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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).