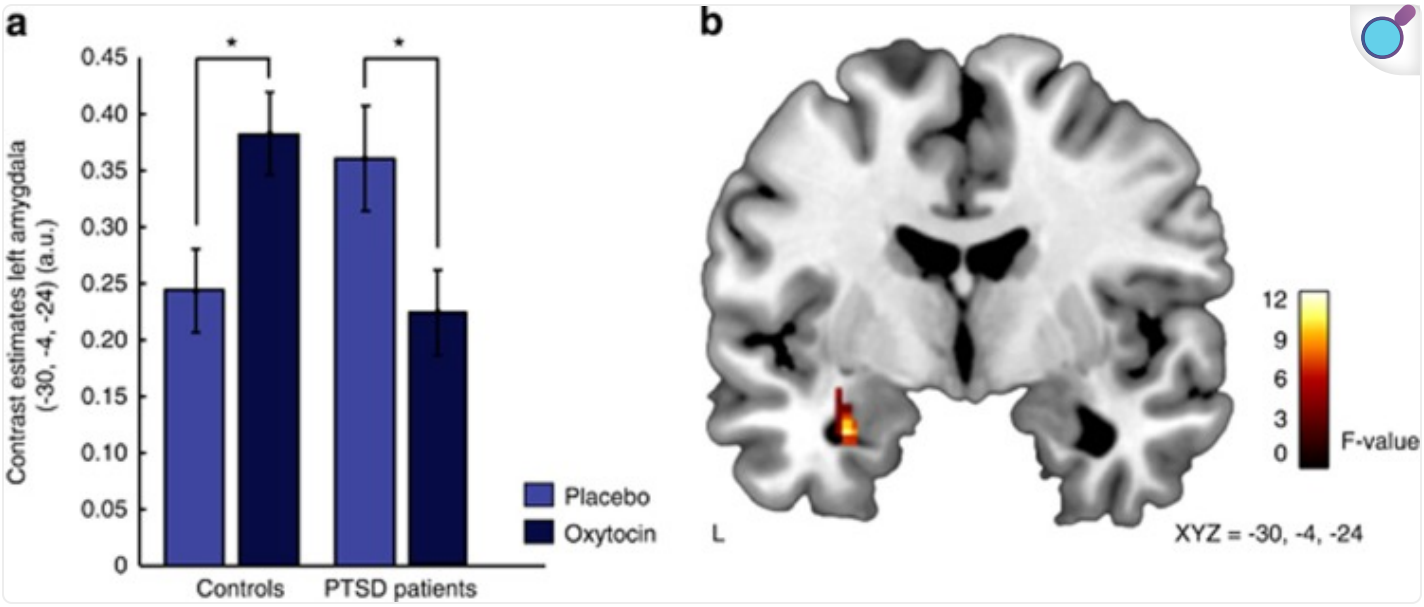
### Main effect of medication

No significant main effect of OT administration on left and right amygdala reactivity toward emotional faces was found (all $P_{FWE}$>0.05).

### Interaction effects

A significant group by medication interaction effect was found for the left amygdala ($P_{FWE}$=0.047, see Figure 2; Table 2), but not for the right amygdala ($P_{FWE}$=0.188). Further testing using *post hoc t*-tests revealed enhanced left amygdala reactivity in trauma-exposed controls ($P_{FWE}$=0.016) and dampened left amygdala reactivity ($P_{FWE}$=0.034) in PTSD patients after OT administration compared with placebo. These effects of OT were independent of sex and stimulus valence (all $P_{FWE}$>0.05). No other significant interaction effects of OT administration on bilateral amygdala reactivity in PTSD patients or control participants were found (all $P_{FWE}$>0.05).

Figure 2.




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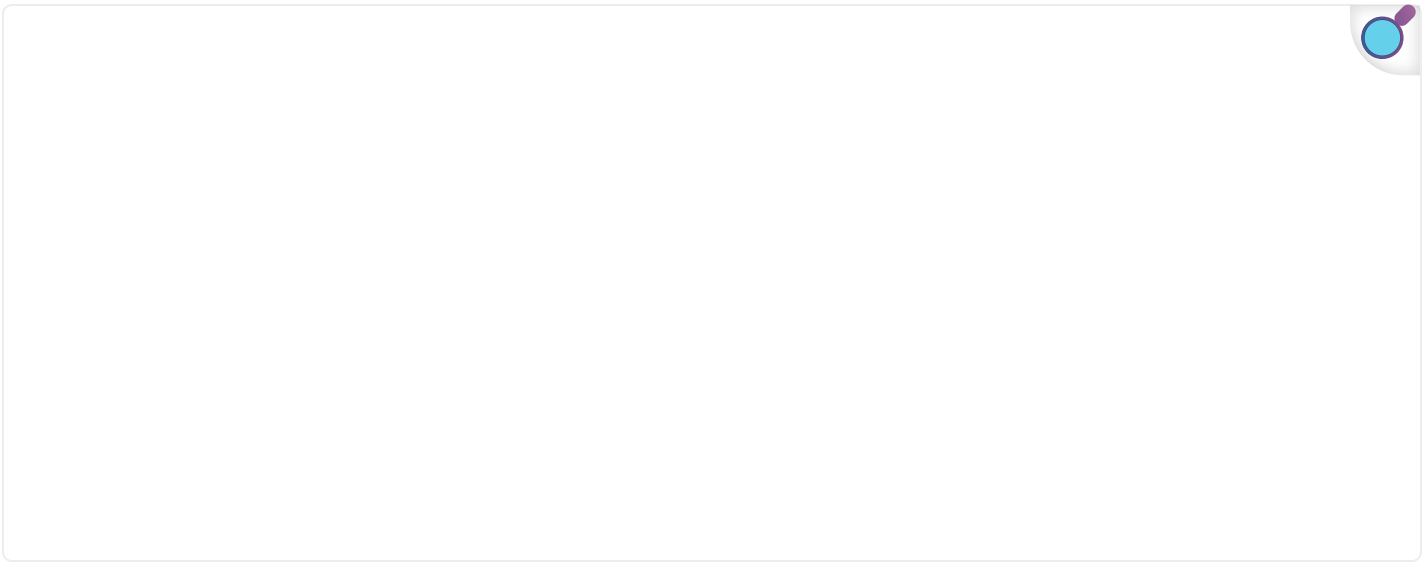
Effect of OT on amygdala reactivity. (a) Mean contrast estimates (± standard errors) in arbitrary units (a.u.) of the left amygdala cluster (peak *xyz*=−30 −4 −24) during the processing of emotional faces (all emotional faces combined *versus* the visuomotor control condition) in PTSD patients and trauma-exposed controls (males and females combined) after placebo and oxytocin (OT) administration. OT administration resulted in dampened amygdala reactivity in PTSD patients and in enhanced amygdala reactivity in trauma-exposed controls. (b) Statistical map of the medication by group interaction effect, overlaid on single-subject template using a statistical threshold of $p<0.01$ (uncorrected) (unmasked) for display purposes. *$p<0.05$.

## Association between Amygdala Reactivity and Clinical Characteristics in PTSD Patients

Subjective anxiety of patients prior to intranasal placebo administration was positively related to left amygdala reactivity toward emotional faces under placebo ($r=0.393$, $p=0.021$, Figure 3). The association between state anxiety and left amygdala reactivity was significant for reactivity toward happy-neutral faces ($r=0.412$, $p=0.014$), but not for reactivity toward fearful-angry faces

($r$=0.274, $p$=0.117). State anxiety prior to OT administration was not related to left amygdala reactivity toward emotional faces after OT administration ($r$=0.064, $p$=0.731), indicating that OT administration abolished the association between left amygdala reactivity and anxiety prior to scanning. In addition, the difference in contrast estimates between OT and placebo administration was trend significant positively related to state anxiety prior to placebo administration ($r$=0.298, $p$=0.089, Figure 3). Notably, this effect was mediated by left amygdala reactivity after placebo administration (indirect effect: 95% confidence interval=0.0018–0.0248, effect=0.0114, Boot SE=0.057), indicating that PTSD patients with higher state anxiety and hence higher left amygdala reactivity during the placebo session showed stronger dampening of amygdala reactivity after OT administration. No significant associations between left amygdala reactivity toward emotional faces and CAPS total score or subscales were found (all $p$>0.05).

Figure 3.



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Relationship between state anxiety and amygdala reactivity in PTSD patients. Scatterplots of correlations between: (a) state anxiety before placebo and oxytocin administration and left amygdala reactivity toward all emotional faces (compared with the visuomotor control condition) after placebo and OT administration: (b) state anxiety before placebo administration and difference in left amygdala reactivity (placebo—OT). Contrast estimates of left amygdala reactivity in arbitrary units (a.u.) were extracted using a 5-mm sphere surrounding the peak voxel (*xyz*=−30 −4 −24) of the OT administration effect in PTSD patients. STAI-state=State-Trait Anxiety Inventory (state-version).

## DISCUSSION

This is the first study showing intranasal OT administration effects on amygdala reactivity in male and female PTSD patients and trauma-exposed controls. Under placebo, the trauma-exposed controls showed greater amygdala reactivity toward fearful-angry faces compared with happy-neutral faces, whereas this differential amygdala reactivity was absent in PTSD patients (ie, equivalent amygdala reactivity toward happy-neutral and fearful-angry faces). When collapsing across all emotional faces, OT administration enhanced left amygdala reactivity in trauma-exposed controls, but dampened left amygdala reactivity in PTSD patients, independent of participants' sex

and valence of the stimuli. Notably, the amygdala dampening effect of OT in PTSD patients was greatest in those patients with high state anxiety and hence high amygdala reactivity under placebo.

The valence-dependent amygdala reactivity (ie, greater amygdala reactivity toward fearful-angry faces compared with happy-neutral faces) followed the expected pattern in trauma-exposed controls (Morris *et al*, 1996), but was absent in PTSD patients. Possibly, PTSD patients may be specifically sensitive to show greater amygdala responsiveness to the neutral, socially ambiguous faces in the happy-neutral condition. Indeed, a previous study showed elevated amygdala responses towards neutral pictures in PTSD patients compared with trauma-exposed controls (Brunetti *et al*, 2010). In addition, we found that PTSD patients with higher state anxiety showed more amygdala reactivity especially toward happy-neutral faces under placebo. Notably, OT administration dampened left amygdala reactivity toward all emotional faces in PTSD patients, independent of stimulus valence and participants' sex. This finding corresponds with previous intranasal OT administration studies in healthy individuals (Kirsch *et al*, 2005) and psychiatric patients with GSAD and BPD (Bertsch *et al*, 2013; Labuschagne *et al*, 2010). Our findings extend accumulating evidence that OT may have anxiolytic properties, possibly by inhibiting fear-associated output of the central amygdala to the brainstem and hypothalamus (Huber *et al*, 2005).

We did not find amygdala hyperresponsiveness in PTSD patients compared with trauma-exposed controls under placebo. This findings is in line with the meta-analysis of Patel *et al* (2012), who found amygdala hyperactivity in PTSD patients compared with non-trauma-exposed, but not compared with trauma-exposed controls. Thus, amygdala hyperresponsiveness may be a consequence of trauma exposure rather than of PTSD. Alternatively, amygdala hyperactivity in PTSD may only become apparent during presentation of trauma-related stimuli and not during processing of non-trauma-related stimuli (van Rooij *et al*, 2014), such as the emotional faces used in the present study.

Contrary to our expectations, OT administration enhanced left amygdala reactivity toward emotional faces in healthy male and female trauma-exposed controls. Notably, we found an overall amygdala enhancing effect, for all emotional faces, which may indicate generally enhanced processing of socially salient environmental cues (ie, salience processing, Seeley *et al*, 2007). Although OT administration has predominantly been found to dampen amygdala reactivity (eg, Domes *et al*, 2007; Kirsch *et al*, 2005; Petrovic *et al*, 2008), increased amygdala reactivity has also been observed after OT administration. OT administration resulted in enhanced amygdala reactivity toward happy faces in healthy males (Gamer *et al*, 2010), and toward fearful (Domes *et al*, 2010) and angry faces (Bertsch *et al*, 2013) and threatening scenes (Lischke *et al*, 2012) in healthy

females. In addition, increased amygdala reactivity toward neutral faces was observed after OT administration in male patients with Asperger's syndrome (Domes *et al*, 2013, 2014). Notably, we found that OT enhanced amygdala reactivity in both male and female trauma-exposed controls. This is in line with previous observations in healthy females, but at odds with previous findings in healthy males, which generally showed dampened amygdala reactivity toward negative stimuli after OT administration (eg, Domes *et al*, 2007; Kirsch *et al*, 2005; Petrovic *et al*, 2008). Our findings underline previous observations that OT administration effects depend on inter-individual factors (eg, psychopathology and/ or trauma exposure).

Notably, we found opposite OT administration effects on amygdala reactivity in PTSD patients *versus* trauma-exposed controls (ie, dampening *versus* enhancing effects). This fits with the hypothesis that OT administration effects may be especially beneficial in those who lack proficiency in fear regulation (Labuschagne *et al*, 2010) or social functioning (Olff *et al*, 2013; Weisman and Feldman, 2013). We included highly trauma-exposed, but apparently resilient control participants, who did not have any current psychopathology or history of PTSD and MDD, despite having experienced numerous traumatic events in their lives. Presumably, our trauma-exposed controls did have little to gain regarding fear regulation, whereas PTSD patients may benefit from improved fear regulation. In support of this hypothesis, we found that PTSD patients, with higher state anxiety under placebo, showed more dampening of amygdala reactivity after OT administration. This indicates that PTSD patients with high anxiety prior to scanning and high baseline amygdala reactivity may especially benefit from OT administration. Alternatively, the observed difference in OT administration effects may be explained by differences in sensitivity to effects of OT administration between PTSD patients and (resilient) trauma-exposed controls. In healthy individuals, OT effects seem to follow an inverted u-shape (Rilling *et al*, 2014), with doses ~24 IU, resulting in more anxiolytic effects than higher doses of OT (Cardoso *et al*, 2013). Moreover, OT applied at higher doses (eg, 40 IU used in this study) may result in anxiogenic effects in healthy individuals, owing to competitive binding to arginine–vasopressin (AVP) receptors (Cardoso *et al*, 2013). Our observation of increased amygdala reactivity on OT administration in our control group fits with this notion. PTSD patients, on the other hand, may be less sensitive to OT administration, owing to alterations at the level of AVP and/or OT receptors, and therefore show dampened amygdala reactivity upon administration of this relatively high dose. The notion that OT system functioning may be affected in PTSD patients is supported by our observation of lower salivary OT levels in male PTSD patients compared with male trauma-exposed controls (Frijling *et al*, 2015), in the same sample reported in this manuscript.

Notably, OT administration effects were lateralized to the left amygdala, although the same (albeit non-significant) directionality of effects was observed in the right amygdala. In line with our

findings, OT administration effects in left amygdala reactivity toward emotional faces have been found in healthy males (Gamer *et al*, 2010; Kirsch *et al*, 2005), healthy females (Domes *et al*, 2010) and male patients with Asperger's syndrome (Domes *et al*, 2014). On the other hand, OT administration effects on right-sided amygdala reactivity toward emotional faces has also been observed in healthy males (Domes *et al*, 2007; Petrovic *et al*, 2008), females with and without BPD (Bertsch *et al*, 2013) and males with Asperger's syndrome (Domes *et al*, 2013). Only one study (in male GSAD patients) found OT administration effects on bilateral amygdala reactivity (Labuschagne *et al*, 2010). Functional lateralization of amygdala reactivity has previously been found in healthy individuals: the right amygdala is associated with rapid, automatic detection and general arousal toward emotional stimuli, whereas the left amygdala is better able to distinguish stimuli associated with different levels of arousal, resulting in a more subtle emotional reaction (Gläscher and Adolphs, 2003). To date, no studies have explicitly investigated lateralization of OT administration effects on amygdala reactivity. Given the previous mixed findings of OT administration on left *versus* right amygdala reactivity, future studies are necessary to resolve this issue.

Dampening amygdala reactivity toward fearful stimuli in PTSD may be beneficial during exposure therapy. Greater amygdala reactivity during extinction learning has been associated with impaired extinction learning (Milad *et al*, 2009) and greater amygdala reactivity toward fearful faces before treatment resulted in worse treatment outcome (Bryant *et al*, 2008). In addition, higher amygdala (and dACC and insula) reactivity toward negative emotional pictures prior to treatment predicted persistence of PTSD symptoms after treatment (van Rooij *et al*, 2015). It has been suggested that excessive (amygdala) fear processing during psychotherapy may result in impaired extinction learning and difficulties in regulating anxiety (Bryant *et al*, 2008). By dampening excessive fear processing during exposure-based therapies, OT administration could result in enhanced treatment response. Besides this anxiolytic mechanism, OT is hypothesized to enhance treatment response via pro-social effects (Olff *et al*, 2010). OT has been found to increase in-group trust, pro-social behavior and neural reward sensitivity to social stimuli in men and women (eg, Groppe *et al*, 2013; Van IJzendoorn and Bakermans-Kranenburg, 2012; Preckel *et al*, 2014; Striepens *et al*, 2014). This way, OT could potentially enhance motivation for treatment, as well as the therapeutic alliance (Olff *et al*, 2010). Strength of therapeutic alliance, defined as the affective bond between the therapist and patient, is an important and consistent predictor of treatment success (Ormhaug *et al*, 2014) and depends on the patient's attachment security: more secure attachment is related to stronger therapeutic alliance and vice–versa (see Diener and Monroe, 2011 for a meta-analysis). Attachment style may be particularly relevant in PTSD: insecure attachment, has been associated with higher PTSD symptom severity in trauma-exposed individuals (see Woodhouse *et al*, 2015 a meta-analysis). Notably, perception of attachment security was improved after OT administration in healthy male students (Buchheim *et al*, 2009). However, opposite effects of OT administration on

attachment have also been found: anxiously attached healthy males remembered their mother as less caring after OT administration, compared with placebo (Bartz *et al*, 2010). In addition, OT administration in anxiously attached BPD patients and healthy controls decreased cooperation and trust (Bartz *et al*, 2011). This emphasizes the need to investigate the effects of OT administration on social processes in PTSD, including the therapeutic alliance and attachment security.

To our knowledge, this is the first study investigating neurobiological effects of OT administration in PTSD patients, as a first step to show the potential clinical importance of OT administration in PTSD patients. Moreover, we investigated sex-differential OT administration effects on amygdala reactivity toward emotional faces, including both male and female PTSD patients within one intranasal OT fMRI study. However, several limitations should be mentioned. First, we included females using oral contraceptives. Also, we did not standardize the phase of menstrual cycle our female participants were scanned in, to minimize time and hence potential differences in symptom severity between the two scanning sessions. We cannot exclude the possibility that this may have influenced our results, although similar effects of OT on amygdala reactivity previously were found in females tested in the follicular phase (Domes *et al*, 2010) and luteal phase (Bertsch *et al*, 2013). At last, to control for the potential confounding effect of trauma exposure, we included a trauma-exposed sample of police officers without PTSD, limiting the generalizability of our findings.

Taken together, we showed that OT administration dampened left amygdala reactivity in male and female PTSD patients, which could presumably enhance treatment response in PTSD. As a next step, effects of OT administration should be thoroughly investigated in clinical settings before considering routine clinical application of OT as medication-enhanced treatment in PTSD.

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## Footnotes

Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)

## Supplementary Material

Supplementary Figure S1

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*This section collects any data citations, data availability statements, or supplementary materials included in this article.*

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Supplementary Figure S1

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