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The role of oxytocin in social bonding, stress regulation and mental health: An update on the moderating effects of context and interindividual differences

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Summary In this review we summarize the results and conclusions of five studies as presented in a symposium at the 42nd annual meeting of the International Society for Psychoneuroendocrinology, in New York in September 2012. Oxytocin administration has received increasing attention for its role in promoting positive social behavior and stress regulation, and its potential as a therapeutic intervention for addressing various aspects of psychiatric disorders. However, it has been noted that the observed effects are not uniformly beneficial. In this paper we present five new studies each concluding that contextual and interindividual factors moderate the effects of oxytocin, as well as peripheral oxytocin levels. These findings are in accordance with the recent idea that oxytocin administration may increase sensitivity to social salience cues and that the interpretation of these cues may be influenced by contextual (i.e. presence of a stranger versus friend) or interindividual factors (i.e. sex, attachment style, or the presence of psychiatric symptoms). When social cues in the environment are interpreted as "safe" oxytocin may promote prosociality but when the social cues are interpreted as "unsafe" oxytocin may promote more

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defensive and, in effect, ''anti-social'' emotions and behaviors. Likewise, oxytocin appears to promote such agonistic tendencies in individuals who are chronically pre-disposed to view the social milieu in uncertain and/or in negative terms (e.g., those with borderline personality disorder, severe attachment anxiety and/or childhood maltreatment). In all, these studies in pre-clinical animal, healthy humans and patients samples further reinforce the importance of considering both contextual and interindividual factors when trying to understand the role of oxytocin as a biological substrate underlying social bonding and stress regulatory processes and when studying the effects of oxytocin administration in particular in patients with (increased risk for) psychiatric disorders.

1. Introduction

Recently oxytocin has received increasing attention, both scientifically for its role in social bonding, stress regulation, and mental health, as well as in the more popular media. It has been advertised as a universal ''love hormone'', as the remedy against loneliness, fears, partner relationship and sexual problems. In this review, we will briefly discuss evidence for oxytocin's role in social bonding, stress regulation and mental health. Specifically, it has been argued that the social effects of oxytocin are, more often than not, moderated by features of the context in which oxytocin is administered and/or the individuals to whom it is administered (Bartz et al., 2011b). Here, we review more recent data supporting this hypothesis, and highlight findings from five studies as presented at the 42nd annual meeting of the International Society for Psychoneuroendocrinology (ISPNE), New York, September 2012. The goal of the symposium was to gain more insight in the influence of a broad variety of contextual and interindividual factors on the effects of exogenous oxytocin administration as well as peripheral oxytocin levels. Finally, the findings of these new studies will be integrated and discussed. Taken together, the integrated results and discussion further support the idea that oxytocin is not simply a ''love hormone'', but instead that oxytocin may increase sensitivity to social salience and subsequent effects of oxytocin administration depend on the attributed salience of the situation (Bartz et al., 2011b).

1.1. Oxytocin and social bonding

Work in a wide variety of mammalian and non-mammalian species contributed important insights into the critical involvement of oxytocin in the formation and continuation of social bonds. Oxytocin is physiologically primarily involved in events associated with reproduction, including stimulation of uterine contraction and lactation (Fuchs et al., 1984). These physiological effects are likely mechanistically linked to regulating attachment behaviors, since these early critical periods represent privileged times during which mothers bond with their offspring, and newly born infants collect information about safety and threat in their environment (for review see Carter, 1998). Early work in animals demonstrated oxytocin's ability to induce maternal behavior (e.g. Pedersen and Prange, 1979) and its role in forming pair-bonds (e.g. Insel, 1997; Williams et al., 1994), setting the stage for investigations of oxytocin's role in social bonding and attachment more generally. In humans, markers of the oxytocinergic system have been linked to parental behavior and parent–infant bonding. For example, high endogenous oxytocin levels peripartum are associated with increased mother–infant bonding (Feldman et al., 2007). In line with this finding, higher plasma and salivary oxytocin levels in mothers and fathers were positively associated with the parent's and child's social engagement, affect synchrony, as well as positive communicative sequences between parent and child (Feldman et al., 2011).

Moreover, early experiences seem to influence the oxytocin system later in life. It has been observed that experiencing childhood trauma, which is a major predisposing factor for the development of insecure attachment and mental health problems, may dysregulate functioning of the oxytocin system. For example, it was shown that adult women who were exposed to any form of childhood maltreatment had lower oxytocin levels in the cerebrospinal fluid compared to controls (Heim et al., 2009). Furthermore, intranasal oxytocin administration studies in humans confirm the overall idea that oxytocin is involved in a broad variety of other processes that are associated with social bonding in healthy individuals, including elevation of (in-group) trust (van Ijzendoorn and Bakermans-Kranenburg, 2012) and improved recognition of facial emotions (Shahrestani et al., 2013).

1.2. Oxytocin and stress regulation

The formation of enduring bonds may play an important role in structuring adaptive responses to stressors, since the mechanisms that arose to facilitate their development likely evolved in environments that presented numerous survival challenges. A large body of evidence links oxytocin to stress regulation in rodents. Central and peripheral oxytocin levels have been found to increase in response to a wide variety of stressful stimuli, such as conditioned fear stimuli and restraint stress (Neumann et al., 2000; Onaka, 2004). In humans an increase in plasma oxytocin was found after exposure to uncontrollable noise in women (Sanders et al., 1990) and in response to several types of psychosocial stressors (Hoge et al., 2008; Marazziti et al., 2006; Taylor et al., 2010). It has been hypothesized that oxytocin release during stressful situations serves to dampen physiological stress levels, for it has also been observed that high basal plasma oxytocin levels are associated with low norepinephrine levels, blood pressure and heart rate (Light et al., 2004). In addition, in lactating women, i.e. women with high oxytocin levels, cortisol and ACTH responses to a physical exercise stressor were attenuated compared to non-breastfeeding women (Altemus et al., 1995). It was shown that oxytocin administration has stress-regulating effects in

rodents (Windle et al., 2004), as well as humans. In healthy humans, effects of oxytocin administration on stress reactivity include decreases in subjective stress ratings (Heinrichs et al., 2003), as well as increases in parasympathetic cardiac control (Norman et al., 2011) and decreases in salivary cortisol levels (Ditzen et al., 2009; Linnen et al., 2012). One of the underlying mechanisms behind these stress regulatory findings appears to be that oxytocin has direct and indirect inhibitory effects on the (central) amygdala (LeDoux, 1994). In rats it was shown that oxytocin-binding to its receptor in the amygdala inhibited activity of neural populations that project to hypothalamic and brainstem areas regulating peripheral stress and fear responses respectively (Huber et al., 2005; Viviani et al., 2011). In support of these findings, neuroimaging studies have shown that intranasal oxytocin administration diminished amygdala activity (e.g. Domes et al., 2007) and decreased functional coupling between the amygdala and brainstem (Kirsch et al., 2005) in healthy males in response to negative emotional stimuli. In addition, also during rest intranasal oxytocin influenced amygdala functioning by increasing amygdala-prefrontal cortex (PFC) connectivity (Sripada et al., 2012). Little is known about the effects of oxytocin administration on amygdala reactivity in females, but thus far it has been shown that intranasal oxytocin may actually increase amygdala reactivity compared to placebo in response to negative emotional stimuli, at least in healthy females (Domes et al., 2010;Lischke et al., 2012).

1.3. Oxytocin and mental health

Findings from preclinical and clinical studies on the effects of oxytocin administration on social processes and stress regulation have led to the conceptual idea that the oxytocin system is a promising therapeutic target for alleviating psychiatric symptoms, since psychopathology is often associated with disturbed stress regulation as well as disrupted attachment and/or deficits in social cognition (Striepens et al., 2011). However, most oxytocin administration studies were single administration trials in individuals without a diagnosed mental disorder. As MacDonald and Feifel recently suggested, findings from these studies cannot be uniformly translated to expected effects in patients with a psychiatric illness, since it has been shown before that short-term effects of drugs may differ between psychiatric patients and healthy controls (Macdonald and Feifel, 2013).

Currently, single oxytocin intranasal administration studies have been conducted in patients with various psychiatric disorders, including autism spectrum disorder, borderline personality disorder (BPD), major depressive disorder, post-traumatic stress disorder (PTSD), schizophrenia and social anxiety disorder (for review see Macdonald and Feifel, 2013). Besides findings that oxytocin may decrease trust and prosocial behavior in BPD patients (Bartz et al., 2011a) and increased sadness in mother with postnatal depression (Mah et al., 2013) findings generally show attenuated subjective and physiological stress reactivity and improved emotion recognition (Macdonald and Feifel, 2013).

Although a single administration of oxytocin still may exert different effects than a long-term treatment schedule, these single-administration studies provide us with some insight into expected effects in psychiatric populations. However, to be able to establish whether oxytocin indeed has therapeutic potential for psychiatric disorders, randomized placebo-controlled trials with long-term administration of the peptide, either as stand-alone treatment or combined with evidence-based treatments, are needed (for more detail see Macdonald and Feifel, 2013). Currently, results from a variety of small study samples indicate that administration of intranasal oxytocin for several days to weeks may lead to improved functioning in a variety of psychiatric disorders, including schizophrenia and autism spectrum disorder (for review see Macdonald and Feifel, 2013; Striepens et al., 2011), but these studies are still sparse. Notably, 2 small sample studies in patients with obsessive compulsive disorder (OCD) failed to show an effect of multiple doses of oxytocin on OCD symptoms in patients (den Boer and Westenberg, 1992; Epperson et al., 1996) and beneficial effects of oxytocin administration on generalized anxiety disorders symptoms were observed in males but not in females (Feifel et al., 2011).

1.4. Contextual cues and interindividual differences moderate effects of oxytocin

Even though it has now become widely acknowledged that endogenous release or exogenous administration of oxytocin may facilitate social bonding and stress regulation, and may even promote mental health, over the past few years it has become clear that these beneficial effects of oxytocin may occur only under specific circumstances (for review see Bartz et al., 2011b). The emerging research has raised doubt as to whether the effects of oxytocin uniformly promote the formation of bonds and adaptive stress responses. Instead, there appear to be conditional effects depending on contextual and interindividual factors (Bartz et al., 2011b). We define contextual factors as external cues stemming from the environment (e.g. the presence of a (un)familiar person) and interindividual factors as internal characteristics that may differ between persons (e.g. sex and hormonal status, attachment style, childhood trauma, presence of psychiatric symptoms, and genetic variation), which may influence the sensitivity to and interpretation of the emotional significance or salience of a situation. Regarding contextual factors, oxytocin administration was for example shown to decrease cooperation when participants interacted with strangers compared to familiar persons (Declerck et al., 2010) or out-group members compared to in-group members (De Dreu et al., 2011), although a recent meta-analysis could not confirm that intranasal oxytocin significantly decreases out-group trust (van Ijzendoorn and Bakermans-Kranenburg, 2012). Similarly, interindividual factors have also been shown to moderate the effects of oxytocin administration. Bartz et al. (2011a) administered intranasal oxytocin or placebo to adults with BPD, which is marked by pervasive fears about separation and abandonment, high levels of emotional reactivity and impulsive aggression. They showed that oxytocin treatment decreased trust and the likelihood of cooperation during a social dilemma game compared to placebo treatment. On the other hand, the administration of intranasal oxytocin in individuals with BPD did dampen stress reactivity behaviourally and at the level of the HPA axis (Simeon et al.,

2011). In another study investigating the effects of oxytocin on attachment representations, which develop in response to early caregiving experiences (Bowlby, 1977), Bartz et al. (2010b) found that differences in attachment anxiety in healthy adults moderated the effects of oxytocin, with more securely attached individuals remembering their mothers as more caring and close in childhood following oxytocin relative to placebo, but more anxiously attached individuals actually remembering their mother as less caring and close following oxytocin relative to placebo. These data suggest that, at least in some individuals, oxytocin may amplify the influence of pre-existing interpersonal schemas, be they positive or negative (Bartz et al., 2011a). In addition, De Dreu (2012) observed that intranasal oxytocin increased cooperation and trust, and reduced betrayal aversion in healthy males who scored high on attachment avoidance, but oxytocin did not have these pro-social effects in individuals scoring high on attachment anxiety. In addition, in a recent study in females it was shown that intranasal OT only increased prosocial behavior during a ball-tossing game in those women who reported having experienced low levels of maternal love withdrawal as a disciplinary measure when they were young, but not in those who had experienced high levels of maternal love withdrawal (Riem et al., 2013). Furthermore, in a recent study by Declerck et al. (2013) it was demonstrated that contextual cues and interindividual factors interact in determining effects of oxytocin: here it was observed that the effects of intranasal oxytocin on prosocial behavior depended on social value orientation (i.e. being pro-self or pro-other oriented) as well as the presence or absence of contact with the opponent prior to the prisoner's dilemma, a well-validated experiment representing a social dilemma.

As we already mentioned above, effects of oxytocin are expected to differ between healthy individuals and psychiatric populations (Macdonald and Feifel, 2013). Interestingly, some studies comparing effects of oxytocin administration between several groups of participants have shown favorable effects of intranasal oxytocin only in individuals who could gain with regard to social or emotional functioning, with those who already functioned adequately not impacted by the oxytocin administration. For example, intranasal oxytocin attenuated subjective stress response and cortisol levels in response to stress only in those with poor coping and emotion regulation abilities respectively, but not in individuals with adequate coping or emotion regulation abilities (Cardoso et al., 2012b; Quirin et al., 2011). Furthermore, intranasal oxytocin increased empathetic accuracy only in individuals who were less socially proficient (Bartz et al., 2010b).

Other important interindividual factors involved in effects of oxytocin are sex and hormonal status (for review see Macdonald, 2012). For example, animal and human studies have shown that gonadal steroids influence the production of oxytocin (Patisaul et al., 2003) and oxytocin receptors (OTR)(Richard and Zingg, 1990) and OTR-binding in the brain (Johnson et al., 1991). Additionally, intranasal oxytocin studies show that males and females may respond differentially to oxytocin administration. As described above, males show attenuated amygdala reactivity, and women increased reactivity of the amygdala to similar emotional stimuli (Domes et al., 2007, 2010; Lischke et al., 2012). In addition, Feifel et al. (2011) observed within a small sample of individuals with generalized anxiety disorder that males benefited from a 3 week oxytocin-treatment regimen, while women showed a trend significant increase in anxiety. The presence of different effects of oxytocin treatment in males and females is of particular interest since females have an increased risk of developing anxiety disorders compared to males (Kessler et al., 2012). In contrast, the prevalence of several disorders characterized by more pervasive disruptions in social cognition and functioning, such as autism spectrum disorders and schizophrenia, is higher in males than in females (Aleman et al., 2003; Fombonne, 2005).

Clearly, the moderating effects of these contextual and interindividual factors on the outcomes of oxytocin administration warrant further investigation, especially in studies investigating long-term administration of oxytocin (e.g. Bartz et al., 2011b).

Next we present findings from five studies on effects of oxytocin, as presented in a symposium at the 42nd annual meeting of the international society for Psychoneuroendocrinology (ISPNE). The goal of the symposium was to discuss findings from a variety of oxytocin studies and integrate the findings within the broader literature on contextual and interindividual factors that influence the effects of oxytocin administration.

2. The role of oxytocin at the interface of stress and social behavior in the socially monogamous prairie vole

Yee and colleagues examined the role of oxytocin at the interface of stress and social behavior in the socially monogamous prairie vole. In 71 female prairie voles Yee and colleagues applied intraperitoneal pre-treatment of oxytocin, saline or oxytocin antagonist prior to a brief flooded cage stressor and subsequently assessed plasma levels of corticosterone and oxytocin, social behavior and neural activation patterns. What follows is a preliminary analysis of the data. Oxytocin pre-treatment resulted in a greater amount of time spent in sedentary social contact (t (26) = 2.57; p = 0.02), but did not differ in the amount of time spent rearing (t (52) = 0.68; p = *n.s.*). Voles pretreated with oxytocin exhibited elevated concentrations of oxytocin in plasma 95 min after the original injection (t (51) = 2.95; p = 0.005), suggesting positive feedback potentiation of oxytocin release in the context of stress, similar to that seen in the context of parturition (Russell et al., 2003). Oxytocin pre-treatment did not change overall neural activation as determined by Fos expression in the paraventricular nucleus (PVN), a brain region critically involved in coordinating neuroendocrine and autonomic responses to stress, and a major site of oxytocin synthesis. However, voles pretreated with oxytocin displayed increased functional coupling between the PVN and cardioregulatory nuclei in the brainstem; blocking oxytocin activity with an antagonist resulted in decoupling of activity in the PVN and brainstem as was seen in voles pretreated with saline. Interestingly, functional coupling with the PVN was seen in brainstem nuclei that exert both sympathetic (Rostral Ventrolateral Medulla) and parasympathetic (Dorsal Vagal Complex; Nucleus Ambiguous) influences on the heart. Although oxytocin pre-treatment seemed to increase neural

control of cardioregulatory processes during a stressor, it also resulted in a trend toward heightened glucocorticoid levels (t (51) = 1.67; p = 0.10). These preliminary findings are consistent with the notion that peripheral pre-treatment of oxytocin in stressed animals results in neurological and endocrine changes that support the maintenance of heightened vigilance without sacrificing heightened social cohesion. Presumably, these changes function adaptively to increase the extent to which individuals are able to share vigilance during a threatening situation in which a safe and familiar social context is available. While the trend toward heightened glucocorticoid levels may initially seem to contradict oxytocin's characterization as an anxiolytic and stress-reducing hormone, the experimental context differs from previous animal studies in at least one of two ways that may better inform oxytocin's function. First, unlike repeated restraint stress (a method commonly used to induce stress in animals) in which immobilization may be adaptive, the flooded cage stressor used in this experiment allowed the animal to move around freely, and was designed to model a stressor that occurs in nature and in which mobilization is necessary for survival. Since glucocorticoids facilitate energy mobilization, oxytocin's augmentation of corticosterone levels may represent an adaptive response. Second, unlike standardized behavioral tests that examine responses while animals are socially isolated, such as the elevated-plus maze, open field, or forced swim test, stress responses occurred in a familiar social context. In conclusion, this new research suggests that oxytocin may function as an anti-stress hormone across varying contexts, by changing physiology and neural connectivity in an adaptive manner that facilitates social cohesion in the face of environmental threats that would otherwise promote dispersal.

3. The effect of oxytocin in response to social stress in men and women

The aim of the study by Kubzansky et al. was to examine whether oxytocin enhances salutary responses to social stress, considering the social conditions under which such responses may occur, and comparing effects across men and women.

Hypotheses were tested using a placebo-controlled, double-blind experimental design. Initial hypotheses were considered with a between subjects 2 (male vs. female) $\times$ 2 (oxytocin vs. placebo) design. In the initial study, participants (n = 99) were randomized to receive either intranasal oxytocin spray or placebo (saline) nasal spray (Kubzansky et al., 2012). Social stress was induced using the Trier Social Stress Test (TSST). Primary outcomes were cardiovascular reactivity, objective behavior during the stress task coded by observers unaware of the oxytocin condition, and self-reported affective responses. In a follow-up study Kubzansky et al. examined effects of oxytocin versus placebo on stress responses under different conditions of social support. Thus, participants were randomized to receive either intranasal oxytocin spray or placebo, and also to participate in the stress task while alone, with a friend, or with a supportive stranger. Primary outcomes were again cardiovascular reactivity, objective behavior during the stress task, and self-reported affect. Cardiovascular reactivity was considered in relation to the biopsychosocial model of challenge and threat (for a review see Blascovich and Mendes, 2010). This model suggests that acute stress reactions may result in either a "challenge" or a "threat" state. While both states are characterized by SNS activation, challenge facilitates goal-directed behavior and is characterized by benign physiological reactions, while threat can impair performance and is characterized by a less benign cardiovascular response.

Participants given oxytocin, relative to placebo, responded to social stress with a *challenge* orientation characterized by a benign pattern of cardiovascular reactivity. Participants given oxytocin, compared to placebo participants, exhibited a trend toward greater increases in cardiac output (F (1, 68) = 3.31, p = 0.07, d = 0.47) and ventricular contractility (indicating more sympathetic activation; F (1, 71) = 2.98, p = 0.09, d = 0.45). Effects of oxytocin on biological responses were more similar than different across men and women. However, men given oxytocin reported less negative affect (i.e., mean change between baseline and social stress task, men = 0.26 vs. women = 2.14) with no effects evident on task performance. Moreover, contrary to expectations, women given oxytocin reported more anger (mean change men = $-$0.62 vs. women = 0.71) but had better math performance.

When considering effects of oxytocin and placebo in the context of different types of social support, additional interesting effects emerged. Findings on biological responses were similar to those reported above, with a more benign pattern of cardiovascular reactivity exhibited by participants given oxytocin, and no sex differences evident in this pattern. Effects of type of support and oxytocin were evident when considering subjective perceptions of the stressful experience. Thus, individuals with stranger support reported receiving less support, more negative affect, and a greater sense of threat in response to the stress task relative to individuals with friend support (all p-values < 0.05) and these effects were significantly exacerbated among those who received oxytocin (p-values for interaction effects < 0.05). Effects on these outcomes of having a friend (with or without oxytocin) appeared to be similar to effects of having oxytocin in the absence of having a friend.

Generally, the findings presented here were somewhat unexpected relative to initial predictions. They do suggest that oxytocin may stimulate an approach-oriented cardiovascular profile during social stress, thereby increasing willingness to engage with the social context. With these alterations, individuals may be somewhat more sensitive to social environmental cues and more strongly influenced by the dominant tone of a situation, be it negative or positive. Thus, in a more positive situation it may be that oxytocin enhances a sense of well-being and attenuates stress response. However, in a more adverse situation, oxytocin may enhance attention to the undesirable features of the experience, leading to more distress or anger, and more negative perceptions of others. With regard to the first study, it is speculated that men found the stress task less difficult than women, so that oxytocin was associated with reduced negative response among the men but not the women. In the second study, participants generally reported that the stranger support condition was more awkward and uncomfortable than being alone; as a result, those with oxytocin compared to those without reported even more discomfort with and negative perceptions of the person (stranger) supposedly

providing support. However, effects are not fully straightforward. For example, in the first study, while oxytocin was associated with more negative subjective response in women, some positive effects were evident: reducing inhibitions actually facilitated math performance among the women who ordinarily might feel less assertive in that situation.

4. Oxytocin, attachment and the shift from self to other

The aim of the research presented by Bartz and colleagues was to understand the paradoxical observations that oxytocin tends to be helpful, socially, for those who are less socially engaged, but unhelpful for those who are preoccupied with closeness. Drawing upon research showing that oxytocin plays a critical role in induction of maternal behavior in animals, Bartz et al. hypothesized that oxytocin may induce a similar other-orientation in humans. However, such a main effect could produce very different outcomes depending on how a person views the self-in-relation-to-other.

This hypothesis was tested by administering either 24 IU oxytocin or placebo to male subjects in a randomized, placebo-controlled, cross-over trial investigating the effects of intranasal oxytocin on self-conceptions of agency (self orientation) and communion (other orientation). Individual differences in attachment were assessed at baseline. Bartz and colleagues found preliminary support for this hypothesis. Specifically, oxytocin increased self-perceptions of communal traits (kind, warm, caring), but this effect was moderated by attachment avoidance, with avoidant individuals, showing the largest increase in communion following oxytocin. Moreover, anxious individuals showed a selective decrease in agency following oxytocin. These data shed light on the variability in extant research on the social effects of oxytocin in humans and help explain both the beneficial and potentially harmful effects of oxytocin. It is interesting to consider whether these person-specific effects are mediated by underlying differences in the endogenous oxytocin system. Indeed, researchers have found that early experiences of abuse and/or neglect are associated with lower CSF oxytocin levels in monkeys (Winslow et al., 2003) and humans (Heim et al., 2009). Given that attachment models develop in response to the infant—caregiver relationship, it may be that the differential effects of intranasal oxytocin administration we observed in anxious versus avoidant individuals are related to the functioning of the endogenous oxytocin system. For example, perhaps because of early caregiving experiences some individuals are more sensitive to the effects of intranasal oxytocin, which could influence how people respond to intranasal oxytocin. Although we think this is an intriguing hypothesis, caution is warranted as Bartz et al. did not measure early abuse in their study of agency and communion, so future work is needed to directly test this hypothesis. That having been said, these findings have potentially important implications for treatment. Although, it is difficult to definitively say at this point who one might select or exclude for oxytocin treatment, Bartz et al.'s data would suggest that the dismissives (i.e., those characterized by high levels of avoidance and low levels of anxiety) might benefit from oxytocin treatment but that one might want to be more cautious with the fearful (i.e., high avoidant/high anxious) types given the mixture with anxiety. Indeed, it was the fearful types who showed the most negative response to oxytocin administration in Bartz et al.'s (2011a) BPD study, being least likely to cooperate in the social dilemma game following oxytocin administration.

5. Dose-dependent effects of oxytocin on autobiographical memory

Cardoso et al. (2012a) previously found that intranasal administration of oxytocin positively altered self-reported personality, including higher ratings of extraversion. One possible mechanism underlying this effect is that oxytocin alters self-perception of traits and behavior by changing the way memories are retrieved. Since memory for past personal events influences goal-striving and self-perception, changes in autobiographical memory may be related to oxytocin-induced changes in personality and affiliative behavior. Therefore, the authors assessed the acute effects of administering intranasal oxytocin on autobiographical memory, predicting that oxytocin would improve participants' recall of specific autobiographical memories (i.e., a greater number of personal memories that occurred within a 24-h period, as per the task instructions). Memories were rated as specific if the recalled personal event was a clearly defined event that occurred, at the longest, within a 24 h period (Williams and Broadbent, 1986). Ratings of specificity are important because difficulties retrieving specific memories are a cardinal cognitive feature of depression (Williams et al., 2007). Further, since depressive symptoms are associated with enhanced sensitivity to oxytocin in some studies (e.g. Ellenbogen et al., 2013) and impaired recall of specific memories for past events (Williams et al., 2007), we examined whether the relation between oxytocin and autobiographical memory would be moderated by self-reported depressive symptoms.

In a within-subject design, seventeen male participants self-administered a placebo and two doses of intranasal oxytocin (24 IU and 48 IU) in random order across three test sessions. This study was part of a larger data collection described elsewhere (see Cardoso et al., 2013). One hundred and ten minutes following oxytocin administration, the participants completed the Autobiographical Memory Test, a well-validated measure of the ability to recall specific (i.e., limited to 24 h) personal events in response to verbally prompted cue words (Williams et al., 2007). While this wait-period is not typical in this area of research, we have reported effects of intranasal oxytocin on cortisol levels up to 130 min post-administration (Cardoso et al., 2013). Memories were rated as specific or "overgeneral" (vague memories extending longer than a period of 24 h) by two independent raters (Williams and Broadbent, 1986). Participants recalled a greater number of specific memories following the 24 IU dose of intranasal oxytocin. The 48 IU dose of intranasal oxytocin, in contrast, did not alter autobiographical memory recall. Participants with higher ratings of depressive symptoms showed a larger increase in the number of specific memories recalled following the 24 IU dose of intranasal oxytocin relative to placebo than participants reporting few symptoms of depression.

Taken together, oxytocin improved autobiographical memory recall, increasing participants' ability to retrieve

specific autobiographical memories. Importantly, the present study is among the few to investigate dose-dependent effects of intranasal oxytocin on indices of cognition. It may be that at higher concentrations of central oxytocin, the molecule begins to occupy structurally related arginine—vasopressin receptors, which often show opposing effects in the literature (Legros, 2001). The finding that intranasal oxytocin alters the recall of personal past memories highlights a putative mechanism by which oxytocin alters self-perceptions (Bartz et al., 2010b; Cardoso et al., 2012a). Of note, the moderating role of depressive symptoms on the acute effects of intranasal oxytocin in humans is in line with previous studies of oxytocin and cognition (e.g. Ellenbogen et al., 2013). Given that sub-threshold depressive symptoms are associated with the later onset of depression (Fergusson et al., 2005), oxytocin may have therapeutic potential in vulnerable populations.

6. PTSD and levels of peripheral oxytocin

The aim of the study by Bradley et al. was to examine peripheral oxytocin, and psychological functioning in a highly traumatized sample in Atlanta. Subjects in this study were recruited as part of the Grady Trauma Project, a 5-year NIH-funded study (MH071537) of risk and resilience factors related to posttraumatic stress disorder (PTSD). Participants were recruited at a publicly funded, not-for-profit healthcare system that serves a low-income population in Atlanta, Georgia. Participants completed a battery of self-report measures assessing trauma history (Traumatic Events Inventory (TEI)), childhood abuse (Childhood Trauma Questionnaire (CTQ)), PTSD (self-report modified PTSD Symptom Scale (mPSS)) and associated symptoms. As described previously (Gillespie et al., 2009), study participants who completed this initial interview were invited to participate in a secondary phase of the study, which included a more thorough psychological and neurobiological assessment. Whole blood samples were collected between 8:00 AM — 9:00 AM under fasting conditions. Separated plasma was stored at −80° C until further analysis using a commercially prepared enzyme-immuno-assay-kit produced by Assay Design (Ann Arbor Michigan).

The sample included 88 study participants. This sample was 26% male and 74% female. All of the participants in this study were African American. The average age of the sample was 40.4 (SD = 13.8). The majority of the participants had a low income, with over 50% reporting a household monthly income less than $1000. As previously reported (Gillespie et al., 2009; Bradley et al., under review), this study population reports a high level of childhood maltreatment and trauma exposure. In this sample 48% reported a history of childhood maltreatment and 92% of the sample reported exposure to at least one traumatic event other than childhood abuse in their lifetime. When the DSM-IV PTSD diagnostic criteria were applied to the mPSS data, 32% met criteria for current PTSD on this proxy variable. When examining the relationship of childhood maltreatment, PTSD and peripheral oxytocin levels controlling for age, sex, prior non-childhood abuse trauma exposure, and current life stress, a significant difference for childhood maltreatment (F (1,75) = 9.96, p = 0.02) was found such that those individuals with a history of childhood maltreatment (M = 823.9, SD = 531.6) had higher levels of peripheral oxytocin than those without a prior history of childhood maltreatment (M = 697.1, SD = 526.9). No significant difference between the two groups based on PTSD (F (1,75) = 0.23, p = 0.61) was observed. However, a significant interaction was found between history of childhood maltreatment and PTSD (F (1,74) = 5.7, p = 0.02). The nature of this interaction was that the lowest levels of peripheral oxytocin were found in those individuals without a history of childhood maltreatment but who did not meet our proxy criteria for current PTSD, while the highest levels of peripheral oxytocin were found in those individuals who had a history of childhood maltreatment as well as a current diagnosis of PTSD (see Fig. 1).

It has been suggested that acute increases in oxytocin levels such as those associated with positive social affiliation or experimental augmentation of oxytocin may serve to decrease stress reactivity (Olff et al., 2010). On the other hand, peripheral oxytocin markers such as plasma oxytocin may be a marker of ongoing social and interpersonal distress (Taylor et al., 2010). In this case increased peripheral oxytocin may serve as a signal of the need to seek social affiliation. This may help to understand the findings of the current study. Even among individuals with current PTSD symptoms, those with a history of childhood maltreatment might be expected to have higher levels of overall interpersonal distress. This might be related to the strong association

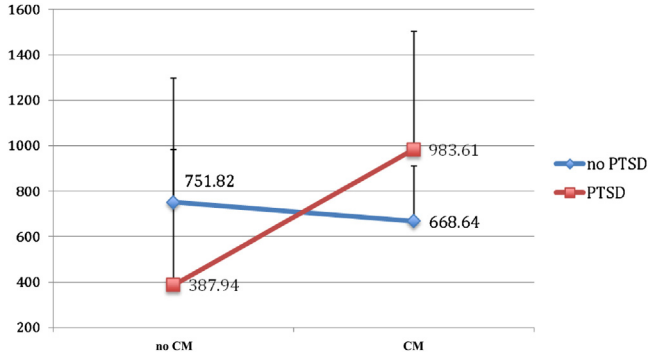

Figure 1 Interaction of PTSD and childhood maltreatment (CM) predicts plasma oxytocin levels. Plasma oxytocin levels (pg/ml, y-axis), collected in the morning (8:00 am — 09:00 am) under fasting conditions in a highly traumatized adult population, with or without a history of childhood maltreatment (groups displayed on the x-axis). The blue line indicates the individuals without PTSD, the red line represents those with PTSD. Displayed are the mean values and the standard deviation (SD).

between childhood maltreatment and impaired attachment. In addition, for those individuals with a history of childhood maltreatment, interpersonal interactions may be more likely to serve as reminders of past traumatic experiences and they may also be more inclined to see others as threatening. Thus the combination of PTSD and childhood maltreatment might be related to particularly high levels of interpersonal distress and disconnection, which is marked by higher levels of peripheral oxytocin. The implications of this data for treatment are not clear. Possibly, these data suggest that further administration of oxytocin to those individuals who already have high basal oxytocin levels, which in this data is the PTSD and child maltreatment group, may not be helpful. On the other hand, if higher peripheral oxytocin levels in this group reflect interpersonal distress cued by reminders of past interpersonal trauma, the combination of administered oxytocin and psychotherapy may lead to increased engagement in new, positive social affiliation and decrease the trauma-associated distress associated with past interpersonal relationships.

The study has a number of significant limitations. It is a cross-sectional study and child maltreatment and PTSD was assessed via self-report. The most notable limitation is the possibility that factors such as medications being taken by participants (e.g., oral contraceptives or psychotropic medications), co-morbid medical diagnoses, menstrual cycle phase or menopausal status might have affected our measurement of oxytocin levels. This was a pilot study, and currently additional data are being gathered on research participants for whom more comprehensive medical data will be available, which will allow to take the factors into account. Given the preliminary nature of these findings, interpretation based on them should be considered speculative and in need of further replication in better-controlled samples.

7. Preventing PTSD by boosting the oxytocin system in acutely traumatized individuals

Frijling et al. focused on the feasibility of a study investigating the effectiveness of oxytocin in the prevention of PTSD in acutely traumatized patients. Increased risk for PTSD development is associated with (pre-existing) dysregulations of the autonomic nervous system, hypothalamic—pituitary—adrenal (HPA) axis and central fear response, as well as a lack of perceived social support early after trauma (Admon et al., 2013; Apfel et al., 2011; Ozer et al., 2003; Shaikh al et al., 2012; van Zuiden et al., 2011). Due to oxytocin's fear and stress regulatory as well as prosocial effects, oxytocin appears to be a promising pharmacological preventive strategy for PTSD, which is both safe and easily applicable (Olff, 2012). When administered early after trauma, oxytocin is hypothesized to ameliorate dysregulated stress and fear responses, as well as facilitate adaptive social functioning. As there is still very little evidence for effective interventions that prevent the development of PTSD examining the preventive effects of oxytocin for PTSD seems worthwhile.

In order to investigate whether intranasal oxytocin administration prevents the development of PTSD, a Randomized Controlled Trial (RCT) is currently conducted by the group of Olff in Amsterdam in recently trauma-exposed individuals who were treated at an Emergency Department (ED). Two-hundred-and-twenty individuals will be included with increased risk of developing PTSD due to high levels of acute PTSD symptoms and/or high levels or peritraumatic distress. Diagnostic clinical interviews are obtained within ten days post-trauma to collect baseline PTSD and other psychopathology symptoms. The intervention starts at the latest on day ten post-trauma. It lasts 7.5 days and consists of 10 puffs of oxytocin (40 IU) or placebo twice a day. At 1.5, 3 and 6 months post-trauma follow-up assessments take place, consisting of diagnostic clinical interviews and stress response measures.

Recruitment has been underway since May 2012 at the Emergency Department (ED) of the Academic Medical Center in Amsterdam. In one year time, 1214 patients visited the ED after experiencing a potentially traumatic event. Based on the patient records, 855 were eligible for screening. Of those eligible individuals, 392 could be contacted and screened. One-hundred-and-fifty-five scored above the cut-off score of the screening instruments. Of these, 40 were excluded based on self-reported exclusion criteria (i.e. pregnancy, current PTSD or severe depression, certain medications or instable medical conditions). Of the remaining eligible participants, 40 consented and met all inclusion and none of the exclusion criteria. Three participants dropped out prior to first intranasal dose. Of the 38 participants who at time of writing were supposed to have completed the first follow-up assessment, 3 were lost to follow-up. Similar inclusion and drop-out percentages apply to our second center, where recruitment was initiated in December 2012. In total, approximately 10% of the contacted individuals ultimately administered at least one dose of the investigational product. One third of the eligible patients consented to participate in the trial, which is comparable to other intervention studies in ED patients (e.g. Rothbaum et al., 2012). Thus far, the RCT on intranasal oxytocin as an early pharmacological intervention for PTSD in trauma-exposed adults seems to be feasible, although the timely screening, assessment and first administration of nasal spray remains a challenge and requires much flexibility from participants as well as the researchers.

PTSD in adulthood has a higher prevalence in women (Olff et al., 2007) and has been associated with increased presence of childhood trauma or maltreatment (Bremner et al., 1993) as well as insecure attachment (Gore-Felton et al., 2012). These factors have been associated with less beneficial effects of oxytocin administration (Bartz et al., 2011a; Feifel et al., 2011; Riem et al., 2013), including the Bartz et al. study described above. In addition, as discussed above, Bradley et al. observed higher levels of plasma oxytocin in women with PTSD who also experienced childhood trauma. However, we do not preclude participation of otherwise eligible individuals with any of these potentially less beneficial predispositions from our trial, since the studies showing those effects were either single-administration studies or performed in healthy populations or psychiatric populations with a very small sample size. It may be expected that effects of multiple administrations of oxytocin differ from effects of single administrations. In addition, effects of oxytocin administration in populations with (developing) psychiatric disorders may be different from effects of oxytocin in healthy populations (Macdonald and Feifel, 2013). Furthermore, several studies, including the study of Ellenbogen and

Cardoso presented above, have shown that the effects of oxytocin administration may be especially prominent in vulnerable populations (e.g. Quirin et al., 2011). Instead of deciding to exclude specific subgroups of traumatized individuals, we will actually carefully investigate potential moderating effects of sex, history of childhood trauma and attachment style to disentangle the paradoxical effects of oxytocin treatment reported in the literature, and to gain insight in the question for which specific subgroups of individuals intranasal oxytocin interventions may result in favorable outcomes in preventing PTSD.

8. Discussion

The collection of studies presented above, varying from preclinical work in prairie voles and healthy participants to studies in patients with (increased risk for) psychiatric disorders, provides additional understanding on the mechanistic role of oxytocin at the interface of social bonding processes, stress regulation and mental health. The presented findings again show that oxytocin can exert beneficial effects on processes thought to promote social bonding. A single oxytocin administration increased sedentary social contact in prairie voles (Yee et al.), promoted other-oriented self-conceptions (Bartz et al.), and improved the retrieval of specific autobiographical memories (Ellenbogen & Cardoso) in healthy humans. In addition, the results show that oxytocin administration regulates stress reactivity, shown as increased functional coupling between PVN and cardioregulatory nuclei in the brainstem in prairie voles (Yee et al.) and changes in affective, behavioral, and cardiovascular responses in humans in response to experimental stressors (Kubzanksy et al.). However, these two studies also showed that oxytocin administration did not necessarily dampen the physiological stress response, but resulted in an approach/vigilance-oriented endocrine and cardiovascular profile, which the authors hypothesize to be benign and promote social affiliation (Kubzansky et al., Yee et al.).

Collectively these studies show that the effects of a single oxytocin administration seem to depend on the salience of the (social) environment, irrespective of whether this was influenced by external cues (i.e. presence of a stranger versus friend in the study of Kubzansky et al.) or differential interpretations due to interindividual factors (i.e. sex in study of Kubzansky et al.; attachment style in study of Bartz et al.; presence of depressive symptoms in study of Ellenbogen & Cardoso), further reinforcing a more nuanced view of oxytocin (Bartz et al., 2011a). Moreover, from the observed approach-oriented endocrine and cardiovascular profile after oxytocin administration by Yee et al. and Kubzansky et al., it can be deduced that effects of oxytocin may not only depend on interpretations of salience derived from contextual or interpersonal cues, but may actually increase the sensitivity to salience cues from the (social) environment (see also Bartz et al., 2011b) and from within the person (i.e. memory for past personal events, Ellenbogen & Cardoso) (see Fig. 2). Notably, a recent meta-analysis showed that single intranasal oxytocin administration enhances the recognition of facial displays of emotion (Shahrestani et al., 2013), which may indicate that increased sensitivity to salience cues due to oxytocin may result in improved social-emotional processing and social cognition.

Thus, altogether the studies presented here provide additional evidence to the hypothesis that contextual and interindividual factors indeed influence the effects that oxytocin exerts (Bartz et al., 2011b). Moreover, among human studies, the effects of oxytocin may vary depending on the dose administered (Ellenbogen & Cardoso), further complicating our understanding of how oxytocin alters social behavior. Together with the studies described in the introduction, the

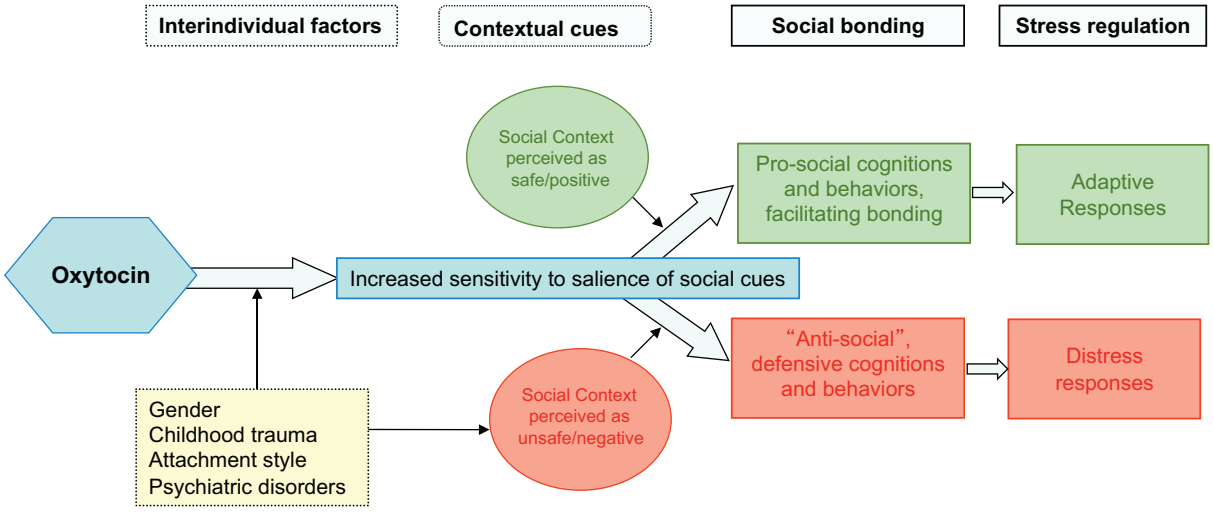

Figure 2 Factors moderating the effects of oxytocin. This figure shows how oxytocin affects social bonding processes and stress regulation dependent on aspects of context and interindividual factors. Oxytocin administration may increase the sensitivity to perceived positive and negative cues from the (social) environment. These are posited externally (e.g. presence of a stranger versus friend), but the interpretation of these cues can be influenced by interindividual factors. When social cues in the environment are interpreted as "safe" or "positive" oxytocin may promote prosocial behaviors and cognitions, and subsequent adaptive stress responses. On the contrary, when the social cues are interpreted as "unsafe" or "negative" oxytocin may promote negative perceptions of others and induce defensive and, in effect, "anti-social" behaviors and also less adaptive stress responses.

findings presented here cast doubt on the popular notion that oxytocin is a universal ''love hormone'' and raise questions about the more basic mechanisms by which oxytocin modulates social bonding behaviors and regulates stress reactivity. Given the complexity of social life, the repeated observation that effects of oxytocin on social bonding processes and stress regulation may not be uniformly positive should not be surprising. As Young et al. (2011) discuss, the formation of pair bonds involves increasing affiliative behavior to select conspecifics (i.e. mates, offspring, kin), but, critically, it also necessarily includes behaviors such as mate-guarding, territoriality, and parental aggression, which all involve agonistic behavior toward potentially threatening conspecifics. Also in humans, oxytocin's critical role in the formation and maintenance of enduring bonds appears to involve both the prosocial and antisocial cognitive, emotional and behavioral associations reported in the literature. This may be understood in an evolutionary perspective, in which the goal is to maximize survival by protecting members of the in-group, irrespective whether this is at potential cost of out-group members. In essence, when the social cues in the environment are interpreted as ''safe'' oxytocin may promote prosociality but when the social cues are interpreted as ''unsafe'' (or even uncertain, e.g. Declerck et al., 2010), oxytocin may promote more defensive and, in effect, ''anti-social'' emotions and behaviors. Likewise, oxytocin may promote such agonistic tendencies in the absence of overtly unsafe social cues in individuals who are chronically predisposed to view the social milieu in uncertain and/or negative terms, such as for those who experienced childhood trauma or maltreatment, and/or with severe attachment anxiety or BPD (e.g., Bartz et al., 2010a). The findings of higher peripheral oxytocin levels in individuals who experienced childhood maltreatment and had adult PTSD (Bradley et al., as described above) further underline the importance of considering developmental history in studies on the effects of oxytocin in patients with (increased risk for) psychiatric disorders.

In conclusion, oxytocin does appear to play an important role in modulation of social bonding processes and stress regulation, and may be crucially involved in the promotion of mental health. Given the beneficial effects of oxytocin administration reported, oxytocin appears to be a promising potential preventive intervention or aid in treatment for a variety of psychiatric conditions, in which it is warranted to improve social bonding processes or stress regulation. However, several recent studies, including the ones reviewed in this paper, reveal that the effects of (single administrations of) oxytocin may not be uniquely beneficial, but depend on interindividual factors as well as (the interpretation of) the context of the situation. In addition, oxytocin may even increase the influence that these contextual and interindividual factors exert on social bonding processes and stress regulation by increasing sensitivity to environmental cues. Thus, it appears increasingly likely that oxytocin will not work as a universal treatment for every individual diagnosed with the same psychiatric condition, which seems to be in line with effectiveness of all current treatment-of-choice psychopharmacological treatments. Future pre-clinical studies in animals and humans, as well as studies investigating oxytocin augmentation as a potential preventive intervention or as an aid in treatment for psychiatric disorders, such as PTSD, will carefully need to consider these contextual and interindividual factors.

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Conflict of interest statement

All authors declare that they have no conflicts of interest.

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