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Intranasal oxytocin enhances neural processing of monetary reward and loss in post-traumatic stress disorder and traumatized controls☆

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ABSTRACT

Background: Anhedonia is a significant clinical problem in post-traumatic stress disorder (PTSD). PTSD patients show reduced motivational approach behavior, which may underlie anhedonic symptoms. Oxytocin administration is known to increase reward sensitivity and approach behavior. We therefore investigated whether oxytocin administration affected neural responses during motivational processing in PTSD patients and trauma-exposed controls.
Methods: 35 police officers with PTSD (21 males) and 37 trauma-exposed police officers without PTSD (19 males) were included in a within-subjects, randomized, placebo-controlled fMRI study. Neural responses during anticipation of monetary reward and loss were investigated with a monetary incentive delay task (MID) after placebo and oxytocin (40 IU) administration.
Results: Oxytocin increased neural responses during reward and loss anticipation in PTSD patients and controls in the striatum, dorsal anterior cingulate cortex and insula, key regions in the reward pathway. Although PTSD patients did not differ from controls in motivational processing under placebo, anhedonia severity in PTSD patients was negatively related to reward responsiveness in the ventral striatum. Furthermore, oxytocin effects on reward processing in the ventral striatum were positively associated with anhedonia.
Conclusions: Oxytocin administration increased reward pathway sensitivity during reward and loss anticipation in PTSD patients and trauma-exposed controls. Thus, oxytocin administration may increase motivation for goal-directed approach behavior in PTSD patients and controls, providing evidence for a neurobiological pathway through which oxytocin could potentially increase motivation and reward sensitivity in PTSD patients.

1. Introduction

Historically, neurobiological research on post-traumatic stress disorder (PTSD) has focused on anxiety and stress responses, reflecting the prominent hyperresponsiveness to trauma-related stimuli in PTSD. However, anhedonia is also a significant problem in PTSD (American Psychiatric Association, 2000). About two-thirds of PTSD patients report diminished interest in significant activities and reduced positive affect, also in the absence of comorbid major depressive disorder (MDD) (Carmassi et al., 2014; Franklin and Zimmerman, 2001). Anhedonic PTSD symptoms are related to increased psychosocial deficits, such as suicidality and interpersonal problems. Moreover, anhedonia predicts chronicity of PTSD and worse treatment outcome (Hassija et al., 2012).

Motivational anhedonia (i.e., reduced anticipation or motivation ('wanting') to engage in significant activities) may be specifically important for PTSD treatment outcome, as it may negatively affect treatment motivation and expectation of treatment success, which are vital for treatment response (Clarke et al., 2013; Schindler et al., 2013). PTSD is related to reduced approach behavior and motivation for positive reinforcers (e.g., money, happy faces, pleasant images) (Nawijn et al., 2015). For example, PTSD patients reported lower expectancy of and satisfaction with monetary reward (Hopper et al., 2008), reduced task-motivation (Sailer et al., 2008) and made less effort to obtain rewards (Elman et al., 2005) compared to trauma-exposed controls. This motivational anhedonia is thought to result from deficits in the reward pathway,

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a neural circuit critical in guiding approach behavior and activated by positive and negative reinforcing stimuli (Der-Avakian and Markou, 2012; Liu et al., 2011). Findings suggest that PTSD is related to hyposensitivity of the reward pathway, such as reduced striatal responses (Admon et al., 2013; Elman et al., 2009; Felmingham et al., 2014; Sailer et al., 2008) and altered prefrontal responses (Aupperle et al., 2012; Frewen et al., 2010; Moser et al., 2015) to positive stimuli. Also, in PTSD patients anhedonic symptom severity was negatively related to responses in the ventral striatum, anterior cingulate cortex (ACC) and insula to positive social and non-social stimuli in PTSD patients (Elman et al., 2009; Felmingham et al., 2014; Frewen et al., 2012), supporting the relation between anhedonia and reward pathway functioning. Several studies investigated motivational processing in response to both positive and negative reinforcers (e.g., winning and losing money/points, positive and negative images). In PTSD patients, increased amygdala and striatal responses (Admon et al., 2009; Elman et al., 2009; Mazza et al., 2012) and altered PFC responses (Aupperle et al., 2012; Mazza et al., 2012; Moser et al., 2015) to negative reinforcers were observed compared to trauma- and non-trauma-exposed controls, although negative results have also been reported (Sailer et al., 2008). These neural findings fit with behavioral observations suggesting increased motivational sensitivity to negative reinforcers in PTSD patients compared to controls (Hopper et al., 2008; Mazza et al., 2012).

Addressing the neural deficits in motivational processing thought to underlie anhedonic symptoms may improve motivational functioning in PTSD. Recently, intranasal oxytocin administration has been proposed as a promising candidate for enhancing efficacy of evidence-based psychotherapy in PTSD by promoting fear regulation and reward processing (Koch et al., 2014; Olff et al., 2010). There is accumulating evidence that oxytocin administration increases motivational salience (i.e., salience due to association with reward) and approach behavior in healthy individuals (Harari-Dahan and Bernstein, 2014). For example, in healthy males and females, intranasal oxytocin was found to increase behavioral approach of social positive stimuli (Preckel et al., 2014; Scheele et al., 2012) and neural responses during reward and punishment anticipation in reward pathway areas such as the striatum, ventral tegmental area (VTA) and insula (Groppe et al., 2013), as well as neural responses during presentation of positive stimuli (Feng et al., 2014; Rilling et al., 2014; Scheele et al., 2013; Striepens et al., 2014).

Oxytocin administration has been studied in various psychiatric populations (Cochran et al., 2013), although not many studies have investigated motivational processing. In schizophrenic patients repeated oxytocin administration decreased negative symptoms, which include anhedonia (Cochran et al., 2013), and improved motivational anhedonic symptoms (Lee et al., 2013). In a group of abstinent cocaine abusers, oxytocin increased behavioral responses to monetary reward, relative to placebo (Lee et al., 2014). In depressed patients, repeated oxytocin administration increased scores on a life enjoyment and satisfaction questionnaire, although these findings should be interpreted with caution due to lack of a placebo group (Scantamburlo et al., 2015). In PTSD patients, Pitman et al. (1993) failed to observe effects of a single oxytocin administration on physiological responses to pleasant images, whereas a pilot study in PTSD patients showed that a single oxytocin administration acutely improved mood and desire for social interaction (Yatzkar and Klein, 2010). Together, these findings suggest that oxytocin may enhance motivational processing in psychiatric populations. Investigating the effects of oxytocin administration on neural motivational processing in PTSD patients can provide valuable insight in the neurobiological effects of oxytocin administration on reward processing and the potential of oxytocin to enhance efficacy of evidence-based psychotherapy. Therefore, we investigated the effect of intranasal oxytocin administration on neural responses during monetary reward and loss anticipation in trauma-exposed police officers with and without PTSD, using a monetary incentive delay (MID) task (Knutson et al., 2000). The anticipation phase of the MID task is a well-established measure of motivational processing, robustly activating the reward pathway (Knutson et al., 2000). Furthermore, it allows for separate investigation of reward and loss anticipation. We hypothesized that oxytocin would increase neural reward pathway responses during motivational processing. As oxytocin was previously found to have differential effects depending on sex (Feng et al., 2014; Rilling et al., 2014), both male and female participants were included and sex-differential effects were examined.

2. Materials and methods

2.1. Participants and procedure

We included 40 police officers with PTSD (21 males) and 40 trauma-exposed police officers without PTSD (20 males). Three participants were excluded prior to analyses due to incomplete scanning data, and five due to low scan data quality (see below), leaving 35 PTSD patients (21 males) and 37 controls (19 males). All participants were current or former police personnel between 18–65 years old. PTSD patients were recruited through a psychotrauma diagnostic outpatient clinic for police personnel (PDC, Diemen, the Netherlands). PTSD patients and controls were additionally recruited through advertisements. PTSD patients had a Clinician Administered PTSD Scale (CAPS, (Blake et al., 1995)) score ≥ 45 and fulfilled DSM-IV (American Psychiatric Association, 2000) criteria for current PTSD. Exclusion criteria for PTSD patients were current severe MDD (MDD with high suicidal risk and/or psychotic symptoms), bipolar disorder, suicidal ideation, alcohol/substance abuse and psychotic disorders, measured with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) or Structured Clinical Interview for DSM–IV (First et al., 2012). Control participants were matched to PTSD patients based on sex, age, education and years of service, had a CAPS score < 15 and experienced at least one traumatic event (DSM-IV A1 criterion). Exclusion criteria for controls were lifetime MDD or PTSD or any current Axis-I psychiatric disorder. Exclusion criteria for all participants were daily use of psychoactive medication (e.g., antidepressants) or systemic glucocorticoids, contraindications for MRI or oxytocin administration, significant medical conditions or history of neurological disorders. Infrequent use of psychoactive medication (e.g., benzodiazepines) was allowed as long as participants abstained from use at least 24 h prior to scanning. All participants provided written informed consent prior to study initiation. The study was approved by the Institutional Review Board of the Academic Medical Center, Amsterdam, The Netherlands.

Each participant participated in two scanning sessions on average 12 days apart (Table S1). Participants abstained from psychoactive medication, drugs and alcohol for 24 hour prior to scanning, and caffeine and nicotine for 2.5 hours prior. Medication allocation was randomized according to a cross-over design, counter-balanced and double-blind (controls: PL-OT $n = 19$, OT-PL $n = 18$; PTSD patients: PL-OT $n = 17$, OT-PL $n = 18$). Participants self-administered 10 puffs of intranasal oxytocin (total 40IU) or placebo (0.9% saline) approximately 50 min prior to the MID task (Table S1). The MID task was presented between 50 and 70 min post-administration, falling within the time-window for central effects of oxytocin administration (i.e., from 25 to at least 78 min post-administration) (Paloyelis et al., 2014; Striepens et al., 2013).

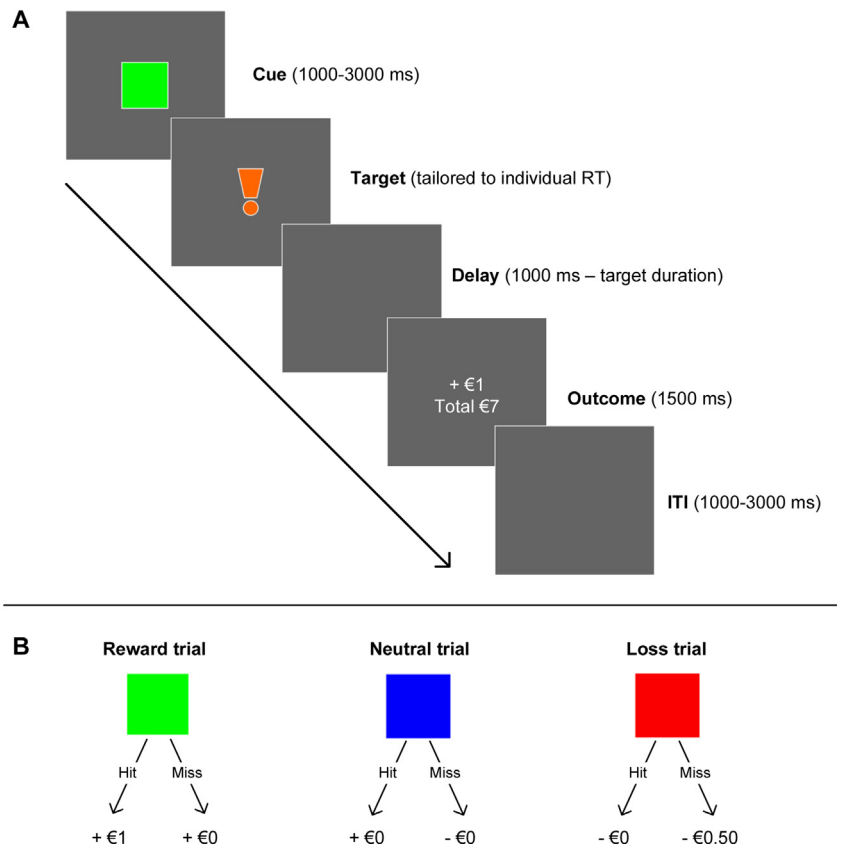

Fig. 1. Monetary incentive delay (MID) task. (A) Stimulus order per trial: anticipation cue (green square for reward trials, blue for neutral, red for loss trials, see (B)), duration jittered between 1000 and 3000 ms; target stimulus, for which duration was tailored to individual mean reaction time (mRT) based on 10 practice trials, to result in feasible target duration (individual mRT + 400 ms) or unfeasible target duration (individual mRT – 150 ms); a delay with a duration of 1000 ms minus target duration; outcome presentation, presented for 1500 ms; and a blank screen inter-trial interval (ITI), duration jittered between 1000 and 3000 ms. (B) Anticipation cues and outcomes per trial type.

2.2. Monetary incentive delay task

The MID task is well-established for fMRI and the anticipation phase reliably elicits reward pathway reactivity including the striatum (Knutson et al., 2000). Prior to each scanning session, participants received task instructions and performed a practice session. Within the scanner, mean reaction times (mRT) were calculated over 10 practice trials performed immediately prior to the start of the task (once per scan session), and used to tailor the task to individual performance. Each trial started with an anticipation cue, informing participants of the trial type (reward, neutral, loss; Fig. 1). Next, the target was presented, to which participants were to push a button as fast as possible. Task difficulty was tailored to individual performance (Knutson et al., 2000). Target presentation time was either feasible (long presentation; mRT + 400 ms) or unfeasible (short presentation; mRT – 150 ms). Responses made before the target disappeared were classified as hits; omissions and responses after target disappearance as misses. After a delay, the outcome was presented (Fig. 1B). For each trial type, 27 trials were presented. For reward and neutral, 18/27 trials were feasible, aimed to result in about 66% hits. For loss, 9/27 trials were feasible, aimed to result in about 66% misses. Trial type order was pseudo-randomized. All participants mastered the task; accuracy was at least 80% of all feasible trials. The MID was presented in two blocks, interleaved with two blocks of a social incentive delay task (results reported elsewhere). To control for potential block-order effects, we counterbalanced the presentation of MID and SID blocks between sessions and between participants, following procedures of Spreckelmeyer et al. (2009) and Rademacher et al. (2010).

2.3. fMRI acquisition

Imaging was performed on a 3T Philips Achieva MR scanner with a 32-channel head-coil (Philips Medical Systems, Best, the Netherlands). Anatomical images were obtained using a high-resolution FAST MP-RAGE sequence (field of view (FOV): 240 × 188 mm; acquisition matrix size (AMS): 240; flip angle: 8°; echo-time (TE): 3.8 ms; repetition time (TR): 8.2s; voxel size: 1 mm^3, 220 slices). Functional images were obtained using an echo-planar imaging (EPI) sequence (FOV: 240 × 240 mm; AMS: 80; flip angle: 76°; TE: 27.63 ms; TR: 2s; voxel size: 3 mm^3, 37 slices).

2.4. fMRI data analyses

fMRI analyses were done using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing consisted of realignment, slice-timing correction, co-registration of functional and anatomical images, segmentation, normalization to the MNI template, resampling to 2 mm^3 voxels and smoothing with an 8 mm full-width half maximum Gaussian kernel. Five subjects were excluded due to low scan quality (scanning artefacts, $n = 2$; excessive movement (>6 mm/degrees), $n = 3$). At the single-subject level, three event types (reward, neutral, loss anticipation) were modelled using a hemodynamic response function at the onset of the anticipation stimuli. Outcome presentation was modelled as regressor of no interest. A high-pass filter of 1/128 Hz was applied and six realignment parameters were included to regress out movement-related signals. Two contrast images were created for each participant and session (reward anticipation > neutral; loss anticipation > neutral)

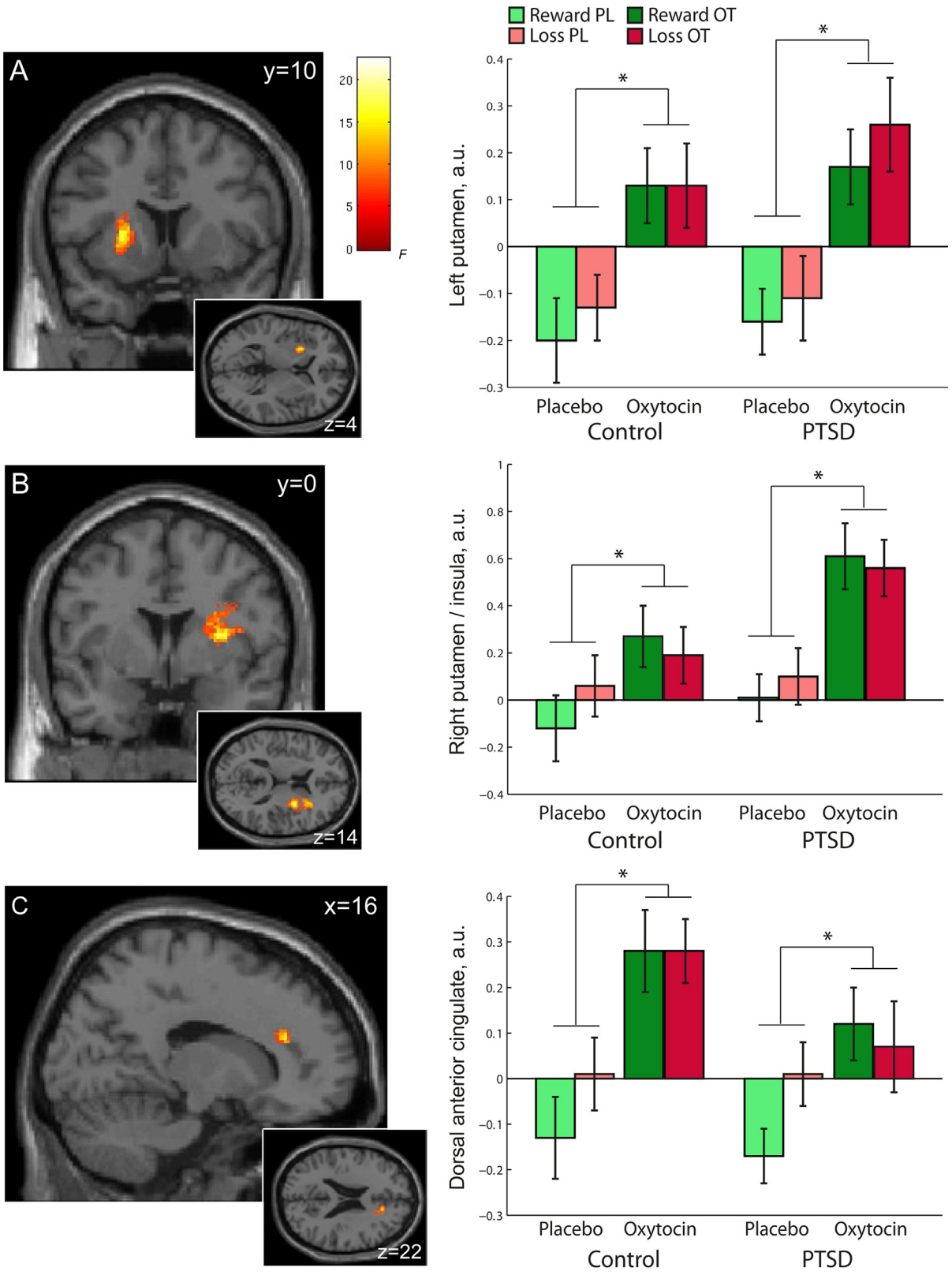

Fig. 2. Main effect of oxytocin administration on reward and loss (vs. neutral) anticipation. (A) Left striatum (putamen, $xyz = -26,10,4$, $Z = 3.93$, $k = 36$, $p_{FWE} = 0.044$); (B) right striatum and insula (putamen, $xyz = 28,0,14$, $Z = 4.10$, $k = 33$, $p_{FWE} = .024$; insula, $xyz = 32,2,14$, $Z = 4.02$, $k = 9$, $p_{FWE} = 0.033$); (C) right dorsal anterior cingulate cortex (dACC, $xyz = 16,34,22$, $Z = 3.79$, $k = 9$, $p_{FWE} = 0.045$). Clusters are overlaid on a single-subject anatomical scan (SPM template), whole brain threshold set at $p < 0.01$ uncorrected for display purposes. Bar-charts show extracted beta-weights (arbitrary units, a.u.) from corresponding functional clusters with a significant main effect of treatment, separately for reward and loss trials in PTSD patients and controls. Error bars indicate standard error of the mean. * = $p < .05$.

and taken to second level. Task effects and baseline group differences were tested in a full-factorial repeated-measures ANOVA of placebo sessions only, with factors group (PTSD/control), sex (male/female) and trial type (reward/loss). Effects of oxytocin administration were tested in a full-factorial repeated-measures ANOVA with factors group, sex, trial type and medication (oxytocin/placebo). In both models, medication-order was included as covariate. To control for potential effects of block-order (MID–SID), we also conducted our analyses while controlling for block-order.

We performed both whole-brain and regions of interest (ROIs) with small volume correction (SVC) analyses. Anatomical ROIs were selected based on a meta-analysis of motivational imaging studies on areas specifically involved in anticipation of positive and negative stimuli (Liu et al., 2011) and a previous study of oxytocin effects on anticipatory reward and punishment processing (Groppe et al., 2013). ROIs of the bilateral striatum, insula and ACC were created with Wake Forest University pickatlas tool (http://fmri.wfubmc.edu/software/pickatlas); VTA ROI was based on Groppe et al. (2013). *P*-values were corrected for family-wise-error rate (p_{FWE}), with p_{FWE} values smaller than 0.05 considered significant. Significant effects were visualized with bar-graphs of average beta-weights of the functional clusters, extracted with Marsbar (http://marsbar.sourceforge.net/). Peak voxels are reported in MNI coordinates.

2.5. Behavioral and clinical analyses

Analyses were conducted in SPSS20 (IBM statistics, Chicago, USA). All variables were checked for outliers, normality and homogeneity of variance between groups, and transformed when necessary. Differences in demographic variables between PTSD patients and controls were tested within males and females separately, using independent sample *t*-tests for continuous variables and χ^2-tests for categorical variables.

Placebo session reaction times (RT, average reaction time in milliseconds on accurate trials) on reward and loss trials were compared to neutral trial RTs to confirm the motivational effect of trial type using a repeated-measures ANOVA, correcting for medication-order. Effects of scan session on average RT and interactions between scan session and group or sex were tested using a repeated-measures ANOVA, correcting for medication received. Reward and loss RTs (relative to neutral RTs) were further tested for effects of group, medication and trial type using repeated-measures ANOVAs, with factors group, sex, trial type and medication, and medication-order as covariate. As task difficulty was tailored to individual performance, accuracy and amount of money won showed very limited variance and were not informative of task performance (Table S2).

We hypothesized that PTSD anhedonia symptom severity would be negatively associated with neural activity during anticipation. As exploratory analyses, we therefore investigated correlations between CAPS anhedonia symptoms and task-reactivity within PTSD patients. As controls reported minimal levels of anhedonia with little within-group variation, only PTSD patients were included in these analyses. Beta-values during reward and loss anticipation were extracted from significant task effect functional activation clusters within the striatum under placebo using Marsbar (http://marsbar.sourceforge.net/) (table S3, left and right ventral striatum/ventral pallidum, peak activation resp. $xyz = 12,8,2$, $p_{FWE} = 0.003$; $xyz = -12,6,0$, $p_{FWE} = 0.014$, whole brain uncorrected threshold of $p = 0.001$). Pearson bivariate correlation coefficients were calculated between striatal activity and anhedonic symptom severity (CAPS items 'diminished interest in significant activities', 'reduced positive affect' and 'feelings of detachment'). Possible confounding effects of PTSD severity and MDD comorbidity were controlled for by performing partial correlation analyses with CAPS total score and by rerunning analyses without PTSD patients with comorbid MDD ($n = 8$).

3. Results

3.1. Sample

Thirty-seven control participants (19 males) and 35 PTSD patients (21 males) were included in the analyses (Table 1). Demographic characteristics did not differ between PTSD patients and controls (age, education, years of service, all *p*-values > 0.050). Male PSTSD patients reported more different types of childhood trauma compared to male controls (ETI, $p = 0.049$). Female PTSD patients reported nominally less different types of work-related trauma exposure compared to female controls (PLES, $p = 0.074$).

3.2. Behavioral data

Under placebo, all participants showed faster RTs on reward and loss trials compared to neutral trials ($F(2,66) = 8.35$, $p = 0.001$), illustrating increased behavioral motivation towards reward and loss trials compared to neutral trials, RTs on reward trials also being faster than loss trials (Reward > Loss > Neutral, Table S2). Scan session (i.e., first vs second scan session) and block-order did not affect average RT ($p > .1$). PTSD, sex and oxytocin administration did not affect RT to reward or loss trials relative to neutral RT (all *p*-values > .1).

3.3. fMRI data

3.3.1. Task and group effects under placebo

Reward and loss (vs. neutral) anticipation activated key nodes of the reward pathway under placebo (ventral striatum/pallidum, amygdala, insula/orbitofrontal cortex, ACC, all $p_{FWE} < 0.05$, whole-brain, Table S3). On whole-brain level, loss anticipation induced significantly higher activation in the right fusiform gyrus, left inferior occipital gyrus and dorsolateral prefrontal cortex compared to reward anticipation ($p_{FWE} < 0.05$, Table S3). No areas showed significantly higher reactivity to reward anticipation compared to loss ($p_{FWE} > 0.05$). Trial type did not affect reactivity in any of the ROIs ($p_{FWE} > 0.05$).

PTSD patients did not show significantly different neural responses during reward and loss anticipation compared to controls under placebo, nor were there any significant interaction effects of group by sex and/or trial type (whole brain or ROI, $p_{FWE} > 0.05$).

3.3.2. Effect of oxytocin administration

Within ROI analyses, oxytocin administration significantly increased reactivity during reward and loss anticipation in the left striatum (putamen, $xyz = -26,10,4$, $Z = 3.93$, $k = 36$, $p_{FWE} = 0.044$, Fig. 2a), right striatum and insula (putamen, $xyz = 28,0,14$, $Z = 4.10$, $k = 33$, $p_{FWE} = 0.024$; insula, $xyz = 32,2,14$, $Z = 4.02$, $k = 9$, $p_{FWE} = 0.033$, Fig. 2b), and right dorsal ACC (dACC, $xyz = 16,34,22$, $Z = 3.79$, $k = 9$, $p_{FWE} = 0.045$, Fig. 2c), compared to placebo, independent of trial type, group and sex. No significant interaction effects of medication by group, sex and/or trial type were observed ($p_{FWE} > 0.05$). No significant oxytocin effects were seen on whole brain level. Oxytocin effects in the putamen, insula and dACC remained significant after controlling for block-order.

3.4. Neural reward responses and anhedonia in PTSD patients

We correlated ventral striatal responses during reward and loss anticipation with anhedonic symptom severity within PTSD patients. As anhedonic symptoms were virtually absent in controls,

Table 1
Participant characteristics.

	Males		*p*-Value	Females		*p*-Value
	Control ($n = 19$)	PTSD ($n = 21$)		Control ($n = 18$)	PTSD ($n = 14$)	
Age (years)	41.11 (10.86)	42.29 (9.83)	0.720	38.06 (9.08)	38.21 (9.85)	0.963
Educational level						
Low	0 (0%)	0 (0%)	0.874	0 (0%)	0 (0%)	0.370
Medium	15 (79%)	17 (81%)		17 (94%)	14 (100%)	
High	4 (21%)	4 (19%)		1 (6%)	0 (0%)	
Years of police service	18.08 (10.21)	19.07 (14.93)	0.819	17.83 (9.56)	15.21 (10.81)	0.473
Police work-related trauma (PLES)	20.32 (6.57)	22.50 (5.95)	0.242	19.44 (7.68)	13.64 (10.09)	0.074#
Childhood trauma (ETI)	3.79 (2.32)	6.10 (4.55)	0.049*	4.22 (5.02)	5.50 (5.43)	0.456
PTSD symptom severity (CAPS)	4.58 (4.89)	68.05 (15.62)	0.000**	4.67 (4.80)	67.79 (10.55)	0.000**
MDD Comorbidity, N(%)	0 (0%)	4 (19%)	0.045*	0 (0%)	4 (29%)	0.015*
Contraceptive use (%)						
None	–	–	–	8 (44%)	6 (43%)	0.910
Hormonal contraceptive	–	–		8 (44%)	7 (50%)	
Menopausal	–	–		2 (11%)	1 (7%)	

Group differences between patients and controls were tested with independent-sample *t*-tests or χ^2-tests, ** = *p*-value < .001; * = *p*-value < .050; # = *p*-value < .100. PLES, police life events scale (Carlier and Gersons, 1992); ETI, early trauma inventory – short version (Bremner et al., 2007); CAPS, Clinician Administered PTSD Scale (Blake et al., 1995).

these analyses were conducted in PTSD patients only (see Supplemental Table S4 for means and standard deviations). Under placebo, severity of diminished interest in activities was significantly negatively correlated with left striatal responses during reward anticipation ($r_{PL} = -0.352$, $p = 0.038$, Fig. 3). After oxytocin administration, diminished interest severity was no longer significantly associated with striatal responses to reward ($r_{OT} = 0.145$, $p = 0.406$). These correlation coefficients were significantly different from each other, as tested with Steiger's *Z*-test (*Z*-score = −2.222, $p = 0.025$). Furthermore, diminished interest was significantly positively correlated with the effect of oxytocin on striatal responses ($r_{\Delta OT\text{-}PL} = 0.362$, $p = 0.033$). Results remained significant after exclusion of PTSD patients with comorbid MDD, and after correction for PTSD severity (CAPS total score) ($p < 0.05$). Diminished interest severity showed similar correlations with right striatal responses and bilateral striatal responses to loss, but these did not reach statistical significance. Severity of reduced positive affect and feelings of detachment were not significantly correlated with striatal responses during reward and loss anticipation in PTSD patients (all $p > 0.05$).

4. Discussion

We investigated whether a single intranasal oxytocin administration affecedt motivational processing in PTSD patients and traumatized controls. We found that oxytocin administration increased neural responses during monetary reward and loss anticipation in the bilateral putamen, right dACC and right insula in male and female PTSD patients and trauma-exposed controls, suggesting that oxytocin increases motivational processing.

Despite previous findings of decreased reward and increased loss sensitivity in PTSD patients compared to controls (Admon et al., 2013; Elman et al., 2009; Felmingham et al., 2014; Frewen et al., 2010; Mazza et al., 2015; Moser et al., 2015; Sailer et al., 2008), we did not observe baseline differences in responses during reward or loss anticipation between PTSD patients and traumatized controls in our sample. However, our exploratory analyses under placebo showed that within PTSD patients, symptom severity of diminished interest in activities was negatively related to ventral striatal responses during reward anticipation (independent of comorbid MDD). This fits with the notion that symptoms of diminished interest, or motivational anhedonia, are related to reduced neural responses specifically during anticipation of reward

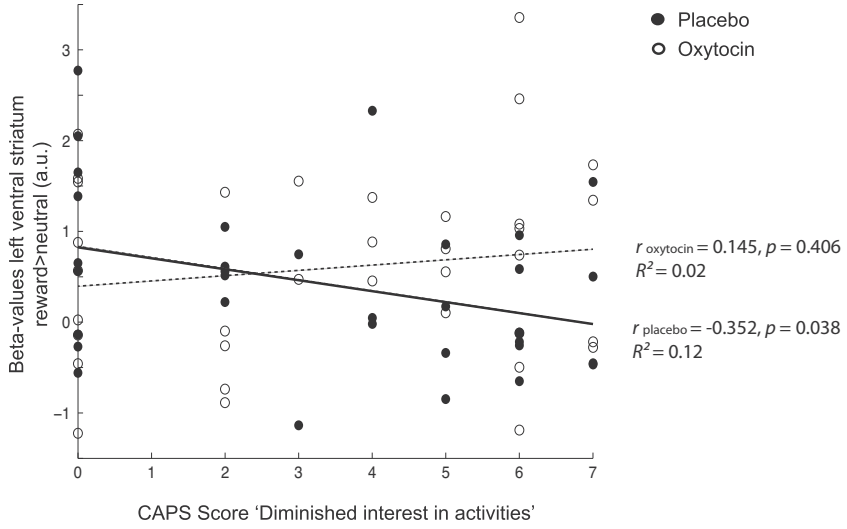

Fig. 3. Anhedonia and ventral striatal responses to reward under placebo and oxytocin. Scatterplot showing the correlation between PTSD symptom severity of 'diminished interest in activities' (*X*-axis, based on Clinician Administered PTSD scale (CAPS) item C4) and beta-values of left ventral striatal responses during reward anticipation (*Y*-axis, arbitrary units) for PTSD patients under placebo (black dots, black regression line, $r_{PL} = -0.352$, $p = 0.038$) and oxytocin (white dots, dotted regression line, $r_{OT} = 0.145$, $p = 0.406$). The effect of oxytocin (oxytocin minus placebo) was significantly related to diminished interest in activities ($r_{\Delta OT\text{-}PL} = 0.362$, $p = 0.033$).

(Der-Avakian and Markou, 2012). We hereby replicate previous findings in PTSD (Elman et al., 2009; Felmingham et al., 2014), as well as other psychiatric populations and healthy individuals (Keedwell et al., 2005; Wacker et al., 2009), suggesting that striatal hyposensitivity is related to anhedonia severity. This may explain inconsistent findings of reward functioning in PTSD patients in the past (Nawijn et al., 2015), as anhedonic symptoms are not equally present in all PTSD patients. Additionally, most previous studies did not include trauma-exposed controls (Elman et al., 2009; Frewen et al., 2010; Sailer et al., 2008), whereas our controls reported high levels of trauma exposure. Trauma exposure in itself is also related to reduced reward processing (Pizzagalli, 2014), and may therefore be a confounding factor in previous research.

Interestingly, the effect of oxytocin administration on striatal responses during reward anticipation in PTSD patients was also dependent on severity of diminished interest; levels of diminished interest were inversely correlated with ventral striatal responses during reward anticipation under placebo, but also positively correlated with increases in ventral striatal responses after oxytocin relative to placebo. This fits with literature suggesting that oxytocin can optimize neural processing specifically in individuals with suboptimal performance (e.g. Bartz et al., 2011; Groppe et al., 2013). It is possible that oxytocin reduced acute anhedonia scores while increasing ventral striatal responses to reward. Unfortunately, acute effects of oxytocin on anhedonia were not measured at the time of scanning, therefore this interpretation cannot be tested in the current dataset.

Besides anhedonia-related effects, oxytocin enhanced neural responses during reward and loss anticipation in the putamen, insula and dACC, in both PTSD patients and controls, independent of sex and valence. The putamen, insula and dACC are functionally connected and part of the reward pathway (Haber and Knutson, 2010). The putamen is involved in reward and loss prediction, establishing stimulus-response contingencies and preparation of approach behavior (Liu et al., 2011), its responses increasing with increasing reward probability (Yacubian et al., 2007). The dACC is involved in weighing reward magnitude relative to effort needed to obtain the reward, crucial for decision making and maintaining goal-directed behavior (Liu et al., 2011). The insula has an important role in valence assessment of positive and negative stimuli, directing attention towards salient cues in the environment (Liu et al., 2011). Reduced activity within these three regions have been linked to anhedonia (e.g. Frewen et al., 2012; Wacker et al., 2009). Taken together, this suggests that by increasing neural responses in these areas during reward and loss anticipation, oxytocin enhances motivational processing. Oxytocin-induced enhanced putamen responses during reward and loss anticipation may increase subjective reward expectancy and facilitate goal-directed behavior to obtain rewards and prevent loss. Oxytocin-induced increased dACC responses to reward and loss anticipation may increase the willingness to expend effort to maximize reward outcome, whereas increased insula activation suggests increased salience and attentional processing. Oxytocin did not affect reaction times, resembling findings by Groppe et al. (2013), nor accuracy. Although Groppe et al. (2013) did observe increased accuracy in a subgroup of participants with low hit rates under placebo, accuracy levels in our sample were relatively high under placebo (>80% of feasible trials), leaving little room for improvement by oxytocin.

Our results of increased putamen and insula responses upon oxytocin administration fit with previous findings of oxytocin-induced increased striatal and insula responses to (social) reward in healthy participants (Feng et al., 2014; Scheele et al., 2013; Striepens et al., 2014) and anticipation of social reward and punishment in healthy participants (Groppe et al., 2013). Regarding the ACC, previous studies reported oxytocin-induced increases in more rostral and ventral parts of the ACC (ventromedial PFC/rostral ACC) in response to positive social stimuli (e.g. Striepens et al., 2014), relative to the more dorsal effects in the current study. Whereas the vmPFC and rACC are involved in value assessment and respond mainly to positive stimuli, the dACC is involved in value- and effort-evaluation and responds to both positive and negative stimuli (Liu et al., 2011), which may explain the more dorsal effects observed in our study.

Oxytocin had similar neural effects in PTSD patients and controls. Previously however, effects of oxytocin were found to depend on clinical status, e.g., dampening amygdala responses towards negative emotional faces in psychiatric patients, but not in controls (Bertsch et al., 2013; Dodhia et al., 2014; Gorka et al., 2015; Labuschagne et al., 2010). Also, in the same sample as the current study, we observed that oxytocin decreased amygdala responses towards emotional faces in PTSD patients compared to placebo, but enhanced responses in controls (Koch et al., 2015). In relation to motivational processing, differential effects of oxytocin have been observed depending on sex (Feng et al., 2014; Rilling et al., 2014, discussed below). In all these studies, oxytocin was beneficial specifically in participants with compromised or sub-optimal neural responsiveness under placebo (Bertsch et al., 2013; Dodhia et al., 2014; Feng et al., 2014; Gorka et al., 2015; Koch et al., 2015; Labuschagne et al., 2010; Rilling et al., 2014). These findings fit with the notion that oxytocin may affect functioning according to an inverted-U-shaped dose-response curve; enhancing functioning in participants with suboptimal performance, but having no effect or even overstimulating participants with already optimal performance (Feng et al., 2014; Rilling et al., 2014). Thus, it is possible that differential oxytocin effects were absent in our study because PTSD patients as a group did not differ from controls under placebo, but it also poses the interesting idea that both PTSD patients and controls were performing suboptimal under placebo, and both groups still had room for improvement.

Only Groppe et al. (2013) have previously investigated oxytocin effects on anticipation of both positive and negative outcomes. Our results are in line with their findings that oxytocin increased striatal and insula responses during social reward and loss anticipation in healthy individuals. We are the first to show that this also holds for monetary reward and loss anticipation, both in PTSD patients and healthy trauma-exposed individuals. Our findings support the notion that oxytocin administration has a more general effect on approach behavior, which extends beyond social stimuli to salient non-social stimuli (Harari-Dahan and Bernstein, 2014). As anticipation of monetary and social reinforcers is processed in the same regions of the reward pathway (Rademacher et al., 2010), this could explain similar effects of oxytocin on social and non-social reward and loss anticipation (Groppe et al., 2013). Future studies may provide further insight in how oxytocin affects motivational sensitivity. Animal studies indicate that oxytocin exerts its effects on motivational processing by interacting with the neurotransmitter dopamine, but its precise mechanisms, especially in humans, remain to be elucidated (Striepens et al., 2014).

It is important to note that increased motivation for loss prevention does not necessarily indicate increased sensitivity for negative stimuli themselves. The occurrence of negative stimuli in the MID task (i.e., monetary loss) can be prevented by a simple button press. Increased striatal responses during reward and loss anticipation have been related to increased motivational behavior, such as faster reaction times on reward and loss trials (Kohls et al., 2013). Thus, the observed effects of oxytocin are thought to increase the motivational salience of reward and loss cues, thereby facilitating the biological readiness for approach behavior, in this case responding to the target stimulus with a button press to obtain reward or prevent loss. By increasing reward pathway responses, oxytocin may induce a state of motivated alertness, optimal for interacting with the environment and maximizing reward retrieval (Harari-Dahan

and Bernstein, 2014). However, as some previous studies have shown increased neural responsiveness and behavioral sensitivity during anticipation of negative reinforcers in PTSD patients compared to controls (Admon et al., 2009; Aupperle et al., 2012; Hopper et al., 2008), albeit in different brain areas and paradigms, oxytocin effects on sensitivity to negative reinforcers must be investigated with care in future studies.

This is one of the first studies looking at sex-dependent effects of oxytocin administration, a topic of debate (Macdonald, 2012). In our study, the effects of oxytocin did not differ by sex. This finding corroborates previous studies, in which oxytocin increased approach behavior and reward responses in both male (Scheele et al., 2013; Striepens et al., 2014) and female populations (Groppe et al., 2013; Preckel et al., 2014). However, it is at odds with two previous studies that have formally tested sex differences in oxytocin effects. In these studies, oxytocin increased putamen responses to positive stimuli in males, but had no effect or even decreased putamen responses in females (Feng et al., 2014; Rilling et al., 2014). Task differences may account for these discrepancies, as both previous studies used a prisoners dilemma task, incorporating social concepts such as trust and cooperation, which are absent in the MID. Also, these previous studies found sex differences under placebo, which were absent in our study. This suggests that baseline sex differences, possibly associated with different task characteristics, may explain the differential effects of oxytocin between our and previous studies. However, compared to Rilling and coworkers (Feng et al., 2014; Rilling et al., 2014), our sample of men and women was relatively small, which may have affected power to detect more subtle sex differences. Furthermore, we have not controlled for menstrual phase in our female participants, which is known to interact with oxytocin (Gimpl and Fahrenholz, 2001). Although the effects of menstrual phase will likely have averaged out over groups and sessions, we cannot exclude the possibility that menstrual cycle influenced the (lack of) sex-specific task and oxytocin effects in our study.

Our results suggest that oxytocin administration can impact the neurobiological mechanisms underlying motivational anhedonia in PTSD patients, and thereby potentially increase motivation to engage in activities. Likewise, in schizophrenic patients, a three-week oxytocin administration regimen reduced motivational and consummatory anhedonic symptoms (Lee et al., 2013). As oxytocin administration is also thought to reduce anxiety and enhance emotion regulation (Koch et al., 2014), it may benefit PTSD patients through several neurobiological pathways (Olff et al., 2010). However, adverse effects of oxytocin administration in healthy and psychiatric populations have also been reported, and are thought to depend on context and inter-individual factors (Bartz et al., 2011). Therefore, applying oxytocin as an add-on to psychotherapy may be more promising than as a stand-alone treatment (Koch et al., 2014). As motivation for treatment and expectancy of treatment success are crucial for treatment response (Clarke et al., 2013; Schindler et al., 2013), enhancing motivational processing may well benefit treatment efficacy. Furthermore, oxytocin effects on reward and loss sensitivity may also increase motivation for social reinforcers (Groppe et al., 2013) in PTSD patients, as anticipatory processing of social and monetary reinforcers are largely dependent on the same neurobiological pathways (Harari-Dahan and Bernstein, 2014; Rademacher et al., 2010). Thus, oxytocin may also enhance sensitivity for social support and therapeutic alliance (Olff et al., 2010), which are important predictors of treatment response (e.g. Clarke et al., 2013; Thrasher et al., 2010). In line with this hypothesis, in a small pilot in PTSD patients, oxytocin increased desire for social interaction (Yatzkar and Klein, 2010).

Some limitations must be noted. The fact that all participants were police officers resulted in a relatively homogeneous group in which controls and patients were comparable in terms of trauma-exposure, leaving less potential confounding factors. However, this also potentially hampers generalization to the whole PTSD population. Furthermore, while we are confident that the carry-over effects between MID and SID are limited and block-order did not affect our findings, we cannot fully exclude the possibility that the SID task may have affected behavioral or neural responses during the MID task. Also, although ventral striatal oxytocin effects in PTSD patients were dependent on clinical symptoms prior to oxytocin intake (i.e., diminished interest), we did not measure the effects of oxytocin on changes in acute (anhedonic) PTSD symptoms. It must further be noted that the measures of anhedonia consisted of single CAPS items. Although item scores were obtained after careful interrogation by an experienced interviewer, these may not fully capture the concept of (motivational) anhedonia. In future studies, it would be of interest to additionally use self-report questionnaires that separately assess motivational and consummatory anhedonia, like the Temporal Experience of Pleasure Scale (Gard et al., 2006). While our findings are encouraging, neural effects on fMRI tasks do not necessarily translate to clinical effects, and future clinical studies are crucial for proper translation into clinical practice.

5. Conclusions

Taken together, we observed that a single oxytocin administration increased reward pathway reactivity during reward and loss anticipation, likely reflecting increased neural motivational processing in both PTSD patients and traumatized controls. Although no baseline differences between PTSD patients and controls were observed, the severity of diminished interest symptoms was negatively related to reward processing in PTSD patients. Additionally, oxytocin administration alleviated these anhedonia-related neural reward deficits, suggesting oxytocin may be specifically beneficial for PTSD patients reporting diminished interest in activities. In sum, our findings provide evidence for a neurobiological pathway through which oxytocin administration can increase motivational behavior and engagement with the environment in PTSD patients. From a clinical perspective, oxytocin may be an interesting candidate to apply in adjunction to psychotherapy, during which it may facilitate motivation for treatment, which is crucial for treatment success. Future clinical trials should be conducted to investigate whether oxytocin administration in adjunct to psychotherapy is indeed beneficial for PTSD patients.

Contributors

All authors have contributed to the manuscript and have approved the present version. Miranda Olff designed the initial concept of the study and obtained funding. All authors contributed to the design of the study. Laura Nawijn and Saskia Koch performed all data acquisition. Laura Nawijn performed all data analyses. Laura Nawijn and Mirjam van Zuiden drafted the manuscript. All authors have performed critical review of the article and have approved the final version.

Conflicts of interest

The authors report no biomedical financial interests and no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.01.020.

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