General introduction
PTSD

Trauma
A major car-accident, being robbed, witnessing or experiencing serious injury: these are some of the most commonly reported traumatic events (Benjet et al., 2016; de Vries and Olff, 2009). Worldwide, about 70% of people are confronted with a traumatic event at some point in their lives, and about 30% of people report four or more of such events (Benjet et al., 2016). After experiencing a traumatic event, initial responses such as flashbacks, difficulty sleeping, reduced interest in activities, and being jumpy are common, and considered a normal response to such an experience. Although memories of the event likely last a lifetime, these acute responses will fade within days or weeks in most people. However, in about 10% of trauma-exposed people, responses do not disappear by themselves, and develop into posttraumatic stress disorder (PTSD). Core symptoms of this psychiatric disorder are intrusive re-experiencing of the traumatic event, avoidance of trauma-related stimuli, persistent negative alterations in mood and cognition, and hyperarousal and reactivity (American Psychiatric Association, 2013). The lifetime prevalence of PTSD is about 8% (e.g. de Vries and Olff, 2009; Kilpatrick et al., 2013). Besides immense personal impact, societal costs of PTSD are high, with high healthcare utilisation, work loss, suicidality and medical morbidity and mortality (e.g. Kartha et al., 2008; Kessler, 2000; Xue et al., 2012). PTSD shows high comorbidity with major depressive disorder (MDD, 50%, e.g. Stander et al., 2014) and drug- and alcohol abuse (10-60%, e.g Debell et al., 2014).
Risk-factors & genetics
Female gender is an important risk factor for development of PTSD (Olff et al., 2007), as well as (familial) psychiatric history and accumulative exposure to (childhood) adversity and/or traumatic events (Brewin et al., 2000). Genetics are also known to play a role; studies estimate the heritability of PTSD at around 30-50% (e.g. Ehlers et al., 2013; Stein et al., 2002). Several candidate genes have been implicated in PTSD (e.g. Broekman et al., 2007), such as genes related to the HPA axis systems (e.g. FKBP5), oxytocin (e.g. OXTR), serotonin (e.g. 5-HTTLPR) and dopamine systems (e.g. DRD2), though only dopamine variants have been confirmed in meta-analyses (Li et al., 2016; Navarro-Mateu et al., 2013). Several genome-wide-association (GWAS) studies have been conducted in PTSD thus far (Logue et al., 2015), implicating several novel genetic pathways. Epigenetic factors may also play a role in PTSD development (Klengel et al., 2014). Epigenetics refer to mechanisms such as methylation that do not affect the genomic code, but can alter gene-expression. These mechanisms can be altered by environmental factors such as stress and trauma (e.g. Mehta et al., 2013; Unternaehrer et al., 2012), thereby providing a potential molecular link between environmental (trauma)-exposure and genetics that may help understand the etiology of PTSD (Klengel et al., 2014; Neylan et al., 2014).

Treatment
Several evidence based psychotherapy treatments for PTSD are available, for example exposure therapy (ET) and cognitive behavioural therapy (CBT) as well as pharmacotherapies (Schnyder, 2014; Watts et al., 2013). However, drop-out rates for PTSD patients in treatment are up to 20% (Imel et al., 2013). Also, even when therapy is completed, about 30% of patients still meet the criteria for the diagnosis of PTSD (Bradley et al., 2005). Therefore, it is crucial to improve currently available treatment for PTSD. Earlier and more effective treatment can potentially increase quality of life and life-years, and substantially decrease societal costs (Kessler, 2000). One way to enhance the efficacy of currently available psychotherapy treatment is to administer pharmacological agents in combination with psychotherapy. With medication-enhanced psychotherapy, or MEP, it is possible to target specific factors known to affect treatment success, thereby potentially boosting the effect of psychotherapy (Dunlop et al., 2012; Johansen and Krebs, 2009).

Social bonding and motivation as predictors of treatment response
Some of the most stable predictors of treatment response in psychiatric disorders including PTSD are related to social and motivational processes. For example, the formation of a collaborative bond between the patient and the therapist, also known as therapeutic alliance, is an important predictor of treatment success (e.g. Martin et al., 2000; Olff et al., 2010; Ormhaug et al., 2015), accounting for about 8% of variability in treatment outcome (Horvath et al., 2011). Perceived social support, both from the therapist and from outside of the therapeutic setting, is another stable predictor (e.g. Thrasher et al., 2010). Furthermore, the motivation for treatment and expectations of
treatment success are known to be important (Clarke et al., 2013; Schindler et al., 2013). Regrettably, these predictors can be critically impacted by social and affective symptoms of PTSD. The inability to experience positive emotions, reduced interest and motivation to engage in significant activities, and feelings of alienation and social withdrawal are core symptoms of PTSD (American Psychiatric Association, 2013), present in the majority of PTSD patients (Carmassi et al., 2014; Franklin and Zimmerman, 2001). These (social) anhedonic features may reduce perceived social support, the ability and motivation to start and/or continue therapy, and perceiving and establishing therapeutic alliance (Charuvastra and Cloitre, 2008; Kaniasty and Norris, 2008; Pietrzak et al., 2010). Thus, anhedonic PTSD symptoms may negatively affect predictors of psychotherapy outcome, leaving PTSD patients at increased risk for negative treatment outcome (Charuvastra and Cloitre, 2008; Hassija et al., 2012).

NEUROBIOLOGY OF PTSD

Anhedonia & reward pathway
From a neurobiological perspective, anhedonia is often explained by deficits in reward functioning, or the drive to seek out and ability to enjoy positive experiences (e.g. Der-Avakian and Markou, 2012). Anhedonic symptoms are thought to arise from aberrations in the reward pathway, a set of neural structures functionally and anatomically connected and crucial for motivational behaviour (Der-Avakian and Markou, 2012; Treadway and Zald, 2013). Dopamine is a key neurotransmitter in this pathway, with mesocorticolimbic projections linking the ventral tegmental area (VTA) with the striatum and amygdala, structures important in signalling positive and negative reinforcing stimuli in the environment. These subcortical structures in turn project to cortical areas such as the anterior insula (AI), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and dorsal prefrontal cortex (PFC). These cortical areas are involved in valence assessment, weighing potential costs and benefits, integrating information from the environment with current needs, and using this information to guide attention, decision making and approach (vs avoidance) behaviour (e.g. Liu et al., 2011) (figure 1). Indeed, neural responses in these areas prior to treatment were predictive of psychotherapy treatment success in PTSD patients (Aupperle et al., 2013; Falconer et al., 2013).

Responsiveness towards positive and negative stimuli in PTSD
PTSD has been associated with reduced sensitivity to positive stimuli such as happy faces, positive memories, and monetary incentives (e.g. Clausen et al., 2016; Felmingham et al., 2014; Frewen et al., 2010; Steuwe et al., 2014). Neurally, PTSD patients show lower responses in the ventral striatum (Admon et al., 2013; Elman et al., 2009; Felmingham et al., 2014; Sailer et al., 2008) towards positive stimuli, compared to controls. Fitting with the idea that reward deficits underlie anhedonia, striatal responses to positive stimuli were specifically negatively correlated with anhedonia symptoms in PTSD patients.
Increased sensitivity to negative stimuli has also been observed in PTSD, e.g. in the amygdala and striatum (non-trauma-related) stimuli (Admon et al., 2013; Elman et al., 2009; Hayes et al., 2012a; Mazza et al., 2012). Interestingly, amygdala, dACC and insula hyperresponsiveness to negative non-trauma related stimuli also predicted subsequent treatment response (Aupperle et al., 2013; Bryant et al., 2008; Falconer et al., 2013; van Rooij et al., 2016). Taken together, these findings suggest that in PTSD, the reward pathway is hyporesponsive to positive stimuli, but hyperresponsive to negative stimuli (Stein and Paulus, 2009).

**Networks**

Besides the reward pathway, other neural networks have been implicated in PTSD. Looking at the brain from a network perspective, Menon postulated the triple network theory, proposing that psychiatric disorders are associated with disturbances in several large intrinsic neural networks, specifically the default mode network (DMN), the salience network (SN) and the central executive network (CEN) (Menon, 2011). The DMN plays an important role in self-referential processing, such as autobiographical memories and social reflection. The SN is important for integration of sensory information, guiding attention and behaviour towards the most salient stimuli in the environment. The CEN is involved in cognitive functions such as working memory, planning and cognitive control. These networks have been implicated in multiple clinical characteristics of PTSD (Lanius et al., 2015), and show aberrant reactivity and connectivity in PTSD patients compared to controls (Koch et al., 2016a). Especially the SN, but also the DMN and CEN, have previously been related to (social) anhedonia and reward function, for example in schizophrenia (Lee et al., 2015) and MDD (Rzepa and McCabe, 2016; Zhang et al., 2017).

**Boosting treatment success in PTSD**

The PTSD-related neurobiological alterations in the reward pathway and other networks are thought to underlie symptoms of (social) anhedonia, and may negatively affect subjective social support, therapeutic alliance, and motivation for treatment, all established predictors of treatment response. Potentially, by addressing these underlying neural processes, we may be able to positively affect these predictive factors and thereby increase the likelihood of successful psychotherapy. A promising pharmacological agent that may influence these processes is the neuropeptide oxytocin (Koch et al., 2014; Olff, 2012; Olff et al., 2010).
Figure 1. Reward pathway and oxytocin pathway in the human brain, sagittal (left) and lateral (right) view. The dopaminergic mesocorticolimbic reward pathway is depicted in blue. Dopamine is the main neurotransmitter in the reward pathway; it is synthesized in the ventral tegmental area (VTA) and projected to the striatum (nucleus accumbens, caudate, putamen), limbic areas such as the amygdala (AMY) and prefrontal areas such as the medial prefrontal cortex (mPFC), ventromedial prefrontal cortex (vmPFC, not shown) and anterior cingulate cortex (ACC). The oxytocin pathway is depicted in purple. Oxytocin is synthesized in the paraventricular nucleus of the hypothalamus (HYP) and centrally projected to limbic areas such as the amygdala, striatum and hippocampus (not shown), acting as a neurotransmitter. Also, it is projected to the VTA, the origin of the dopaminergic mesocorticolimbic pathway (in blue). Via these areas, as well as through extracellular diffusion, oxytocin presumably affects prefrontal and cortical functioning in areas such as the mPFC, ACC and insula. Furthermore, oxytocin is projected to the brainstem, and into the peripheral blood stream via the supraoptic nucleus of the hypothalamus (not shown), where it acts as a hormone, influencing peripheral physiological functions, such as autonomic fear responses. The dopamine and oxytocin pathways partly overlap, and animal studies have shown that the systems interact to influence social motivational behavior.

*Sagittal and lateral brain images adapted from images by Patrick J. Lynch & C. Carl Jaffe, Creative Commons Attribution 2.5 License 2006.*
Neurobiology of oxytocin

The neuropeptide and hormone oxytocin is synthesized in the paraventricular and supraoptic nucleus of the hypothalamus, and subsequently released into the peripheral circulation and projected to various brain regions associated with affective processing such as the amygdala and striatum (Meyer-Lindenberg et al., 2011) (figure 1). Oxytocin binds to the oxytocin receptor (OXTR), a G-protein-coupled receptor. OXTR-localization studies in post-mortem (female) human brains, suggest the presence of OXTR in the amygdala, substantia nigra, striatum and hypothalamus, as well as in the sensory cortices, cingulate and the prefrontal cortex (Bethlehem et al., 2016; Boccia et al., 2013). In rodents, oxytocin was observed to excite specific neurons within the amygdala and thereby modulate fear expression and autonomic stress responses (e.g. Huber et al., 2005). Also, oxytocin was found to interact with dopamine and serotonin in the striatum and ventral tegmental area (VTA), thereby affecting social (reinforcement) behavior and anxiety (e.g. Dölen et al., 2013; Romero-Fernandez et al., 2013; Shahrokh et al., 2010; Yoshida et al., 2009; Young and Wang, 2004).

Plasma levels of oxytocin can be increased by administration of synthetic oxytocin nasal spray. Intranasal oxytocin is currently approved to stimulate lactation, and it is easy to apply and well tolerated (Quintana et al., 2016). Although the precise route of central delivery remains to be elucidated (Evans et al., 2014; Quintana et al., 2014), intranasal oxytocin administration increased oxytocin levels in peripheral blood and cerebrospinal fluid (CSF) in healthy human males up to at least 75 minutes after administration (Striepens et al., 2013), and increased regional cerebral blood flow in the amygdala, striatum, cingulate cortices, anterior insula, and other regions involved in social and affective processing, up to at least 80 minutes after administration (Paloyelis et al., 2014).

Prosocial & anxiolytic effects

Intranasal oxytocin administration was repeatedly found to enhance positive social functioning in healthy individuals; a meta-analysis showed increased (in-group) trust after oxytocin administration (Van IJzendoorn and Bakermans-Kranenburg, 2012). Other studies reported increased perceived social support, increased social motivation, faster approach towards pleasurable social images and reduced bodily distance and increasing eye-contact with the experimenter (Auyeung et al., 2015; Bernaerts et al., 2017; Cardoso et al., 2016; Preckel et al., 2014; Scheele et al., 2012). Oxytocin administration also increased subjective ratings and neural responses towards positive (social) stimuli in the striatum, ventral tegmental area, anterior insula and mPFC in healthy individuals (Cardoso et al., 2014; Groppe et al., 2013; Hu et al., 2015; Mickey et al., 2016; Scheele et al., 2014a, 2013, 2012; Striepens et al., 2014). Furthermore, oxytocin administration reduced anxiety and stress-responses in healthy individuals (de Oliveira et al., 2012; Heinrichs et al., 2003), and was repeatedly found to reduce amygdala responses towards
negative social stimuli (Domes et al., 2007; Kirsch et al., 2005; Petrovic et al., 2008). In healthy males, oxytocin administration facilitated fear extinction, although this was dependent on timing of administration (i.e. prior or post fear memory- reactivation) (Acheson et al., 2013; Eckstein et al., 2014a), suggesting potential for exposure therapy. However, importantly with regard to potential clinical application, opposing findings have also been reported, see discussion below.

Common variants within the OXTR gene coding for the oxytocin receptor have been associated with endogenous oxytocin levels (Feldman et al., 2012). Meta-analyses and large population studies suggest that variants within the OXTR gene are related to sociality (Li et al., 2015), and striatal responses to emotional faces, and interact with life-stress to predict psychopathology (Loth et al., 2013). Null-findings have also been reported however (Bakermans-Kranenburg and van Ijzendoorn, 2013). OXTR variants further moderated intranasal oxytocin effects on neural responses (Feng et al., 2015; Marsh et al., 2012; Montag et al., 2013). On an epigenetic level, OXTR methylation has been related to depression (Bell et al., 2015; Kimmel et al., 2016; Reiner et al., 2015), social anxiety (Ziegler et al., 2015) and neural responses to affective stimuli (Jack et al., 2012; Puglia et al., 2015; Ziegler et al., 2015).

Understandably, these prosocial, motivational and anxiolytic associations have sparked a great interest for oxytocin administration in psychiatric research. For example in affective disorders, experimental neuroimaging studies reported beneficial effects on amygdala reactivity and connectivity in GSAD and borderline patients (Bertsch et al., 2013a; Dodhia et al., 2014; Gorka et al., 2015; Labuschagne et al., 2011, 2010). Not many studies have investigated oxytocin effects on (social) reward functioning in psychiatric patients. Behaviorally, repeated oxytocin administration reduced anhedonia-related measures in schizophrenia and MDD patients (e.g. Lee et al., 2013; Scantamburlo et al., 2015), although both studies were small and the latter did not include a placebo group. Also, repeated oxytocin administration prevented development of PTSD symptoms in recently traumatized individuals with high initial PTSD symptoms (van Zuiden et al., 2016). However, reported effects of intranasal oxytocin have not always been positive, and oxytocin use is not without controversy.

**Controversy on effects of oxytocin**

At the starting point of the current project, literature on oxytocin administration had mainly suggested prosocial and anxiolytic effects (e.g. Kirsch et al., 2005; Macdonald and Macdonald, 2010). Yet over the years, a growing number of contradicting findings were reported, with intranasal oxytocin increasing anxiety and amygdala responses towards negative emotional stimuli and stress (Domes et al., 2010; Eckstein et al., 2014b; Grillon et al., 2013), increasing aggressive rather than prosocial behavior (e.g. Shamay-Tsoory et al., 2009) and decreasing trust (Bartz et al., 2011a; Declerck et al., 2010). The few clinical (pilot) studies that investigated oxytocin administration in combination
with psychotherapy (MEP) have also had mixed results; combined with one session of psychotherapy, oxytocin decreased social avoidance behavior and increased social cognition, but increased anxiety in male MDD patients relative to psychotherapy under placebo (MacDonald et al., 2013b). In arachnophobia patients, it impeded exposure therapy response and there was a trend towards reduced therapeutic alliance in (Acheson et al., 2015). In patients with social anxiety disorder, oxytocin administration in adjunction with exposure therapy did not improve general treatment effects, but did improve positive self-image (Guastella et al., 2009). Also the few small studies carried out in PTSD patients have yielded mixed results; single oxytocin administration increased compassion towards women (Palgi et al., 2016b), but not empathic abilities (Palgi et al., 2016a) or physiological responses to pleasant images (Pitman et al., 1993). Together, these inconsistencies in experimental and clinical literature have led to a heated discussion of the potential and dangers of applying oxytocin in psychiatry (e.g. Cardoso and Ellenbogen, 2013; Leng and Ludwig, 2015; MacDonald et al., 2013a; Macdonald and Feifel, 2013; Quintana and Woolley, 2016).

Interindividual effects
With their social salience theory, Shamay-Tsoory and Abu-Akel aimed to reconcile these seemingly contradictory effects (Shamay-Tsoory and Abu-Akel, 2015). They suggested that oxytocin administration enhances the salience of social stimuli, with the direction of oxytocin effects depending on the context (i.e. positive/safe vs. negative/threatening). Importantly, the interpretation of the context may differ depending on interindividual characteristics. Others have voiced similar notions that intranasal oxytocin effects depend on interindividual characteristics, such as sex, psychopathology and trauma exposure, and contextual factors such as social setting (Bartz et al., 2011b; Hurlemann and Scheele, 2016; Olff et al., 2013), determining on the interpretation of the (social) environment. After Domes et al. reported that oxytocin administration decreased amygdala responses to emotional faces in healthy men (Domes et al., 2007), but increased amygdala responses in healthy women (Domes et al., 2010), more recent studies seem to confirm that oxytocin effects are sex-dependent (Ebner et al., 2016; Feng et al., 2014; Gao et al., 2016; Rilling et al., 2014). These sex-differences may be especially important in PTSD research, with females having two-fold higher risk of developing PTSD. Several biopsychosocial factors thought to influence sex-differences in risk for PTSD, such as acute stress responses and (childhood) trauma exposure (Olff et al., 2007), also moderate the effects of oxytocin administration (Hurlemann and Scheele, 2016; Meyer-Lindenberg et al., 2011).

Oxytocin administration in PTSD
The suggested prosocial, approach-enhancing and anxiolytic effects of oxytocin administration may benefit motivation for therapy and social interaction within the therapeutic setting, and thereby potentially increase success of psychotherapy in PTSD (Koch et al., 2014; Olff et al., 2010; Quirin et al., 2014). However, taking the repeated findings of opposing effects of oxytocin into account, research is needed to investigate
whether the previously observed prosocial, motivational and anxiolytic effects of oxytocin administration indeed hold for PTSD. Also, considering previous reports of sex-dependent effects, it is important to investigate if oxytocin effects are similar for male and female PTSD patients. Therefore, as a first step in investigating the potential of oxytocin administration for MEP in PTSD, we have conducted a neuroimaging study into the effects of intranasal oxytocin administration in males and females with and without PTSD, the BOOSTER study (box 1). To control for potential effects of trauma-exposure we included a sample of highly trauma-exposed police officers.

OBJECTIVES

Part I: Reward functioning in PTSD
In the first part of this PhD thesis, we aim to provide an overview of the nature of reward deficits in PTSD.

Chapter 2: Although responses to negative stimuli have received considerable attention in PTSD research, little is known concerning alterations in responses to positive stimuli. Therefore, in chapter 2, we carried out a systematic review of available research literature on reward functioning in PTSD to investigate if there is evidence for subjective, behavioural or neural reward deficits in PTSD patients compared to healthy controls.

Part II: Oxytocin effects on reward and salience neurocircuitry in PTSD
In the second part of this thesis, we focus on effects of oxytocin administration on reward processing and functional connectivity networks in PTSD. The neuroimaging studies described in chapter 3, 4 and 5 were all part of the BOOSTER study. Our aim is to explore if intranasal oxytocin can positively affect neurobiological (correlates of) predictors of treatment response. This will inform us if intranasal oxytocin has potential to positively influence treatment response in PTSD.

Chapter 3 & 4: We present an investigation of the effects of intranasal oxytocin administration on neural motivational processing during a monetary incentive delay task (chapter 3) and a social incentive delay task (chapter 4), looking at responses to both reward and punishment in male and female PTSD patients and trauma-exposed controls.

Chapter 5: In chapter 5 we describe the effects of oxytocin administration on large intrinsic functional connectivity networks during rest, in male and female PTSD patients and trauma-exposed controls. Considering the association of the DMN, SN and CEN with psychiatric disorders, we specifically focussed on oxytocin effects on these networks.

Part III: Genetic and epigenetic associations with PTSD
In part III, an (epi)genetic approach is adopted towards PTSD and the oxytocin system. Here, our aim is to explore (epi)genetic differences between male and female PTSD
patients and trauma-exposed controls. This may help to further elucidate potential mechanisms and (epi)genetic factors involved in the genetic susceptibility to PTSD.

**Chapter 6:** In chapter 6, we describe findings of an epigenome-wide investigation, used to identify epigenetic and genetic loci associated with PTSD. We investigate whether PTSD patients and trauma-exposed controls show differences in epigenome-wide methylation. Furthermore, we explore differences in single nucleotide polymorphisms (SNPs) in the BOOSTER study and an independent replication cohort.

**Chapter 7:** Next, we compare methylation of the oxytocin receptor gene (*OXTR*) between male and female PTSD patients and trauma-exposed controls, and associating *OXTR* methylation with clinical, subjective and neuroimaging measures.

**Summary & discussion**

**Chapter 8:** In the final chapter, we give a summary of our main findings, integrate these with the current literature and discuss (clinical) implications.

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**Box 1. The BOOSTER study**

We conducted the BOOSTER study (BOosting the Oxytocin System after Trauma: neurobiological effects on Emotion and Reward processing in PTSD), a pharmacological functional magnetic resonance imaging (fMRI) study with a double-blind, randomized, placebo-controlled crossover design (figure 2). The BOOSTER study was conducted in a sample of highly trauma-exposed male and female Dutch police officers with and without PTSD. In total, 40 PTSD patients (21 males) and 40 trauma-exposed healthy controls (20 males) were included, matched on sex, age, years of service, and education. During T0, participants signed informed consent. Subsequently, eligibility was assessed, and clinical interviews were conducted to assess in-and exclusion criteria, most importantly the presence of PTSD symptoms and psychiatric disorders. Also, several biological samples were collected (whole blood, hair). Participants were thereafter randomized to treatment-order for the following two scan sessions (T1 placebo- T2 oxytocin or T1 oxytocin- T2 placebo). Scanning took place at the Spinoza center for neuroimaging (location Roetersseiland), and scan sessions were scheduled at least three days apart. All participants were scanned once after self-administration of oxytocin nasal spray (40 international units (IU), i.e. 10 puffs), and once after self-administration of a saline placebo nasal spray (NaCl 0.9%, 10 puffs) under experimenter supervision. Intranasal oxytocin or placebo administration took place 45 minutes prior to the start of the first functional scan (i.e. emotional faces task), so functional scans would coincide with the active time-window of central effects of intranasal oxytocin (Paloyelis et al., 2014). Medication allocation was double-blind and order was counterbalanced. Within the BOOSTER study, we investigated effects of intranasal oxytocin compared to placebo on several task-based measures of emotion processing (emotional faces and emotion distraction task) and reward processing (monetary and social reward task), as well as resting-state functional connectivity (see also Koch et al., 2016b, 2016c, in prep.). Structural scans (T1-weighted and diffusion tensor imaging (DTI)), (epi)genetic and endocrine measures, questionnaires and clinical interviews were also included (see also Frijling et al., 2015; Koch et al., 2017; van Zuiden et al., in prep.), to allow examination of baseline differences between PTSD patients and controls and relate effects of oxytocin administration to interindividual characteristics.
A. BOOSTER study procedure

B. Scan session procedure

Figure 2. Schematic overview of the BOOSTER study and scan procedures. A. During T0, eligibility and clinical characteristics were assessed. Eligible participants were randomized to treatment-order for the following two scan sessions (T1 placebo- T2 oxytocin or T1 oxytocin- T2 placebo). B. Scan session procedures were identical for the two scan sessions, except for treatment (oxytocin or placebo), and for the structural scan, which was a structural T1-weighted scan during the first scan session, and a DTI scan during the second scan session. Abbreviations: IU=international units, OT=oxytocin, PL=placebo, DTI=diffusion tensor imaging.