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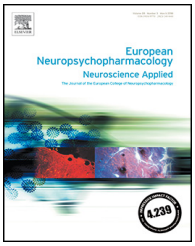

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Effects of intranasal oxytocin on distraction as emotion regulation strategy in patients with post-traumatic stress disorder

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Abstract
Post-traumatic stress disorder (PTSD) is characterized by difficulty down-regulating emotional responses towards trauma-reminders. The neuropeptide oxytocin may enhance treatment response in PTSD, by dampening excessive fear and improving fear regulation. However, oxytocin effects on (neural correlates of) cognitive emotion regulation abilities have never been investigated in PTSD patients. Therefore, we investigated behavioral and neural effects of intranasal oxytocin administration (40IU) on distraction as emotion regulation strategy in male and female police officers with and without PTSD ($n = 76$), using a randomized placebo-controlled cross-over fMRI study. The distraction condition consisted of a working memory task while negative affective pictures were presented. Under placebo, male PTSD patients showed decreased right striatal activity during distraction compared to male trauma-exposed controls, which was unaffected by oxytocin. After oxytocin administration, left thalamus activity during distraction was enhanced in all participants, independent of PTSD status or sex. Although left thalamus activity during distraction did not differ between PTSD patients and controls under placebo, it was negatively correlated with error rates within PTSD patients. Furthermore, oxytocin administration increased functional connectivity between the left thalamus and amygdala in PTSD

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patients and male trauma-exposed controls. Upregulation of thalamus activity during distraction by oxytocin may enhance cognitive emotion regulation abilities during psychotherapy in PTSD, although this should still be investigated in a clinical setting. Our findings open an important research avenue into oxytocin effects on cognitive emotion regulation in PTSD and other psychiatric disorders characterized by deficient emotion regulation abilities. Registered in the Netherlands Trial Registry, registration number: NTR3516

1. Introduction

Post-traumatic stress disorder (PTSD) can develop after exposure to a traumatic event (American Psychiatric Association, 2013). Corresponding with symptoms of ongoing emotional and physiological distress towards trauma reminders (American Psychiatric Association, 2013), PTSD has been conceptualized as disorder of emotion regulation (Lanius et al., 2010). In line with this conceptualization, PTSD is associated with impaired down-regulation of emotional, physiological and neural responding towards (potentially) threatening and trauma-related stimuli (Ehlers et al., 2010; Hayes et al., 2012). Neurobiological correlates of PTSD include hyperactivity and hyperconnectivity in salience processing areas, including the amygdala, anterior insula and dorsal anterior cingulate cortex (dACC) (Hayes et al., 2012; Patel et al., 2012; Sripada et al., 2012b). Furthermore, meta-analytic findings of bilateral thalamus hypo-activity during symptom provocation studies indicate impaired thalamus recruitment towards trauma-related stimuli in PTSD (Hayes et al., 2012). Additionally, observations of ventromedial prefrontal cortex (vmPFC) hypo-activity and decreased connectivity between the vmPFC, amygdala and hippocampus in PTSD suggest diminished top-down prefrontal control over the (amygdala-mediated) fear response (Koch et al., 2016; Sripada et al., 2012a), thought to underlie the aforementioned emotion dysregulation (Rauch et al., 2006). For example, enhanced attentional bias for trauma-related stimuli has been linked to deficits in rapid regulatory activation of the caudate nucleus and midline frontal regions involved in fear regulation (Todd et al., 2015).

Emotion regulation refers to all conscious and non-conscious regulatory processes altering the experience or expression of emotions (Ochsner et al., 2002) and emotional actions (Roelofs et al., 2009). Cognitive emotion regulation strategies include reappraisal (changing the interpretation of the stimulus) (Ochsner et al., 2002) and distraction (diverting attention away from the emotional content, e.g. by performing a working memory (WM) task) (Kanske et al., 2011). In healthy individuals, automatic emotion regulation processes involve the hippocampus, and medial prefrontal cortical structures, including the anterior cingulate cortex (ACC) (Phillips et al., 2008). Cognitive emotion regulation results in more positive affect, recruitment of frontoparietal and dorsal midline cortices and altered activation in emotional processing and salience detection areas, such as the amygdala and insula (Etkin et al., 2015; Kanske et al., 2011). Furthermore, emotion regulation success has been associated with greater recruitment of the ventrolateral prefrontal cortex, caudate nucleus and thalamus during cognitive reappraisal (Wager et al., 2008a). PTSD has been associated with impaired down-regulation of negative affect (Rabinak et al., 2014; Xiong et al., 2013), and with dorsolateral (dlPFC) and dorsomedial prefrontal cortex (dmPFC) hypo-activity during cognitive reappraisal (New et al., 2009; Rabinak et al., 2014), adding to the evidence for impaired (neural) emotion regulation abilities in PTSD.

Treatments of choice for PTSD, such as exposure therapy, cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) therapy, all involve exposure to reminders of the traumatic event as well as emotion regulation aspects (Schnyder et al., 2015). Notably, during EMDR, traumatic memory retrieval is interrupted by a secondary task taxing WM (commonly eye movements), resulting in decreased vividness and emotionality of the traumatic memory (Gunter and Bodner, 2008). Although generally effective, approximately one-third of PTSD patients does not fully recover upon receiving trauma-focused psychotherapy (Bradley et al., 2005), underlining the need for adjuvant interventions to enhance therapy response. Improving cognitive emotion regulation skills prior to or during psychotherapy may result in enhanced treatment response, possibly via increased tolerance to exposure-related distress (Bryant et al., 2013; Cloitre et al., 2010).

Cognitive emotion regulation abilities may be boosted with psychopharmacological agents, such as the neuropeptide oxytocin. Previous studies found blunted amygdala responsiveness towards emotional stimuli (Domes et al., 2007; Kirsch et al., 2005) and increased functional connectivity between the amygdala and vmPFC (Sripada et al., 2013) after oxytocin administration in healthy males, and in psychiatric patients with high anxiety (Bertsch et al., 2013; Dodhia et al., 2014; Labuschagne et al., 2010). Moreover, we recently observed that oxytocin administration in PTSD patients decreased subjective anxiety and nervousness (Koch et al., 2016), dampened amygdala reactivity towards emotional faces (Koch et al., 2015), and normalized functional connectivity of amygdala subregions with the prefrontal cortex to the level of healthy trauma-exposed controls (Koch et al., 2016). Hence, by dampening fear responsiveness and improving fear regulation abilities, oxytocin may enhance treatment response in PTSD (Olff et al., 2010). However, oxytocin effects on the ability to use cognitive emotion regulation strategies, such as distraction, have not been studied in psychiatric patients yet.

Therefore, we investigated effects of oxytocin administration on behavioral and neural correlates of distraction as cognitive emotion regulation strategy in male and female police officers with and without PTSD, using a randomized, placebo-controlled, cross-over fMRI study. We hypothesized to observe impaired down-regulation of negative affect and of activity in emotion processing areas (i.e., amygdala and

insula), as well as deficient up-regulation of emotional control areas (i.e., thalamus, hippocampus, caudate nucleus, anterior cingulate cortex and medial prefrontal cortex) during distraction in PTSD patients, which would be improved after oxytocin administration. We included both male and female participants to investigate possible sex differences in neurobiological and cognitive emotion regulation deficits associated with PTSD- and oxytocin effects.

2. Experimental procedures

2.1. Participants and procedure

We included 36 PTSD patients (21 males) and 40 trauma-exposed controls (20 males). Participants were all (former) police officers, between 18 and 65 years old and eligible for MRI. They did not use psychotropic medication, had no history of neurological disorders, and females were not pregnant or breastfeeding. Participants were recruited via a psychodiagnostic center for police personnel (Diemen, the Netherlands, patients only) and via advertisements in journals and on websites of the Dutch police. PTSD patients met current DSM-IV diagnostic criteria for PTSD, with a Clinician-Administered PTSD Scale (CAPS) score of $\geq$ 45 (Blake et al., 1995). Current comorbidity was assessed with the Mini International Neuropsychiatric Interview (MINI-plus) (Sheehan et al., 1998) or the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002). PTSD patients were excluded if they met DSM-IV criteria for current psychotic disorder, severe major depressive disorder (MDD) (i.e., involving suicidal ideation and/or psychotic symptoms), substance abuse, suicidal ideation, or reported personality disorder. Trauma-exposed controls were matched to patients on sex, age, years of service and educational level. They were exposed to at least one potentially traumatic event (DSM-IV A1 criterion), with a current CAPS score of $<$ 15. Exclusion criteria for controls were lifetime history of PTSD or MDD and any current DSM-IV axis-I or reported personality disorder.

This randomized, placebo-controlled cross-over fMRI study consisted of two scanning sessions, on average 11.51 ($\pm$ 9.89) days apart. Participants abstained from alcohol and drugs 24 h prior to scanning and from rigorous exercise, beverages (except for water) and nicotine 2.5 h before scanning. Participants self-administered either placebo (0.9% saline) or intranasal oxytocin (Syntocinon, 40IU, 5 puffs per nostril) under experimenter supervision. Intranasal spray was applied on average 83.48 ($\pm$ 4.21) minutes before task performance, when neural effects of oxytocin are still observed (i.e., at least up to 80 minutes post-administration) (Paloyelis et al., 2014). Drug-order was randomized, double-blind and counterbalanced between sessions. The study was approved by the Institutional Review Board of the AMC in Amsterdam, the Netherlands and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before study participation.

2.2. Distraction task

The distraction task (McRae et al., 2010) consisted of three conditions: passive viewing of neutral or negative pictures (attend-neutral & attend-negative) and distraction from negative pictures (distract-negative) (Fig. 1A and B). During both passive viewing conditions, participants were instructed to passively attend to the picture. In the distraction condition, participants were first presented

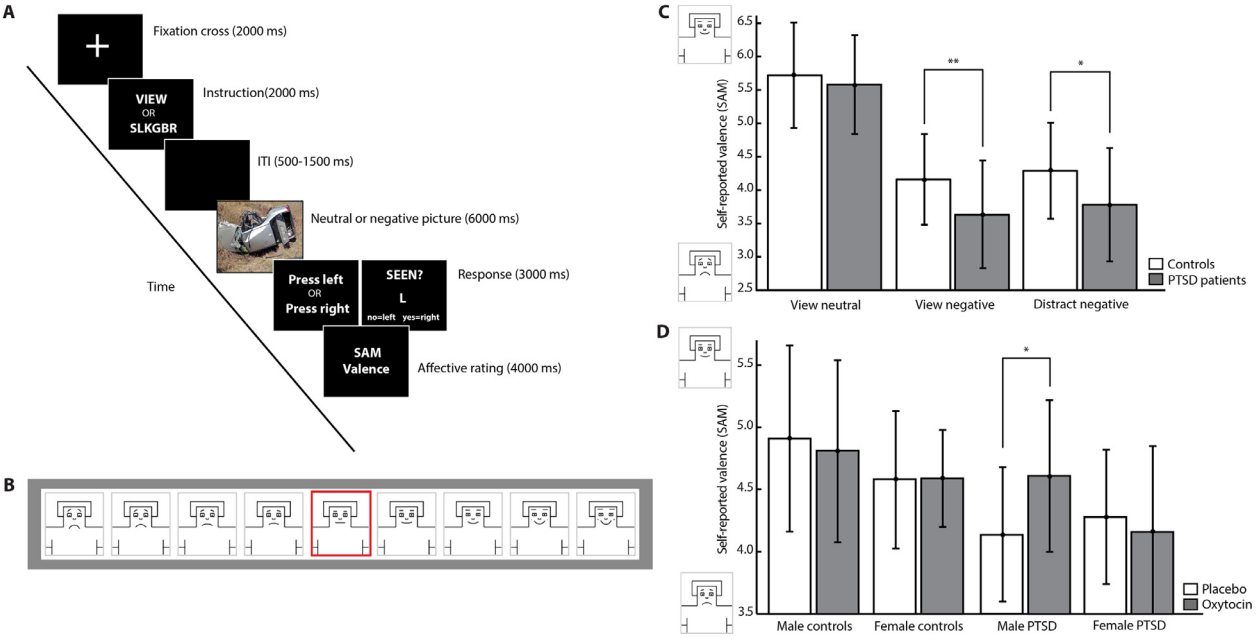

Fig. 1 Distraction task and behavioral effects. A. Design of the distraction task. The distraction task consisted of three conditions: (1) passive viewing of neutral pictures, (2) passive viewing of negative pictures and (3) working memory task (distraction) during the presentation of negative pictures. In the working memory condition, participants had to remember a six letter string. B. After each trial, valence ratings were assessed using self-assessment manikins (SAM) on a 9-point scale, ranging from 1 (negative affect) to 9 (positive affect). C. Mean ($\pm$ standard deviations) of valence ratings of negative and neutral pictures in the distraction task for trauma-exposed controls and PTSD patients (collapsed across sex) under placebo. D. Mean ($\pm$ standard deviations) of valence ratings under placebo and oxytocin for male and female trauma-exposed controls and PTSD patients (collapsed across task versions). $^{*}p < 0.05$; $^{**}p < 0.01$.

with a six letter string, which had to be remembered during subsequent presentation of the negative picture. When the negative picture disappeared, a letter was shown and participants had to indicate with a button press whether that letter was part of the previously presented string. During both passive viewing conditions, participants were asked to press either the left or right button after picture presentation, to keep motor responses constant across conditions. After each picture, emotional state was evaluated with self-assessment manikins (SAM), on a 9-point scale ranging from 1 (negative valence) to 9 (positive valence).

Neutral and negative pictures were selected from the International Affective Picture System (IAPS), based on normative valence and arousal ratings (Lang et al., 2008). Two task versions, each consisting of 20 neutral and 40 negative pictures, were used. Pictures in both tasks were matched for normative valence and arousal ratings, complexity and luminescence (all $p > 0.05$). The order of task versions was randomized and counterbalanced between sessions. After each scanning session, participants rated a random subset of presented pictures (10 images per task condition) on valence and arousal using 9-point SAMs (valence: negative valence (1) - positive valence (9); arousal: aroused (1) - calm (9)) (Supplementary Table S1).

2.3. MRI acquisition

We acquired structural and functional MRI images with a 3T Philips Achieva MR system, using a 32-channel head coil. We used a FAST MPRage sequence to obtain a high-resolution T1-weighted structural image (220 slices; voxel size = 1 mm^3; repetition time = 8.2 s; echo time = 3.8 s; flip angle = 8°) and an echo planar sequence sensitive to the BOLD contrast for functional images (540 volumes; voxel size = 3 mm^3; repetition time = 2 s; echo time = 28 ms; flip angle = 76°).

2.4. Statistical analysis

2.4.1. Behavioral analysis

Significant outliers (standardized value > |3.29|) were removed ($n = 3$ for fMRI valence ratings) and non-normally distributed variables were log-transformed to obtain normal distributions. Differences between PTSD patients and controls on demographics, trauma history and PTSD symptom severity were tested within males and females separately, using independent sample *t*-tests (normally distributed) or Mann Whitney *U* tests (non-normally distributed, i.e., when transformation did not result in normal distribution) for continuous and Chi-square tests for categorical variables.

Repeated measures analyses of covariance (ANCOVA's) were performed on valence ratings, with within-subject factors task condition (attend-neutral, attend-negative, distract-negative) and drug (placebo - oxytocin), between subject-factors group (PTSD - control) and sex (male - female) and covariate drug-order. Group differences in error-rates and reaction times were tested in the distraction condition only, because of high performance accuracy in the passive viewing conditions. Post-hoc tests were corrected for multiple comparisons using the Benjamin-Hochberg false-discovery rate (FDR) correction (Bejamin and Hochberg, 1995). An adjusted *p*-value of < 0.05 was considered significant.

2.4.2. fMRI analysis

Functional images were analyzed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing involved realignment, slice-time-correction, co-registration, segmentation, normalization to the Montreal Neurological Institute (MNI) template, resampling to 2 mm^3 voxels and smoothing with a 6 mm full-width half maximum Gaussian kernel. At first level, we included the six realignment parameters and a high-pass filter (cut-off 1/128 Hz), and removed temporal autocorrelation using the AR(1) process.

First-level contrast images for attend-negative > attend-neutral and distract-negative > attend-negative were used in two separate second-level repeated measures ANCOVA's, with group and sex as between-subjects factors, drug as within-subjects factor and drug-order as covariate. To investigate overall task effects and baseline differences between PTSD patients and trauma-exposed controls, the abovementioned models were additionally estimated for images acquired under placebo only.

Regions of interests (ROIs) for the bilateral amygdala, hippocampus, thalamus, dorsal striatum (i.e., caudate and putamen combined), insula, anterior cingulate cortex (ACC) and middle frontal gyrus (MFG) were anatomically defined using the 50% Harvard-Oxford probability atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and based on previous findings of the neural circuitry of emotion regulation (Kanske et al., 2011; Rive et al., 2015; Tyborowska et al., 2016). For all main and interaction effects, family-wise error (FWE) correction for multiple comparisons was conducted at the whole-brain level ($p_{FWE} < 0.05$) and for each ROI (small volume corrected, SVC), based on an initial cluster-forming threshold of $p < 0.001$. For the volume of interest analyses, we additionally corrected for multiple comparisons of the 7 ROIs with a Bonferroni correction, yielding *p*-values of < 0.0071 (i.e., 0.05/7) significant. We conducted correlation analyses between extracted contrast estimates from significant activation clusters and behavioral task performance (i.e., reaction times, error rates and affective ratings), using Pearson correlations for normally distributed variables (i.e., reaction times and affective ratings) and Spearman rank correlations for non-normally distributed variables (i.e., error rates). Given the age range of our participants (i.e., 22-59 years of age), we additionally investigated whether observed neural (oxytocin) effects were associated with age, by conducting Pearson correlation analyses between the abovementioned extracted contrast estimates and age. Five participants were excluded due to scanning artifacts ($n = 2$) and movement ($n = 3$), leaving 34 PTSD patients (20 males) and 37 trauma-exposed controls (19 males) for the final analyses.

2.4.3. Effective connectivity analysis

Following the results of oxytocin administration on thalamus activity during distraction (see Results below), we explored whether oxytocin administration also affected interregional functional connectivity of the thalamus during distraction. We conducted a psychophysiological interaction (PPI) analysis (Friston et al., 1997), using the main drug effect on left thalamus activity during distraction (MNI *xyz* = −14, −10, 4) as seed region. Subject-specific contrast images of the PPI between time courses of the left thalamus and the distraction vs attend negative pictures conditions were generated for each drug condition. These contrast images were entered in a second-level full-factorial model with group and sex as between-subjects factors, drug as within-subjects factor and drug-order as covariate. To investigate overall task effects and baseline differences between PTSD patients and trauma-exposed controls, the abovementioned model was additionally estimated for images acquired under placebo only. Given previous findings of effective connectivity between the thalamus and amygdala during emotion regulation (Tyborowska et al., 2016), volume of interest analyses were conducted on the bilateral amygdala (based on the 50% Harvard-Oxford probability atlas).

3. Results

3.1. Participant characteristics

PTSD patients and trauma-exposed controls did not differ on demographic characteristics. Male PTSD patients experienced significantly more types of childhood traumatic events than male trauma-exposed controls ($t(39) = -2.180$,

Table 1 Participant characteristics.

	PTSD patients ($n=37$)		Healthy controls ($n=40$)		Statistics	
	Males ($n=21$)	Females ($n=16$)	Males ($n=20$)	Females ($n=20$)	Males	Females
Age (years)	42.29 (9.83)	37.56 (9.78)	41.35 (10.62)	38.65 (9.48)	$t(39)=-0.293$ $p=0.771$	$t(34)=0.337$ $p=0.738$
Years of service	16.29 (10.82)	14.53 (10.74)	18.42 (10.05)	18.60 (9.84)	$t(39)=0.655$ $p=0.516$	$t(33)=1.163$ $p=0.253$
Educational level						
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
					$\chi^2=0.006$	$\chi^2=1.694$
Middle	14 (67%)	15 (93%)	16 (85%)	17 (90%)		
					$p=0.939$	$p=0.193$
High	7 (33%)	1 (7%)	4 (15%)	3 (10%)		
CAPS total score	68.05 (15.62)	67.56 (11.83)	4.7 (4.79)	4.45 (4.66)	$t(39)=-17.728$ $p<0.0001$	$t(34)=-21.123$ $p<0.0001$
Current comorbidity						
MDD	4 (19%)	4 (25%)				
Dysthymia	2 (9.5%)	1 (6.3%)	n/a	n/a	n/a	n/a
Panic Disorder	1 (4.8%)	-				
Specific phobia	1 (4.8%)	-				
Work-related traumatic events (PLES)	22.50 (5.95)	13.50 (4.49)	20.45 (6.42)	19.4 (7.27)	$t(39)=-1.047$ $p=0.302$	$t(34)=2.114$ $p=0.042^*$
Childhood traumatic events (ETI)	6.09 (4.55)	5.25 (5.18)	3.65 (2.35)	4.25 (4.82)	$t(39)=-2.18$ $p=0.037^*$	$t(34)=-0.598$ $p=0.554$
Hormonal contraceptive use						
None	n/a	7 (44%)	n/a	8 (40%)	n/a	$\chi^2=0.690$
Hormonal		8 (50%)		9 (45%)		$p=0.708$
Menopause		1 (6%)		3 (15%)		
Alcohol use (AUDIT total score	3.52 (3.40)	4.06 (4.79)	3.40 (1.67)	3.15 (1.75)	$t(34.31)=0.723$ $p=0.474$	$t(34)=0.102$ $p=0.920$

Mean (±standard deviation) of demographics, trauma history and PTSD symptom severity for male and female PTSD patients and trauma-exposed controls. Number of different types of police-related traumatic events was measured with the Police life events scale (PLES) (total score) (Carlier and Gersons, 1992). The number of different types of childhood traumatic events was assessed with the early trauma Inventory - Short Form (ETI-SF) (Bremner et al., 2007).
PTSD = post-traumatic stress disorder; MDD = major depressive disorder; CAPS = clinician administered PTSD scale (Blake et al., 1995); AUDIT = alcohol use disorder identification test (Bush, 1998).

$p=0.037$), whereas female trauma-exposed controls experienced significantly more types of work-related traumatic events than female PTSD patients ($t(34)=2.114$, $p=0.042$) (Table 1). To ensure that observed results were not confounded by differences in trauma-exposure between PTSD patients and trauma-exposed controls, we repeated all fMRI analyses with number of different childhood and work-related traumatic events as covariates in the models. Severity of PTSD, anxiety and depression symptoms did not differ between scanning sessions (all $p>0.05$) (Supplementary Table S2).

3.2. Behavioral results

A significant main effect of task condition was found ($F(1.2,80.68)=7.85$, $p=0.004$): neutral pictures were rated more positive than negative pictures (attend-negative vs attend-neutral: $F(1,67)=9.38$, $p=0.003$; distract-negative vs attend-neutral: ($F(1,67)=7.07$, $p=0.010$) ($\alpha FDR=0.050$). We observed a nominally significant task condition by group interaction effect ($F(1.2,80.68)=3.56$, $p=0.055$): PTSD patients rated negative (attend-negative: $p=0.003$; distract-negative: $p=0.018$), but not neutral (attend-neutral: $p=0.5$) pictures as significantly more negative than trauma-exposed controls ($\alpha FDR=0.033$). For all participants, distraction did not result in less negative ratings of negative pictures compared to passive viewing ($p>0.5$) (Fig. 1C). Noteworthy, a significant drug by group by sex interaction was found ($F(1,67)=8.25$, $p=0.005$): male PTSD patients rated all pictures more positive after oxytocin compared to placebo ($p=0.003$). No significant oxytocin effects on affective ratings were found for trauma-exposed controls (males: $p=0.325$; females: $p=0.638$) or female PTSD patients ($p=0.089$) ($\alpha FDR=0.0125$) (Fig. 1D).

3.2.1. Online error rates and reaction time during distraction

PTSD patients tended to make more errors during distraction compared to trauma-exposed controls (group main effect: $F(1,69)=3.17$, $p=0.062$), irrespective of drug or sex.

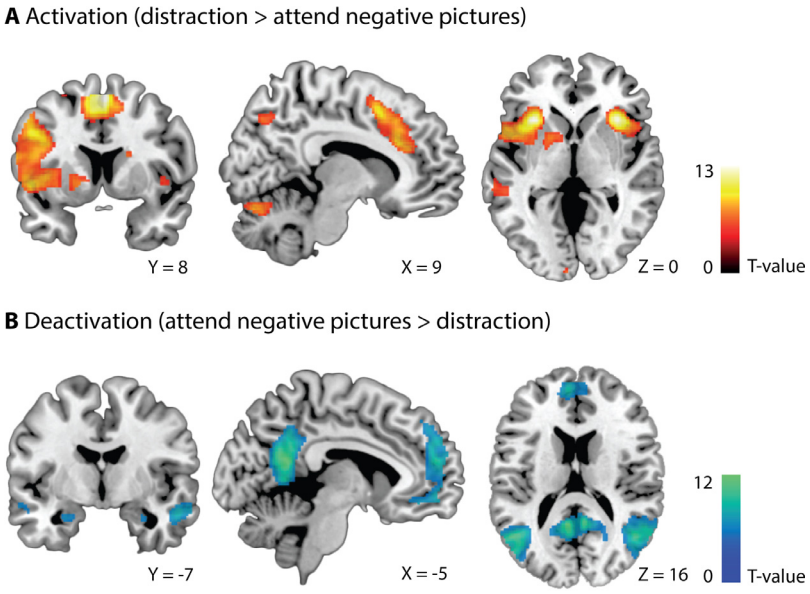

Fig. 2 Effects of distraction under placebo. Statistical maps of the overall task effect under placebo across all participants for A. activation during distraction (distraction > attend negative pictures) and B. deactivation during distraction (attend negative pictures > distraction). All $p_{FWE} < 0.05$ whole-brain corrected, minimal cluster-size = 20; Coordinates are given in MNI stereotaxic space.

All participants made more errors during distraction after oxytocin compared to placebo (main effect of drug: $(F(1,69) = 6.56,\ p = 0.013)$. These effects were driven by misses (i.e., no answer given within the allotted time: group main effect $p = 0.012$; drug main effect $p = 0.001$), and not by incorrect answers (all $p > 0.05$). No significant effects were found regarding reaction times in the distraction condition.

3.2.2. Post-scan ratings

Compared to the normative IAPS ratings, neutral and negative pictures were rated as significantly more positive and less arousing by all participants (all $p < 0.05$). Direct comparison between trauma-exposed controls and PTSD patients revealed higher arousal ratings of neutral and negative pictures and more negative valence ratings of negative pictures in PTSD patients (all $p < 0.05$; $\alpha FDR = 0.046$).

3.3. fMRI results

3.3.1. Effects of distraction

Under placebo, and across all participants, distraction activated emotional control areas, including the supplementary motor area (extending into the dorsal anterior cingulate cortex), anterior insula and middle frontal gyrus, as well as salience processing areas, such as the striatum and thalamus. Distraction down-regulated activity in the amygdala and hippocampus, precuneus and ventromedial prefrontal cortex (i.e., passive viewing negative pictures > distraction) (all $p_{FWE} < 0.05$, whole-brain corrected (See Fig. 2). See the supplementary material for all task effects under placebo, including results for the negative-attend > neutral-attend contrast.

3.3.2. Group differences under placebo

Under placebo, a significant group by sex interaction was found in the right caudate nucleus (peak voxel $xyz = 18, 6, 22$, $Z = 4.39$, $p_{SVC} = 0.006$; Fig. 3). Right caudate activity was found during distraction in male trauma-exposed controls ($p_{SVC} < 0.001$), but not in female trauma-exposed controls ($p_{SVC} = 0.411$), male ($p_{SVC} = 0.030$) or female PTSD patients ($p_{SVC} = 0.052$). Compared to male trauma-exposed, male PTSD patients showed decreased right caudate activity during distraction (peak voxel $xyz = 18, 6, 22$, $Z = 4.97$, $p_{SVC} < 0.001$), whereas no group differences were found for female participants ($p_{SVC} = 0.611$). No other significant effects of group, sex or group by sex interactions were found, both at the whole-brain level, nor in any of the ROIs (all corrected $p > 0.05$). These effects were not associated with participants' age, and comparable results were obtained after controlling for baseline group differences in trauma exposure.

3.3.3. Oxytocin effects

Oxytocin administration significantly enhanced left thalamus activity during distraction relative to passive viewing of negative pictures, compared to placebo (main effect of drug: peak voxel $xyz = -14, -10, 4$, $Z = 4.26$, $p_{SVC} = 0.007$; Fig. 4A and B), independent of PTSD status and sex (all $p > 0.05$ for all interaction effects). To functionally characterize this effect, we correlated contrast estimates of left thalamus activity with behavioral task performance during distraction, both under placebo and oxytocin. As error rates during distraction significantly differed between PTSD patients and trauma-exposed controls (see behavioral results and Supplementary Table 2), we conducted analyses for both groups separately. Under placebo, thalamus activity was negatively correlated with error rates during distraction in PTSD patients (spearman $\rho = -0.382$, $p = 0.031$;

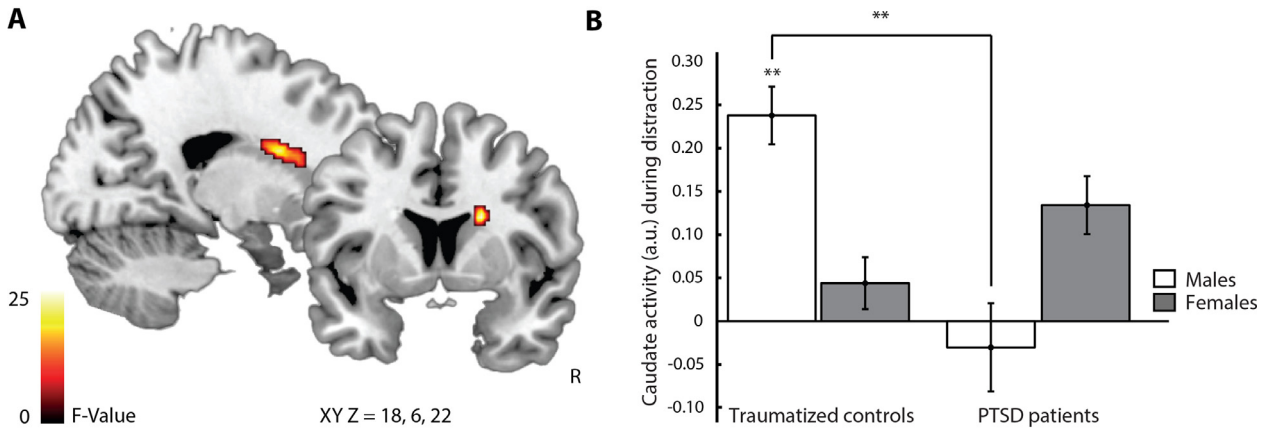

Fig. 3 Group differences in striatum activity during distraction. Group differences under placebo. A. Statistical map of the group by sex interaction in the right caudate nucleus, overlaid on a single-subject template and statistically thresholded at $p_{uncorrected} < 0.001$. B. Contrast estimates in arbitrary units (a.u.) of right caudate activity during distraction (compared to passive viewing of negative pictures) extracted from the group by sex interaction cluster. Male trauma-exposed controls showed significant right caudate activity during distraction, which was greater compared to male PTSD patients. $^{**}p < 0.001$.

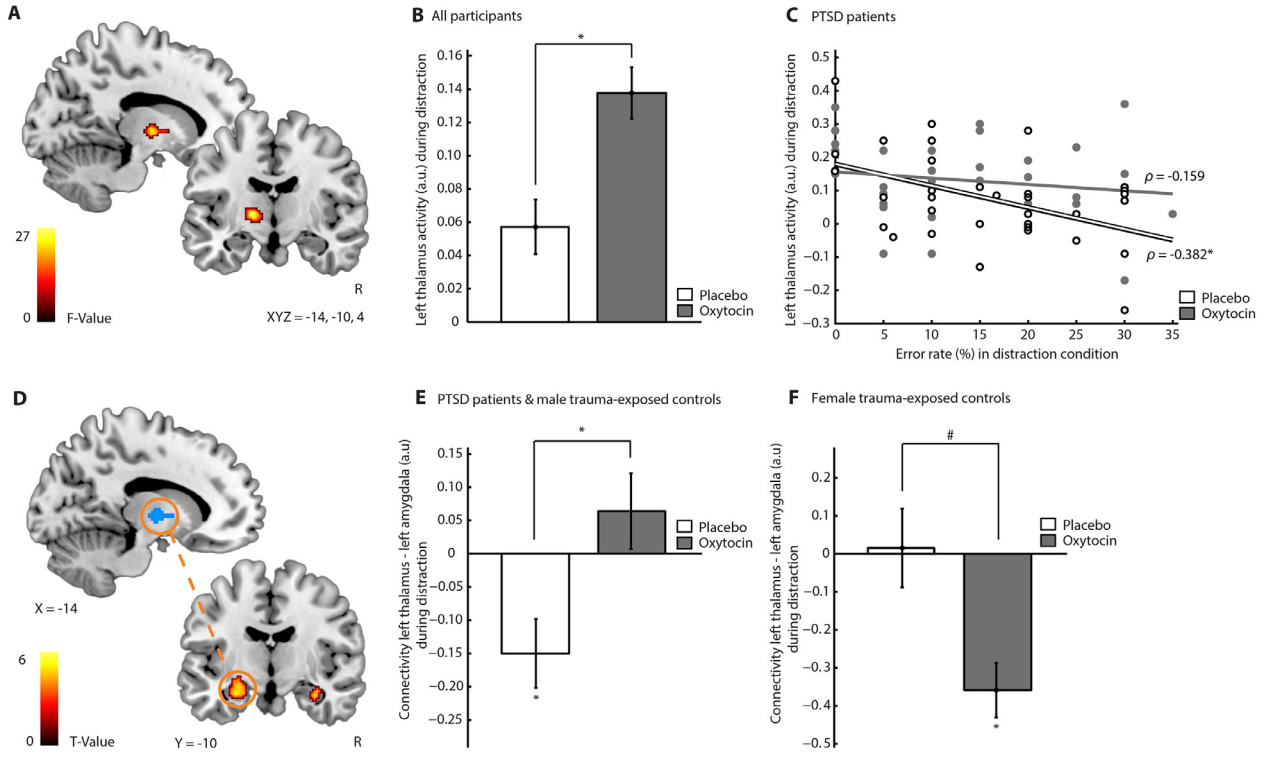

Fig. 4 Oxytocin effects on thalamus activity and connectivity. A. Statistical map of the main drug effect in the left thalamus, overlaid on a single-subject template and statistically thresholded at $p_{uncorrected} < 0.001$. B. Contrast estimates in arbitrary units (a.u.) of left thalamus activity during distraction, compared to passive viewing of negative pictures. Oxytocin administration resulted in increased left thalamus activity during distraction in all participants. C. Within PTSD patients, left thalamus activity during distraction was negatively correlated with error rate (%) during distraction under placebo, but not under oxytocin. D. Under placebo, the left thalamus cluster showed decreased functional connectivity with the left amygdala (extending into the hippocampus) during distraction, compared to passive viewing of negative pictures. E. Contrast estimates (a.u.) of left thalamus – amygdala functional connectivity, showing increased connectivity during distraction after oxytocin administration in PTSD patients and male trauma-exposed controls. F. In female trauma-exposed controls, oxytocin administration resulted in marginally decreased left thalamus – amygdala functional connectivity during distraction. $^{\#}p < 0.1$; $^{*}p < 0.05$; $^{**}p < 0.001$.

Fig. 4C): greater recruitment of the left thalamus was associated with relatively less errors during distraction. After oxytocin administration, left thalamus activity and error rates during distraction were not significantly correlated within PTSD patients (spearman $\rho = -0.159$, $p = 0.385$), and the correlation coefficient magnitudes under placebo and oxytocin were marginally different (Steiger's $Z = -1.515$, $p = 0.065$). Within trauma-exposed controls, no significant correlations between left thalamus activity and error rates during distraction were observed, both under placebo and oxytocin (all $p > 0.05$). Left thalamus activity during distraction was not significantly correlated with other behavioral task performance measures (i.e., reaction times and affective ratings). These effects were not associated with participants' age, and comparable results were obtained after controlling for baseline differences in trauma exposure. No other significant effects of group, sex or group by sex interactions were found, both at the whole-brain level, and for each ROI (all $p > 0.05$).

Given our previous findings of oxytocin administration effects on amygdala activity (Koch et al., 2015) and amygdala functional connectivity with the prefrontal cortex (Koch et al., 2016, 2015), we additionally explored whether oxytocin administration affected amygdala activity during distraction using a lenient statistical threshold. Under placebo, female PTSD patients showed greater right amygdala down-regulation during distraction compared to female trauma-exposed controls, whereas this amygdala down-regulating effect of distraction was absent within male PTSD patients. After oxytocin, the group difference in distraction-induced amygdala downregulation between female trauma-exposed controls and PTSD patients was abolished. Additionally, all females showed up-regulation of left amygdala activity during distraction after oxytocin (see Supplementary Results).

3.3.4. Effective connectivity of the left thalamus

To further elucidate the effects of oxytocin administration on thalamus functional connectivity, we performed a PPI analysis with the left thalamus oxytocin-effect as seed. Under placebo, decreased functional connectivity between the left thalamus and left amygdala, extending into the hippocampus, was found during distraction compared to passive viewing of negative pictures (left: MNI $xyz = -26, -10, -14$, $Z = 4.13$, $p_{SVC} = 0.003$; right: MNI $xyz = 30, -2, -24$, $Z = 3.13$, $p_{SVC} = 0.086$; Fig. 4D). No significant effects of group, sex or group by sex interactions were found regarding functional connectivity under placebo (all $p_{SVC} > 0.05$).

When investigating oxytocin effects on left thalamus-amygdala functional connectivity during distraction, we found a group by sex by drug interaction effect in the left amygdala, extending into the hippocampus (MNI $xyz = -18, -6, -20$, $Z = 3.41$, $p_{SVC} = 0.039$). Oxytocin administration increased left thalamus - left amygdala functional connectivity during distraction in male trauma-exposed controls, and male and female PTSD patients (MNI $xyz = -22, -6, -22$, $Z = 3.33$, $p_{SVC} = 0.048$; Fig. 4E). This effect was also found at a subthreshold level in the right amygdala (MNI $xyz = 22, -4, -22$, $Z = 3.16$, $p_{SVC} = 0.079$). In female trauma-exposed controls, on the other hand, oxytocin tended to decrease functional connectivity between the left thalamus and left amygdala during distraction (MNI $xyz = -18, -8, -18$, $Z = 3.12$, $p_{SVC} = 0.087$; Fig. 4F). These effects were not associated with participants' age, and comparable results were obtained after correcting for baseline differences in trauma exposure.

4. Discussion

We investigated neural and behavioral effects of oxytocin administration on distraction as cognitive emotion regulation strategy in male and female PTSD patients and trauma-exposed controls. The distraction condition consisted of a working memory task while negative affective pictures were presented. During distraction, oxytocin administration enhanced left thalamus activity in all participants, and increased functional coupling between the left thalamus and amygdala in all PTSD patients and male trauma-exposed controls.

Under placebo, distraction resulted in robust down-regulation of neural activity in emotion processing areas (e.g., the amygdala), as well as upregulation of neural activity in (prefrontal) emotional control areas. Compared to male trauma-exposed controls, male PTSD patients showed diminished activity in the right caudate nucleus during distraction. This finding is in line with a meta-analysis showing diminished right caudate activity across experimental designs in PTSD patients, compared to non-trauma exposed controls (Patel et al., 2012). The caudate nucleus is a key node of the reward pathway and implicated in (goal-directed) affective processing (Goldin et al., 2008). Previous meta-analyses of cognitive emotion regulation neuroimaging studies found caudate nucleus involvement, both during down-regulation of negative affect (Kalisch, 2009) and up-regulation of (predominantly) positive affect (Frank et al., 2014). Whereas the putamen is involved in motor control, the caudate nucleus is predominantly associated with cognitive control processes, such as working memory, via afferent projections from the dorsolateral prefrontal cortex as part of the frontostriatal circuit (Haber, 2016). Notably, PTSD has been associated with impaired neurocognitive functioning, including decreased working memory performance (Polak et al., 2012; Scott et al., 2015). Hyperarousal and bias towards threat in PTSD may switch attentional resources towards external negative stimuli, at the cost of (prefrontally-mediated) neurocognitive functioning (Etkin et al., 2013; Scott et al., 2015). This suggestion fits with observations of decreased caudate nucleus activity in PTSD patients vs controls associated with attentional bias towards trauma-related stimuli (Todd et al., 2015), and during working memory updating (Moores et al., 2008). Our findings provide additional support of diminished caudate nucleus involvement in PTSD during cognitive (emotional) control using a working memory task.

Under placebo and across all participants, we observed increased thalamus activity and negative thalamus-amygdala functional connectivity when using distraction as cognitive emotion regulation strategy, compared to passively watching negative pictures. The thalamus is involved in multiple cognitive functions and supports integration of information processing across various functional brain networks (Hwang et al., 2017). Furthermore, the thalamus is part of the salience network, integrating salient information

from various subcortical and cortical areas, including the amygdala, within the network (Seeley et al., 2007). Thalamus recruitment may be important for effective emotional control (Tyborowska et al., 2016), and alterations in thalamic activity and connectivity have been suggested to underlie the pathophysiology of PTSD (Yin et al., 2011). A quantitative meta-analysis found lower bilateral thalamus activity in PTSD patients during symptom provocation (Hayes et al., 2012), indicating deficient recruitment of the thalamus towards trauma-related stimuli in PTSD. For example, compared to trauma-exposed controls, lower thalamus activity was previous observed in PTSD patients during exposure to trauma reminders, using script-driven imagery (Lanius et al., 2001). Furthermore, altered functional connectivity of the thalamus with cortical regions was observed in PTSD patients compared to trauma-exposed controls (Yin et al., 2011), as well as lower thalamus-amygdala connectivity, which was associated with greater PTSD symptom severity (Zhu et al., 2017).

Although we did not observe group differences in thalamus activity and connectivity under placebo, we observed that greater thalamus activity during distraction was associated with higher distraction WM task accuracy in PTSD patients. The thalamus may be important in allocating attentional resources to the cognitive WM task (Wright et al., 2015), thereby diminishing potential interference of negative stimuli processing on WM performance (Etkin et al., 2013) and improving the effectiveness of distraction to down-regulate negative affect. Of note, our observation is in line with findings in healthy participants showing positive associations between thalamus activity during emotion regulation and reappraisal success (Wager et al., 2008b). Contrary to our findings, however, previous emotion regulation studies in healthy participants found decreased thalamus activity when down-regulating negative affect (Dörfel et al., 2014; Kanske et al., 2011; Ochsner et al., 2004), and increased thalamus activity when upregulating (predominantly) positive affect (Frank et al., 2014).

Oxytocin administration resulted in enhanced left thalamus activity during distraction in all participants, and in increased left thalamus-amygdala functional connectivity during distraction in all PTSD patients and male controls. Previous intranasal oxytocin fMRI studies found mixed effects of oxytocin administration on thalamus activity (Wigton et al., 2015), reporting increased (Baumgartner et al., 2008; Domes et al., 2010; Hu et al., 2015), decreased (Domes et al., 2007) and unaltered (Riem et al., 2011) thalamus activity after oxytocin administration. Possibly, these mixed effects could be explained by differences in task design, such as stimulus type, with different types of emotional information being differentially modulated and relayed from the thalamus to other brain regions (Wigton et al., 2015). Given previous (Tyborowska et al., 2016; Wager et al., 2008b) and our present observations of thalamus recruitment during emotional control, which was positively associated with task performance, and previous findings of thalamus hypo-activity towards trauma reminders in PTSD patients (Hayes et al., 2012; Lanius et al., 2001), our finding of enhanced thalamus activity during distraction after oxytocin administration tentatively suggests improved neural emotional control. In line with previous findings that reduced thalamus-amygdala resting-state functional connectivity in PTSD patients was related to symptom severity (Zhu et al., 2017), we suggest that this enhanced neural emotional control was achieved via enhanced communication with the amygdala. Fitting with suggestions of improved affect regulation after oxytocin administration, male PTSD patients rated all pictures as more positive after oxytocin administration.

Clinically, down-regulating exposure-related distress using cognitive emotion regulation could facilitate effective exposure therapy (Bryant et al., 2013): greater reduction in PTSD symptom severity after CBT was found in PTSD patients who received pre-treatment emotion regulation skills training (including distraction) compared to those who received supportive counseling (Bryant et al., 2013). Therefore, oxytocin administration could potentially enhance treatment response to CBT by facilitating neural emotional control abilities, although this clinical effect remains to be investigated. The effects of oxytocin administration have been suggested to follow an inverted U-shaped dose response curve: anxiolytic effects of oxytocin may be strongest in individuals with suboptimal baseline emotion regulation abilities (Labuschagne et al., 2010; Spengler et al., 2017), the latter depending on individual differences such as sex and psychopathology (Bartz et al., 2011). Regarding sex differences, gonadal steroid hormones were found to influence fear regulation abilities (Glover et al., 2015; Gruene et al., 2015), as well as oxytocin (receptor) production (Patisaul et al., 2003; Richard and Zingg, 1990), and oxytocin receptor binding in the brain (Johnson et al., 1991). In individuals with optimal fear regulation abilities, on the other hand, oxytocin administration may have no or even anxiogenic effects. For example, we previously observed that oxytocin administration resulted in increased rather than decreased amygdala activity in trauma-exposed controls, and that (anxiolytic) oxytocin effects on amygdala down-regulation in PTSD patients were positively associated with higher baseline anxiety symptoms (Koch et al., 2015). In the present study, we observed different baseline thalamus-amygdala functional coupling during distraction under placebo in female trauma-exposed controls compared to male and female PTSD patients and male trauma-exposed controls, which was nominally *decreased*, rather than *increased* after oxytocin administration. It remains to be investigated how individual differences in (neural) emotion regulation abilities moderate the effects of oxytocin administration on emotion regulation neurocircuitry in healthy and clinical samples.

We included a homogeneous sample of trauma-exposed police officers to control for potential confounding effects of trauma-exposure on neurobiology. However, this also limits the generalizability of our findings. Additionally, as we aimed to minimize time and hence fluctuations in symptom severity between sessions, we did not test our females during the same phase of the menstrual cycle. This may have confounded our findings in our female participants (Caldwell et al., 1994). Further, we did not explicitly present distraction as cognitive emotion regulation strategy to not influence behavioural responding. This would presumably be different in a clinical setting during CBT, where distraction would be introduced as an explicit cognitive emotion regulation strategy to down-regulate exposure-related distress. Finally, a recent study showed the largest neural

oxytocin effects within 70 minutes post-administration (Spengler et al., 2017), suggesting that our timing of the task relative to oxytocin administration (i.e., 83 min) may have been suboptimal. On the other hand, another recent pharmacodynamic study showed neural oxytocin effects up to at least 80 minutes post-administration (Paloyelis et al., 2014), in agreement with our findings of oxytocin administration effects on thalamus activity and functional connectivity within a comparable time-window.

To conclude, oxytocin administration during distraction modulated thalamus activity and functional connectivity with the amygdala. Oxytocin may hold therapeutic promise in PTSD as potential enhancer of cognitive emotion regulation ability during psychotherapy. Our findings open the way for future research into oxytocin effects on cognitive emotion regulation and its neural correlates in psychiatric patients characterized with deficient emotion regulation abilities.

Conflict of interest

All authors declare that they have no biomedical financial interests and no potential conflicts of interest.

Contributions

MO obtained funding. SBJK and MvZ drafted the manuscript. All authors contributed to development and implementation of the study protocol. LN, JLF and SBJK conducted all participant-related study procedures and collected the data. SBJK analyzed the data, and all authors contributed to data interpretation. All authors contributed to editing the manuscript and have approved the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2018.12.002.

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