Oxytocin – the prosocial molecule?

Intranasal oxytocin effects on social approach behavior, social cognition, volitional and emotional ambivalence in healthy human beings

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Summary

Oxytocin (OXT) is a highly conserved neuropeptide, regarding both its chemical structure and its functionality. It has been traced back at least 700 million years. OXT's fundamental role lies in reproduction and parenting behavior. OXT findings in animal models, which provided the initial interest for OXT research in humans, are presented in this thesis to clarify the importance of biochemical mechanisms, sexual-dimorphism and species-specificity of the OXT system. In the past few years, OXT has become a very prominent molecule because it may improve social deficits, even in psychiatric illnesses, e.g. social phobia or schizophrenia. However, past research findings have produced highly controversial results in regard to OXT's prosocial role, which might also be due to the complexity of the biochemical mechanisms which are still widely unknown. This dissertation examines modulatory influences of intranasal OXT on different social domains in healthy women and men to further distinguish the prosocial – and possibly beneficial – effects of this neuropeptide. The first study revealed prosocial effects of intranasal OXT in women, who selectively approached social positive stimuli quicker and more closely after OXT administration. In the second study, OXT was also found to have a prosocial effect. It increased the willingness to induce *happy* emotions, while it reduced the willingness to induce *anger* or *fear*. The willingness to induce positive, but not negative emotions, was accompanied by (for example) reduced or increased inferior frontal gyurs (IFG) activity, respectively. In the third study, OXT was *indirectly* investigated as a prosocial neuropeptide. The fMRI study revealed that OXT diminished neural activity in the dorsal anterior cingulate cortex (dACC) in response to volitional (Experiment 1) as well as emotional (Experiment 2) ambivalence. Behaviorally, the OXT effect was apparent in faster reaction times (Experiment 1) and reduced arousal ratings (Experiment

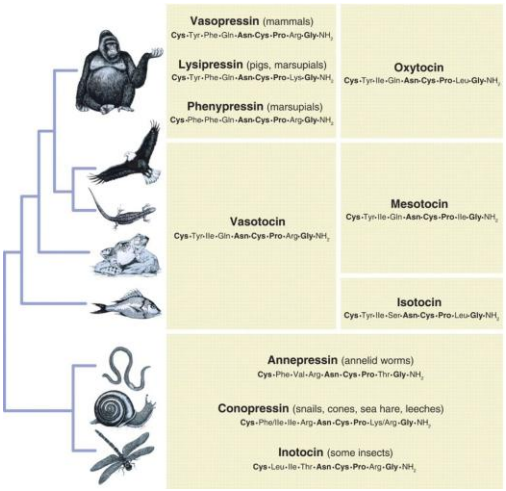
2). In conclusion, the results of the three presented studies indicate that OXT does primarily act as a prosocial molecule, however the prosocial tendencies of OXT may be tilted by many different moderators such as genetic predispositions, early life experiences or strong personality traits.

Chapter 1: Introduction

The molecular evolution of oxytocin

Oxytocin (OXT) and vasopressin (AVP) are well preserved neuropeptides that only differ in two amino acids. Homologs of these two neuropeptides have been traced back for at least 700 million years. Homologs have been found in many diverse species, such as: insects (inotocin), snails (conopressin), annelid worms (annepressin), fish (isotocin, vasotocin), birds (mesotocin, vasotocin), marsupials (phenypressin), pigs (lysipressin) and other mammals (oxytocin, vasopressin).

Figure 1: Oxytocin and vasopressin homologs. (Copied from Donaldson & Young, 2008).



These two neuropeptides have been associated with a general role in modulation of reproductive and social behaviors, even though these behaviors are species-specific (Donaldson & Young, 2008). Most invertebrates only possess one of the two neuropeptide homologes. OXT,

AVP and their vertebrate homologs have most likely occurred after gene-duplication, before vertebrates diverged (Acher, Chauvet, & Chauvet, 1995; H. K. Caldwell & Young, 2006). It is possible that only one member of the oxytocin/vasopressin gene family occurs in invertebrates because the amino acid changes distinguishing the two neuropeptides remain neutral in their functionality (in invertebrates) (Van Kesteren et al., 1995). In vertebrates, OXT and AVP are predominately produced in the hypothalamus, more specifically in secreting magnocellular neurons of the paraventricular nucleus (PVN) and the supraoptic (SON) nucleus (Knobloch & Grinevich, 2014). From an evolutionary perspective it is remarkable that OXT homologs are found in primitive species like insects (Garrison et al., 2012) where no typical neuropeptide pathway is present, however the more primitive homologs are expressed within comparable neurosecretory regions. The occurrence of OXT and AVP in ancient species suggests that these neuropeptides possess a primordial functionality.

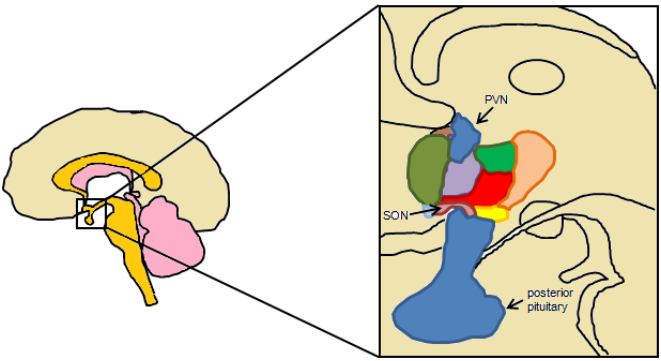


Figure 2. The hypothalamus, locus of OXT synthesis. [1]

[1] This figure was redrawn, but inspired by the following pictures: http://images.sciencedaily.com/2014/10/141030133308-large.jpg, http://www.medidesign.de/Media/Hypothalamus-Hypophyse.jpg

Approximately 80% of the mammalian brain regions which surround the ventricles and the subarachnoid space express OXT receptors. This implies that OXT diffusion within the fluid of extracellular space (e.g. into the blood) could result in behavioral effects of OXT in mammals, as research studies with intracerebroventricular administration have shown (Veening, de Jong, & Barendregt, 2010).

The relationship between peripheral, cerebrospinal fluid concentrations of oxytocin and behavior

In humans, peripheral samples such as saliva, urine or blood are often obtained to measure OXT concentrations, because cerebrospinal fluid (CSF) samples require a more invasive procedure. However, the relationship of peripheral samples to behavior is not extensively known. Thus, a debate whether intranasal OXT administration can account for the behavioral changes and neural modulations – which have been observed in numerous studies – is controversial. An increase in plasma levels of OXT after intranasal administration has been found (Burri, Heinrichs, Schedlowski, & Kruger, 2008; Landgraf, 1985). It is, however, not clear whether elevated plasma concentrations of OXT reflect CSF concentrations. Kagerbauer and colleagues (2012) collected plasma and CSF samples simultaneously from 41 non-neurological and non-psychiatric patients and did not find a correlation between these two samples. The general idea that most intranasal OXT studies rely on assumes that peripheral samples – e.g. saliva samples – represent a correlational neuropeptide amount to OXT brain levels. Therefore, studies assume that these peripheral measurements of OXT and AVP can predict and/ or explain behavioral findings. OXT – said to be produced in the hypothalamus and released into the brain and the periphery – does not cross the blood-brain barrier (BBB) in high amounts because of tight junctions formed by the epithelial cells that are impermeable to large

molecules (Landgraf & Neumann, 2004). It has been suggested that intranasal administration is not potent enough to deliver a sufficient amount of the neuropeptide to the brain to effect behavior and neural activity (Ludwig et al., 2013). In conclusion, it is not entirely clear whether the peripheral OXT levels are a good measure or indicator for OXT brain levels (Kagerbauer et al., 2013a). However, two studies have found a significant positive correlation between plasma and CSF concentrations of OXT (Landgraf, 1985) and a negative correlation between plasma and CSF concentrations to anxiety (Carson et al., 2014). Given these controversial findings in combination with the numerous studies that report changes in neural activity and behavior after intranasal OXT administration, we assume that OXT can cross the BBB and reach the CSF to a sufficient degree in order to operate in a delayed but also long lasting fashion (Born et al., 2002) on neural activity and behavior. This assumption has been confirmed by Burri et al. (2008) who ascertained a significant OXT plasma increase 40 minutes after intranasal administration, lasting for more than one hour (Burri, Heinrichs, Schedlowski, & Kruger, 2008). Due to the delayed plasma increase and functional onset of OXT, experiments normally start 30 – 45 minutes after intranasal OXT administration. It is noteworthy, the intranasally administered OXT has a 1000-fold higher concentration than the concentration in the blood (Neumann, Maloumby, Beiderbeck, Lukas, & Landgraf, 2013), and that the OXT concentration in the CSF is much higher than in blood (Kagerbauer et al., 2013b).

The relationship between oxytocin, oxytocin receptor genes and behavior

Oxytocin pathways are influenced by genetic variations that shall be discussed in this section. The genes which encode OXT and AVP are *neurophysin I* (NPI) and *neurophysin II* (NPII), respectively. OXT has only

one receptor (OXTR), in contrast to AVP which has three different receptors (V1a, V1b, V2). Both neuropeptides can bind, with reduced affinity, to each other's receptor(s). Human genes that encode the four receptors are single-copy genes derived from a common antecedent, even though they are located on different chromosomes. Except for the V2 receptors, they are all expressed in the brain (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012). There are indications that V1a, V2 and the OXTR proteins form heteromeric dimers (Cottet et al., 2010), and these receptors can be expressed in the same cell line; but is not certain that they can be co-expressed. The existence of heteromeric dimers could point to possible confounds regarding the interpretation of OXT or AVP effects. The action of the heteromeric receptor after OXT or AVP binding leaves some ambiguity for interpreting the results, since it cannot be determined which part of the dimer acted upon the binding (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012). More detailed genetic studies are needed to clarify this aspect of heterodimer binding.

Another open question is whether there are any functional polymorphic variants in the promoter region of the OXTR that may be related to social traits. Different genetic variants in the OXTR gene are characterized by single nucleotide polymorphisms (SNPs). The variant that has been linked to behavior and neural activity in different social contexts is the rs53676, with the three allele combinations: A/A, A/G and G/G (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012). Multiple studies have investigated this gene variant in relation to different social contexts. One study examined the relationship between positive/ negative affect and loneliness and the OXTR polymorphisms. In total the authors tested 285 healthy adults and revealed that men with the rs53576 A/A genotype displayed reduced positive affect scores (Lucht et al., 2009). Another study testing the relationship between empathy and stress reactivity and the OXTR genotype rs53576 revealed that individuals with a homozygous G-allele displayed higher

behavioral dispositional empathy than individuals who carried one or even two A-alleles in the "Reading the Mind in the Eyes Test" (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) and the Interpersonal Reactivity Index (Davis, 1980). A/A and A/G carriers also revealed an increased stress reactivity than G/G individuals, during a startle anticipation task, which was strengthened by an affective reactivity scale rating (Rodrigues, Saslow, Garcia, John, & Keltner, 2009; Saphire-Bernstein, Way, Kim, Sherman, & Taylor, 2011). Furthermore, A-allele carriers showed reduced levels of optimism and self-esteem compared to G/G homozygous individuals (Saphire-Bernstein, Way, Kim, Sherman, & Taylor, 2011), while investigations of adult attachment styles in relation to this OXTR polymorphism did not reveal any significant associations (Gillath, Shaver, Baek, & Chun, 2008). Cortisol levels could be reduced when social support was given, however, only in individuals who were carriers of at least one G-allele (Chen et al., 2011). One research group suggests that the social advantage which has been found for the G/G genotype might be linked to better hearing and understanding when talking to people in a room with substantial background noise (Tops, van Ijzendoorn, Riem, Boksem, & Bakermans-Kranenburg, 2011). A multimodal neuroimaging study revealed that A-allele carriers displayed a significantly reduced gray matter volume in the hypothalamus (Tost et al., 2010).

The OXTR SNP rs2268493, has been associated with as a risk gene for autism spectrum disorder and additionally it has been found to decrease mesolimbic responses in reward anticipation (Damiano et al., 2014). Consequently, the OXTR gene can – to some extent – explain the differences in behavior and neural activity. The gene can also be modified by epigenetic changes that occur through different experiences the individual makes along the lifetime as shall be discussed in the following section.

The sites of OXTR gene expression that have been identified in the human brain (see Table 1) have been associated with diverse pathophysiologies in fMRI studies. The amygdala, for example, displayed hyperactivity in borderline personality disorder patients while they were performing the Thematic Apperception Test (Schnell, Dietrich, Schnitker, Daumann, & Herpertz, 2007), which probes for underlying motives, concerns and perceptions of the social world (Bogen, 1998). Similarly, increased amygdala activation was found in autistic patients compared to healthy individuals during a face processing task (Dalton, Nacewicz, Alexander, & Davidson, 2007). Another region with abundant OXTRs is the ACC, which has been associated with sexual arousal (Karama et al., 2002), emotion decision-making and goal–directed behavior (Cannon et al., 2007). Psychiatric disorders that have been related to ACC dysfunction, such as schizophrenia (Adams & David, 2007) and posttraumatic stress disorder (Hou et al., 2007) might benefit for OXT treatment.

Table 1: Distribution of OXTR in the human brain

Brain Regions
Amygdala
Medial preoptic area
Anterior and ventromedial hypothalamus
Olfactory nucleus
Vertical limb of the diagonal band
Anterior cingulate
Solitary nucleus
Islands of Calleja
Basal nucleus of Meynert
Ventral pallidum
Globus pallidus
Lateral septal nucleus
Paraventricular thalamic nucleus
Anterior medial preoptic area
Lateral mammillary nucleus
Medial mammillary nucleus
Substantia nigra pars compacta
Dorsal raphe nucleus
Hypoglossal nucleus
Dorsal motor nucleus of the vagus nerve
Inferior olive nucleus
Substantia gelatinosa of trigeminal nucleus

(Boccia, Petrusz, Suzuki, Marson, & Pedersen, 2013; Gimpl & Fahrenholz, 2001)

Epigenetic changes on the oxytocin receptor in relation to social behavior

As explained above, OXT actions are mediated by its receptor and its polymorphism. Even though one may link the genotype to phenotypical behavior, the biological mechanisms which influence gene transcription are not well understood. Epigenetic changes, such as the methylation of DNA which reduces OXTR transcription has not been taken into consideration yet.

In autism spectrum disorders, a functional relationship between OXTR gene methylation and behavior was found (Gregory et al., 2009). A study in healthy humans which investigated DNA methylation patterns of the OXTR gene revealed individual differences concerning brain regions that are involved in social perception, such as the temporoparietal junction (TPJ) and the dACC (Jack, Connelly, & Morris, 2012). The study by Jack et al. (2012) determined the methylation pattern via blood samples. It might be argued that, again, peripheral blood methylation patterns might not be comparable to those in the brain, however it has been suggested that methylation patterns are moderately conserved across different tissue types within one individual (Byun et al., 2009). Furthermore, DNA methylation patterns assessed in the periphery have been found to be useful indicators of the same methylation patterns in the brain (Kaminsky et al., 2012). Jack et al. (2012) revealed a significant relationship between the OXTR gene methylation degree and brain activity while participants were performing a classic social perception task, first developed by Heider and Simmel (1944). In this task, geometric shapes move around on the screen in two different manners. First, they move around and appear to interact in a somewhat social manner and secondly they move around randomly. OXT being called the "social molecule" might very well have an influence on the perception of the first condition. And indeed, the authors found a relationship between the methylation pattern and neural activity. Surprisingly, elevated neural activity in the TPJ and the

dACC was found when methylation levels were high compared to low in the contrast "social movement" – "random movement". At first the elevated activity in the individuals with high DNA methylation might not appear intuitive, because it means reduced OXTR gene transcription (Gregory et al., 2009) and if the processes under investigation shall be mediated by OXT action one would expect higher perturbation in these individuals. However, the interpretation provided by the authors is, that increased neural activity can also indicate extensive resource recruitment which is strengthened by the finding that dACC activity is increased when ambiguously expressed emotions are resolved (Nomura et al., 2003). Jack et al. (2012) claim that the positive correlation between dACC activity and methylated OXTR may indicate a more ambiguous perception of the "social movement" compared to the "random movement" (Jack, Connelly, & Morris, 2012).

It has been suggested that the epigenetic OXTR gene methylation is an adaptive strategy to down-regulate the OXTR, thereby encouraging up-regulation of OXT synthesis via a negative feedback loop. Changes in the OXT pathway may mainly occur in early life and it is well known that social experiences during early childhood can have lifelong consequences (Carter, Boone, Pournajafi-Nazarloo, & Bales, 2009). Animal studies with prairie voles show that animal handling after birth influences the offspring. For example, OXTR binding and OXT injection at the first day of life facilitates pair-bonding behavior in males, while an OXT antagonist leads to the opposite effect (Carter, Boone, Pournajafi-Nazarloo, & Bales, 2009). This assumption is supported by a human study which found an interaction effect of OXT and early life experiences (Riem, Bakermans-Kranenburg, Huffmeijer, & van Ijzendoorn, 2013), stating that positive life-experiences resulted in increased prosocial behavior after intranasal OXT treatment, while the opposite was true for individuals who reported negative childhood experiences. Unfortunately, this study did not determine methylation

patterns, but with regards to content, this study supports the impact of early life experiences on social behavior. The lasting consequences of early life events might reflect a special aptitude of early OXT exposure to regulate the OXTR gene via methylation.

The influences of sex steroids on oxytocin

OXT and its pathway are influenced by sex steroids, which can in part explain the apparent sexually-dimorphic findings throughout the OXT literature (for examples see Preckel, Scheele, Kendrick, Maier, & Hurlemann, 2014; Rilling et al., 2014). The biochemical underpinnings of sexual differences in the OXT system are, however, not well established.

In the rat, progesterone binds with high affinity to OXTR and thus inhibits the receptor function. A similar mechanism could also take place in humans, namely that progesterone might negatively modulate the OXTR, offering an explanation for progesterone's action on uterine quiescence (Grazzini, Guillon, Mouillac, & Zingg, 1998). However, these results have not been able to be replicated and thus the finding remains uncertain (Burger, Fahrenholz, & Gimpl, 1999). It has been stated, however, that high progesterone concentration blocked the signaling of multiple G protein-coupled receptors in general, to which the OXTR belongs (Gimpl & Fahrenholz, 2001). Another mechanism by which progesterone might influence OXTR binding is through the modulation of cholesterol concentrations which stabilize the OXTR, especially in high – affinity states (Gimpl, Burger, Politowska, Ciarkowski, & Fahrenholz, 2000). Progesterone might inhibit cholesterol esterification and its transport to and from the plasma membrane (Liscum & Munn, 1999). Interestingly, progesterone also stimulates the key enzyme responsible for de novo cholesterol biosynthesis (Metherall, Waugh, & Li, 1996). Therefore, precursors of cholesterol

simultaneously enrich the cell membrane. The exact mechanism by which progesterone acts on the OXT system remains unclear.

Regarding brain activity, estrogen has only little influence on OXT synthesis. OXTRs are extensively regulated by steroid hormones. In the rat for example, an inhibition of aromatase (an enzyme responsible for estrogen biosynthesis) results in a reduced activity of the OXTR, while both estradiol and testosterone enhance OXT binding (Tribollet, Audigiers, Dubois, & Dreifuss, 1990). OXTR affinity was increased after estrogen treatment in the medial preoptic area-anterior hypothalamus (J. D. Caldwell, Walker, Pedersen, Barakat, & Mason, 1994) and further receptor binding was increased by progesterone (Coirini, Schumacher, Flanagan, & McEwen, 1991). Effects of progesterone are very diverse: another study reported that chronic treatment with progesterone resulted in a decreased basal OXTR density in the ventromedial nucleus, for example, while an increase was observed in the limbic structures and estrogen-induced OXT binding was reduced (Patchev, Schlosser, Hassan, & Almeida, 1993). It needs to be noted that OXTR binding and OXT action in the brain vary across species in regard to steroid regulations. Estrogen, for example, increases OXTR binding in rats but decreases OXTR binding in the mouse brain (in homologous regions) (Insel, Young, Witt, & Crews, 1993).

In women, estrogen and progesterone (and inflammatory cytokines) are shown to influence OXT action. Central OXT, for example, increases social contact and reduces aggression in estrogen-treated female prairie voles (Witt, Carter, & Walton, 1990), and exogenous OXT results in increased social contact and grooming, in rats (Argiolas & Gessa, 1991). OXT and VPN neurons express a G protein-coupled receptor which possesses a non-genomic estrogen receptor (ER). Through these ERs, membrane-mediated actions of estrogen can have immediate, rapid actions on these neurons, changing their electrical activity by fast perfusion (100

pM) and thereby hyperpolarizing them (e.g. in the hypothalamus or the amygdala) (Brailoiu et al., 2007; Kelly & Ronnekleiv, 2008). In rats, estrogen-sensitive brain areas (e.g. the hypothalamus) displayed increased amounts of OXTR gene mRNA after estrogen perfusion while no significant mRNA increase was found in estrogen-insensitive brain areas (e.g. the olfactory nuclei) (Breton & Zingg, 1997).

The *challenge hypothesis* suggests that testosterone (T) levels rise when males compete, be it for food and territory or mating with a female, and that T decreases when males have to care for their offspring (Wingfield, Hegner, Dufty, & Ball, 1990). Moreover, it has been shown that urinary T levels in male monkeys (marmosets) was lowest in those animals that carried offspring the most (Nunes, Fite, Patera, & French, 2001). Also, the smell of marmoset babies reduced serum T levels in male marmosets (Prudom et al., 2008). Human studies have shown that lower T levels are related to infant responsiveness (Fleming, Corter, Stallings, & Steiner, 2002). Knowing that OXT is involved in parenting behavior, it is likely that OXT is – at least partly – responsible for the decreased T levels in the situations described. And indeed, Feldman and colleagues (2012) found a relationship between genetic variations of the OXTR gene and paternal contact quality to their infant. There are two OXTR gene "risk" variants (rs22254298 and rs1042778) that are associated with lower OXT concentrations in plasma, which in turn are linked to less parental touch (Feldman et al., 2012). Interestingly, the peripheral OXT levels of fathers and children positively correlate and seem to be mediated by the interaction of father and child (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010). In addition, OXT administration has been shown to increase the exploratory behavior of fathers toward their toddlers (Naber, Poslawsky, van Ijzendoorn, van Engeland, & Bakermans-Kranenburg, 2013). OXT may increase T levels in order to increase sexual receptivity (Gossen et al., 2012; MacDonald &

Feifel, 2012). Weisman et al. (2014) implied that the T system might concomitantly be involved in endocrinological patterns of mating and parenting efforts rather than just being responsible for one or the other (Weisman, Zagoory-Sharon, & Feldman, 2014). The observed associations between OXT-induced T and social behaviors may be related to the reward system (Hermans et al., 2010). The testosterone induced OXT may thereby facilitate the investment in care-giving.

However, it needs to be acknowledged that modulation by steroid hormones is species specific. In birds for example, the modulation by estrogen on the social behavior brain network (SBBN) appears to be much bigger than in mammals (Maney, Goode, Lange, Sanford, & Solomon, 2008). The SBBN consists of the amygdala, the lateral septum, medial preoptic area, periaqueductal gray and the ventromedial hypothalamus. The SBBN is built of neural groups and each group fulfills multiple criteria. These groups are interconnected: each group contains neurons with gonadal hormone receptors and is considered important for more than one social behavior (Newman, 1999).

Steroid hormones have a huge impact on the developmental period, prenatally. Gonadal hormones influence important organizational matters of the AVP system and thereby trigger sexual differentiation (Albers, 2014). In Syrian hamsters, rats and humans, gender differences in the AVP concentrations in the magnocellular neurons of the SON have been observed (Delville, Koh, & Ferris, 1994; Ishunina & Swaab, 1999; Madeira, Sousa, Cadete-Leite, Lieberman, & Paula-Barbosa, 1993; P. V. Taylor et al., 2012). In hyenas, the AVP expression is negatively correlated with testosterone, and in gonadoectomized females the AVP expression in the lateral septum is decreased (Rosen et al., 2006). In Syrian hamsters on the other hand steroid hormones do not seem to influence the expression of AVP in either sex (Huhman & Albers, 1993).

Human studies revealed that AVP increases forgiveness in women, while OXT and AVP administration guided women to treat computer counterparts more like humans. Men responded with an increased cooperation behavior towards human as well as computer counterparts following AVP administration (Williams, Insel, Harbaugh, & Carter, 1994). This sex-difference is somewhat in line with animal studies that suggest AVP to be more potent in males, while OXT appears to have more impact on females. Interestingly, OXT as well as AVP frequently increased activity in the striatum, the basal forebrain, the insula, the amygdala and the hippocampus when men engaged in cooperative behavior. These brain regions are involved in reward, memory, social bonding and arousal. In women, OXT and AVP either had no effect at all or they decreased activity in the regions. However, both peptides can bind to both receptors and a clear interpretation is therefore not possible. A dose-response curve could offer a more detailed interpretation basis (Rilling et al., 2014).

The menstrual cycle and oxytocin levels

Due to the different effects of estradiol in particular, it might be interesting to take the female menstrual cycle into consideration to discover, whether OXT fluctuates in females throughout the month.

Fluctuations of the OXT hormonal level during different time points of the menstrual cycle has been shown by many studies (Altemus, Roca, Galliven, Romanos, & Deuster, 2001; Shukovski, Healy, & Findlay, 1989). In rats, OXT released from the paraventriculospinal pathway acts on OXT receptors in the spinal cord, resulting in modulations of the menstrual-cycle (Benoussaidh, Maurin, & Rampin, 2004), and a human study showed that endogenous OXT suppression in women may alter the ovulatory cycle (Evans, Reid, Wakeman, Croft, & Benny, 2003). Another study aimed at elucidating the plasma OXT levels in healthy, sexually active women

throughout the menstrual cycle and at correlating these OXT values with steroid hormones present at different cycle times (Salonia et al., 2005). Half of the women in this study were taking oral contraceptives while the other half was not. A significant difference between the two different phases (luteal phase, ovulatory phase) of the menstrual cycle could not be found, for either group. Plasma OXT fluctuated significantly in those women who did not take oral contraceptives. OXT levels were significantly higher in the ovulatory than during the luteal phase. No significant OXT plasma level fluctuations could be observed in women taking oral contraceptives. Steroid hormone fluctuation in these two groups was similar: estrogen and progesterone fluctuated throughout the menstrual cycle in women without oral contraceptives, but no fluctuations occurred in women with oral contraceptives. Surprisingly, there were no significant correlations between the OXT and the steroid hormones (Salonia et al., 2005).

In postmenopausal women, an increase in OXT was related to gaps in social relationships (Taylor et al., 2006). It might be surprising that a reduction in relationships lead to an increase of OXT: this might, however, be a compensation mechanism of mammals to deal with isolation. Additionally, a rise in OXT might facilitate new social engagement (S. E. Taylor, Saphire-Bernstein, & Seeman, 2010)

Sexual-dimorphic differences of the oxytocin system

Neuroendocrinology studies are abundantly done with men, because they are the easier model – they do not have a menstrual cycle that is accompanied by substantial endogenous hormonal changes. However, it is important to discuss the differences between the genders and acknowledge that endocrine studies with men cannot be transferred to women. This section is focused on the sexual-dimorphic differences of the OXT system that have been

discovered so far and how these differences are interlinked with sex-hormones, the female menstrual cycle and hormonal contraceptives.

The most prominent animal model in which OXT and AVP effects are studied is the prairie vole. Prairie voles are a good animal model for pair-bonding and other social human behaviors, because they are – like humans – socially monogamous. The most interesting sexual-dimorphic finding in prairie voles, in regard to this dissertation, is that OXT facilitates partner preference in females but not males. In males, the partner preference is facilitated by AVP (Winslow, Hastings, Carter, Harbaugh, & Insel, 1993).

When female prairie voles shared the same territory with a male, they developed a preference for that male over a stranger. This preference was measured by the amount of time the female spent with the familiar male compared to the amount of time spent with the stranger. When the voles mated, the female developed a partner preference after only six hours, while the preference was developed much later (after more than twelve hours) when no mating occurred (Williams, Catania, & Carter, 1992). Physical contact, especially vaginal stimulation leads to OXT release (Williams, Insel, Harbaugh, & Carter, 1994). In prairie voles, OXT and OXT receptor antagonists changed the sexual behavior in males and reduced their reproductive potential (Bales, Pfeifer, & Carter, 2004).

In male rats, more AVP neurons and projections have been discovered compared to females. The most prominent sources of sexually dimorphic AVP innervations are the bed nucleus of the stria terminalis and the medial amygdala (Caffe, van Leeuwen, & Luiten, 1987; De Vries & Buijs, 1983; DeVries, Buijs, Van Leeuwen, Caffe, & Swaab, 1985). Regarding the AVP receptors binding, sex differences have so far only been found in zebra finches. Male zebra finches show significantly higher binding in the hippocampal septum regions to the V1a receptor than females (Goodson, Evans, & Wang, 2006). Male Siberian hamsters display a higher

density of V1a binding in the ventromedial hypothalamus, the ventrolateral hypothalamus and the premammillary nucleus than females (Dubois-Dauphin et al., 1991). Interestingly, V1a receptor binding in the hypothalamus also displays species-specific sexually-dimorphic characteristics, and is increased in female mice (Dubois-Dauphin, Barberis, & de Bilbao, 1996).

When male prairie voles are treated with OXT antagonists, they show a reduction in AVP-immunoreactive cells, even though the number of OXT-immunoreactive cells was not altered (Yamamoto et al., 2004). The effects of OXT and OXT receptor antagonists were not as pronounced in female prairie voles as they were in males, but postnatal exposure to OXT or an OXT antagonist led to an increase of OXT-immunoreactive cells in the paraventricular nucleus of the hypothalamus, when the females were 21 days old (Yamamoto et al., 2004). Furthermore, mate guarding behavior of pair-bonding in adult females was increased after neonatal OXT exposure (Bales & Carter, 2003) and females that were postnatally (on the first day of life) treated with an OXT receptor antagonist displayed increased neural activity in the central amygdala when they were exposed to a male prairie vole (Kramer, Choe, Carter, & Cushing, 2006). Interestingly, human studies revealed that OXT reduces amygdala reactivity to social and emotional stimuli in healthy men, while left amygdala activity in women was increased after intranasal OXT administration when social emotional stimuli, of different valence, were shown (Domes et al., 2010).

Another well-known gender difference in neuroendocrinology, is the response to stress, first described by the "flight-fright-fight" (FFF) response (Hoffman, 1964). In more recent years, it became clear that this FFF response to stress appears in men, but not in women. Women's responses to stress reflect more a "tend and be-friend" mechanism in which they seek out the company of other women (S. E. Taylor et al., 2000).

Women show a strongly decreased stress response when social support is provided in stressful situations (Gerin, Milner, Chawla, & Pickering, 1995). In humans, OXT may inhibit glucocorticoid release (Chiodera et al., 1991) and it is hypothesized that women release OXT in stressful situations, thereby reducing anxiolytic effects (McCarthy, 1995). OXT release after a stressful event seems to be greater in females and also androgens (e.g. testosterone and progesterone) are said to reduce OXT release in stressful situations (Jezova, Jurankova, Mosnarova, Kriska, & Skultetyova, 1996). This suggests that OXT release after a stressful situation is less helpful in men, because it is counteracted by testosterone. It has been suggested that there is an alternative biochemical mechanism in females to prevent the abandonment of the infant in a stressful or threatening situation (McCarthy, 1995) that may be dependent on increased OXT release, and which concomitantly strengthens the attachment between mother and infant (S. E. Taylor et al., 2000). Sex differences concerning OXT effects are becoming more prevalent. A further major difference between males and females is that the OXT pathways have likely developed differently (Carter, 2014).

The prairie vole as an animal model for human oxytocin research

Influences of OXT have been studied in different species, but – as already mentioned – the most important animal model for pair-bonding and social behavior in research is the prairie vole.

The prairie voles are rodents that naturally live in the Central America (Hall, 1981). These rodents develop a monogamous pair-bonding behavior, such as nesting, breeding and caring for the offspring together (Getz & Hofmann, 1986) and typically stay together until one of them dies (Getz & Carter, 1996). It has been suggested that monogamy in prairie voles evolved due to their natural habitat in which resources of food and water are scarce (McGuire, Gretz, Hofmann, Pizzuto, & Frase, 1993). Some authors

suggest that monogamy only develops when resources are scarce, because both parents are needed to support the offspring (Emlen & Oring, 1977).

The monogamous behavior which prairie voles display remains the same in laboratory environments. Mating, for instance, is preferably done with the own partner and, voles stay together during gestation and show biparental care for their offspring (Carter & Getz, 1993; Dewsbury, 1987; Getz & Carter, 1996; Mcguire & Novak, 1984; Oliveras & Novak, 1986; Thomas & Birney, 1979). Mating induced partner preference development is attended by aggressive behavior against conspecifics (Bowler, Cushing, & Carter, 2002; Wang, Hulihan, & Insel, 1997; Winslow, Hastings, Carter, Harbaugh, & Insel, 1993), which arises to protect the mate and the territory from invaders (Carter & Getz, 1993). These important findings suggest that they follow a similar social behavioral pattern as humans, and thus serve as a good animal model for human pair-bonding and other social behavioral studies.

Most studies that involve medical treatments are first tested on animals for various reasons. Before animal studies have shown promising clinical potential of a substance, experiments on humans are not feasible. Animal studies offer a relatively broad degree of environmental and genetic manipulations. Furthermore, substances need to be tested for toxicity and proven safe before human studies can be conducted. Finally, studies on an animal model organism offer exclusive insights into pathophysiologies and new treatments can be challenged (Hackam, 2007). However, it is ‘just’ an animal model and in many cases the therapeutic value of the discoveries of animal research cannot directly be translated to humans (Perel et al., 2007). Therefore, human research is the final important piece of the puzzle before a new therapeutic substance can be released.

Oxytocin and its role in the human social life

Mammalian physical traits evolved simultaneously with OXT. It is not known why these evolutionary changes occurred, but they may have contributed to the development of the human nervous system and the large human neocortex, allowing for language and high social cognition (Carter, 2014).

Human behavior (or mammalian behavior in general) is highly dependent on social interactions. The most basic explanation for this can be found in child upbringing. Children are dependent on their parents or caretakers (Hrdy, 2009). The child's emotional and physiological well-being is influenced by the parents (especially their mother), both prenatally and after birth. A newborn baby cannot survive on its own and this vulnerability and dependence remain for several years (Mateo, 2009). Much of the neocortex develops after birth and in humans the maturation process can continue into the fourth decade of life (Rakic, 2009). Mechanisms such as mother-infant interaction and lactation offer a biological example for selective bonding and sociality. These mechanisms are extremely important in humans and can result in lifelong relationships and social support, which allow for learning many different social and cognitive behaviors and the acquisition of a large social network (Carter, 1998). In some communities, other group members aside from the parents are crucially important to raising children (Seema & Begum, 2008), which might explain why OXT influences a broader social behavioral range than mother-child interactions. Social, as well as emotional, structures seem to be evolutionary based. It has been suggested that physiological regulators were entrenched in social behavior and reach out for proximity (Hofer, 1987). Even though there seems to be a strong biological bias toward social interactions, there may also be other factors influencing human social behavior, e.g. cognitive experience. Social interactions are built on repetitive experiences that are

learned and gradually internalized. Over time, these repetitive behavioral experiences develop into a person to person specific pattern which depends on the experiences with the respective individual(s) (Feldman, 2012). Even though social relationships are person-specific a child tends to use his or her first social experiences as a template for new social interactions and future relationships (Malekpour, 2007). Thus, the quality of the relationship between parents/ caregivers and the child may predict later relationships and their quality.

Falling in love with a new spouse is exciting and initiates arousal (Fisher, Aron, & Brown, 2006). A critical feature in the early passionate love stage is eye gaze, which OXT has been shown to influence (Guastella & MacLeod, 2012). The perceived arousal during the passionate love stage may be caused by OXT and maybe also AVP release (Carter, 1992). The word love entails a broad meaning, including: "a feeling of strong or constant affection for a person", "unselfish loyal and benevolent concern for the good of another", "warm attachment, enthusiasm" (www.merriam-webster.com/dictionary/) and "reciprocal trust" (Hardin, 2002). There are multiple OXT studies investigating different aspects of "love" as well as broader aspects of social interactions. Emotional responses to moral elevation, which describe an emotion that people may experience after witnessing someone else act forgiving or compassionate in an unexpected context (Acevedo, Aron, Fisher, & Brown, 2012), might underlie the same neurophysiological processes as those associated with falling in love. One study which investigated moral elevation found neural synchronization in brain areas (between subjects) that were previously associated with self-referential processing, such as the medial prefrontal cortex and the insula (Englander, Haidt, & Morris, 2012). But importantly, close interactions between humans is not limited to mother-child or romantic partner bonding: humans also share emotions with and of others and experience emotional

contagion (Hatfield, Cacioppo, & Rapson, 1994). We become enthusiastic when we play team sports and witness other people's achievements (Pepping & Timmermans, 2012). Being able to experience the emotional states of others may promote human behavior, such as positive emotion expression or solidarity (Kok & Fredrickson, 2010).

Social interaction benefits were increased in a computerized task in which intranasal OXT increased trust among humans (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Hurlemann et al. (2010) discovered that emotional empathy and performance on feedback-guided item-category association tasks were facilitated by intranasal OXT administration. The authors found that participants were generally better in learning performance when social versus nonsocial reinforcement was shown, and that this effect was increased following OXT administration. The Multifaceted Empathy Test showed that OXT facilitated emotional, but not cognitive empathy (Hurlemann et al., 2010). OXT's effects on cooperation revealed an increase in the caudate nucleus in response to reciprocal cooperation of the other player compared to AVP and PLC (Rilling et al., 2012). This neural activation might trigger reward perceptions for cooperative behavior and thereby facilitate trusting behavior. Behavioral data strengthened neural findings in that OXT was associated with increased cooperative behavior, even after the other player did not reciprocate (Rilling et al., 2012). Taken together, these results suggest that OXT's effects on behavior contribute to the ability to be close to someone else.

It is not known whether social bonds in humans can be formed without OXT or AVP. Social bonds are formed in diverse conditions which are most likely all supported by OXT and possibly also by AVP action (Carter, 2014). Presumably, OXT and AVP are the foundation of powerful positive social behaviors and experiences. This assumption is supported by the finding that OXT's effects on emotion regulatory processes are coupled

with high levels of parasympathetic activity (high vagal tone) (Kok & Fredrickson, 2010). High vagal tone is associated with a quicker increase in self-described positive emotions as well as a feeling of connectedness. This association is bidirectional, and an increase in positive emotions and connectedness predicts an elevation in vagal tone, independent of the initial vagal tone. The vagal tone and psychosocial well-being thus predict each other (Kok & Fredrickson, 2010). Furthermore, this finding suggests an effect of OXT on the autonomous nervous system (ANS) and explains the importance of social engagement and attachment. In addition to this study, OXT and social support increase wound healing (Gouin et al., 2010), prevent cardiovascular dysfunction (Karelina & DeVries, 2011) and display anti-inflammatory effects (Szeto et al., 2011). These "healing" characteristics underline the strength of positive relationships and psychological well-being in stressful and difficult situations. People who feel socially supported are more likely to endure illnesses and usually live longer than people who are socially isolated (Ozbay et al., 2007). However, the individual perception of loneliness and social support is also important for its consequences (Ali et al., 2010).

Nevertheless, OXT effects are not always prosocial per se and might thus not necessarily directly reflect positive health effects. As mentioned before, there are many individual differences that influence the OXT system. Individuals, who have a difficult life history in regards of family background and attachment, may display asocial behavior in response to OXT administration (Bartz, Zaki, Bolger, & Ochsner, 2011). These behavioral responses might for example occur by an increased perception of threat in social groups (De Dreu, 2012). Ambivalent OXT findings might also reflect different neuroendocrine activity (Dai et al., 2012). As has been discussed above, there are many uncertainties about the exact mechanism of

OXT and how this mechanism might differ depending on genes, methylation patterns, developed attachment styles or a combination of these aspects.

Study designs and concepts of the oxytocin studies in this dissertation

Much more knowledge – especially regarding the biochemical mechanisms of OXT in humans – needs to be acquired to get a whole picture of OXT's potential on social interactions. Many methods used in animal research are not applicable to humans. The most common method used to investigate brain activity in relation to behavior (in humans) is the functional magnetic resonance imaging (fMRI) technique, which was applied in studies 2 and 3 of this dissertation. The acquired blood-oxygenated level dependent (BOLD) responses indicate (indirectly) brain activity during task performance. BOLD responses arise due to the different magnetic properties of oxygenated hemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic). When blood properties change from the diamagnetic to the paramagnetic, or deoxygenated state, brain activation displays decreased signal intensity on the MRI. Thus, the term *brain activation*, or rather *neural activity* reflects brain regions in which neural activity is high, because high neural activity requires more oxygen which is delivered via hemoglobin from the blood. The fMRI BOLD technique is favored over positron emission tomography (PET) because it does not require injections of radioactive substances to generate images. However, PET would be a promising technique to further discover the human OXT system, because it could display OXT receptor locations. The fMRI method has been used to investigate a broad range of neural activity that corresponds to motion, smell, memory (Sato, Kubota, & Toichi, 2014) and social-emotional processes (Adolphs, 2009; Kim et al., 2014). The *social brain*, which has been illustrated mostly by fMRI, constitutes a large portion of the human brain and is involved in social interaction and understanding others (Brett, Anton, Valabregue, & Poline,

2002). The main areas belonging to the social brain include the amygdala, the ventral striatum, the hypothalamus (Dinstein, Hasson, Rubin, & Heeger, 2007), the anterior insula (Etzel, Gazzola, & Keysers, 2008), the superior temporal sulcus (STS) (Gazzola, Aziz-Zadeh, & Keysers, 2006), the medial prefrontal cortex (mPFC) (Gazzola, Rizzolatti, Wicker, & Keysers, 2007), the inferior parietal lobe (IPL) (Zaki, Ochsner, Hanelin, Wager, & Mackey, 2007), the inferior frontal gyrus (IFG) (Etkin, Egner, & Kalisch, 2011) and the anterior cingulate cortex (ACC) (Klumpp, Post, Angstadt, Fitzgerald, & Phan, 2013). The aim of social neuroscience is to understand the complex interactions between social cues and their impact on behavior, neural activity, cognition and hormonal processes (Ochsner & Gross, 2005) because social environment is essential for every human individual. This social proximity comprises communities, such as families, friends, neighborhoods, religious groups, nationalities, as well as types of employment and hobbies that provide a context for individual behavior (Haslam, Jetten, Postmes, & Haslam, 2009). The social environment offers OXT a broad range of action, which results in different explanations for the OXT mechanism. Some hypotheses support OXT's role as a prosocial peptide, such as the *social approach/ withdrawal hypothesis*, which suggests that OXT up-regulates social approach behavior while it down-regulates social avoidance behavior (Kemp & Guastella, 2011). Other theories, such as the *social salience hypothesis,* suggest that OXT up-regulates the salience of positive as well as negative social stimuli. Thus, the behavioral action that follows OXT administration is more dependent on the social context (Shamay-Tsoory et al., 2009). Another suggestion by De Dreu and colleagues (2010), which complements the salience hypothesis to some extent, is that OXT increases positive in-group behavior while reducing kindness towards out-group members. Out-group members are not perceived as negative per se, however, which differentiates this suggestion from the approach/ withdrawal theory. A

new hypothesis, the *general approach-avoidance hypothesis of OXT* (GAAO), has recently been posited (Harari-Dahan & Bernstein, 2014). The GAAO suggests that OXT's effects may not be restricted to social behaviors, but instead that OXT modulates non-social (mal)adaptive behaviors as well. This modulation is assumingly moderated by approach-avoidance (AA) motivation. Thus, the GAAO hypothesis questions whether OXT's influence on AA behaviors is necessarily *socially* determined (Harari-Dahan & Bernstein, 2014). The predominant effects of OXT on social behavior are, according to this theory, attributed to the higher emotion evocative properties of social stimuli compared to non-social task stimuli. Another hypothesis which appears very plausible, especially in regard to the biological background, suggests that OXT effects are modulated by contextual and individual differences (Bartz, Zaki, Bolger, & Ochsner, 2011). The context- and person-specific modulation of OXT effects is a rather vague hypothesis which may nonetheless account for all findings and is additionally very reasonable, given the current knowledge of the influence of epigenetic mechanisms, which may arise due to different life events.

This dissertation presents three different studies, each investigating one aspect of the effects of intranasal OXT on different social-emotional behavior or cognition. The first study compared social approach behavior in women who received either intranasal OXT or PLC. Our research group previously showed an effect of OXT on social approach behavior in heterosexual pair-bonded men. Now, we investigated whether OXT has similar or divergent effects on women. It is very important to perform endocrine studies, here OXT studies, in both sexes because the effects may be very different. Thus, we investigated whether OXT influences the AA behavior of women, testing its effects on sociality. We hypothesized that women display an increased approach behavior to positive social stimuli after OXT administration. It might be assumed that OXT also modulates

avoidance behavior, particularly to social stimuli, but avoidance behavior is not as crucial as approach behavior for social interactions. Therefore, our hypothesis focused on approach behavior towards positive social stimuli only.

The second study examined whether OXT can influence the willingness to induce emotions of different emotional categories (anger, fear, happy, neutral) in healthy men. It has previously been reported that OXT increases the willingness to share emotions (Lane et al., 2012), but whether OXT also influences the willingness to induce emotions, valence-dependent or not, has not been investigated yet. Emotion induction takes place in every conversation. An interplay of *who says what* results in emotional reactions in conspecifics and thus plays a key role in social behavior. We hypothesized that OXT would increase the willingness to say *happy* emotion evocative statements (EES) and, decrease the willingness to state *anger* and *fear* EES, while no difference between OXT and PLC on *neutral* EES was expected. We expected neural activation in brain areas that are involved in the mirror neuron system such as the premotor area (PM). The mirror neuron system allows the observer to grasp a goal-directed action of a conspecific (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; G. Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). Additional neural activation was expected in areas that are responsible for higher cognitive functions, e.g. emotion regulation, such as the medial prefrontal cortex (mPFC) or the anterior cingulate cortex (ACC) (Etkin, Egner, & Kalisch, 2011).

In the third study, we investigated intranasal OXT effects on volitional and emotional ambivalence, in healthy men. The terms *volitional* and *emotional ambivalence* were introduced by Bleuler (1950). Volitional ambivalence describes the dilemma when making an emotional decision between two equally attractive or repulsive options, while emotional

ambivalence entails the simultaneous presence of two aversive emotions towards the same person, e.g. loving and hating someone. In this study, we conducted two experiments to test volitional and emotional ambivalence separately. As has been stated above, when postmenopausal women lack social contacts, their plasma OXT levels were increased (Taylor et al., 2006), which may compensate for reduced social contacts. Therefore it is plausible that OXT also reduces the perceived negativity of various stressful events. Even though this study is slightly different from the first two studies because it concentrates on OXT's effect on the emotional well-being of one individual, disregarding the *direct* interaction with another individual, the prosocial aspect of OXT is also present in this study. It has been shown that happy people show more kindness and that showing kindness increases happiness (Otake, Shimai, Tanaka-Matsumi, Otsui, & Fredrickson, 2006), implying that the basis for positive social interactions and prosocial behavior lies within oneself. Conclusively, if OXT is able to increase positive feelings within oneself, it could also increase kind behavior towards others. To probe volitional ambivalence, we chose a moral dilemma study which was previously designed by Harrison et al. (2012). We hypothesized that OXT alleviates the perceived ambivalence that is present during dilemmas, being reflected by an increased reaction time and a decreased neural activity in the dACC which is important for emotional conflict. To probe emotional ambivalence, we chose an infidelity task, previously designed by Takahashi and his colleagues (2006). Participants were asked to imagine their romantic partner in different situations with another man. We again hypothesized that OXT would alleviate the perceived emotional ambivalence towards their partner. We expected that activation in the dACC as well as arousal ratings when imagining the ambivalent situations would be decreased in the OXT group.

In conclusion, this dissertation presents three distinct studies in which the effects of intranasal OXT on social and emotional behavior were investigated, controlling for non-social and non-emotional stimuli. One prominent question, that encompasses all studies, is: “Does OXT act as a prosocial molecule?” This is followed by the second question: “Does OXT only show effects in *direct* interactions with others?” In the general discussion, these questions will be answered and findings of the three presented studies will be discussed in light of the existing OXT theories.

Chapter 2: Manuscript 1

Foreword

Social approach is an essential behavior for humans to indicate interest in their conspecifics and to build liaisons (Baumeister & Leary, 1995). In the following publication we investigated whether OXT influences social approach in women. We also compared the results to a previous study done in men because it is important to consider both sexes in neuroendocrinologcial studies in order to reveal potential sexually-dimorphic effects. This study entails three different behavioral experiments, two which aimed at elucidating OXT's effects on social approach in women and one control experiment which was conducted to test whether OXT might have a general effect on distance perception, regardless of sociality and valence.

We hypothesized that OXT, as a prosocial molecule, increases approach behavior in women to positive social stimuli.

Manuscript 1: Oxytocin facilitates social approach behavior in women

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Abstract

In challenging environments including both numerous threats and scarce resources, the survival of an organism depends on its ability to quickly escape from dangers and to seize opportunities to gain rewards. The phylogenetically ancient neurohormonal oxytocin (OXT) system has been shown to influence both approach and avoidance (AA) behavior in men, but evidence for comparable effects in women is still lacking. We thus conducted a series of pharmacological behavioral experiments in a randomized double-blind study involving 76 healthy heterosexual women treated with either OXT (24 IU) or placebo intranasally. In Experiment 1, we tested how OXT influenced the social distance subjects maintained between themselves and either a female or male experimenter. In Experiment 2, we applied a reaction time based AA task. In Experiment 3 we investigated effects on peri-personal space by measuring the lateral attentional bias in a line bisection task. We found that OXT specifically decreased the distance maintained between subjects and the male but not the female experimenter and also accelerated approach towards pleasant social stimuli in the AA task. However, OXT did not influence the size of peri-personal space, suggesting that it does not alter perception of personal space per se, but rather that a social element is necessary for OXT's effects on AA behavior to become evident. Taken together, our results point to an evolutionarily adaptive mechanism by which OXT in women selectively promotes approach behavior in positive social contexts.

Keywords: Approach; avoidance; female; sexual dimorphic; oxytocin; social distance.

Introduction

For humans as with all social species, approach behavior has a pivotal function in signaling interest in conspecifics, thereby providing a means to establish and cultivate close relationships (Baumeister and Leary, 1995). The phylogenetically ancient neuropeptide oxytocin (OXT) has been implicated in modulating both approach/avoidance (AA) behavior and pair-bonding in men (Kemp and Guastella, 2011; Scheele et al., 2012; Striepens et al., 2014). However, it is still unknown whether OXT influences these fundamental behavioral tendencies equivalently in both sexes.

Despite mounting evidence that OXT can affect a broad repertoire of sophisticated human behaviors (Kosfeld et al., 2005; Hurlemann et al., 2010), few studies have examined the peptide's effect on AA behavior as a probe for appetitive and aversive motivation. We have shown that intranasal OXT administration motivates men in a monogamous heterosexual relationship, but not single men, to keep a larger social distance from unfamiliar attractive women, suggesting that OXT may strengthen the existing monogamous pair-bond (Scheele et al., 2012). On the other hand, Liu and colleagues (2012) failed to find an effect of OXT administered to both interacting male and female subjects on the physical distance maintained between them using a microcoded video-recording approach. However, since the experimental design in their study included concomitant treatment of both male and female subjects (Liu et al., 2012) the influence that cross-partner interaction has on the readiness for social engagement (Weisman et al., 2012) may have interfered with OXT effects. Another study utilizing a reaction time based AA task observed that OXT diminished the differential response to angry and happy faces in men (Radke et al., 2013). These findings are in stark contrast with the results of another study reporting an accelerated response selectively for disgusted facial expressions (Theodoridou et al., 2013) and where the authors propose that OXT may

play a role in behavioral prophylaxis. This latter interpretation resonates well with previous findings of enhanced defensive reactions after OXT administration (Striepens et al., 2012; Grillon et al., 2013). Thus, it appears OXT can promote approach behavior in men, but only under certain circumstances and with heightened caution.

Sexual-dimorphic effects of OXT are not surprising, since gonadal steroids play a role in early morphogenesis of the OXT system (de Vries, 2008), influence the production of OXT (Patisaul et al., 2003), and regulate the density of OXT receptors (OXTR) and OXTR binding (Johnson et al., 1991; Young et al., 1998; Choleris et al., 2008). In female prairie voles, OXT is critical for the formation of a partner preference, while in male voles, the related neuropeptide vasopressin appears to be more important for pair bonding (Insel and Hulihan, 1995; Cushing et al., 2001; Ross et al., 2009). In humans, common OXTR gene variants interact with sex to predict harm avoidance (Stankova et al., 2012) and the behavioral and neural effect profile of intranasally administered OXT is profoundly different between male and female players of an interactive social game (Rilling et al., 2014). Furthermore, Fischer-Softy et al. (2013) reported that OXT improves kinship recognition in women and competition recognition in men and Herzman and coworkers (2013) found that OXT impairs recollection judgments only in men, but not in women. Perhaps the most prominent sex-specific OXT effect is the peptide's modulatory influence on amygdala activity. OXT suppresses amygdala activity to fear-inducing visual stimuli in men (Kirsch et al., 2005), but it enhanced neural responses to threatening scenes in women (Lischke et al., 2012). However, sex differences are not evident in all behavioral domains (Cardoso et al., 2012) and there is also evidence for a decreased amygdala responsibility after OXT treatment in nulliparous women (Rupp et al., 2014).

To gauge potential sex-specific effects of OXT on AA behavior, we submitted 76 healthy heterosexual women to a series of randomized, placebo-controlled between-subject design experiments, which we had previously carried out in males (Scheele et al., 2012). In Experiment (Exp.) 1 we applied a stop distance paradigm to measure the social distance maintained by subjects when encountering an unfamiliar male or female experimenter. In Exp. 2 we assessed reaction times in a computerized AA task entailing a broad range of pleasant and aversive emotional scenes. Lastly, in Exp. 3, we probed whether there needs to be a social context for OXT to unfold its effects by using a modified line bisection task which provides an estimate of the extent or "size" of the subjects' non-social peri-personal space.

Materials and methods

Subjects and protocols

A total of 76 healthy heterosexual female adults (mean age ± SD = 23.76 ± 2.60) participated in this study after giving written informed consent. In Exp. 2, nine participants were excluded, because their reaction time was either more than two SDs above or below the mean. In Exp. 3, four left-handed subjects were excluded. The study was approved by the institutional review board of the Medical Faculty of the University of Bonn (Germany) and was performed in compliance with the latest revision of the Declaration of Helsinki. All subjects were free of current and past physical or psychiatric illness, as assessed by medical history and the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Participants also completed a comprehensive neuropsychological test battery including the Social Interaction Anxiety Scale (SIAS) and Social Phobia Scale (SPS) (Heinrichs et al., 2002), the Family Conflict Resolution Scale (German

abbreviation: KLSE) (Kog et al., 1987), the Positive and Negative Affect Schedule (PANAS) (Krohne et al., 1996), the State and Trait Anxiety Inventory (STAI-S and STAI-T) (Englert et al., 2011), and the Letter-Number-Sequence (BZF) (Schächtele, 2009). In total, the screening and test session lasted approximately 1.5 and 2 hours, respectively. All female participants were not pregnant, not lactating and used oral contraceptives. Nineteen participants in the OXT group and 20 participants in the PLC were in a stable monogamous relationship. Estimation of which treatment was received was comparable between the OXT and PLC groups ($\chi^2_{(1)} = 0.91$; $P = 0.34$), indicating that subjects were unaware of whether they had received OXT or PLC. Participants were asked to maintain their regular sleep-wake cycle and to abstain from caffeine and alcohol intake on the day of the experiment. In addition, they were naive to prescription-strength psychoactive medication, and had not taken any over-the-counter psychoactive medication in the past four weeks. There were no significant pretreatment differences (Table 1). Personality traits possibly affecting the attitude towards social distance were also assessed (e.g. Social Interaction Anxiety Scale and Social Phobia Scale) (Mattick and Clarke, 1998). Using a double-blind, counter-balanced, randomized, parallel-group design, either intranasal OXT (n = 38) (24 IU, Syntocinon-Spray, Sigma Tau; 3 puffs per nostril, each with 4 IU OXT) or PLC (n = 38) (PLC, containing all ingredients except for the peptide) was given 45 min before the start of the experiments. The intranasal administration of OXT has been shown to increase not only peripheral OXT plasma levels but also central OXT concentration in the cerebrospinal fluid (Striepens et al., 2013). In Exp. 1, we used the stop-distance paradigm to determine both the ideal distance for an interaction with an unfamiliar attractive male and an attractive female experimenter and the distance at which the subjects felt slightly uncomfortable (Fig. 1A and B). Next, the subjects were asked to rate the

attractiveness, sympathy and trustworthiness of the experimenters on a scale from 1-9 as well as their feelings during the testing (stress, embarrassment and reflection on their own emotions). Likewise, the experimenters evaluated the subjects on these scales. In Exp. 2, subjects performed an AA-task at which the speed of manual approach and avoidance response to stimuli varying in both valence and social content was measured. Subjects had to discriminate between positive (attractive men or beautiful landscapes) and negative (mutilations or dirt) pictures selected from the International Affective Picture System (IAPS) (Lang et al., 2005) as fast as possible by pulling a joystick toward (positive) or away (negative) from their own body. Since pleasant pictures in our previous study mostly displayed nude women, we had to replace these stimuli in the present study. Importantly, based on the normative valence and arousal IAPS ratings, the picture sets for female and male participants were comparable. Finally, Exp. 3 served as a non-social control task in which participants had to bisect a line in the middle as accurately as possible.

Stop-distance paradigm

An adapted version of the stop-distance paradigm was used (Kennedy et al., 2009). Subjects met both experimenters for the first time. A standardized appearance of the experimenters was ensured for all subjects across all sessions and all subjects were tested in the same room. One half of the subjects started with the female experimenter and the other half started with the male experimenter. Subjects were positioned at one end of the room with their toes placed on a marking line. Trials were administered in a fixed order and each subject completed a practice trial before the start of the experiment. In the first half of the trials, the male or female experimenter was the one moving at a natural gait either toward ("far", i.e. start distance of 2 m) or away ("close", i.e. start distance of 30 cm) from the subject, whereas in the

second half, the female volunteer was the one moving. This experimental variation served to mimic approach or withdrawal during influential first encounters. The experimenter avoided eye contact (EC) in half the trials, although subjects were not informed of this during initial task instruction. Subjects were asked to tell the experimenter to stop at their preferred distance in the first half of the trials and choose their ideal distance in the second half, when personally moving. The preferred or ideal distance was described as the distance at which the participants would feel most comfortable to have a conversation with a complete stranger. Subjects could fine-tune the distance by moving the experimenter slightly further backward or forward. After measuring the ideal distance, the experimenter/subject returned to the starting position and the same procedure was used to determine the slightly uncomfortable distance. All different trial conditions were repeated twice and in total there were 32 trials involving each experimenter. The final chin-to-chin distance was measured with a digital laser measurer (model DLR165K; Bosch; error = 0.003 m). Finally, the subjects were asked to estimate the distance that an average person would regard as optimal and as slightly uncomfortable.

Approach-avoidance task

The pictures presented during the task were carefully adjusted for luminance using a self-written script in Matlab 7 (MathWorks). Each trial started with the presentation of a fixation cross for 1 to 2 s. Pictures were then presented randomly in four blocks (one block contained five pictures of each positive social/nonsocial and negative social/nonsocial category). Each picture was presented for 2000 ms. Participants were instructed to place their head on a chin rest at a viewing distance of 50 cm to the computer screen. Approach and avoidance behavior was simulated by increasing or decreasing the picture size. Pulling the joystick replaced the picture by the same one

enlarged by a factor of 1.1, while pushing the joystick reduced the picture size by a factor of 0.9. Reaction times were obtained by using the joystick displacement measurements for each trial. Trials showing an extreme reaction time (> 200 ms or < 1500 ms) or movements in the wrong direction were excluded. Participants (n = 9) who deviated more than two SDs from the mean reaction time were also excluded.

Figure 1: The stop-distance paradigm

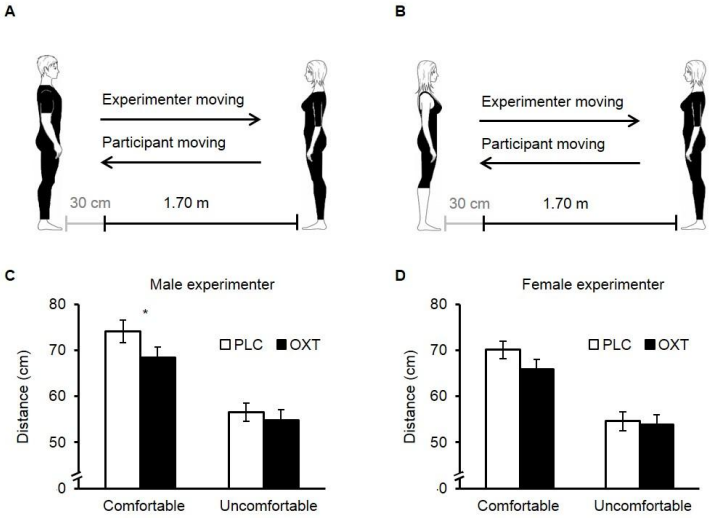


Figure Legend: Figure 1

Effects of OXT in the stop-distance-paradigm. Experimental setup for the male (A) and female experimenters (B). In the first half of the trials the experimenter was the one moving either towards ('far', i.e. start distance of 2 m) or away from the subject ('close', i.e. start distance of 30 cm), whereas in the second half the female volunteer was the one approaching or withdrawing. An additional condition was gaze direction, with the female

experimenter avoiding eye contact in half of the trials. Mean ideal (comfortable) distances and slightly uncomfortable distances across all conditions for the male (C) and female (D) experimenter. OXT significantly decreased the ideal distance that women maintained in relation to the unknown attractive man. Error bars indicate the standard error of the mean (SEM). Abbreviations: OXT, oxytocin; PLC, placebo; * $P < 0.05$.

Figure 2: (A) The Joystick Approach-Avoidance Task and (B) the Line Bisection Task

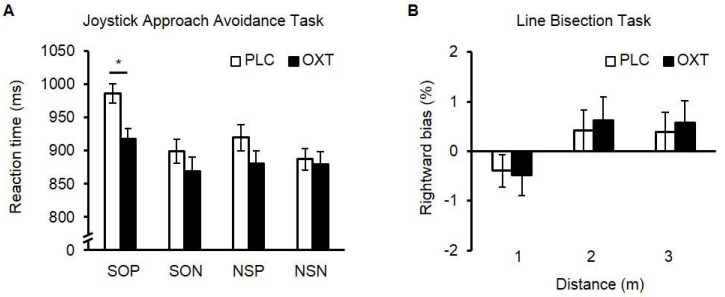


Figure Legend: Figure 2

Effects of OXT in the Joystick Approach-Avoidance (A) and Line Bisection Task (B). OXT specifically accelerated the approach towards social positive stimuli, but did not influence motor responses to negative or non-social cues. In the Line Bisection Task a left pseudo-neglect occurred if the line was presented in a near distance and this bias shifted rightward at farther distances. This shift reflects the extent of the peri-personal space and OXT had no effect on this non-social component. Error bars indicate the standard error of the mean (SEM). Abbreviations: NSN, non-social negative; NSP,

non-social positive; OXT, oxytocin; PLC, placebo; SON, social negative; SOP, social positive; * $P < 0.05$.

Line bisection task

When participants have to bisect horizontally-oriented lines, they generally show a small left bias in near space (pseudo-neglect). At greater distances this bias shifts rightward and the rate at which this occurs can be taken as an index of the extent/size of the near space (Varnava et al., 2002). In the present paper, the line bisection task included three different distances (1, 2, and 3 m) from which participants had to bisect a horizontal line which was presented on a large screen (93x51cm). From each distance the participants had to bisect the line 10 times by moving a cursor using a wireless mouse that was placed on a table next to the participants' right hand. We measured the bisection bias (in %) as dependent variable in this task, with positive and negative values indicating a rightward or leftward bias, respectively. The cursor had two different starting positions; it started at random either in the upper left or right corner of the screen. All trials for each distance were averaged in order to eliminate a possible effect of cursor starting position.

Statistical analysis

Demographical, neuropsychological, and behavioral data were analyzed using SPSS 20 (SPSS Inc., Chicago, IL, USA). Quantitative behavioral data were compared by mixed-model analysis of variance (ANOVA) and Pearson's product-moment correlation was used for correlation analysis. Eta-squared and Cohen's d were calculated as measures of effect size. The assumption of sphericity was assessed with Mauchly's test, and for significant violations Greenhouse-Geisser's correction was applied. For qualitative variables Pearson's chi-squared tests were used. All reported P-

values are two-tailed, if not otherwise noted, and *P*-values of $P < 0.05$ were considered significant.

Results

Exp. 1: Stop-distance paradigm

A repeated-measures ANOVA was carried out with the ideal or slightly uncomfortable distances as dependent variables, 'eye contact' (EC; with or without), 'person moving' (PM; experimenter or subject), and 'starting position' (SP; close or far) as within-subject factors, and 'treatment' (OXT or PLC) as between-subject factor. For the ideal distance involving the male experimenter as a stimulus, we observed main effects for EC ($F_{(1,74)} = 6.99$, $P = 0.01$, $\eta^2 = 0.09$), PM ($F_{(1,74)} = 24.10$, $P < 0.01$, $\eta^2 = 0.25$), and SP ($F_{(1,74)} = 15.80$, $P < 0.01$, $\eta^2 = 0.18$), and an interaction between PM and SP ($F_{(1,74)} = 37.47$, $P < 0.01$, $\eta^2 = 0.34$). The female participants maintained a larger distance between themselves and the experimenter if the latter avoided EC, and the interaction was qualified by a larger distance if the experimenter instead of the subject was moving in trials with a far SP. In the case of a close SP this effect was reversed. Importantly, there was a main effect of treatment with OXT treatment resulting in a closer approach across all conditions ($F_{(1,74)} = 4.39$, $P = 0.04$, $\eta^2 = 0.06$, Fig. 1C). For the slightly uncomfortable distance, the main effects of PM ($F_{(1,74)} = 16.43$, $P < 0.01$, $\eta^2 = 0.18$) and SP ($F_{(1,74)} = 100.77$, $P < 0.01$, $\eta^2 = 0.58$) and the interaction between both factors ($F_{(1,74)} = 11.68$, $P < 0.01$, $\eta^2 = 0.14$) remained significant, but there were no further significant results (all *P*s > 0.05).

For the ideal distance between the subjects and the female experimenter, we also found main effects of EC ($F_{(1,74)} = 71.92$, $P < 0.01$, $\eta^2 = 0.49$), PM ($F_{(1,74)} = 4.97$, $P < 0.03$, $\eta^2 = 0.06$), and SP ($F_{(1,74)} = 21.79$, $P < 0.01$, $\eta^2 = 0.23$; Fig. 1D). There was no significant treatment effect ($P =$

0.14), but there were interactions between EC and PM ($F_{(1,74)}$ = 9.61, P < 0.01, η^2 = 0.12), EC and SP ($F_{(1,74)}$ = 10.82, P < 0.01, η^2 = 0.13) as well as SP and PM ($F_{(1,74)}$ = 29.26, P < 0.01, η^2 = 0.28). Participants showed a closer approach if the experimenter kept EC, if they were the person moving and if the SP was far. The EC effect was more pronounced if the starting position was close and if the experimenter was moving and a close SP led to a larger distance only if the subject was moving. For the estimate of the slightly uncomfortable distance between participants and the female experimenter, the main effects of PM ($F_{(1,74)}$ = 3.94, P = 0.05, η^2 = 0.05) and SP ($F_{(1,74)}$ = 45.63, P < 0.01, η^2 = 3.81) remained significant, but no further effects were detected (P > 0.05). The distances for all conditions are shown in Tab. 2.

The OXT effect cannot be attributed to a generally altered space perception since no significant effect was observed for participants' judgment of the ideal and uncomfortable distances of an average woman (all Ps > 0.05). Furthermore, the male experimenter perceived the OXT-treated female participants as more attractive ($F_{(1,71)}$ = 11.23, P < 0.01, η^2 = 0.14; Tab. 3) and likable ($F_{(1,71)}$ = 4.23, P = 0.04, η^2 = 0.06) than PLC-treated subjects. There were also trends such that the experimenter reported increased reflective thinking about the women in the OXT group ($F_{(1,71)}$ = 3.34, P = 0.07, η^2 = 0.05) and he rated women under OXT as more trustworthy ($F_{(1,71)}$ = 3.70, P = 0.06, η^2 = 0.05). None of these effects were evident for the female experimenter and the participants from the two treatment groups did not rate either experimenter significantly differently on any of these measures (all Ps > 0.05). For the male experimenter, in the OXT group subjects estimates of the ideal and slightly uncomfortable distances were negatively correlated with attractiveness (ideal: r = -0.33, P = 0.05; uncomfortable: r = -0.44, P < 0.01), likability (ideal: r = -0.35, P = 0.04; uncomfortable: r = -0.35, P = 0.04) and trustworthiness ratings (ideal: r = -0.30, P = 0.08; uncomfortable: r = -0.35, P = 0.04). No significant

correlations were found in the PLC group (all *P*s > 0.05). For the female experimenter, the pattern of correlations was reversed, with significant associations being present only in the PLC group. The ideal and slightly uncomfortable distances were negatively correlated with likability (ideal: r = -0.55, $P < 0.01$; uncomfortable: r = -0.45, $P < 0.01$) and trustworthiness ratings (ideal: r = -0.59, $P < 0.01$; uncomfortable: r = -0.51, $P < 0.01$) and positively linked to embarrassment (ideal: r = 0.52, $P < 0.01$; uncomfortable: r = 0.64, $P < 0.01$) and stress (ideal: r = 0.37, P = 0.02; uncomfortable: r = 0.35, P = 0.03).

A comparison of the ideal and uncomfortable social distances obtained for heterosexual dyads in the present study with our previous findings (Scheele et al., 2012) in male participants revealed a significant main effect of the participants' sex (ideal: $F_{(1,230)}$ = 20.88, $P < 0.01$, η^2 = 0.08; uncomfortable: $F_{(1, 230)}$ = 135.48, $P < 0.01$, η^2 = 0.37) and a significant interaction between the participants' gender and treatment for the ideal distance ($F_{(1, 230)}$ = 13.12, $P < 0.01$, η^2 = 0.05). Under PLC, women kept a larger social distance to the attractive opposite-sex experimenter than men (women, 78 cm; men, 57 cm). In line with previous findings on empathy (Hurlemann et al., 2010), OXT reduced this a-priori sex difference and motivated women and men to approximate their preference for the comfortable social distance (women, 71 cm; men, 65 cm). Considering effect sizes, the OXT effects were larger in men (ideal: η^2 = 0.14, uncomfortable η^2 = 0.08) than in women (ideal: η^2 = 0.06, uncomfortable η^2 = 0.01). This difference is likely related to a floor effect since a further reduction of the social space in women would lead to uncomfortable distances.

Exp. 2: Approach-avoidance task

A repeated-measures ANOVA with 'sociality' (social or non-social) and 'valence' (positive or negative) as within-subject factors, 'treatment' (OXT

vs. PLC) as between subject factor and the reaction time as dependent variable yielded main effects of sociality ($F_{(1,65)}$ = 13.08, P < 0.01, η^2 = 0.17) and valence ($F_{(1,65)}$ = 13.02, P < 0.01, η^2 = 0.17), a trend for a treatment effect ($F_{(1,65)}$ = 3.72, P = 0.075, η^2 = 0.05) and an interaction of sociality and valence ($F_{(1,65)}$ = 9.88, P < 0.01, η^2 = 0.13). All participants showed faster responses to non-social and to negative stimuli. The reaction time difference between positive and negative items was more pronounced for the social condition. Importantly, exploratory post-hoc t tests revealed that OXT elicited faster approach behavior only for positive social stimuli ($t_{(65)}$ = 2.45, P = 0.02, d = 0.61, Fig. 2A) and had no effect on other categories (all Ps > 0.05).

Exp. 3: Line bisection task

A repeated measures ANOVA with 'distance' as a within-subject variable and 'treatment' as a between-subject variable revealed a main effect of distance ($F_{(2,140)}$ = 9.15, P < 0.01, η^2 = 0.12; Fig. 2B), but no further main or interaction effects (all Ps > 0.05). In line with previous literature (Varnava et al., 2002), all participants displayed a right pseudo-neglect in near space and increasing left pseudo-neglect in far space. No significant differences were found between the two treatment groups in any of the three distances in the line bisection task. The pattern of results in all three experiments did not change if relationship status was incorporated as an additional between-subject factor and there were no interactions between treatment and the relationship status (all Ps > 0.05).

Discussion

In the present study, we aimed at elucidating the influence of OXT on AA behavior in healthy women. OXT decreased the social distance that female participants kept between themselves and an unfamiliar attractive and

friendly male experimenter in Exp. 1 and accelerated the motor responses towards pleasant social scenes in Exp. 2. Notably, in Exp. 3 OXT did not alter lateral attentional bias used as an index of space perception and the extent/size of peri-personal space. Taken together, our results point to an evolutionarily adaptive mechanism by which OXT is promoting approach behavior in women specifically in positive social contexts.

Our findings are consistent with the biobehavioral synchrony model which posits that the temporal concordance of micro-level social behaviors in the gaze, vocal, affective, and touch modalities interacts with OXT responses to create dyad-specific affiliations (Feldman, 2012). In the present study, OXT may have influenced micro-level behaviors in the female participants such that they were perceived as more attractive and more likeable by the male experimenter. The negative association between these ratings and the social distance measured under OXT underscores that this improved interaction quality may have contributed to the closer approach. However, given the correlational nature of this finding, it is also conceivable that the enhanced approach behavior could itself have led to an altered perception of female subjects resulting in them being given higher ratings. If the OXT effect on social distance is mediated by subtle behavioral changes, this could explain the absence of a significant OXT effect in trials with a female experimenter where heterosexual women might be less perceptive or responsive to these subtle female behavioral cues. On the other hand, floor effects in the female-female interaction and uncomfortable distance conditions could have prevented a significant effect since in both conditions a smaller than the ideal distance determined in the mixed-sexes dyads was exhibited.

In contrast to our previous study with male subjects (Scheele et al., 2012), we did not observe an interaction between treatment and relationship status in women. An evolutionary explanation for these sexually-dimorphic

results arises from the different mating strategies that men and women may have developed to maximize their evolutionary fitness in view of their asymmetric parental investments (Buss et al., 1992). Men benefit from impregnating as many women as possible, while women benefit from choosing their mates more carefully (Levy and Kelly, 2010). These different mating strategies may have contributed to sex-specific jealousy behaviors, with men perceiving sexual infidelity as more threatening and women being more sensitive to emotional infidelity (Buss et al., 1992). Thus, men may endorse social approach and physical proximity as more distressing signals of potential infidelity compared to women. By increasing the reward value of their female partner (Scheele et al., 2013), OXT may further enhance these signals in men and trigger the avoidance of unfamiliar attractive females. For OXT effects on AA behavior in women, the relationship status appears to be less relevant. We acknowledge that mate choice preferences not only vary across the menstrual cycle but may also depend on the use of hormone-based contraceptives (Alvergne and Lummaa, 2010). We exclusively recruited women who took oral contraceptives since plasma OXT levels have been found to fluctuate throughout the menstrual cycle in normally cycling women, but not in women using oral contraceptive pills (Salonia et al., 2005). Women taking oral contraceptives display a significantly reduced sensitivity to social odors (Renfro and Hoffmann, 2013) and it has been proposed that OXT is responsible for the modulatory influence of romantic love on the ability of women to identify body odors of potential partners (Lundstrom and Jones-Gotman, 2009). Notwithstanding, by focusing on a homogenous sample we can exclude that any menstrual cycle-dependent hormonal changes contributed to our results.

Current perspectives on the central effects of OXT emphasize its pleiotropic contributions to sociality, although a substantial diversity in behavioral functions is evident across taxa (Anacker and Beery, 2013; Goodson, 2013).

Our present results also highlight the crucial role of a social component for OXT actions in women, since in Exp. 2 facilatory OXT effects were restricted to positive social stimuli and we did not observe alterations in 'non-social' peri-personal space in Exp. 3. Notably, these results are consistent with previous studies in men demonstrating that OXT specifically potentiated the social reinforcement advantage in a feedback-guided item-category association task (Hurlemann et al., 2010) and that it also affected social, but not financial information, in a decision-making paradigm (Evans et al., 2010). In both sexes, OXT improved the sensitivity to detect biological, but not non-biological motion (Keri and Benedek, 2009). The peptide also enhanced the suppression of electrophysiological oscillations in the mu/alpha and beta bands during the perception of biological motion, suggesting that OXT may act by allocating cortical resources to the social task (Perry et al., 2010). Clearly, it will be relevant to disambiguate whether these differential effects are due to a-priori higher salience of social stimuli or whether OXT truly requires a social component.

While the importance of sociality appears to be generalized, valence-dependent effects may differ between sexes. In men, OXT can augment defensive responses if threatening scenes are presented (Striepens et al., 2012). Furthermore, Theodoridou et al. (2013) argued that OXT may fulfill a prophylactic function by accelerating motor responses to disgusted facial expressions which signify threat to perceivers. Interestingly, in the latter study, no significant interaction between treatment and sex was found, however, the experimental design did not control for the hormonal status of the women and the applied stimulus set mainly consisted of face photographs. Emotional face photographs are highly salient and usually have no contextual information whereas ambiguous emotional stimuli and emotional scenes do contain contextual information.

Our data suggest a sexual-dimorphic effect of OXT on AA behavior such that in men it elicits social approach with caution even if the context is experienced as aversive and stressful, whereas in women social approach behavior appears to be restricted to safe situations. This discrepancy could perhaps be related to sex differences in brain OXT receptor distribution as well as in endogenous OXT levels. So far there is only a single autoradiography mapping study on the brains of eight males and four females which failed to establish any correlation between OXT receptor distribution or density and sex (Loup et al., 1991). There is also no evidence for higher or lower OXT plasma concentrations in women than in men (Feldman, 2012; Zhong et al., 2012), but there is an ongoing controversial debate about the relationship of peripheral and central measurement (Churchland and Winkielman, 2012). Consequently, future studies are warranted to test this hypothesis of sex-difference by employing modern OXT receptor mapping techniques and by measuring cerebrospinal fluid concentration in larger samples.

In conclusion, we here provide the first evidence that OXT in women facilitates approach behavior not only in response to various pleasant scenes but also in a real-life setting with other people. Notably, several psychiatric disorders have been associated with dysfunctional AA behavior. In particular, patients with social anxiety may benefit from a pharmacological enhancement of their approach behavior (Roelofs et al., 2009). Our findings emphasize the necessity to generate gender-tailored treatments by identifying features for each patient that constitute a safe social context in which OXT is most effective.

References

Alvergne, A., and Lummaa, V. (2010). Does the contraceptive pill alter mate choice in humans? *Trends Ecol Evol* 25**,** 171-179. doi: 10.1016/j.tree.2009.08.003.

Anacker, A.M.J., and Beery, A.K. (2013). Life in groups: the roles of oxytocin in mammalian sociality. *Frontiers in Behavioral Neuroscience*. doi: 10.3389/fnbeh.2013.00185.

Baumeister, R.F., and Leary, M.R. (1995). The Need to Belong - Desire for Interpersonal Attachments as a Fundamental Human-Motivation. *Psychological Bulletin* 117**,** 497-529. doi: Doi 10.1037/0033-2909.117.3.497.

Buss, D.M., Larsen, R.J., Westen, D., and Semmelroth, J. (1992). Sex Differences in Jealousy: Evolution, Physiology, and Psychology. *Psycholgical Science* 3**,** 251-255. doi: 10.1111/j.1467-9280.1992.tb00038.x

Cardoso, C., Ellenbogen, M.A., and Linnen, A.M. (2012). Acute intranasal oxytocin improves positive self-perceptions of personality. *Psychopharmacology (Berl)* 220**,** 741-749. doi: 10.1007/s00213-011-2527-6.

Choleris, E., Devidze, N., Kavaliers, M., and Pfaff, D.W. (2008). "Steroidal/neuropeptide interactions in hypothalamus and amygdala related to social anxiety," in *Progress in Brain Research*, eds. D.N. Inga & L. Rainer. Elsevier), 291-303.

Churchland, P.S., and Winkielman, P. (2012). Modulating social behavior with oxytocin: how does it work? What does it mean? *Horm Behav* 61**,** 392-399. doi: 10.1016/j.yhbeh.2011.12.003.

Cushing, B.S., Martin, J.O., Young, L.J., and Carter, C.S. (2001). The effects of peptides on partner preference formation are predicted by

habitat in prairie voles. *Horm Behav* 39**,** 48-58. doi: 10.1006/hbeh.2000.1633.

De Vries, G.J. (2008). "Sex differences in vasopressin and oxytocin innervation of the brain," in *Progress in Brain Research,* eds. D.N. Inga & L. Rainer. Elsevier), 17-27.

Englert, C., Bertrams, A., and Dickhäuser, O. (2011). Entwicklung der Fünf-Item-Kurzskala STAI-SKD zur Messung von Zustandsangst. *Zeitschrift für Gesundheitspsychologie* 19**,** 173-180.

Evans, S., Shergill, S.S., and Averbeck, B.B. (2010). Oxytocin decreases aversion to angry faces in an associative learning task. *Neuropsychopharmacology* 35**,** 2502-2509. doi: 10.1038/npp.2010.110.

Feldman, R. (2012). Oxytocin and social affiliation in humans. *Horm Behav* 61**,** 380-391. doi: 10.1016/j.yhbeh.2012.01.008.

Goodson, J.L. (2013). Deconstructing sociality, social evolution and relevant nonapeptide functions. *Psychoneuroendocrinology* 38**,** 465-478. doi: 10.1016/j.psyneuen.2012.12.005.

Grillon, C., Krimsky, M., Charney, D.R., Vytal, K., Ernst, M., and Cornwell, B. (2013). Oxytocin increases anxiety to unpredictable threat. *Mol Psychiatry* 18**,** 958-960. doi: 10.1038/mp.2012.156.

Heinrichs, N., Hahlweg, K., Fiegenbaum, W., Frank, M., Schröder, B., and Witzleben (Van), I. (2002). Validität und Reliabilität der Social Interaction Anxiety Scale (SIAS) und der Social Phobia Scale (SPS). *Verhaltenstherapie***,** 26-35.

Hurlemann, R., Patin, A., Onur, O.A., Cohen, M.X., Baumgartner, T., Metzler, S., Dziobek, I., Gallinat, J., Wagner, M., Maier, W., and Kendrick, K.M. (2010). Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *J*

Neurosci 30**,** 4999-5007. doi: 10.1523/JNEUROSCI.5538-09.2010.

Insel, T.R., and Hulihan, T.J. (1995). A gender-specific mechanism for pair bonding: oxytocin and partner preference formation in monogamous voles. *Behav Neurosci* 109**,** 782-789.

Johnson, A.E., Coirini, H., Insel, T.R., and Mcewen, B.S. (1991). The regulation of oxytocin receptor binding in the ventromedial hypothalamic nucleus by testosterone and its metabolites. *Endocrinology* 128**,** 891-896. doi: 10.1210/endo-128-2-891.

Kemp, A.H., and Guastella, A.J. (2011). The Role of Oxytocin in Human Affect: A Novel Hypothesis. *Current Directions in Psychological Science* 20**,** 222-231. doi: 10.1177/0963721411417547.

Kennedy, D.P., Glascher, J., Tyszka, J.M., and Adolphs, R. (2009). Personal space regulation by the human amygdala. *Nat Neurosci* 12**,** 1226-1227. doi: 10.1038/nn.2381.

Keri, S., and Benedek, G. (2009). Oxytocin enhances the perception of biological motion in humans. *Cogn Affect Behav Neurosci* 9**,** 237-241. doi: 10.3758/CABN.9.3.237.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., Gruppe, H., Mattay, V.S., Gallhofer, B., and Meyer-Lindenberg, A. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *J Neurosci* 25**,** 11489-11493. doi: 10.1523/JNEUROSCI.3984-05.2005.

Kog, E., Vertommen, H., and Vandereycken, W. (1987). Minuchin's psychosomatic family model revised: A concept-validation study using a multitrait-multimethod approach. *Famliy Process* 26**,** 235-252.

Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., and Fehr, E. (2005). Oxytocin increases trust in humans. *Nature* 435**,** 673-676. doi: 10.1038/nature03701.

Krohne, H.-W., Egloff, B., Kohlmann, C.W., and Tausch, A. (1996). Untersuchung mit einer deutschen Form der Positive and Negative Affect Schedule (PANAS). *Diagnostica* 42**,** 139-156.

Lang, P.J., Bradley, M.M., and Cuthbert, B.N. (2005). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-6.* Gainesville, FL: University of Florida.

Levy, K.N., and Kelly, K.M. (2010). Sex Differences in Jealousy: A Contribution From Attachment Theory. *Psycholgical Science* 21**,** 168-173. doi: 10.1177/0956797609357708

Lischke, A., Gamer, M., Berger, C., Grossmann, A., Hauenstein, K., Heinrichs, M., Herpertz, S.C., and Domes, G. (2012). Oxytocin increases amygdala reactivity to threatening scenes in females. *Psychoneuroendocrinology* 37**,** 1431-1438. doi: 10.1016/j.psyneuen.2012.01.011.

Liu, J.C.J., Guastella, A.J., and Dadds, M.R. (2012). Effects of oxytocin on human social approach measured using intimacy equilibriums. *Horm Behav* 62**,** 585–591.

Loup, F., Tribollet, E., Dubois-Dauphin, M., and Dreifuss, J.J. (1991). Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. *Brain Res* 555**,** 220-232.

Lundstrom, J.N., and Jones-Gotman, M. (2009). Romantic love modulates women's identification of men's body odors. *Horm Behav* 55**,** 280-284. doi: 10.1016/j.yhbeh.2008.11.009.

Mattick, R.P., and Clarke, J.C. (1998). Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behav Res Ther* 36**,** 455-470.

Patisaul, H.B., Scordalakes, E.M., Young, L.J., and Rissman, E.F. (2003). Oxytocin, but not oxytocin receptor, is rRegulated by oestrogen receptor beta in the female mouse hypothalamus. *J Neuroendocrinol* 15**,** 787-793. doi: 10.1046/j.1365-2826.2003.01061.x.

Perry, A., Bentin, S., Shalev, I., Israel, S., Uzefovsky, F., Bar-On, D., and Ebstein, R.P. (2010). Intranasal oxytocin modulates EEG mu/alpha and beta rhythms during perception of biological motion. *Psychoneuroendocrinology* 35**,** 1446-1453. doi: 10.1016/j.psyneuen.2010.04.011.

Radke, S., Roelofs, K., and De Bruijn, E.R. (2013). Acting on anger: social anxiety modulates approach-avoidance tendencies after oxytocin administration. *Psychol Sci* 24**,** 1573-1578. doi: 10.1177/0956797612472682.

Renfro, K.J., and Hoffmann, H. (2013). The relationship between oral contraceptive use and sensitivity to olfactory stimuli. *Horm Behav* 63**,** 491-496. doi: 10.1016/j.yhbeh.2013.01.001.

Rilling, J.K., Demarco, A.C., Hackett, P.D., Chen, X., Gautam, P., Stair, S., Haroon, E., Thompson, R., Ditzen, B., Patel, R., and Pagnoni, G. (2014). Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. *Psychoneuroendocrinology*. doi: 10.1016/j.psyneuen.2013.09.022.

Roelofs, K., Minelli, A., Mars, R.B., Van Peer, J.M., and Toni, I. (2009). On the neural control of social emotional behavior. *Social Cognitive and Affective Neuroscience* 4**,** 50-58. doi: 10.1093/scan/nsn036.

Ross, H.E., Freeman, S.M., Spiegel, L.L., Ren, X., Terwilliger, E.F., and Young, L.J. (2009). Variation in oxytocin receptor density in the nucleus accumbens has differential effects on affiliative behaviors in monogamous and polygamous voles. *J Neurosci* 29**,** 1312-1318. doi: 10.1523/JNEUROSCI.5039-08.2009.

Rupp, H.A., James, T.W., Ketterson, E.D., Sengelaub, D.R., Ditzen, B., and Heiman, J.R. (2014). Amygdala response to negative images in postpartum vs nulliparous women and intranasal oxytocin. *Soc Cogn Affect Neurosci* 9**,** 48-54. doi: 10.1093/scan/nss100.

Salonia, A., Nappi, R.E., Pontillo, M., Daverio, R., Smeraldi, A., Briganti, A., Fabbri, F., Zanni, G., Rigatti, P., and Montorsi, F. (2005). Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. *Horm Behav* 47**,** 164-169. doi: 10.1016/j.yhbeh.2004.10.002.

Schächtele, B. (2009). "Buchstaben-Zahlen-Folgen (BZF). Untertest aus dem Wechsler-Intelligenztest. für Erwachsene (WIE)," in *Handbuch neuropsychologischer Testverfahren. Band 1: Aufmerksamkeit, Gedächtnis, exekutive Funktionen,* eds. D. Schelling, R. Drechsler, D. Heinemann & W. Sturm. (Göttingen: Hogrefe), 804-809.

Scheele, D., Striepens, N., Güntürkün, O., Deutschländer, S., Maier, W., Kendrick, K.M., and Hurlemann, R. (2012). Oxytocin Modulates Social Distance between Males and Females. *J Neurosci* 14**,** 16074-16079. doi: 10.1523/JNEUROSCI.2755-12.2012.

Scheele, D., Wille, A., Kendrick, K.M., Stoffel-Wagner, B., Becker, B., Güntürkün, O., Maier, W., and Hurlemann, R. (2013). Oxytocin enhances brain reward system responses in men viewing the face of their female partner. *PNAS* 110**,** 20308 - 20313. doi: 10.1073/pnas.1314190110.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amoriam, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., and Dunbar, G. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59**,** 22 - 33.

Stankova, T., Eichhammer, P., Langguth, B., and Sand, P.G. (2012). Sexually dimorphic effects of oxytocin receptor gene (OXTR) variants on Harm Avoidance. *Biology of Sex Differences* 17**,** 1-5. doi: 10.1186/2042-6410-3-17.

Striepens, N., Kendrick, K.M., Hanking, V., Landgraf, R., Wullner, U., Maier, W., and Hurlemann, R. (2013). Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. *Sci Rep* 3**,** 3440. doi: 10.1038/srep03440.

Striepens, N., Matusch, A., Kendrick, K.M., Mihov, Y., Elmenhorst, D., Becker, B., Lang, M., Coenen, H.H., Maier, W., Hurlemann, R., and Bauer, A. (2014). Oxytocin enhances attractiveness of unfamiliar female faces independent of the dopamine reward system. *Psychoneuroendocrinology* 39**,** 74-87. doi: 10.1016/j.psyneuen.2013.09.026.

Striepens, N., Scheele, D., Kendrick, K.M., Becker, B., Schafer, L., Schwalba, K., Reul, J., Maier, W., and Hurlemann, R. (2012). Oxytocin facilitates protective responses to aversive social stimuli in males. *Proc Natl Acad Sci U S A* 109**,** 18144-18149. doi: 10.1073/pnas.1208852109.

Theodoridou, A., Penton-Voak, I.S., and Rowe, A.C. (2013). A direct examination of the effect of intranasal administration of oxytocin

on approach-avoidance motor responses to emotional stimuli. *PLoS One* 8**,** e58113. doi: 10.1371/journal.pone.0058113.

Varnava, A., Mccarthy, M., and Beaumont, J.G. (2002). Line bisection in normal adults: direction of attentional bias for near and far space. *Neuropsychologia* 40**,** 1372-1378. doi: 10.1016/S0028-3932(01)00204-4.

Weisman, O., Zagoory-Sharon, O., and Feldman, R. (2012). Oxytocin administration to parent enhances infant physiological and behavioral readiness for social engagement. *Biol Psychiatry* 72**,** 982-989. doi: 10.1016/j.biopsych.2012.06.011.

Young, L.J., Wang, Z., Donaldson, R., and Rissman, E.F. (1998). Estrogen receptor alpha is essential for induction of oxytocin receptor by estrogen. *Neuroreport* 9**,** 933-936.

Zhong, S., Monakhov, M., Mok, H.P., Tong, T., Lai, P.S., Chew, S.H., and Ebstein, R.P. (2012). U-shaped relation between plasma oxytocin levels and behavior in the trust game. *PLoS One* 7**,** e51095. doi: 10.1371/journal.pone.0051095.

Tables

Table 1. Demographics and neuropsychological performance

	OXT (*N* = 38)	**PLC (*N* = 38)**
Age (years)	23.61 (2.71)	23.74 (2.47)
Education (years) [1]	15.88 (4.36)	14.44 (5.71)
Months of being single [1]	5.62 (19.06)	13.74 (13.69)
Months of being in a relationship [1]	34.16 (28.48)	32.63 (27.67)
Social Interaction Anxiety Scale (SIAS) [1]	16.13 (11.11)	17.97 (12.12)
Social Phobia Scale (SPS) [1]	6.66 (7.19)	7.73 (8.49)
Family conflict resolution (KLSE)	31.89 (4.63)	32.5 (5.51)
Positive affect (PANAS)	32.79 (6.31)	30.29 (6.22)
Negative affect (PANAS) [1]	44.82 (4.16)	43.13 (7.45)
State Anxiety (STAI)	1.76 (0.36)	1.83 (0.23)
Trait Anxiety (STAI) [1]	2.14 (0.17)	2.14 (0.23)
Visual attention (D2)	13.32 (2.45)	13.09 (2.84)
Letter-Number-Span-Test (BZT) [1]	17.76 (2.47)	17.66 (2.12)

Notes. Given are mean values (SD). There were no significant differences between the OXT and PLC group (all *P*s > 0.05). Data derived from not normally distributed populations were compared by using [1] non-parametric Mann-Whitney U tests. Anxiety and mood were assessed before the experiment with the STAI (State Trait Anxiety Inventory for State and Trait) and the PANAS (Positive and Negative Affective Schedule). Family conflict resolutions were assessed using a German questionnaire 'Konfliktlösungsstile im Elternhaus' (KLSE). Social anxiety was measured with the SIAS (Social Interaction Anxiety Scale) and the SPS (Social Phobia Scale). Visual attention and concentration were assessed using the d2 (Aufmerksamkeits- und Belastungstest d2) and working memory performance was assessed using the German version of the Letter-Number-Span Test ('Buchstaben-Zahlen-Test'; BZT). Abbreviations: OXT, oxytocin; PLC, placebo.

Table 2. Ideal and slightly uncomfortable distances (cm) in Exp. 1

	OXT male experimenter (*N* = 38)	**PLC male experimenter (*N* = 38)**	**OXT female experimenter (*N* = 38)**	**PLC female experimenter (*N* = 38)**
Comfortable distance				
Experimenter moves				
from far (EC)	72.54 (18.75)	81.32 (18.71)	67.95 (15.85)	73.71 (14.33)
from far (NEC)	73.10 (18.03)	81.85 (17.08)	70.21 (14.43)	74.99 (13.79)
from close (EC)	73.38 (12.72)	76.69 (15.66)	69.11 (11.20)	70.76 (10.31)
from close (NEC)	73.15 (12.31)	79.93 (12.98)	73.08 (13.05)	75.42 (11.34)
Participant moves				
from far (EC)	64.35 (16.96)	71.26 (16.19)	62.48 (17.64)	69.05 (14.17)
from far (NEC)	64.42 (15.87)	72.34 (15.91)	64.30 (17.05)	69.33 (14.23)
from close (EC)	73.25 (15.05)	79.36 (17.95)	70.32 (15.11)	74.66 (16.60)
from close (NEC)	74.01 (16.12)	81.45 (16.85)	71.57 (15.61)	77.39 (18.50)
Uncomfortable distance				
Experimenter moves				
from far (EC)	51.21 (16.63)	55.73 (19.11)	49.45 (12.15)	52.65 (11.97)
from far (NEC)	50.88 (16.51)	55.41 (18.10)	50.36 (11.78)	51.71 (12.12)
from close (EC)	64.61 (12.77)	65.78 (13.51)	57.46 (9.68)	57.63 (11.52)
from close (NEC)	63.43 (12.87)	64.73 (13.16)	58.58 (10.07)	57.82 (11.72)
Participant moves				
from far (EC)	46.19	48.38	48.00	49.78

	(12.83)	(12.55)	(13.18)	(12.80)
from far (NEC)	46.18	48.06	46.36	49.43
	(13.12)	(11.81)	(11.92)	(11.36)
from close (EC)	61.73	65.01	56.99	57.98
	(14.04)	(15.04)	(12.92)	(18.94)
from close (NEC)	62.71	65.78	56.39	59.79
	(13.78)	(15.81)	(12.17)	(19.66)

Notes. Mean values (SD) are given. Abbreviations: EC, eye contact; NEC, no eye contact; OXT, oxytocin; PLC, placebo.

Table 3. State measurements in Exp. 1

	OXT (***N*** **= 38)**	**PLC** (***N*** **= 38)**
From male experimenter		
Stressful	2.06 (1.26)	1.87 (1.19)
Embarrassing	1.69 (0.83)	1.79 (0.96)
RooF	2.91 (2.09)	3.89 (2.46)
Likable	**7.37 (0.97)**	**6.68 (1.74)**
Attractive	**6.29 (1.15)**	**5.13 (1.71)**
Trustworthy	6.91 (1.36)	6.21(1.73)
For male experimenter		
Stressful	4.37 (2.05)	4.55 (2.31)
Embarrassing	2.58 (1.75)	3.16 (2.02)
RooF	5.34 (2.46)	4.97 (2.48)
Likable	7.45 (1.41)	7.71 (1.31)
Attractive	7.29 (0.98)	7.45 (0.95)
Trustworthy	7.47 (1.11)	7.37 (1.32)
From female experimenter		
Stressful	3.46 (1.61)	2.95 (1.29)
Embarrassing	1.11 (0.31)	1.13 (0.41)
RooF	4.43 (1.44)	4.42 (1.15)
Likable	7.38 (0.92)	7.18 (1.09)
Attractive	6.86 (0.89)	6.53 (1.01)
Trustworthy	7.11 (1.10)	7.08 (1.22)
For female experimenter		
Stressful	3.92 (1.88)	3.92 (2.16)
Embarrassing	2.24 (1.60)	2.58 (1.88)
RooF	4.71 (2.55)	4.89 (2.54)
Likable	8.26 (0.79)	8.08 (1.36)
Attractive	6.87 (1.19)	6.92 (1.32)
Trustworthy	8.39 (0.72)	8.08 (0.75)

Notes. Mean values (SD) are given. Bold numbers indicate a significant treatment difference ($P < 0.05$). Ratings were given on a scale from 1 (not true at all) to 9 (absolutely true). Abbreviations: OXT, oxytocin; PLC, placebo; RooF, Reflection on own feelings.

Supplementary Information on manuscript 1

Supplementary Data

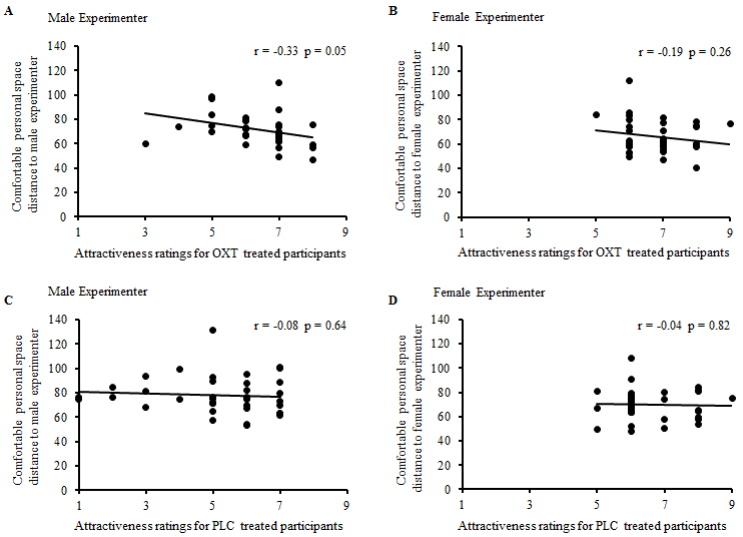
Given the complex design of experiment 1, we decided to stratify the analysis based on the only variable entailing a short temporal break between the trials. During this break, the male experimenter left the testing room and the female experimenter entered the room (or vice versa). Nevertheless, we also conducted a repeated-measures ANOVA with "gender" as an additional within-subject factor in order to control for a possible gender x treatment interaction. We found a main effect of gender ($F_{(1,74)} = 12.67$, $P < 0.01$, $\eta^2 = 0.15$), with female participants preferring a larger distance to the male experimenter (74.52 cm) than to the female experimenter (67.95 cm). However, there was no gender x treatment interaction and the pattern of significant results did not differ from the results pattern obtained by the stratified repeated measures ANOVAs in the main manuscript.

In a further supplementary analysis of Experiment 1, we restricted the sample to subjects (placebo (PLC) $n = 28$, oxytocin (OXT) $n = 27$) who perceived the female experimenter as highly attractive (rating ≥ 7). A univariate ANOVA with the ideal distance as dependent variable revealed a significant main effect of treatment ($F_{(1,53)} = 4.58$, $P < 0.04$, $\eta^2 = 0.08$). Applying the same selection criteria (rating ≥ 7) to the attractiveness ratings for the male experimenter yielded a sub-sample of 62 participants (PLC $n = 33$, OXT $n = 29$). In this sub-sample the treatment effect remained significant ($F_{(1, 60)} = 4.13$, $P < 0.05$, $\eta^2 = 0.06$). In the small sample of 14 participants who did not perceive the male experimenter as attractive (i.e. attractiveness rating < 7), the OXT effect did not reach statistical significance ($F_{(1, 12)} = 2.10$, $P = 0.17$, $\eta^2 = 0.15$), but OXT-treated subjects

(Mean = 76.50 cm, SD = 15.27cm) still preferred a smaller distance than PLC-treated participants (Mean = 92.25 cm, SD = 25.90cm).

Supplementary Figures

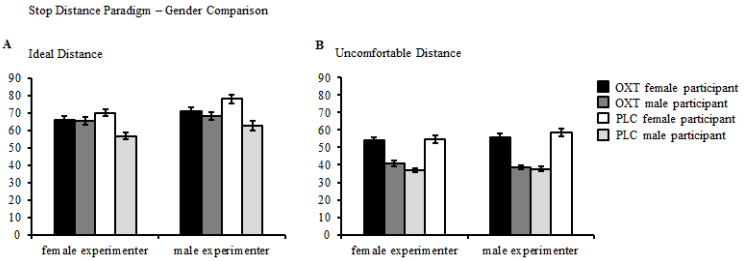
Supplementary Figure 1: Associations between ideal social distance and experimenter's attractiveness



Supplementary Figure 1

Associations between the ideal social distance and the participants' attractiveness as rated by the experimenters. A significant correlation was evident only for OXT-treated participants and the male experimenter (**A**), but not for the female experimenter (**B**). Under PLC, there was neither a correlation for the male (**C**) nor the female experimenter (**D**). Abbreviations: OXT, oxytocin; PLC, placebo.

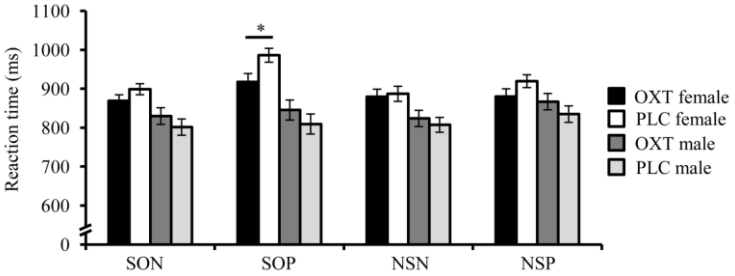
Supplementary Figure 2: Comparison of ideal and uncomfortable social distance between women and men



Supplementary Figure 2

The effect of OXT on the ideal (**A**) and uncomfortable (**B**) social distance between women and men. Overall, female participants preferred a larger distance than male participants and this difference became smaller if OXT was administered. The increase of social distance after OXT treatment in men was driven by pair-bonded participants (cf. Scheele et al., 2012). Data for male participants are derived from Scheele et al. (2012). Error bars indicate the standard error of the mean (SEM). Abbreviations: OXT, oxytocin; PLC, placebo.

Supplementary Figure 3: OXT's influence on reaction time in the Joystick approach avoidance task in both sexes



Supplementary Figure 3

The effect of OXT on reaction time based approach and avoidance behavior. OXT accelerated the approach of positive social stimuli in women. OXT had no general effect on approach and avoidance behavior in men, but selectively decelerated the approach of positive social stimuli in pair-bonded men (cf. Scheele et al., 2012). Data for male participants are derived from Scheele et al. (2012). Error bars indicate the standard error of the mean (SEM). Abbreviations: NSN, non-social negative; NSP, non-social positive; OXT, oxytocin; PLC, placebo; SON, social negative; SOP, social positive; * $P < 0.05$.

Supplementary References

Scheele, D., Striepens, N., Güntürkün, O., Deutschländer, S., Maier, W., Kendrick, K.M., and Hurlemann, R. (2012). Oxytocin Modulates Social Distance between Males and Females. *J Neurosci* 14**,** 16074-16079. doi: 10.1523/JNEUROSCI.2755-12.2012.

Chapter 3: Manuscript 2

Foreword

Social approach was revealed to be increased in the OXT compared to the PLC group. Thus, the first study emphasized OXT's role as a prosocial molecule, even though some context specificity was also observed in that, women in the OXT group only approached the attractive male experimenter significantly more, but not the attractive female experimenter. However, this lack of significance in approaching the female experimenter might have occurred due to ceiling effects because participants in both the OXT and the PLC group stepped closer to the female experimenter than to the male experimenter.

The next study, a functional magnetic resonance imaging (fMRI) study, was focused on whether healthy men who received OXT show an increased or decreased willingness to express positive or negative emotions. The different contexts in this study are presented by four different emotional categories: anger, fear, happiness and neutral. Emotions are expressed in almost all situations in everyday life. As soon as someone expresses emotions, he or she also inevitably induces emotions in his or her counterpart. The process of emotion induction requires complex cognitive processes. First, the participant needs to be able to imagine what emotion a presented sentence would induce in himself, then he needs to decide whether he is willing to induce the experienced emotion in someone else by stating the sentence, assuming that the counterpart also perceives the message of the sentence the same way.

Brain regions that are necessary for these processes, include the inferior frontal gyrus, the inferior parietal lobe and the medial prefrontal cortex which we expected to be activated during this task. We hypothesized that OXT, as a prosocial molecule, would increase the willingness to induce

happy emotions and decrease the willingness to induce anger and fear. We did not expect OXT to have any impact on emotionally neutral sentences. We assumed that the brain activity would be decreased in the OXT group for happy sentences and increased for anger and fear sentences, while we did not expect any activation differences between the OXT and the PLC group for neutral sentences.

Manuscript 2: Oxytocin increases the willingness to induce happy emotions and decreases the willingness to induce negative emotions

Note: This manuscript is currently under review by the co-authors

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Abstract

The willingness to induce positive or negative emotions requires highly cognitive abilities, including the capacity to deduce from what might make another person happy or sad. Additionally, for this task it is necessary to distinguish oneself from the other. Brain regions known to be involved in these processes include the inferior frontal gyrus (IFG), the ventral premotor area (vPM), the medial prefrontal cortex (mPFC) and the inferior parietal lobe (IPL). To investigate the effects of the neuropeptide hormone oxytocin (OXT) on neural and behavioral correlates of the willingness to induce emotions we have conducted a randomized, between-subject, double-blind, placebo-controlled, functional magnetic resonance imaging experiments involving 42 healthy male volunteers. We chose a paradigm in which participants had to indicate how well they could imagine to make an emotion evocative statement (EES) to someone they know. Our results show that the intranasal administration of OXT (24 IU) diminished neural responses in the IFG, the vPM, the mPFC and the IPL to happy EES, while it enhanced activity to anger, fear EES. Neutral EES received region-specific activation patterns after OXT administration. Under OXT, the willingness to induce happy or neutral feelings was increased, while the willingness to make anger or fear EES was decreased. Thus, enhancing the willingness to induce positive emotions and decreasing the willingness to induce negative emotions paralleled by a modulated neural activity, OXT may qualify as a positive emotion inducer.

Key words: Inferior frontal gyrus, mirror neuron network, fMRI, oxytocin, willingness to induce emotions

Introduction

Emotions are expressed in countless situations in everyday life. People always express emotions to others, thereby inducing emotions in, and receiving emotional responses from their conspecifics (Leggitt & Gibbs, 2000). This interaction of emotion expression and emotion induction is crucial for social relationships and can influence dynamics in partnerships or groups (Kelly & Barsade, 2001). A crucial mechanism for emotional exchange is the neural mapping of other people's emotions. The successful mapping promotes social support and benefits social interactions and social bonding by facilitating the understanding of another individual (Hatfield, Cacioppo, & Rapson, 1993; Keysers, Kaas, & Gazzola, 2010; Niedenthal, 2007).

Oxytocin (OXT), an ancient and highly conserved neuropeptide that mediates relationship quality in human pair-bonds (Scheele et al., 2012; Scheele et al., 2013) has been found to improve social emotional inference of others (Aoki et al., 2014) and it facilitates the distinction between self and other (Colonnello, Chen, Panksepp, & Heinrichs, 2013). Therefore, OXT is likely to be involved in unillumined emotional processing, which is as well suggested by its ability to increase trustwothy perception of briefly presented faces (Theodoridou, Rowe, Penton-Voak, & Rogers, 2009). The neural circuits that are involved in mapping emotions of others involve the mirror neuron network, which allows the observer to grasp a goal-directed action of a conspecific (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). The similar activation pattern between observer and executer allows the observer to directly infer the actions of others (Rizzolatti, Fogassi, & Gallese, 2001). However, representing the observed brain activity in one's own brain is not sufficient to grasp the intention of the executer. The mirror

neuron network cannot be regarded as a directly corresponding mechanism between movement representations and emotions (Caggiano, Fogassi, Rizzolatti, Thier, & Casile, 2009; G. Rizzolatti et al., 1996). The network, which has been identified to encode the goal of motor actions is the parieto-frontal mirror system (Rizzolatti & Sinigaglia, 2010). A previous study (Keysers & Gazzola, 2007) which involved verbal presentations of other people's mental states and judgments which were related to the self and others, revealed the ventro (v)mPFC to be a shared neural network of introspection and theory of mind. Being involved with physiological or emotional states of others, activation of shared neural circuits are likely to transform states of another person into empathic perception (Keysers & Gazzola, 2007). Taken together with the observation that emotional processing influences thoughtful choices (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994), it may be suggested that the emotion induction can also take the opposite direction, meaning that unconscious emotional processing of information leads to a specific decision. We believe, that this emotional mechanism underlies the task in this study which aims at investigating the neural and behavioral correlates of the willingness to induce specific emotions from four categories (anger, fear, happiness, neutral) in another individual. There are, however, further functions which should be taken into consideration, inlcuding emotional processing, self-referential processing and inducing emotions in others and thereby making a distinction between self and other, but also planning could be involved in this task. Brain areas that have been related to these functions and which we believe to be involved in this task, include the medial prefrontal cortex (mPFC) (planning and emotional control), the ACC (emotional control) (Etkin, Egner, & Kalisch, 2011), the anterior insula (AI) (self-referential processing) the IFG (intention) (Iacoboni et al., 2005) and the IPL (mirror neuron system, self-other distinction) (Decety & Sommerville, 2003).

Further evidence is provided by a transcranianal magnetic stimulation (TMS) study which showed reduced reaction times to 'adapted' motor actions after stimulating the premotor and the inferior parietal lobe (IPL) (Cattaneo, Sandrini, & Schwarzbach, 2010). IPL mirror neurons enable the observer to identify the executer's intention of movement (Rizzolatti & Sinigaglia, 2010) and the IPL is involved in the distinction between self and other (Uddin, Molnar-Szakacs, Zaidel, & Iacoboni, 2006). Further evidence for involvement of the parieto-frontal mirror network in intention encoding, is delivered by an fMRI study with three different conditions (Iacoboni et al., 2005). In condition one, participants were shown a photo on which a person was either having breakfast or just finished having breakfast. In the second condition, participants were exposed to a photo of a hand which reached for a mug, no context was provided in this photo. The third condition entailed photos displaying the same hand, but this time two context situations were provided which indicated the intention of the person grasping the mug. Iacobini et al. (2005) revealed a stronger activation in the IFG for the last condition, which encompassed an intention, compared to the other two conditions. The authors concluded that the IFG and the premotor cortex are involved in embedding actions into a context and that neurons in these areas are involved in the understanding of other's intentions (Rizzolatti & Sinigaglia, 2010) (for further evidence, please refer to: (Hamilton & Grafton, 2008). Thus, we can predict actions of other people on the basis of our own action system. Multiple neuroimaging studies revealed shared neural activation for observing others in pain or pleasure and experiencing pain or pleasure directly (Jabbi, Swart, & Keysers, 2007; Jackson, Meltzoff, & Decety, 2005; Saarela et al., 2007; Singer et al., 2004). Empathy for pain revealed anterior insula (AI) activation (Singer et al., 2004), another reason for expecting the AI to be involved when testing for the willingness to

induce emotions. Given OXT's influence on abundant social interactions, it is likely that OXT plays a major role in emotion regulation and induction.

Thinking about what sentence would please or hurt someone else exemplifies a very reflective, cognitive capacity. This capacity is required for our task in which participants are meant to say how likely they would make different emotion evocative statements (EES) to someone they know. Midline structures are involved in these processes which involve conscious thinking of what we know about the other person to deduce what might please or hurt this individual (Amodio & Frith, 2006; Kilner & Frith, 2008).

In our study, we directly investigated the modulatory effects of OXT on the neural processing and behavioral responses on the willingness to induce emotions. We probed this willingness by presenting emotion evocative sentences (EES) of four emotional categories (anger, fear, happiness, neutral). Participants had to rate each statement on how well they could imagine to say it to someone they know. This fMRI-experiment, originally designed by Marsh & Cardinale, (2012), was adapted and conducted with 42 healthy male volunteers after they had received intranasal OXT (24 IU) or placebo (PLC). Due to OXT's frequently posited role as a prosocial molecule (e.g. see Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), we hypothesize that OXT increases the willingness to induce happy emotions and decrease the willingness to induce negative emotions, while we do not expect any OXT modulation on neutral EES. We expect the behavioral outcomes to be accompanied by altered neural activations in the mirror neuron network and midline structures.

Materials and Methods

Subjects

Forty-two healthy, non-smoking male adults (mean age ± SD = 24.88 ± 4.48 years) participated in the present study. All subjects were free of current and past physical or psychiatric illness, as assessed by medical history and a Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). All participants were recruited by local advertisement at the University Bonn, Germany. They provided written informed consent before study enrollment. All subjects were naïve to prescription-strength psychoactive medication and had not taken any over-the-counter psychoactive medication in the past 4 weeks. Participants were asked to maintain their regular bed and wake times and to abstain from caffeine and alcohol intake on the day of the experiment. To control for pre-treatment cognitive differences participants completed a comprehensive neuropsychological test battery. We assessed cognitive performance using the Cambridge Neuropsychological Test Automated Battery (CANTAB), a computerized neurocognitive assessment presented through a touch-screen computer (Sahakian & Owen, 1992). For details of the outcome measure see CANTABeclipse™ Test Administration Guide (CANTABeclipse, 2011). The ability to retain spatial information, and visual memory were measured with the spatial working memory task (SWM), and the paired associates learning task (PAL), respectively. All subjects were within a normal range of cognitive performance and there were no a priori differences in age and education (**Table T1**). We did not find a priori differences in potential moderator variables like mood: positive or negative affect (PANAS) (Watson, Clark, & Tellegen, 1988), state or trait anxiety (STAI) (Spielberger, Gorsuch, & Lushene, 1970), regular social interaction: social network (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997), the ability to verbally express emotions: alexithymia subscales (Taylor et al.,

1988), or task-relevant personality traits: psychopathic personality inventory (Zemack-Rugar, Bettman, & Fitzsimons, 2007) or ethical attitudes: ethical idealism and realism (Forsyth, 1980) between the OXT (n = 21) and PLC (N = 21) groups (all p > .05) (**Table 1, Table 3**). The experiment was approved by the institutional review board of the Medical Faculty of the University of Bonn and carried out in compliance with the latest revision of the Declaration of Helsinki.

Experimental design and fMRI paradigm

We applied a double-blind, between-subject, placebo-controlled, design. Subjects were randomly assigned to either intranasal administration of OXT (24 IU; Syntocinon-Spray, Novartis; three puffs per nostril, each with 4 IU OXT) or PLC (sodium chloride solution), approximately 45 ± 10 min before the start of the fMRI session.

The paradigm consisted of an introduction sentence that was presented for 5 s: "How well can you imagine saying the following sentence to a person you know?", afterwards there was a total of 80 EES. These sentences belonged to four emotional categories with 20 sentences of each emotion: *fear*, *anger*, *happiness* and *neutral*. The statements were translated into German from the task developed by Marsh et al (2012), instead of *sadness* we included *fear* and these sentences were newly created, the EES from the condition *disgust* were not included. Participants had to rate each EES, e.g. "I could easily hurt you", on a scale ranging from 0 (not at all) – 100 (very well). Each EES was presented for 6 sec, after 3 s the rating scale appeared underneath the sentence and the participant was able to give his answer; after a decision was made, the participant was asked to confirm his choice by button press. Between each trial, a fixation cross was presented. The order of emotional categories was alternated and prevented sentences from the same emotional category to be presented directly after each other.

The intertrial time interval (ITI) was between 4 s and 6 s. The answer anchor *very good* vs. *not at all* were alternated randomly. The answer scale was in form of a triangle and the anchor indicating "very good" was always on the high end (**see FIG. 1**).

Analysis of behavioral data

Demographical, neuropsychological, and behavioral data were analyzed using IBM SPSS Statistic 20 (IBM, New York, NY, USA). Quantitative behavioral data were compared using repeated measures ANOVAs and t tests. Pearson's product-moment correlation was used for correlation analysis. Eta-squared and Cohen's d were calculated as measures of effect size. For qualitative variables Pearson's chi-squared tests were used. All reported P-values are two-tailed, if not otherwise noted, and P-values of $P < 0.05$ were considered significant.

We received answer ratings for each EES on a scale from 0-100, we summed up all ratings from one category to examine how well participants could imagine to induce the four different emotions to a person they know. We excluded participants from the behavioral analysis who strongly deviated (± 1.5 SD) from the mean, we chose a very strict exclusion of participants, because OXT effects are subtle and measuring behavioral data in the fMRI is difficult, therefore we wanted to minimize answer deviations. We calculated a repeated measures analysis with the four EES categories (anger, fear, happy, neutral) as within-subject variables and treatment (OXT, PLC) as a between-subject variable. To disentangle the directionality of the effects, we performed one-tailed t tests, because we expected only one direction to be important for each emotion, depending on the valence.

Additionally, we performed a correlational analysis with the behavioral ratings of the four emotional categories of the EES and the cold-

heartedness scale of the psychopathy questionnaire. This questionnaire has 10 separate scales (social influence, fearlessness, stress immunity, Machiavellian egocentricity, rebellious nonconformity, blame externalization, carefree non-planfulness and cold-heartedness and the total). We are only interested in two sub-scales of this questionnaire which appear relevant for this experiment: cold-heartedness and social influence, because these two sub-scales are thought to have an impact on our task. High scores on the cold-heartedness subscale indicate careless behavior towards others; people with high scores do not have difficulties to deliver bad news. High scores on the social influence scale indicate that these individuals are self-conscious and like attention and they are able to influence others in their own interest.

Acquisition and analysis of fMRI data

The MRI data were acquired with a Siemens Avanto MRI system (Siemens, Erlangen, Germany) operating at 1.5T. T2*-weighted echoplanar (EPI) images with blood-oxygen-level-dependent contrast were obtained (repetiton time (TR) = 3,000 ms, echo time (TE) = 35 ms, matrix size: 64 x 64, pixel size: 3 mm x 3 mm x 3 mm, slice thickness = 3.0 mm, distance factor = 10%, field of view (FoV) = 192, flip angle = 90°, 36 axial slices). High-resolution anatomical images were acquired on the same scanner with a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1,570 ms, TE = 3.42 ms, matrix size: 256 x 256, pixel size: 1 mm x 1mm x 1 mm, slice thickness = 1.0 mm, FoV = 256, flip angle = 15, 160 sagittal slices).

The MRI data were preprocessed and analyzed using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7 (The MathWorks Inc., Natick, MA). Images were first preprocessed using a standardized procedure including reorientation, affine registration, realignment, and

spatial normalization to the current Montreal Neurological Institute (MNI) template using the unified segmentation function in SPM8 (41, 42). The normalized images were spatially smoothed using an 8 - mm FWHM Gaussian kernel. On the first level, the four emotional categories (fear, anger, happy, neutral) and the rating were modeled as separate conditions. The analysis was corrected for movement parameter. To examine the effects of OXT on the willingness to induce the emotions, the statements were defined and modeled in an event-related design convolved with a hemodynamic response function (Friston et al., 1994). Region of interest (ROI) analyses was conducted in SPM8 and focused on main and interaction effect of treatment (OXT, PLC) on the four emotional categories. In order to disentangle the direction and specificity of OXT effects, parameter estimates were extracted from regions showing significant treatment effects using MarsBaR toolbox (see also http://marsbar.sourceforge.net/). Parameter estimates (of anger vs baseline, fear vs baseline, happy vs baseline and neutral vs baseline) were assessed using a repeated measures analysis of variance (ANOVA) with the between-subject factor treatment (OXT, PLC).

To evaluate the neural mechanisms that might underlie the behavioral effects, we conducted a flexible factorial design with the four emotions as within subject factors and treatment as the between subject factor. Our task requires multiple skills, like perspective taking, self-other distinction and planning, because consequences of one's action need to be considered. Therefore, we expect the IFG, and the PM to play a major role, because they are involved in integrating actions into a context, in the understanding other's intentions (G. Rizzolatti & Sinigaglia, 2010). The medial prefrontal cortex (mPFC) is responsible for goal-directed actions and emotion regulation (Shimamura, 2000) while the TPJ integrates information from the external environment and from within the body (Abu-Akel & Shamay-Tsoory, 2011) which makes them likely candidates to be involved

in this task. We further expected the IPL (Fan, Duncan, de Greck, & Northoff, 2011; Lawrence et al., 2006) to be involved, because it enables the distinction between self and other. Also the interoceptive network, including the anterior cingulate cortex (ACC), and the insula, may be important in our task due to necessary self-reflection on what this sentence would trigger in oneself (McKiernan, D'Angelo, Kaufman, & Binder, 2006; Northoff et al., 2006; Zaki, Davis, & Ochsner, 2012).

To increase the power, the analysis was restricted to WFU Pickatlas automatic anatomic labeling (aal, brodmann, TD labels) (Brett, Anton, Valabregue, & Poline, 2002; Lancaster et al., 2000; Maldjian, Laurienti, Kraft, & Burdette, 2003) atlas-based regions of interest (ROIs) for the IFG, PM, IPL, TPJ, mPFC, ACC and the insula (significance threshold $P < .05$ family-wise error (FWE) corrected).

Results

Behavioral results

A 2x4 repeated-measures analysis of variance (ANOVA) with emotions (anger, fear, happy, neutral) as a within-subject variable and treatment (OXT vs. PLC) as the between-subject variable revealed a significant main effect of emotion ($V = 0.962$ $F_{(3.\ 24)} = 203.820$, $P < 0.05$, $\eta 2 = 0.962$), no main effect of group, and an interaction-effect between treatment and emotion ($V = 0.310$, $F_{(3.\ 24)} = 3.587$, $P < 0.05$, $\eta 2 = 0.310$). This indicates differential effects of emotions. In the OXT group compared to the PLC group, the willingness to induce happy (OXT: 89.507 ± 10.175, PLC: 82.965 ± 10.641) and neutral (OXT: 83.627 ± 10.607, PLC: 75.700 ± 12.711) emotions was significantly higher than the willingness to induce anger (OXT: 32.823 ± 13.811, PLC: M = 45.889 ± 19.831) or fear (OXT: 18.620 ± 8.870, PLC: 23.539 ± 5.749). The interaction with treatment revealed that OXT increases

the willingness to induce happy and neutral feelings, while it decreases the willingness to induce anger and fear. Post-hoc one-tailed independent t tests comparing OXT and PLC groups for the specific emotions revealed a significant (trend) difference in the OXT group for happy (P = 0.055) and neutral (P = 0.042) EES, and a significant difference for anger (P = 0.026) and fear (P = 0.050). We did not expect neutral EES to show a significant difference.

Additional correlational analysis revealed that OXT seems to strengthen pre-existing traits like *cold-heartedness* and *social influence* (sub-scales of the psychopathy questionnaire). We found a significant positive correlation in the OXT group for anger (P = 0.044, r = 0.546) and fear (P = 0.008, r = 0.678) sentences with the cold-heartedness scale, in addition to a negative correlation trend of this scale to happy (P = 0.066, r = -0.504) EES. In the PLC group, we only found a significant positive correlation between the cold-heartedness scale and fear (P = 0.010, r = 0.683) EES. A significant correlation for the social influence scale was found in the OXT group for happy (P = 0.029, r = 0.583) and a trend for neutral (P = 0.084, r = 0.478) EES.

FMRI results

As expected from previous literature, the evaluation of EES, elicited broad activity in the mirror neuron network and the emotional reflection related brain regions in the PLC group, including the cingulate gyrus, the medial frontal gyrus, the insula and the inferior parietal lobe which is involved in distinction between self and other feelings (cf. **Table T2)** (Decety & Sommerville, 2003; McKiernan et al., 2006).

The statistical parametric mapping (SPM) ROI analysis of the regions we anticipated to be involved in this task, including the IFG, IPL, BA6, the ACC the mPFC the insula and the TPJ, were performed. Main

effects of the different emotional categories were observed in the left IFG ($F_{(1,160)}$ = 18.82, P_{FWE} < 0.05), the right IPL ($F_{(1,160)}$ = 16.92, P_{FWE} < 0.05), the left ACC ($F_{(1,160)}$ = 18.21, P_{FWE} < 0.05), the right mPFC ($F_{(1,160)}$ = 26.04, P_{FWE} < 0.05) and the bilateral TPJ (right: $F_{(1,160)}$ = 33.06, P_{FWE} < 0.05, left: $F_{(1,160)}$ = 21.80, P_{FWE} < 0.05), no main effects were revealed in the ventral premotor area (Brodmann area 6) and the insula. Parameter estimate extraction was used to determine the directionality of these main effects. Paired t tests with the extracted parameter estimates revealed that in the IFG, happy EES resulted in significantly lower reduction in activation than anger and fear EES. The IPL main effect displays a significantly increased activity of happy EES compared to neutral EES, significantly lower activation of anger compared to happy and neutral. In the ACC, EES of anger and fear revealed significantly lower activation than happy and neutral EES. In the mPFC, anger and fear statements elicited significantly lower activation than happy or neutral statements. In the left TPJ, anger and fear EES displayed significantly lower activation compared to happy and neutral EES. Happy sentences sparingly, revealed significantly reduced (almost none) activity compared to neutral EES. In the right TPJ, we find that anger and fear EES are significantly more reduced than neutral EES.

Interaction effects of treatment x emotion were revealed in the left IFG (MNI x, y, z: -48, -1, 22, $F_{(3,160)}$ = 9.21, P_{FWE} < 0.05 **FIG. 2**) and the right IPL (MNI x, y, z: 30, -40, 52, $F_{(3,160)}$ = 7.99, P_{FWE} < 0.05 **FIG. 3**). A trend to significance was observed in the ventral premotor area (MNI x, y, z: -51, -4, 25, $F_{(3,160)}$ = 7.70, P_{FWE} < 0.057 **FIG. 4**) and the right mPFC (MNI x, y, z: 12, 8, 52, $F_{(3,160)}$ = 7.45, P_{FWE} = 0.059 **FIG. 5**). Parameter estimates were extracted to determine the directionality of the interaction effects from the contrasts emotion (anger, fear, happy, neutral) vs baseline and revealed that OXT increased activation anger and fear EES and decreased activation for happy and neutral EES in the left IFG, the PMv as well as in the mPFC

(**FIG. 2, 4, 5**). In the IPL, OXT increased activity for anger, fear and neutral while we found an activity reduction for happy EES (**FIG 3**). We did not expect to find a significant interaction between treatment and neutral EES, therefore we again conducted a repeated-measures ANOVA with emotions (anger, fear, happy) as within-subject variables and treatment (OXT vs. PLC) as between-subject variable and the interaction effect remained in the IPL (MNI x, y, z: 30, -40, 52, $F_{(2,120)} = 12.72$, $P_{FWE} < 0.05$).

Figure 1: Triangle rating scale on which participants selected their answer

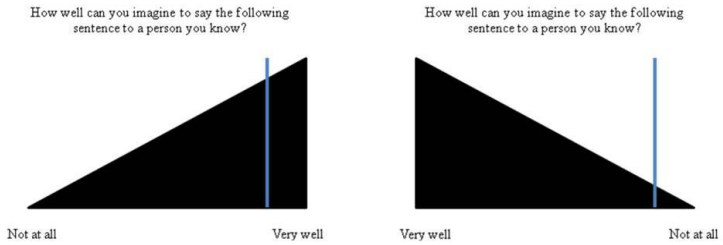

Figure Legend: Figure 1

The triangle flipped randomly between trials, but the *very well* anchor always corresponded to the high side of the triangle while the *not at all* anchor always corresponded to the flat side of the triangle

Figure 2: Oxytocin (OXT) effects on emotion induction in the inferior frontal gyrus (IFG)

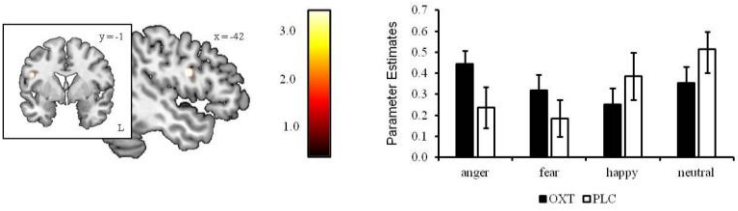

Figure Legend: Figure 2

A significant interaction between treatment (OXT vs PLC) and emotion (anger, fear, happy, neutral) was found in the IFG (**B**). Post-hoc t-tests revealed that OXT decreased activity for *happy* EES while it increased activity for *anger*, *fear* and *neutral* EES. Error bars indicate the standard

error of the mean (SEM). Abbreviations: EES, emotion evocative statement, IPL, inferior parietal lobe; OXT, oxytocin; PLC, placebo

Figure 3: (OXT) effects on emotion induction in the inferior parietal gyrus (IPL)

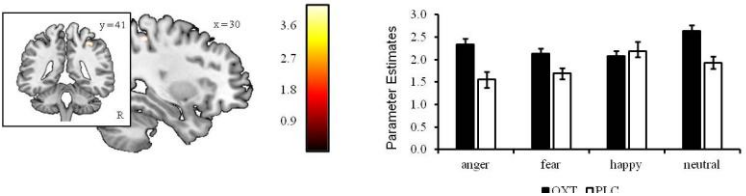

Figure Legend: Figure 3

A significant interaction between treatment (OXT vs PLC) and emotion (anger, fear, happy, neutral) was found in the IPL. Post-hoc t-tests revealed that OXT decreased activity for *happy* EES while it increased activity for *anger*, *fear* and *neutral* EES.

Figure 4: (OXT) effects on emotion induction in the ventral premotor area (BA6)

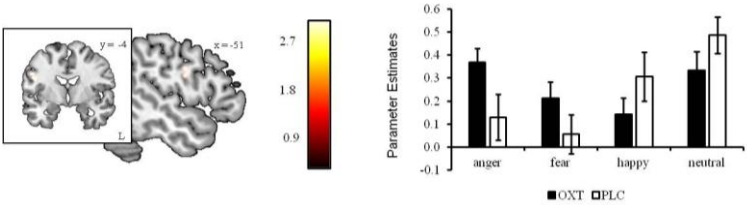

Figure Legend: Figure 4

A significant interaction between treatment (OXT vs PLC) and emotion (anger, fear, happy, neutral) was found in the BA6. Post-hoc t-tests revealed that OXT decreased activity for *happy* EES while it increased activity for *anger*, *fear* and *neutral* EES. Error bars indicate the standard error of the mean (SEM). Abbreviations: EES, emotion evocative statement, IPL, inferior parietal lobe; OXT, oxytocin; PLC, placebo

Figure 5: Oxytocin (OXT) effects on emotion induction on the medial prefrontal cortex (mPFC)

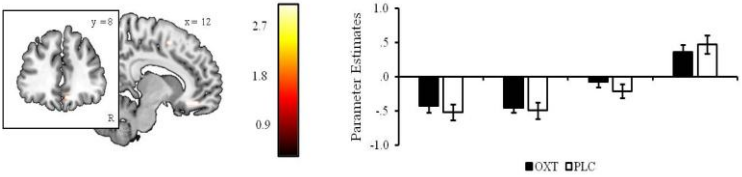

Figure Legend: Figure 5

A significant interaction between treatment (OXT vs PLC) and emotion (anger, fear, happy, neutral) was found in the mPFC. Post-hoc t-tests revealed that OXT decreased reduced activity for *happy*, *anger* and *fear* EES and reduced activity for *neutral* EES. Error bars indicate the standard error of the mean (SEM). Abbreviations: EES, emotion evocative statement, IPL, inferior parietal lobe; OXT, oxytocin; PLC, placebo

Figure 6: Behavioral ratings on EES

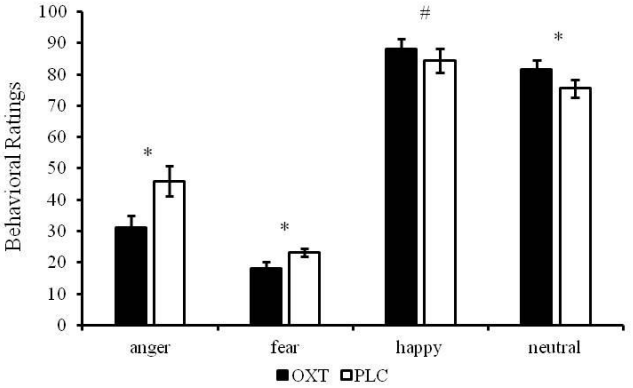

Figure Legend: Figure 6

The behavioral responses show that OXT facilitated the willingness to state *happy* and *neutral* EES, while it reduced the willingness to state *anger* or *fear* EES. Error bars indicate the standard error of the mean (SEM). Abbreviations: EES, emotion evocative statement, IPL, inferior parietal lobe; OXT, oxytocin; PLC, placebo, *significant difference, #trend to significant difference.

Discussion:

In the present study, we aimed at elucidating the influence of OXT on the willingness to induce emotions of different valences in healthy men. This study provides the first evidence that OXT increases people's willingness to induce positive emotions, while it decreases people's willingness to induce negative emotions. The behavioral finding is strongly supported by neural modulation of OXT in the IFG (**FIG. 2**), the BA6 (**FIG. 4**) and the mPFC (**FIG. 5**) which display increased activity for the willingness to induce negative emotions and decreased activity for the willingness to induce positive emotions after intranasal OXT administration. Furthermore, the IPL displayed similar activation patterns, but the neutral EES resulted in an increased activation which was not expected and is surprising, especially because the other brain areas show an increase of activation for neutral EES after OXT administration (**FIG. 3**). Nevertheless, excluding neutral EES from our analysis did not change the neural nor the behavioral pattern, and the interaction of treatment x emotion stayed significant, showing that the neutral condition alone does not fully explain the significant interaction effect of treatment x emotion. Neural up-regulation by OXT (in the IFG, mPFC, BA6 and the IPL) is associated with decreased willingness to induce negative emotions and vice versa. Consequently, OXT enhances the willingness to induce positive emotions and reduces the willingness to induce negative emotions in healthy men.

Our results are consistent with previous literature, because brain structures which were activated and modulated by OXT in this task have already been associated with emotion regulation, mentalizing and anticipation. OXT suppressed activity to the willingness to induce positive emotions in the left IFG, the right mPFC and the ventral premotor area, while it up-regulated neural activity in these regions while evaluating the willingness to induce negative emotions. The IFG has been suggested to

have different functions, the right part is associated with speech and emotion processing as well as with the evaluation of affective salience (Rota et al., 2009). The left part is associated with reappraising the emotions of others (Grecucci, Giorgetta, Bonini, & Sanfey, 2013) and reading other people's mind (Dal Monte et al., 2014). Dal Monte and colleagues (2014) reported that patients with a lesion in the left IFG performed poorly in the Reading the Mind in the Eyes Test (RMET), compared to other lesion patients. The REMT requires decoding as well as reasoning about mental states. Furthermore, findings have shown OXT modulation on the IFG, and these findings suggest that OXT increases activity in the IFG, thereby as well increasing the responsiveness to infant cries (Riem et al., 2011). Thus, our finding of OXT induced increased activity in the left IFG in response to happy emotions is very plausible, because as discussed, other studies also found that increased IFG activity reflects improved social behavior.

The mPFC is involved in social cognition and reward (Harris, McClure, van den Bos, Cohen, & Fiske, 2007), it is important for the interplay of cognitive tasks and emotion (Simpson, Snyder, Gusnard, & Raichle, 2001). The study by Harris et al. (2007) showed positive vs negative pictures to their participants that either displayed persons or objects. The authors found the anterior rostral region of the mPFC to be specifically activated for social stimuli, while positive social stimuli elicited stronger activation than negative stimuli. This result is consistent with our finding; we also found comparably highly reduced activation in the mPFC for negative vs positive stimuli (**FIG. 5**). The mPFC has also been suggested to play an important role in emotion regulation (Opialla et al., 2014). Emotion regulation is one example for cognitive control and its dysfunction may result in mood disorders (Ochsner & Gross, 2005). The uniqueness of human social cognition is shown by its ability to strategically organize behavior to persue certain goals, either to positively contribute to the greater good or to

manipualte others (Adolphs, 2009). Usually emotion induction occurs involuntarily and without conscious intentions. Theories of decision-making have stated that intentional choices are often influenced by automatic and emotional processing (Damasio et al., 1994) and that social judgments on, for example trustworthiness, can be made after brief facial picture presentation (Bar, Neta, & Linz, 2006), indicating an uncoscious processing.

The ventral premotor area (BA6) has previously been linked to goal-directed actions as part of the mirror neuron network. In our study, the activation pattern in the ventral premotor area is identical to the activation pattern in the IFG. These similar patterns strongly indicate an interacting communication between these areas, also with the mPFC in which the activation patter is also similar even though we found a reduced activation pattern for all EES, except for neutral.

The IPL has been identified as a region that distinguishes between self and other (Uddin, Molnar-Szakacs, Zaidel, & Iacoboni, 2006) and it is as well part of the mirror neuron system. Furthermore, the IPL, including the supramarginal gyrus has been proposed to function as a 'bottom-up' attentional subsystem that mediates automatic attributions of attention to task-relevant information (Ludwig et al., 2013). After receiving OXT, the task-relevant information, whether EES were positive, negative or neutral, may have become more salient, as has been suggested before (Prehn et al., 2013). The increased stimuli salience might have influenced the responses to specific emotionally different EES. These observations are consistent with our previous findings, which show that OXT reduces ACC activity in emotionally difficult situations and thereby facilitating the emotional burden experienced as well as the decision making of these situations (Preckel, Scheele, Eckstein, et al., 2014).

Current perspectives on the central effects of OXT emphasize its pleiotropic contributions to sociality, although a substantial diversity in behavioral

functions is evident across taxa (Anacker & Beery, 2013; Goodson, 2013). It has been shown that OXT increases people's willingness to share emotions (Lane et al., 2013). And happy people show more kindness than unhappy people and become even happier through their kind actions (Otake, Shimai, Tanaka-Matsumi, Otsui, & Fredrickson, 2006). Another study states that OXT increases positive communication between couples while they discuss conflict-laden topics (Ditzen et al., 2009), and the ability to produce normative ratings of others' emotions was improved after OXT administration (Carson et al., 2014). Also given the previous findings of OXT on the strong context-dependency (Bartz, Zaki, Bolger, & Ochsner, 2011) and emotion specificity (Gamer & Buchel, 2012), our observations that OXT enhanced the willingness to induce positive emotions (*happy*) and reduce the willingness to induce negative emotions (*anger*, *fear*) is highly plausible. Our results strengthen these previous observations and take them one step ahead by showing that OXT can influence the willingness to induce positive emotions in someone else, thereby improving social communication.

There are multiple and controversial findings about OXT's role in social interactions (Kosfeld et al., 2005; Shamay-Tsoory et al., 2009). Even though, results in this study reflect purely prosocial actions of OXT, it also appears that personality traits such as psychopathy, are strengthened by OXT. This is suggested by the positive correlation between anger and fear EES and the negative correlation between happy EES and the *cold-heartedness* scale as well as the *social influence* scale of the psychopathy questionnaire. This correlational finding might partly explain the vast amount of diverse findings in the OXT literature. Participants in our study generally scored very low on the psychopathy questionnaire, and we still found indications for OXT's strengthening effect of personality traits that may be able to turn the prosocial findings around. Riem et al. (2013) found an interaction of OXT and childhood experiences on prosocial behavior

towards ostracism, stating that individuals who received supportive upbringing increased their prosocial behavior toward socially excluded individuals, while the opposite was true for individuals with unsupportive family backgrounds. OXT crucially influences social interactions, thereby providing a basis for psychological well-being (Knobloch & Grinevich, 2014). OXT effects should however be treated with caution since the diversity of findings points out that OXT has wide-ranging influences of which we might not yet be aware.

A shortcoming of our study is that we only tested men and as previous studies have shown, there are various sexually-dimorphic effects of OXT (Preckel, Scheele, Kendrick, et al., 2014; Stankova, Eichhammer, Langguth, & Sand, 2012). Therefore, the generalization of the results is restricted to men. One of the most discussed OXT matters is its role in psychiatric populations. We can, however, only speculate about possible clinical implications of OXT on the basis of our results, because we only tested healthy individuals. Though, we believe that OXT might enhance social-emotional functions. Assuming that OXT has the same effects on autistic men as it had in healthy men, it could improve their judgment of whether an EES is appropriate to make for prosocial interaction or not. OXT could function as a social reinforcer and initiate an upward spiral, by increasing the readiness to make positive statements.

Taken together, we here provide first evidence that the neuropeptide hormone OXT influences the willingness to induce emotions in others and more importantly that it enhances positive emotion induction and reduces negative emotion induction.

References

Abu-Akel, A., & Shamay-Tsoory, S. (2011). Neuroanatomical and neurochemical bases of theory of mind. Neuropsychologia, 49(11), 2971-2984.

Adolphs, R. (2009). The social brain: neural basis of social knowledge. Annu Rev Psychol, 60, 693-716.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci, 7(4), 268-277.

Anacker, A. M. J.;, & Beery, A. K. . (2013). Life in groups: The roles of oxytocin in mammalian sociality. *Front Behav Neurosci*. doi: 10.3389/fnbeh.2013.00185

Aoki, Y., Yahata, N., Watanabe, T., Takano, Y., Kawakubo, Y., Kuwabara, H., Yamasue, H. (2014). Oxytocin improves behavioural and neural deficits in inferring others' social emotions in autism. *Brain, 137*(Pt 11), 3073-3086. doi: 10.1093/brain/awu231

Bar, M., Neta, M., & Linz, H. (2006). Very first impressions. Emotion, 6(2), 269-278.

Bartz, J. A., Zaki, J., Bolger, N., & Ochsner, K. N. (2011). Social effects of oxytocin in humans: context and person matter. Trends Cogn Sci, 15(7), 301-309.

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. . (2002). *Region of interest analysis using an spm toolbox*. Paper presented at the 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan.

CANTABeclipse. (2011). Test administration guide: Cambridge Cognition Limited.

Caggiano, V., Fogassi, L., Rizzolatti, G., Thier, P., & Casile, A. (2009). Mirror neurons differentially encode the peripersonal and extrapersonal space of monkeys. Science, 324(5925), 403-406.

Carson, D. S., Berquist, S. W., Trujillo, T. H., Garner, J. P., Hannah, S. L., Hyde, S. A., Parker, K. J. (2014). Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children. *Mol Psychiatry*. doi: 10.1038/mp.2014.132

Cattaneo, L., Sandrini, M., & Schwarzbach, J. (2010). State-dependent TMS reveals a hierarchical representation of observed acts in the temporal, parietal, and premotor cortices. Cereb Cortex, 20(9), 2252-2258.

Cohen, S., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M., Jr. (1997). Social ties and susceptibility to the common cold. *JAMA*, *277*(24), 1940-1944.

Colonnello, V., Chen, F. S., Panksepp, J., & Heinrichs, M. (2013). Oxytocin sharpens self-other perceptual boundary. *Psychoneuroendocrinology*, *38*(12), 2996-3002. doi: 10.1016/j.psyneuen.2013.08.010

Dal Monte, O., Schintu, S., Pardini, M., Berti, A., Wassermann, E. M., Grafman, J., et al. (2014). The left inferior frontal gyrus is crucial for reading the mind in the eyes: Brain lesion evidence. Cortex, 58, 9-17.

Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., & Damasio, A. R. (1994). The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science, 264(5162), 1102-1105.

Decety, J., & Sommerville, J. A. (2003). Shared representations between self and other: A social cognitive neuroscience view. *Trends Cogn Sci*, *7*(12), 527-533. doi: DOI 10.1016/j.tics.2003.10.004

Dimberg, U., & Thunberg, M. (1998). Rapid facial reactions to emotional facial expressions. *Scand J Psychol*, *39*(1), 39-45.

Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U., & Heinrichs, M. (2009). Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. [Controlled Clinical Trial

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., & Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. Exp Brain Res, 91(1), 176-180.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci, 15(2), 85-93.

Fan, Y., Duncan, N. W., de Greck, M., & Northoff, G. (2011). Is there a core neural network in empathy? An fmri based quantitative meta-analysis. *Neurosci Biobehav Rev, 35*(3), 903-911. doi: 10.1016/j.neubiorev.2010.10.009

Forsyth, D. R. (1980). A taxonomy of ethical ideologies. *Journal of Personality and Social Psychology, 39*(1), 175-184. doi: Doi 10.1037//0022-3514.39.1.175

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. Brain, 119 (Pt 2), 593-609.

Gamer, M., & Buchel, C. (2012). Oxytocin specifically enhances valence-dependent parasympathetic responses. *Psychoneuroendocrinology, 37*(1), 87-93.

Garrison, J. L., Macosko, E. Z., Bernstein, S., Pokala, N., Albrecht, D. R., & Bargmann, C. I. (2012). Oxytocin/vasopressin-related peptides have an ancient role in reproductive behavior. *Science, 338*(6106), 540-543. doi: 10.1126/science.1226201

Grecucci, A., Giorgetta, C., Bonini, N., & Sanfey, A. G. (2013). Reappraising social emotions: the role of inferior frontal gyrus,

temporo-parietal junction and insula in interpersonal emotion regulation. Front Hum Neurosci, 7, 523.

Goodson, J. L. (2013). Deconstructing sociality, social evolution and relevant nonapeptide functions. *Psychoneuroendocrinology, 38*(4), 465-478. doi: 10.1016/j.psyneuen.2012.12.005

Hamilton, A. F., & Grafton, S. T. (2008). Action outcomes are represented in human inferior frontoparietal cortex. Cereb Cortex, 18(5), 1160-1168.

Harari-Dahan, O., & Bernstein, A. (2014). A general approach - avoidance hypothesis of Oxytocin: Accounting for social and non-social effects of oxytocin. Neurosci Biobehav Rev, 47C, 506-519.

Harris, L. T., McClure, S. M., van den Bos, W., Cohen, J. D., & Fiske, S. T. (2007). Regions of the MPFC differentially tuned to social and nonsocial affective evaluation. Cogn Affect Behav Neurosci, 7(4), 309-316.

Hatfield, E., Cacioppo, J. L., & Rapson, R. L. (1993). Emotional contagion. *Current Directions in Psychological Sciences, 2*, 96-99.

Hietanen, J. K., Surakka, V., & Linnankoski, I. (1998). Facial electromyographic responses to vocal affect expressions. *Psychophysiology, 35*(5), 530-536.

Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J. C., & Rizzolatti, G. (2005). Grasping the intentions of others with one's own mirror neuron system. PLoS Biol, 3(3), e79.

Jabbi, M., Swart, M., & Keysers, C. (2007). Empathy for positive and negative emotions in the gustatory cortex. *Neuroimage, 34*(4), 1744-1753. doi: DOI 10.1016/j.neuroimage.2006.10.032

Jackson, P. L., Meltzoff, A. N., & Decety, J. (2005). How do we perceive the pain of others? A window into the neural processes involved in

empathy. *Neuroimage, 24*(3), 771-779. doi: DOI 10.1016/j.neuroimage.2004.09.006

Kanske, P., & Kotz, S. A. (2011). Emotion speeds up conflict resolution: a new role for the ventral anterior cingulate cortex? *Cereb Cortex, 21*(4), 911-919.

Kelly, J. R., & Barsade, S. G. (2001). Mood and emotions in small groups and work teams. *Organizational Behavior and Human Decision Processes, 86*(1), 99-130. doi: 10.1006/obhd.2001.2974

Keysers, C., & Gazzola, V. (2007). Integrating simulation and theory of mind: from self to social cognition. *Trends Cogn Sci, 11*(5), 194-196.

Keysers, C., Kaas, J. H., & Gazzola, V. (2010). Somatosensation in social perception. *Nat Rev Neurosci, 11*(6), 417-428. doi: 10.1038/nrn2833

Kilner, J. M., & Frith, C. D. (2008). Action observation: inferring intentions without mirror neurons. Curr Biol, 18(1), R32-33.

Knobloch, H. S., & Grinevich, V. (2014). Evolution of oxytocin pathways in the brain of vertebrates. *Front Behav Neurosci, 8*, 31. doi: 10.3389/fnbeh.2014.00031

Kohler, E., Keysers, C., Umilta, M. A., Fogassi, L., Gallese, V., & Rizzolatti, G. (2002). Hearing sounds, understanding actions: action representation in mirror neurons. Science, 297(5582), 846-848.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., Fox, P. T. (2000). Automated talairach atlas labels for functional brain mapping. [Research Support, U.S. Gov't, P.H.S.]. *Hum Brain Mapp, 10*(3), 120-131.

Lane, A., Luminet, O., Rime, B., Gross, J. J., de Timary, P., & Mikolajczak, M. (2013). Oxytocin increases willingness to socially share one's

emotions. *Int J Psychol, 48*(4), 676-681. doi: 10.1080/00207594.2012.677540

Lawrence, E. J., Shaw, P., Giampietro, V. P., Surguladze, S., Brammer, M. J., & David, A. S. (2006). The role of 'shared representations' in social perception and empathy: An fmri study. *Neuroimage, 29*(4), 1173-1184. doi: 10.1016/j.neuroimage.2005.09.001

Leggitt, J. S., & Gibbs, R. W. (2000). Emotional reactions to verbal irony. *Discourse Processes, 29*(1), 1-24. doi: 10.1207/S15326950dp2901_1

Ludwig, M., Tobin, V. A., Callahan, M. F., Papadaki, E., Becker, A., Engelmann, M., & Leng, G. (2013). Intranasal application of vasopressin fails to elicit changes in brain immediate early gene expression, neural activity and behavioural performance of rats. [Research Support, N.I.H., Extramural

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fmri data sets. *Neuroimage, 19*(3), 1233-1239.

Marsh, A. A., & Cardinale, E. M. (2012). When psychopathy impairs moral judgments: Neural responses during judgments about causing fear. *Soc Cogn Affect Neurosci, 9*(1), 3-11. doi: doi: 10.1093/scan/nss097

McKiernan, K. A., D'Angelo, B. R., Kaufman, J. N., & Binder, J. R. (2006). Interrupting the "stream of consciousness": An fmri investigation. *Neuroimage, 29*(4), 1185-1191. doi: 10.1016/j.neuroimage.2005.09.030

Niedenthal, P. M. (2007). Embodying emotion. *Science, 316*(5827), 1002-1005. doi: 10.1126/science.1136930

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain--a meta-analysis of imaging studies on the self. [Meta-Analysis

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. Trends Cogn Sci, 9(5), 242-249.

Onoda, K., Okamoto, Y., Toki, S., Ueda, K., Shishida, K., Kinoshita, A., et al. (2008). Anterior cingulate cortex modulates preparatory activation during certain anticipation of negative picture. Neuropsychologia, 46(1), 102-110.

Opialla, S., Lutz, J., Scherpiet, S., Hittmeyer, A., Jancke, L., Rufer, M., et al. (2014). Neural circuits of emotion regulation: a comparison of mindfulness-based and cognitive reappraisal strategies. Eur Arch Psychiatry Clin Neurosci.

Otake, K., Shimai, S., Tanaka-Matsumi, J., Otsui, K., & Fredrickson, B. L. (2006). Happy people become happier through kindness: A counting kindnesses intervention. *Journal of Happiness Studies, 7*, 361 - 375. doi: 10.1007/s10902-005-3650-z

Preckel, K., Scheele, D., Eckstein, M., Maier, W., & Hurlemann, R. (2014). The influence of oxytocin on volitional and emotional ambivalence. *Soc Cogn Affect Neurosci, in press*.

Preckel, K., Scheele, D., Kendrick, K. M., Maier, W., & Hurlemann, R. (2014). Oxytocin facilitates social approach behavior in women. *Front Behav Neurosci, 8*. doi: Artn 191 Doi 10.3389/Fnbeh.2014.00191

Prehn, K., Kazzer, P., Lischke, A., Heinrichs, M., Herpertz, S. C., & Domes, G. (2013). Effects of intranasal oxytocin on pupil dilation indicate increased salience of socioaffective stimuli. *Psychophysiology, 50*(6), 528-537. doi: Doi 10.1111/Psyp.12042

Research Support, Non-U.S. Gov't]. *Psychoneuroendocrinology, 38*(8), 1418-1425. doi: 10.1016/j.psyneuen.2012.12.023

Research Support, Non-U.S. Gov't]. *Neuroimage, 31*(1), 440-457. doi: 10.1016/j.neuroimage.2005.12.002

Research Support, Non-U.S. Gov't]. *J Neuroendocrinol, 25*(7), 655-667. doi: 10.1111/jne.12046

Research Support, Non-U.S. Gov't]. *Biol Psychiatry, 65*(9), 728-731. doi: 10.1016/j.biopsych.2008.10.011

Research Support, Non-U.S. Gov't]. *Neuroimage, 62*(1), 493-499. doi: 10.1016/j.neuroimage.2012.05.012

Riem, M. M., Bakermans-Kranenburg, M. J., Pieper, S., Tops, M., Boksem, M. A., Vermeiren, R. R., et al. (2011). Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: a randomized controlled trial. Biol Psychiatry, 70(3), 291-297.

Riem, M. M., Bakermans-Kranenburg, M. J., Huffmeijer, R., & van Ijzendoorn, M. H. (2013). Does intranasal oxytocin promote prosocial behavior to an excluded fellow player? A randomized-controlled trial with cyberball. [Randomized Controlled Trial

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. Brain Res Cogn Brain Res, 3(2), 131-141.

Rizzolatti, G., Fadiga, L., Matelli, M., Bettinardi, V., Paulesu, E., Perani, D., et al. (1996). Localization of grasp representation in humans by PET: 1. Observation versus execution. Exp Brain Res, 111(2), 246 - 252.

Rizzolatti, G., Fogassi, L., & Gallese, V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci, 2(9), 661-670.

Rizzolatti, G., & Sinigaglia, C. (2010). The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. Nat Rev Neurosci, 11(4), 264-274.

Rota, G., Sitaram, R., Veit, R., Erb, M., Weiskopf, N., Dogil, G., et al. (2009). Self-Regulation of Regional Cortical Activity Using Real-Time fMRI: The Right Inferior Frontal Gyrus and Linguistic Processing. Human Brain Mapping, 30(5), 1605-1614.

Saarela, M. V., Hlushchuk, Y., Williams, A. C., Schurmann, M., Kalso, E., & Hari, R. (2007). The compassionate brain: Humans detect intensity of pain from another's face. *Cereb Cortex, 17*(1), 230-237. doi: 10.1093/cercor/bhj141

Sahakian, B. J., & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using cantab: Discussion paper. [Research Support, Non-U.S. Gov't]. *J R Soc Med, 85*(7), 399-402.

Scheele, D., Striepens, N., Güntürkün, O., Deutschländer, S., Maier, W., Kendrick, K. M., & Hurlemann, R. (2012). Oxytocin modulates social distance between males and females. *Journal of Neuroscience, 14*, 16074-16079. doi: 10.1523/JNEUROSCI.2755-12.2012

Scheele, D., Wille, A., Kendrick, K. M., Stoffel-Wagner, B., Becker, B., Güntürkün, O., Hurlemann, R. (2013). Oxytocin enhances brain reward system responses in men viewing the face of their female partner. *PNAS, 110*(50), 20308 - 20313. doi: 10.1073/pnas.1314190110

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amoriam, P., Janavs, J., Weiller, E., Dunbar, G. (1998). The mini-international neuropsychiatric interview (m.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for dsm-iv and icd-10. *J Clin Psychiatry, 59*(20), 22 - 33.

Shimamura, A. P. (2000). The role of the prefrontal cortex in dynamic filtering. Psychobiology, 28(2), 207-218.

Simpson, J. R., Jr., Snyder, A. Z., Gusnard, D. A., & Raichle, M. E. (2001). Emotion-induced changes in human medial prefrontal cortex: I. During cognitive task performance. Proc Natl Acad Sci U S A, 98(2), 683-687.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Firth, C.D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science, 303*(5661), 1157-1162.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press.

Stankova, T., Eichhammer, P., Langguth, B., & Sand, P. G. (2012). Sexually dimorphic effects of oxytocin receptor gene (oxtr) variants on harm avoidance. *Biology of Sex Differences, 17*, 1-5. doi: 10.1186/2042-6410-3-17

Striepens, N., Scheele, D., Kendrick, K. M., Becker, B., Schafer, L., Schwalba, K., Hurlemann, R. (2012). Oxytocin facilitates protective responses to aversive social stimuli in males. *Proc Natl Acad Sci U S A, 109*(44), 18144-18149. doi: 10.1073/pnas.1208852109

Taylor, G. J., Bagby, R. M., Ryan, D. P., Parker, J. D., Doody, K. F., & Keefe, P. (1988). Criterion validity of the toronto alexithymia scale. *Psychosomatic Medicine, 50*(5), 500-509.

Theodoridou, A., Rowe, A. C., Penton-Voak, I. S., & Rogers, P. J. (2009). Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. Horm Behav, 56(1), 128-132.

Uddin, L. Q., Molnar-Szakacs, I., Zaidel, E., & Iacoboni, M. (2006). rTMS to the right inferior parietal lobule disrupts self-other discrimination. [Research Support, N.I.H., Extramural

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The panas scales. *J Pers Soc Psychol, 54*(6), 1063-1070.

Wild, B., Erb, M., & Bartels, M. (2001). Are emotions contagious? Evoked emotions while viewing emotionally expressive faces: Quality, quantity, time course and gender differences. *Psychiatry Res, 102*(2), 109-124.

Zaki, J., Davis, J. I., & Ochsner, K. N. (2012). Overlapping activity in anterior insula during interoception and emotional experience. [Research Support, N.I.H., Extramural

Zemack-Rugar, Y., Bettman, J. R., & Fitzsimons, G. J. (2007). The effects of nonconsciously priming emotion concepts on behavior. *J Pers Soc Psychol, 93*(6), 927-939.

Tables

Table T1. Demographics and neuropsychological performance

	OXT (n = 21) Mean (± SD)	PLC (n = 21) Mean (± SD)
Age (years)	25.10 (4.67)	24.67 (4.41)
Education (years)	16.78 (2.44)	16.61 (1.72)
Idealism (EPQ) [a]	60.20 (7.97)	58.71 (10.10)
Realism (EPQ) [a]	55.00 (8.62)	55.94 (8.94)
Positive affect (PANAS) [b]	27.62 (4.79)	28.67 (4.49)
Negative affect (PANAS) [b]	10.62 (0.74)	12.24 (2.51)
State Anxiety (STAI) [c]	44.05 (1.63)	45.14 (1.93)
Trait Anxiety (STAI) [c]	42.25 (4.89)	40.40 (3.86)
PAL [d]		
Total errors	21.33 (14.17)	19.67(18.71)
SWM – 6 [e]		
Between errors	5.76 (8.41)	5.57 (8.44)
Strategy score	12.90 (3.43)	12.19 (3.64)
Social Network Questionnaire	21.35 (6.23)	21.31 (8.04)
Toronto Alexithymia Scale		
Difficulty Describing Feelings	12.68 (3.07)	15.05 (10.81)
Difficulty Identifying Feeling	25.79 (5.37)	22.84 (5.19)
Externally-Oriented Thinking	11.37 (2.93)	12.05 (3.55)

Notes. There were no significant differences between the OXT and PLC group (all Ps > 0.05). Moral thoughts were measured by using Forsyth's [a] Ethics Position Questionnaire (EPQ). Anxiety and mood were assessed before the experiment with the [b] Positive and Negative Affective Schedule (PANAS) and the [c] State Trait Anxiety Inventory for State and Trait (STAI). [d] Paired Associate Learning (PAL) reports the number of errors made. [e] Social Working Memory (SWM) Strategy tests whether participants have cognitive dysfunctions, which was not the case in either group. Abbreviations: OXT, oxytocin; PLC, placebo.

Table T2. Activation table of the GLM under PLC

Region	Right/ left	Cluster size (voxels)	*t-score*	*MNI-coordinates*		
				x	*y*	*z*
PLC: anger+fear+happy > neutral						
Middle Occipital Lobe*	L	1866	12.72	-30	-82	19
Lingual Gyrus*	R		12.47	21	-70	-5
Middle Occipital Gyrus*	L		11.54	-45	-64	-8
Parietal Inferior Lobe*	L	3826	10.72	-54	-25	40
Postcentral*	L		10.23	-48	-34	49
Parietal Inferior Lobe*	R		9.21	36	-43	49
Middle Cingulate Gyrus*	L	75	7.94	-12	-25	40
Pallidum*	L	570	7.17	-18	2	4
Precentral Gyrus*	L		6.74	-54	5	25
Insula*	L		6.47	-42	-4	10
Thalamus*	L	137	6.40	-18	-28	1
	L		6.04	-9	-25	1
	R		5.44	6	-25	1
Middle Frontal Gyrus	R	15	4.32	36	41	25
	R		4.16	42	32	28

Notes. Abbreviations: PLC, placebo; *Significant at $P < 0.05$ family wise error corrected with a cluster extent threshold of $k = 10$ voxels.

Table T3. State measurement of anxiety, mood and attention

	OXT session (n = 22) Mean (± SD)	PLC session (n = 22) Mean (± SD)	t	P
State Anxiety (STAI)	31.95 (4.74)	31.45 (5.11)	0.43	0.67
State Anxiety (STAI) – post [a]	32.95 (5.32)	32.14 (4.42)	0.95	0.35
Positive affect (PANAS) – pre [b] positive	28.68 (6.61)	28.41 (5.86)	0.28	0.78
Positive affect (PANAS) – post [b]	27.77 (6.59)	28.14 (7.03)	-0.40	0.69
Negative affect (PANAS) – pre [b]	11.23 (1.57)	12.00 (3.45)	-1.07	0.30
Negative affect (PANAS) – post [b]	11.55 (3.19)	11.09 (2.76)	0.66	0.52
D2 [c]	221.09	218.77	0.29	0.77

Notes. State anxiety before and after the experiment was assessed using the [a]STAI = State Trait Anxiety Inventory. Mood before and after the experiment was assessed using the [b] PANAS = Positive and Negative Affect Schedule. Attention performance after the experiment was assessed using the [c] D2 = Aufmerksamkeits- und Belastungstest. Abbreviations: OXT, oxytocin; PLC, placebo.

Chapter 4: Manuscript 3

Foreword

The willingness to induce happy emotions was increased in the OXT group, while the willingness to induce anger or fear was decreased. The willingness to induce these different emotions was accompanied by neural activation patterns in various brain regions, mainly in the mirror neuron network. Happy sentences that were more easily stated in the OXT group, generally, displayed a decreased neural activation, and the opposite relationship was observed between anger and fear sentences and neural activity. Thus, the second study emphasized OXT's role as a prosocial molecule. The third study, which also included fMRI measurements, focused on a more internal process. Social isolation and the feeling of "not belonging" cause emotional distress and may result in asocial behavior. Emotional distress can arise every day, e.g. due to conflicting/ ambivalent emotions or opposing/ ambivalent thoughts. Assuming that OXT can decrease the feeling of ambivalence and emotional distress, people may feel more content and act more kindly (Otake, Shimai, Tanaka-Matsumi, Otsui, & Fredrickson, 2006). Ambivalence as such is a very general term, which has been classified in three different aspects: 1) volitional ambivalence, 2) emotional ambivalence and 3) intellectual ambivalence (Bleuler, 1950). This study entails two separate fMRI experiments. The first experiment investigated volitional ambivalence using a previously developed paradigm of moral dilemmas (Harrison et al., 2012) and the second fMRI experiment investigated emotional ambivalence using an adapted infidelity paradigm that was originally designed by Takahashi and colleagues (2006).

A brain region that is extensively connected to emotional conflict is the dACC. We hypothesized that OXT, as a prosocial molecule, would

decrease the feeling of ambivalence, accompanied by decreased dACC activation in both fMRI studies, reflecting decreased perceived emotional conflict.

Manuscript 3: The influence of oxytocin on volitional and emotional ambivalence

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Abstract

Moral decisions and social relationships are often characterized by strong feelings of ambivalence which can be a catalyst for emotional distress and several health-related problems. The anterior cingulate cortex (ACC) has been identified as a key brain region monitoring conflicting information, but the neurobiological substrates of ambivalence processing are still widely unknown. We have conducted two randomized, double-blind, placebo-controlled, functional magnetic resonance imaging experiments involving 70 healthy male volunteers to investigate the effects of the neuropeptide oxytocin (OXT) on neural and behavioral correlates of ambivalence. Exemplarily, we chose moral decision-making and the imagery of partner infidelity to probe volitional and emotional ambivalence. In both experiments, intranasal OXT diminished neural responses in the ACC to ambivalence. Under OXT, moral dilemma vignettes also elicited a reduced activation in the orbitofrontal cortex, and the imagery of partner infidelity was rated as less arousing. Interestingly, the OXT-induced differential activation in the ACC predicted the magnitude of arousal reduction. Taken together, our findings reveal an unprecedented role of OXT in causing a domain-general decrease of neural responses to ambivalence. By alleviating emotional distress OXT may qualify as a treatment option for psychiatric disorders with heightened ambivalence sensitivity such as schizophrenia or obsessive compulsive disorder.

Key words: ambivalence, anterior cingulate cortex, fMRI, jealousy, moral, oxytocin

Introduction

Ambivalence, that is the experience of conflicting emotions or opposing thoughts, is a hallmark of countless situations in everyday life. At the root of his concept of tripartite, Bleuler (1908) differentiated between volitional, intellectual, and emotional ambivalence. Moral decision-making can be considered as an instance of volitional ambivalence, since divergent moral values have to be evaluated. Intellectual ambivalence is related to philosophical skepticism, while emotional ambivalence describes a situation in which an individual simultaneously loves and hates another person.

Ambivalence can be the cause of emotional distress (van Harreveld *et al.*, 2009) and it may have detrimental influence on health-relevant processes. Ambivalent relationships are associated with coronary-artery calcification (Uchino *et al.*, 2014) and social support from an ambivalent friend is linked to greater cardiovascular reactivity during psychosocial stress (Gramer and Supp, 2014; Holt-Lunstad and Clark, 2014). The number of ambivalent network ties is correlated with depression (Uchino *et al.*, 2001) and task-measured ambivalence is elevated in patients with schizophrenia (Docherty *et al.*, 2014). On the neural level, the evaluation of ambivalent target stimuli elicits activation in the anterior cingulate cortex (ACC) (Nohlen *et al.*, 2014), which is consistent with previous conflict-monitoring accounts of ACC function (Botvinick *et al.*, 1999). As it stands, not much is known concerning the neurobiological underpinnings of ambivalence.

The neuropeptide hormone oxytocin (OXT) is a key factor mediating relationship quality in human pair-bonds (Scheele *et al.*, 2012; Scheele *et al.*, 2013) and OXT has been found to enhance the buffering effect of social support on stress responsiveness (Heinrichs *et al.*, 2003). OXT also increases positive communication and reduces cortisol levels during an instructed couple conflict (Ditzen *et al.*, 2009). Interestingly, the

ACC is a region of high OXT receptor (OXTR) density in the human brain (Boccia *et al.*, 2013) and adolescents with the minor CC-genotype of a OXTR polymorphism (rs237915) exhibited lower ACC activity in response to animated angry faces and were more resilient against the effect of stressful experiences (Loth *et al.*, 2014). Likewise, the intranasal administration of OXT reduces ACC activity during the pre-feedback period of a trust game (Baumgartner *et al.*, 2008). On the other hand, OXT can also facilitate the initial sensation of social stress and increase ACC activity (Eckstein *et al.*, 2014).

The present study was designed to directly investigate the modulatory effects of OXT on the neural processing of volitional and emotional ambivalence. In Experiment 1 (Exp. 1), we probed volitional ambivalence by measuring neural responses to moral dilemmas (Harrison *et al.*, 2012) in 48 healthy male volunteers after they had received intranasal OXT (24 IU) or placebo (PLC). These moral dilemmas primarily entailed difficult decisions about life and death trade-offs. In Experiment 2 (Exp. 2), we assessed emotional ambivalence in another sample of 22 healthy male participants with a task more proximate to OXT's bonding-related effects. We used description-based imagery of sexual and emotional infidelity of the participants' female partner (Takahashi *et al.*, 2006). Subsequently, the participants had to rate the arousal induced by the sentences depicting infidelity. Given the previous equivocal findings and the strong context-dependency of OXT effects (Preckel *et al.*, 2014), we expected that OXT would either alleviate or enhance the perceived ambivalence evident by an altered ACC response in both experiments or changed arousal ratings in Exp. 2.

Materials and Methods

A detailed synopsis of all experimental procedures is provided in the Supplementary Information.

Subjects

Forty-eight healthy, non-smoking male adults (mean age ± SD = 24.6 ± 4.56 years) participated in Exp. 1 and twenty-two men (26.73 ± 3.60 years) volunteered in Exp. 2. Prior to the test sessions, the participants completed a comprehensive neuropsychological test battery and questionnaires assessing ethical ideology (Forsyth, 1980) and love styles (e.g. Eros, a committed romantic relationship) (Lee, 1988). All subjects were within a normal range of cognitive performance and there were no a-priori differences between the OXT and PLC groups in Exp. 1 (**Supplementary Table S1 and S2**). All subjects in Exp. 2 were in a romantic heterosexual relationship for more than six months, were unmarried, and had no children. Both experiments were approved by the institutional review board of the Medical Faculty of the University of Bonn and carried out in compliance with the latest revision of the Declaration of Helsinki. Subjects were free of current and past physical or psychiatric illness, as assessed by medical history and a Mini-International Neuropsychiatric Interview.

Experimental design and fMRI tasks

For both experiments we applied a randomized, placebo-controlled, double-blind design. Subjects were randomly assigned to either intranasal administration of OXT (24 IU; Syntocinon-Spray, Novartis; three puffs per nostril, each with 4 IU OXT) or PLC (sodium chloride solution), approximately 45 ± 10 min before the start of the fMRI.

We decided to use a between-subject design study for Exp. 1 to avoid the repetition of the same moral decisions. The task consisted of twenty-four non-dilemma story vignettes and twenty-four moral dilemma story vignettes taken from Harrison et al. (2012). Prior to the fMRI experiment, participants were familiarized with the vignettes and the corresponding stories. In the non-dilemma condition, participants had to recall each scenario and indicate the correct outcome by button press. In the moral dilemma condition, participants had to provide their own moral judgment by button press. For instance, the participants had to decide whether they want to endorse a utilitarian (e.g. suffocate your crying child to prevent the detection by enemy soldiers) or deontological action (e.g. remove your hand from the child's mouth). The paradigm featured a block design which included 8 blocks of 6 moral dilemma or non-moral vignettes. Moral dilemma and non-moral blocks were presented in an alternating order.

Exp. 2 consisted of a within-subject design study. The participants were confronted with three types of short sentences describing neutral actions of the partner or sexual and emotional infidelity. We used the same definition of sexual and emotional infidelity as Takahashi et al. (2006), with the former pertaining to a condition explicitly or implicitly indicating a sexual relationship or physical contact and the latter indicating diversion of the partner's emotional commitment to someone else. All sentences were written in German and started with "My girlfriend". The sentences were presented in six blocks for each of the three conditions. In each 24 s block, three different sentences were shown for 8 s each. The sequence of blocks was randomized, and blocks were separated from each other by a low-level baseline period of 20 s duration, where a fixation cross was depicted in the center of the screen. The subjects were instructed to attentively read the sentences and to imagine the described situations. To assure attentive stimulus processing, subjects were asked to press a keypad button whenever

a stimulus was presented (percent correct responses OXT 99.38 ± 2.03, PLC 98.65 ± 2.15, P = 0.25). After scanning, subjects were seated in front of a computer and were asked to rate arousal induced by the imagery of each sentence on a visual analog scale (ranging from 0, not arousing, to 100, most arousing). The sequence of the sentences was randomized.

Acquisition and analysis of fMRI data

In Exp. 1, the MRI data were acquired with a Siemens Avanto MRI system (Siemens, Erlangen, Germany) operating at 1.5T. T2*-weighted echoplanar (EPI) images with blood-oxygen-level-dependent contrast were obtained (retention time (TR) = 3,000 ms, echo time (TE) = 35 ms, matrix size: 64 x 64, pixel size: 3 mm x 3 mm x 3 mm, slice thickness = 3.0 mm, distance factor = 10%, field of view (FoV) = 192, flip angle = 90°, 36 axial slices). High-resolution anatomical images were acquired on the same scanner with a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1,570 ms, TE = 3.42 ms, matrix size: 256 x 256, pixel size: 1 mm x 1mm x 1 mm, slice thickness = 1.0 mm, FoV = 256, flip angle = 15, 160 sagital slices).

In Exp. 2, a Siemens Trio MRI system (Siemens, Erlangen, Germany) operating at 3T was used to obtain T2*-weighted echoplanar (EPI) images with blood-oxygen-level-dependent contrast (TR = 3000 ms, TE = 35 ms, matrix size: 64 x 64, pixel size: 3 mm x 3 mm x 3 mm, slice thickness= 3.0 mm, distance factor = 10%, FoV = 192, flip angle = 90°, 36 axial slices). In addition, high-resolution anatomical images were acquired on the same scanner using a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1570 ms, TE = 3.42 ms, matrix size: 256 x 256, pixel size: 1 mm x 1 mm x 1 mm, slice thickness = 1.0 mm, FoV = 256, flip angle = 15°, 160 sagital slices).

The MRI data were preprocessed and analyzed using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK;

http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7 (The MathWorks Inc., Natick, MA). The first five volumes of each functional time series were discarded to allow for T1 equilibration. Images were corrected for head movement between scans by an affine registration. For realignment, images were initially realigned to the first image of the time-series and subsequently realigned to the mean of all images. For spatial normalization, the mean EPI image of each subject was normalized to the current Montreal Neurological Institute (MNI) template (Evans *et al.*, 1992; Holmes *et al.*, 1998) using the unified segmentation function in SPM8. This algorithm combines image registration, tissue classification, and bias correction within the same generative model. In Exp. 1, all images were thereby transformed into standard stereotaxic space and resampled at 3 mm x 3 mm x 3 mm voxel size. The normalized images were spatially smoothed using an 8-mm full width at half maximum Gaussian kernel. In Exp. 2, all images were resampled at 2 mm x 2 mm x 2 mm voxel size and spatially smoothed using a 6-mm full width at half maximum Gaussian kernel. Raw time series were detrended by the application of a high-pass filter (cutoff period, 128 s). A two-level random effects approach based on the general linear model as implemented in SPM8 was used for statistical analyses for both experiments.

On the first level in Exp. 1, the two conditions (‘moral‘ and ‘non-moral‘) of the block design were defined and modeled by a boxcar function convolved with a hemodynamic response function. The movement parameters were included as confounds in the design matrix. Each experimental condition was compared relative to the low-level baseline and differences between each condition were computed separately for the OXT and PLC group. To examine the effects of OXT in Exp. 1, parameter estimates of all contrasts were used to perform two-sample *t*-tests on the second level with a significance threshold of $P < 0.05$ corrected for multiple comparisons (family-wise error (FWE)).

On the first level in Exp. 2, six conditions ('$Sexual_{OXT}$', '$Neutral_{OXT}$', '$Emotional_{OXT}$', '$Sexual_{PLC}$', '$Neutral_{PLC}$', '$Emotional_{PLC}$') were modeled by a boxcar function convolved with a hemodynamic response function. The movement parameters were included as confounds in the design matrix. Each condition was compared relative to the low level baseline and non-specific effects of OXT were analyzed by comparing all items with the low level baseline. Differences between each condition were computed separately for the OXT and PLC sessions and we built the contrasts [$Sexual_{OXT}$ > $Sexual_{PLC}$], [$Neutral_{OXT}$ > $Neutral_{PLC}$], and [$Emotional_{OXT}$ > $Emotional_{PLC}$] to specifically examine the modulatory effects of OXT. Parameter estimates for each contrast were subjected to one-sample *t*-tests on the second level for the whole-brain with a significance threshold of $P < 0.05$ corrected for multiple comparisons (family-wise error (FWE)). Based on the previous finding that patients with obsessive-compulsive disorder exhibit an increased neural response to moral task vignettes in the orbitofrontal cortex (OFC) (Harrison *et al.*, 2012), we used 6-mm spheres as regions of interest (ROI) centered at the coordinates of the reported maximum value for the orbitofrontal cortex (MNI x, y, z: ±4, 38, -20). Given the strong OXT effect on ambivalence-related activation of the ACC in Exp. 1, we used an anatomically defined ROI of the ACC in Exp. 2. The ACC ROI was defined using the Wake Forest University (WFU) Pickatlas (Version 3.0), which provides a method for generating ROI masks based on the Talairach Daemon database (Maldjian *et al.*, 2003). ROI-based two-sample (Exp. 1) or one-sample (Exp. 2) *t*-tests were computed with a threshold of $P < 0.05$ and FWE-corrected for multiple comparisons based on the size of the ROI. Anatomical classification was done using the WFU pick atlas, automatic anatomic labeling (aal) or Talairach Daemon (TD) labels (Lancaster *et al.*, 2000; Maldjian *et al.*, 2003). In order to further examine the specific OXT effect, the parameter estimates were extracted from the

activated clusters in the ACC, orbitofrontal cortex, the posterior cingulate cortex and the precuneus using the MarsBaR toolbox (Brett *et al.*, 2002) (see also http://marsbar.sourceforge.net/) with a sphere size of 6-mm.

Results:

Experiment 1

Behavioral results

OXT had no significant effect on the rejection rate of moral dilemmas (mean % rejected OXT = 54.83 ± 12.31, PLC = 53.44 ± 18.83, $t_{(37.39)} = 0.30$, $P = 0.77$, $d = 0.09$). Furthermore, a repeated-measures analysis of variance (ANOVA) with treatment as between-subject factor (OXT vs. PLC), morality (moral dilemma vs. non-moral vignettes) as within-subject variable, and reaction time (RT) as a dependent variable yielded a main effect of morality ($F_{(1,46)} = 84.62$, $P < 0.001$, $\eta^2 = 0.65$), but no further significant main or interaction effects. The RT for moral dilemma decisions (3.00 s ± 0.28 s) was significantly longer than the RT for responses in the non-moral condition (2.62 s ± 0.39 s).

FMRI results

Under PLC, the evaluation of moral dilemmas, compared to the non-dilemma condition, elicited broad activations in a moral decision-making network including the medial-frontal lobe, the cingulate cortex, the temporal lobe, and the angular gyrus (cf. **Supplementary Table S3)** (Greene *et al.*, 2001; Heekeren *et al.*, 2005). As expected, there were no significant activations for the contrast "non-dilemma > dilemma". The OXT treatment reduced the neural responses to ambivalent moral dilemmas ("moral > non-moral") in the ACC (MNI x, y, z: 12, 41, 1, $t_{(46)} = 5.35$, $P_{FWE} < 0.01$; cf. **Fig.**

1A), the posterior cingulate cortex (MNI x, y, z: 0, -46, 31, $t_{(46)} = 4.31$, $P_{FWE} = 0.02$), the precuneus (MNI x, y, z: 0, -58, 37, $t_{(46)} = 3.68$, $P_{FWE} = 0.02$), and the medial cingulate cortex (MNI x, y, z: 9, -43, 34, $t_{(46)} = 3.61$, $P_{FWE} = 0.02$). Interestingly, a ROI-based analysis revealed that the OXT group also exhibited decreased activation in the OFC for the contrast moral > non-moral (MNI x,y,z: 0, 35, -20, $t_{(46)} = 2.97$, $P_{FWE} = 0.03$; cf. **Fig. 1B**).

Experiment 2

Behavioral results

A repeated-measures ANOVA with treatment (OXT vs. PLC) and type (emotional, neutral, sexual) as within-subject variables and arousal ratings as dependent variable yielded a main effect of type ($F_{(1.24,26.07)} = 240.17$, $P < 0.01$, $\eta^2 = 0.92$), a main effect of treatment ($F_{(1,21)} = 5.10$, $P = 0.04$, $\eta^2 = 0.20$), and a trend for an interaction of type and treatment ($F_{(1.47,30.95)} = 2.67$, $P = 0.099$, $\eta^2 = 0.11$; **Fig. 2A**). The imagery of both sexual and emotional infidelity elicited stronger arousal than neutral sentences ($t_{(21)} = 17.99$, $P < 0.01$, $d = 5.31$ and $t_{(21)} = 14.46$, $P < 0.01$, $d = 4.37$) and consistent with previous findings in men (Buss *et al.*, 1992), the description of sexual infidelity was perceived as more arousing than emotional infidelity ($t_{(21)} = 4.74$, $P < 0.01$, $d = 0.52$). Post-hoc *t*-tests revealed that OXT diminished arousal ratings for sexual ($t_{(21)} = 2.30$, $P = 0.03$, $d = 0.22$) and emotional infidelity ($t_{(21)} = 2.29$, $P = 0.03$, $d = 0.28$), but had no effect on the neutral category ($t_{(21)} = 0.31$, $P = 0.76$, $d = 0.04$). Participants with higher scores on a questionnaire measurement of romantic love, Eros, were more likely to rate both emotional (PLC: $r = 0.46$, $P = 0.03$; **Fig. 2A**; OXT: $r = 0.34$, $P = 0.13$)

and sexual infidelity (PLC: $r = 0.43$, $P = 0.048$; OXT: $r = 0.40$, $P = 0.07$) as more arousing, but there was no correlation for neutral items (PLC: $r = -0.17$, $P = 0.45$; OXT: $r = -0.004$, $P = 0.99$). Furthermore, OXT did not influence subjective anxiety, mood ratings, or attention (cf. ***Supplementary Table S4***).

FMRI results

At the whole-brain level, under PLC treatment the imagery of sexual infidelity, compared to the neutral condition, produced widespread activations in a fronto-temporal network including the middle and medial frontal gyrus, anterior cingulate cortex, and middle and superior temporal gyrus (cf. ***Supplementary Table S5***). As expected, there were no significant activations for the contrast "neutral > sexual", but surprisingly the neutral condition elicited a stronger activation than emotional infidelity. Neutral imagery of the partner, compared to emotional infidelity, produced activation in the inferior parietal lobule, cingulate cortex, middle and superior frontal gyrus, occipital gyrus, pallidum, and insula (cf. ***Supplementary Table S5***).

Importantly, a diminished neural response in the cingulate cortex to sexual infidelity was evident after OXT treatment (MNI x, y, z: -2, 30, -8, $t_{(21)} = 4.38$, $P_{FWE} = 0.04$; **Fig. 2B**). This OXT effect in the ACC positively correlated with the behavioral OXT effect on arousal ratings of sexual infidelity (MNI x, y, z: 0, 10, 30, $t_{(21)} = 5.06$, $P_{FWE}= 0.01$; MNI x, y, z: 0, 20, 30, $t_{(21)} = 4.92$, $P_{FWE} = 0.02$; MNI x, y, z: -2, 38, 12, $t_{(21)} = 4.68$, $P_{FWE} = 0.03$; **Fig. 2C**).

Discussion:

In the present study, we aimed at elucidating the modulatory influence of OXT on the neural processing of volitional and emotional ambivalence. The

OXT treatment reduced ACC activation during both moral decision-making (Exp. 1) and the imagery of sexual infidelity (Exp. 2). In addition, OXT diminished activation in the ventromedial prefrontal cortex in response to moral evaluations. On the behavioral level, these neural effects were paralleled by decreased arousal ratings of imagined infidelity. Importantly, a stronger reduction of ACC activity was associated with an enhanced decrement of arousal, thus indicating that the ACC recruitment reflects the psychological response to ambivalence.

Consistent with our previous findings, the OXT treatment had no effect on the endorsement of utilitarian or deontological options (Scheele *et al.*, 2014b). However, during the evaluation of moral dilemmas compared to non-dilemma scenarios, OXT suppressed activity in the cingulate cortex and precuneus, which have been identified as regions distinguishing difficult from easy personal moral judgments (Greene *et al.*, 2004). We have recently shown that OXT can induce a self-referential processing bias in moral decision-making (Scheele *et al.*, 2014b) and greater self-congruence may subsequently produce a diminished sense of volitional ambivalence. Current neurobiological concepts of human morality (Koenigs *et al.*, 2007; Shenhav and Greene, 2010) further emphasize the function of the ventromedial prefrontal cortex and OFC for producing moral emotions such as guilt or shame. In fact, patients with obsessive-compulsive disorder (OCD) display a moral hyper-sensitivity which has been linked to increased engagement of these brain regions (Harrison *et al.*, 2012). It is currently still elusive to what extent OXT is involved in the pathogenesis of OCD. An early case study reported anti-obsessive effects of an intranasal OXT treatment (Ansseau *et al.*, 1987), but two small clinical trials (den Boer and Westenberg, 1992; Epperson *et al.*, 1996) failed to detect significant improvements. Cerebrospinal fluid measurements of OXT levels in OCD patients are inconsistent (Leckman *et al.*, 1994; Altemus *et al.*, 1999). Nevertheless, anti-

obsessive effects of serotonin reuptake inhibitors may be partly exerted through oxytocinergic mechanisms (Humble *et al.*, 2013) and our results suggest that an OXT treatment could be particularly beneficial for a subtype of OCD patients with moral-related compulsions.

Figure 1: (A) Activity in the anterior cingulate cortex and (B) orbitofrontal cortex during the evaluation of moral dilemmas

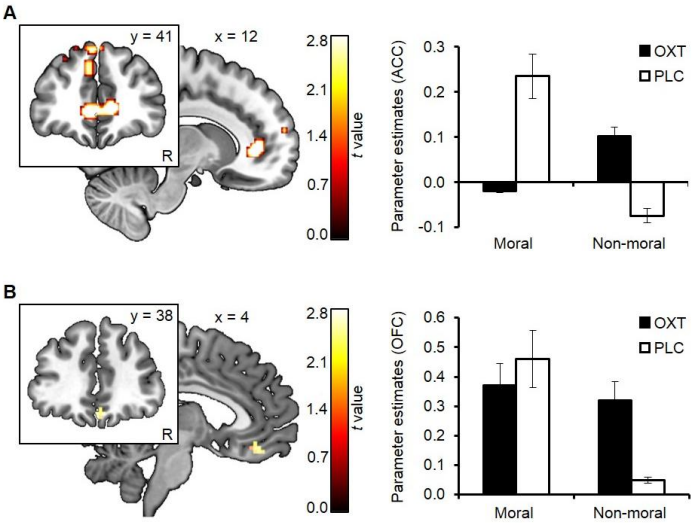


Figure Legend: Figure 1: Oxytocin OXT compared to placebo (PLC) significantly reduced brain activity in the anterior cingulate cortex (A) and orbitofrontal cortex (B) during the evaluation of moral dilemmas. Error bars indicate the standard error of the mean (SEM). Abbreviations: ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; OXT, oxytocin; PLC, placebo (Experiment 1).

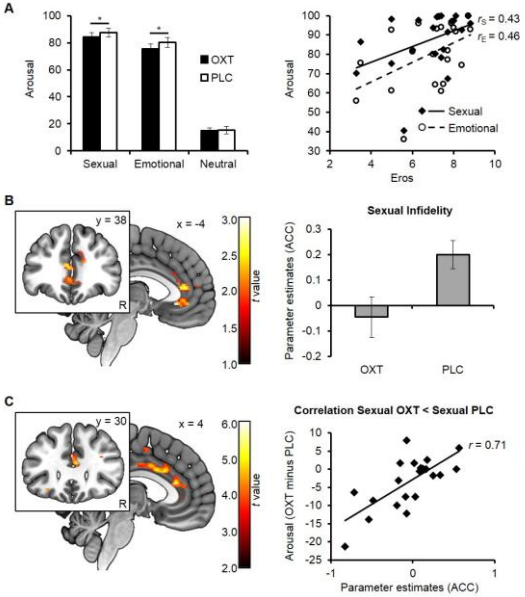
Jealousy is often the consequence of assumed partner infidelity and constitutes a risk factor for domestic violence (Kingham and Gordon, 2004). In addition, delusional jealousy, also called Othello's syndrome, frequently occurs from neurological disorders (Graff-Radford *et al.*, 2012). In contrast to Takahashi et al. (2006), we did observe significant activations during the imagery of sexual infidelity in the cingulate cortex and frontal regions, but not in the amygdala or hippocampus. This discrepancy and the diminished neural responses in the emotional condition could result from intercultural differences between a European and Asian sample, but it is more likely to reflect distinct features in bonding-related sample characteristics such as the clearly longer relationship duration in our study (36 months vs. 15 months in the study of Takahashi et al. (2006); cf. ***Supplementary Table S6***). The ACC has been previously found to signal distress due to exclusion from an opposite-sex player in a cyberball game, suggesting that the social attachment system recruits the ACC to promote social connectedness (Eisenberger *et al.*, 2003). Aside from reducing ACC activity during the pre-feedback period of a trust game (Baumgartner *et al.*, 2008), OXT also abolishes the negative evaluation of aversely conditioned faces by attenuating ACC and amygdala response (Petrovic *et al.*, 2008). The absence of an amygdala downregulation in the present study corroborates the results of Petrovic and colleagues (2008) who reported that the amygdala modulation varies as a function of task features.

Figure 2: Behavioral and neural findings of the sexual- and emotional infidelity task

Figure legend: Figure 2: Oxytocin (OXT) significantly decreased arousal ratings of sentences describing sexual as well as emotional partner infidelity and these ratings positively correlated with Eros (a romantic love style) (A). OXT diminished the neural response to imagery of sexual infidelity in the

anterior cingulate cortex (ACC) (B) and this OXT effect on ACC activity predicted the behavioral OXT effect on arousal ratings of sexual infidelity (C). Abbreviations: ACC, anterior cingulate cortex; OXT, oxytocin; PLC, placebo; *P < 0.05 (Experiment 2).

The intriguing findings of reduced arousal ratings of and ACC responses to the imagery of sexual infidelity, along with our previous finding of increased activity in reward-associated brain regions after OXT treatment (Scheele *et al.*, 2013) indicate that OXT may decrease emotional ambivalence by promoting and strengthening the pair-bond representation. Our results therefore complement the interactionist component process model (Bartz *et al.*, 2011; Scheele *et al.*, 2014a) which posits that social OXT effects are contingent upon contextual and interindividual factors. In ambivalent situations, OXT may bias an individual towards favoring a prosocial interpretation of conflicting emotions or cognitions.



In accordance with Bleuler's (1908) description of ambivalence as a core symptom of schizophrenia, several recent studies document elevated levels of relationship-associated or task-measured ambivalence in patients with schizophrenia (Tremeau *et al.*, 2009; Antonius *et al.*, 2013; Docherty *et al.*, 2014). Since an exploratory meta-analysis of four randomized controlled trials investigating OXT's influence on psychosis found only weak treatment effects (Gumley *et al.*, 2014), the promise of OXT seems to instead lie more in augmentation of therapies to alleviate ambivalence related symptoms. Given that OXT is known to increase the willingness to socially share one's emotion (Lane *et al.*, 2013), we predict that OXT would enhance the therapeutic effect of ambivalence-tailored treatment protocols.

A limitation to the present study is that we have exclusively tested male participants. Future studies are warranted to unravel possible sexual-dimorphic effects of OXT (Preckel *et al.*, 2014) on neural and behavioral substrates of ambivalence. Furthermore, the block design in Exp. 1 precluded a differential analysis of the moral dilemmas pertaining to the extent of potential self-benefit which can moderate behavioral OXT effects (Scheele *et al.*, 2014b).

Taken together, we here provide first evidence that the neuropeptide hormone OXT can reduce volitional and emotional ambivalence in the domains of moral decision-making and imagery of partner infidelity. Our findings can help to inform the design of future clinical trials probing the therapeutic potential of an OXT treatment for psychiatric disorders with altered ambivalence processing such as schizophrenia or OCD.

References

Altemus, M., Jacobson, K. R., Debellis, M., Kling, M., Pigott, T., Murphy, D. L., et al. (1999). Normal CSF oxytocin and NPY levels in OCD. *Biological Psychiatry, 45*, 931-933.

Ansseau, M., Legros, J. J., Mormont, C., Cerfontaine, J. L., Papart, P., Geenen, V., et al. (1987). Intranasal oxytocin in obsessive-compulsive disorder. *Psychoneuroendocrinology, 12*, 231-236.

Antonius, D., Bruce, K. L., Moisa, B., Sinclair, S. J., Malaspina, D. & Tremeau, F. (2013). Familiarity preference in schizophrenia is associated with ambivalent attitudes towards others. *Schizophrenia Research, 150*, 229-234.

Bartz, J. A., Zaki, J., Bolger, N. & Ochsner, K. N. (2011). Social effects of oxytocin in humans: context and person matter. *Trends in Cognitive Sciences, 15*, 301-309.

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U. & Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron, 58*, 639-650.

Bleuler, E. (1908). Die Prognose der Dementia praecox (Schizophreniegruppe). *Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin, 65*,436-464.

Boccia, M. L., Petrusz, P., Suzuki, K., Marson, L. & Pedersen, C. A. (2013). Immunohistochemical localization of oxytocin receptors in human brain. *Neuroscience, 253*, 155-164.

Botvinick, M., Nystrom, L. E., Fissell, K., Carter, C. S. & Cohen, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature, 402*, 179-181.

Brett, M., Anton, J.-L., Valabregue, R. & Poline, J.-B. (2002) *Region of interest analysis using an SPM toolbox.* Presented al: 8th

International Conference on Functional Mapping of the Human Brain, Sendai, Japan.

Buss, D. M., Larsen, R. J., Westen, D. & Semmelroth, J. (1992). Sex-Differences in Jealousy - Evolution, Physiology, and Psychology. *Psychological Science*, *3*, 251-255.

den Boer, J. A. & Westenberg, H. G. (1992). Oxytocin in obsessive compulsive disorder. *Peptides*, *13*, 1083-1085.

Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U. & Heinrichs, M. (2009). Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. *Biological Psychiatry*, *65*, 728-731.

Docherty, A. R., Sponheim, S. R. & Kerns, J. G. (2014). Further examination of ambivalence in relation to the schizophrenia spectrum. *Schizophrenia Research*, doi: 10.1016/j.schres.2014.06.015.

Eckstein, M., Scheele, D., Weber, K., Stoffel-Wagner, B., Maier, W. & Hurlemann, R. (2014). Oxytocin facilitates the sensation of social stress. *Human Brain Mapping*, *35*, 4741-4750.

Eisenberger, N. I., Lieberman, M. D. & Williams, K. D. (2003). Does rejection hurt? An FMRI study of social exclusion. *Science*, *302*, 290-292.

Epperson, C. N., McDougle, C. J. & Price, L. H. (1996). Intranasal oxytocin in obsessive-compulsive disorder. *Biological Psychiatry*, *40*, 547-549.

Evans, A. C., Marrett, S., Neelin, P., Collins, L., Worsley, K., Dai, W., et al. (1992). Anatomical mapping of functional activation in stereotactic coordinate space. *Neuroimage*, *1*, 43-53.

Forsyth, D. R. (1980). A Taxonomy of Ethical Ideologies. *Journal of Personality and Social Psychology*, *39*, 175-184.

Graff-Radford, J., Whitwell, J. L., Geda, Y. E. & Josephs, K. A. (2012). Clinical and imaging features of Othello's syndrome. *European Journal of Neurology*, *19*, 38-46.

Gramer, M. & Supp, N. (2014). Social support and prolonged cardiovascular reactivity: The moderating influence of relationship quality and type of support. *Biologcial Psychology*, *101*, 1-8.

Greene, J. D., Nystrom, L. E., Engell, A. D., Darley, J. M. & Cohen, J. D. (2004). The neural bases of cognitive conflict and control in moral judgment. *Neuron*, *44*, 389-400.

Greene, J. D., Sommerville, R. B., Nystrom, L. E., Darley, J. M. & Cohen, J. D. (2001). An fMRI investigation of emotional engagement in moral judgment. *Science*, *293*, 2105-2108.

Gumley, A., Braehler, C. & Macbeth, A. (2014). A meta-analysis and theoretical critique of oxytocin and psychosis: prospects for attachment and compassion in promoting recovery. *British Journal of Clinical Psychology*, *53*, 42-61.

Harrison, B. J., Pujol, J., Soriano-Mas, C., Hernandez-Ribas, R., Lopez-Sola, M., Ortiz, H., et al. (2012). Neural correlates of moral sensitivity in obsessive-compulsive disorder. *Archives of General Psychiatry*, *69*, 741-749.

Heekeren, H. R., Wartenburger, I., Schmidt, H., Prehn, K., Schwintowski, H. P. & Villringer, A. (2005). Influence of bodily harm on neural correlates of semantic and moral decision-making. *Neuroimage*, *24*, 887-897.

Heinrichs, M., Baumgartner, T., Kirschbaum, C. & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry*, *54*, 1389-1398.

Holmes, C. J., Hoge, R., Collins, L., Woods, R., Toga, A. W. & Evans, A. C. (1998). Enhancement of MR images using registration for signal averaging. *Journal of Computer Assisted Tomography*, *22*, 324-333.

Holt-Lunstad, J. & Clark, B. D. (2014). Social stressors and cardiovascular response: Influence of ambivalent relationships and behavioral ambivalence. *International Journal of Psychophysiology*, *93*, 381-389.

Humble, M. B., Uvnas-Moberg, K., Engstrom, I. & Bejerot, S. (2013). Plasma oxytocin changes and anti-obsessive response during serotonin reuptake inhibitor treatment: a placebo controlled study. *BMC Psychiatry*, *13*, 344.

Kingham, M. & Gordon, H. (2004). Aspects of morbid jealousy. *Advances in Psychiatric Treatment*, *10*, 207-215.

Koenigs, M., Young, L., Adolphs, R., Tranel, D., Cushman, F., Hauser, M., et al. (2007). Damage to the prefrontal cortex increases utilitarian moral judgements. *Nature*, *446*, 908-911.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., et al. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping*, *10*, 120-131.

Lane, A., Luminet, O., Rime, B., Gross, J. J., de Timary, P. & Mikolajczak, M. (2013). Oxytocin increases willingness to socially share one's emotions. *International Journal of Psychology*, *48*, 676-681.

Leckman, J. F., Goodman, W. K., North, W. G., Chappell, P. B., Price, L. H., Pauls, D. L., et al. (1994). Elevated cerebrospinal fluid levels of oxytocin in obsessive-compulsive disorder. Comparison with Tourette's syndrome and healthy controls. *Archives of General Psychiatry*, *51*, 782-792.

Lee, J. A. (1988). Love styles. In: M. H. Barnes & R. J. Sternberg (eds). *The Psychology of love*, New Haven, Conn, Yale University Press. p. 38–67.

Loth, E., Poline, J. B., Thyreau, B., Jia, T., Tao, C., Lourdusamy, A., et al. (2014). Oxytocin Receptor Genotype Modulates Ventral Striatal Activity to Social Cues and Response to Stressful Life Events. *Biological Psychiatry, 76*, 367-376.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A. & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*, *19*, 1233-1239.

Nohlen, H. U., van Harreveld, F., Rotteveel, M., Lelieveld, G. J. & Crone, E. A. (2014). Evaluating ambivalence: social-cognitive and affective brain regions associated with ambivalent decision-making. *Social Cognitive and Affective Neuroscience*, *9*, 924-931.

Petrovic, P., Kalisch, R., Singer, T. & Dolan, R. J. (2008). Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *Journal of Neuroscience*, *28*, 6607-6615.

Preckel, K., Scheele, D., Kendrick, K. M., Maier, W. & Hurlemann, R. (2014). Oxytocin facilitates social approach behavior in women. *Frontiers in Behavioral Neuroscience*, *8*, 191.

Scheele, D., Kendrick, K. M., Khouri, C., Kretzer, E., Schlapfer, T. E., Stoffel-Wagner, B., et al. (2014a). An Oxytocin-Induced Facilitation of Neural and Emotional Responses to Social Touch Correlates Inversely with Autism Traits. *Neuropsychopharmacology, 39*, 2078-2085.

Scheele, D., Striepens, N., Güntürkün, O., Deutschlander, S., Maier, W., Kendrick, K. M., et al. (2012). Oxytocin Modulates Social Distance between Males and Females. *Journal of Neuroscience*, *32*, 16074-16079.

Scheele, D., Striepens, N., Kendrick, K. M., Schwering, C., Noelle, J., Wille, A., et al. (2014b). Opposing effects of oxytocin on moral judgment in males and females. *Human Brain Mapping*, doi: 10.1002/hbm.22605.

Scheele, D., Wille, A., Kendrick, K. M., Stoffel-Wagner, B., Becker, B., Güntürkün, O., et al. (2013). Oxytocin enhances brain reward system responses in men viewing the face of their female partner. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 20308-20313.

Shenhav, A. & Greene, J. D. (2010). Moral judgments recruit domain-general valuation mechanisms to integrate representations of probability and magnitude. *Neuron*, *67*, 667-677.

Takahashi, H., Matsuura, M., Yahata, N., Koeda, M., Suhara, T. & Okubo, Y. (2006). Men and women show distinct brain activations during imagery of sexual and emotional infidelity. *Neuroimage*, *32*, 1299-1307.

Tremeau, F., Antonius, D., Cacioppo, J. T., Ziwich, R., Jalbrzikowski, M., Saccente, E., et al. (2009). In support of Bleuler: objective evidence for increased affective ambivalence in schizophrenia based upon evocative testing. *Schizophrenia Research*, *107*, 223-231.

Uchino, B. N., Holt-Lunstad, J., Uno, D. & Flinders, J. B. (2001). Heterogeneity in the social networks of young and older adults: prediction of mental health and cardiovascular reactivity during acute stress. *Journal of Behavioral Medicine*, *24*, 361-382.

Uchino, B. N., Smith, T. W. & Berg, C. A. (2014). Spousal relationship quality and cardiovascular risk: dyadic perceptions of relationship ambivalence are associated with coronary-artery calcification. *Psychological Science*, *25*, 1037-1042.

van Harreveld, F., Rutjens, B. T., Rotteveel, M., Nordgren, L. F. & van der Pligt, J. (2009). Ambivalence and decisional conflict as a cause of psychological discomfort: Feeling tense before jumping off the fence. *Journal of Experimental Social Psychology*, *45*, 167-173.

Supplementary Information

The influence of oxytocin on volitional and emotional ambivalence

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Supplementary Experimental Procedures:

1. Study subjects

Forty-eight healthy, non-smoking male adults participated in Experiment 1 (Exp. 1; oxytocin (OXT) group: n = 25; mean age ± S.D. = 25.04 ± 4.69 years; placebo (PLC) group: n = 23; age = 24.13 ± 4.48 years). Twenty-three were in a romantic heterosexual relationship and twenty-five were singles, all were unmarried and had no children. In Experiment 2 (Exp. 2), twenty-two, non-smoking adult males participated (age = 26.73 ± 3.60 years). All subjects were in a romantic heterosexual relationship for more than six months, were unmarried and had no children. Subjects in both studies were free of current and past physical or psychiatric illness, as assessed by medical history and the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al.*, 1998). All participants were recruited by local advertisement at the University Bonn, Germany. They provided written informed consent before study enrollment. All subjects were naïve to prescription-strength psychoactive medication and had not taken any over-the-counter psychoactive medication in the past 4 weeks. Participants were asked to maintain their regular bed and wake times and to abstain from caffeine and alcohol intake on the day of the experiment. All subjects were within a normal range of cognitive performance and there were no a-priori

differences between the OXT and PLC groups in Exp. 1 (**Supplementary Table S1 and S2**). In Exp. 2, the subjects reported to be passionately in love, and the time intervals since they last saw their partners and had intimate contact were comparable between the OXT and PLC sessions (**Supplementary Table S6**). We also controlled if the subjects had an argument with their partners in the week before both test sessions and if anything important in their relationship changed between the two test sessions. Participants also completed the Positive and Negative Affective Scale (PANAS) (Watson *et al.*, 1988) and the State-Trait Anxiety Inventory (STAI) (Spielberger *et al.*, 1970) immediately before the nasal spray administration and after the experimental task (in Exp. 2), to control for potentially confounding effects of OXT on mood and anxiety. Furthermore, in Exp 2. all subjects completed the d2 Test of Attention (Aufmerksamkeits- und Belastungstest d2) (Brickenkamp and Zillmer, 1998) after the experimental task. There were no differences between the PLC- and OXT-treated participants in either experiment (all *P* values > 0.05) (**Supplementary Table S1 and S4**). The estimation of the received treatment was comparable between the OXT and PLC session (Exp. 1: $\chi^2_{(1)} = 1.44$, $P = 0.26$; Exp. 2: $\chi^2_{(1)} = 0.29$, $P = 0.86$), showing that the subjects were unaware of whether they had received OXT or PLC.

Neuropsychological screening. To control for possible pretreatment differences in cognitive performance, all participants completed a comprehensive neuropsychological test battery. Cognitive performance was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB), a computerized neurocognitive assessment presented through a touch-screen computer (Sahakian and Owen, 1992). For details of the outcome measure see CANTABeclipse^{TM} Test Administration Guide (CANTABeclipse, 2011). Subjects' speed of response to a visual target (only in Exp. 2), the ability to retain spatial information, and visual memory were

measured with the simple and reaction time task (RTI), the spatial working memory task (SWM), and the paired associates learning task (PAL), respectively. All subjects were within a normal range of cognitive performance (**Supplementary Table S1 and S2**). There were also no differences in ethical ideology between the OXT- and PLC-treated group in Exp. 1 as assessed with the Ethic Position Questionnaire (EPQ) (Forsyth, 1980). Furthermore, all subjects in Exp. 2 completed the Marburg Attitude Scales towards Love Styles (MEIL), which is a German version of Love Styles developed by Lee (Lee, 1988). It contains three primary styles of loving: the first one is Eros, a romantic love style that is similar to passionate love and is characterized by a powerful attraction to the beloved individual. The second is Ludus, which describes lovers who view love as a game and often have several partners simultaneously. The third is Storge, a slow developing, friendship-based love. These primary love styles can be combined to form secondary styles of love: Pragma (Storge and Ludus combined; pragmatic view on the relationship), Mania (Eros and Ludus combined; obsessive and possessive lover), and Agape (Storge and Eros combined; altruistic love style). In the German version, each love style is assessed with 10 items.

2. FMRI paradigms

Experiment 1

The stories for all task vignettes were translated into German. Prior to the fMRI experiment, participants were familiarized with the vignettes and the corresponding stories. They were asked to memorize all stories before the fMRI experiment. During the fMRI experiment, the pictures corresponding to the memorized stories were presented in the scanner. Below each picture the words "Yes" and "No" were presented and the participants had to make a decision by pressing a button. The number of correct responses to the non-dilemma conditions was equally high in the OXT (88.50 ± 14.40 %) and PLC group (85.51 ± 17.72 %, $t_{(46)} = 0.65$, $P = 0.52$). The response buttons for "Yes" and "No" changed depending on the random lateralization of "Yes" and "No" on the screen. The total stimulus interval for each presented illustration was five seconds. After one second, the corresponding dilemma or non-dilemma question and the words "Yes" and "No" were shown below the picture for four seconds. There was a total of 8 blocks (4 non-moral and 4 moral dilemma illustration blocks). The order of blocks was alternated. Each block contained 6 stimulus pictures and lasted for 30 seconds.

Experiment 2

We adapted an fMRI paradigm used by Takahashi et al. (2006). The participants were confronted with three types of short sentences describing neutral actions of the partner or sexual and emotional infidelity. The sentences were validated in two pilot studies involving ten healthy men in study 1 (age = 25.70 ± 4.11 years) as well as 137 healthy women (age = 21.71 ± 2.66 years) and 69 healthy men (age = 23.20 ± 4.54) in study 2. None of these women and men participated in the fMRI study. In study 1, the participants had to classify the sentences twice as either neutral or as

describing emotional or sexual infidelity. After the first evaluation, sentences with a low inter-rater agreement were adjusted. The final set contained only sentences with high concordance (for each sentence ≥80% of the participants were in agreement about the category). In study 2, the participants had to rate their arousal induced by sentences depicting sexual or emotional infidelity. A repeated measures analysis of variance (ANOVA) with gender as a between-subject variable, type (sexual vs. emotional infidelity) as within-subject factor, and the arousal ratings as dependent variable yielded a main effect of type ($F_{(1, 204)} = 120.08$, $P < 0.01$, $\eta^2 = 0.37$), with the participants assigning higher arousal ratings to sexual infidelity than to the emotional condition. Importantly, the validity of our sentences is further corroborated by an interaction between type and gender ($F_{(1, 204)} = 5.48$, $P = 0.02$, $\eta^2 = 0.03$). Consistent with previous findings (Buss *et al.*, 1992), female participants (7.90 ± 1.14) rated emotional infidelity as slightly more arousing than male participants (7.65 ± 1.22), while there was no difference for the ratings of sexual infidelity (women: 8.35 ± 1.06; men: 8.34 ± 0.88). Both tasks were programmed in Presentation 14 (Neurobehavioral Systems, Albany, CA) and stimuli were presented via liquid crystal display (LCD) video goggles (Nordic NeuroLab, Bergen, Norway).

3. Statistical analysis

Demographical, neuropsychological, and behavioral data were analyzed using IBM SPSS Statistic 20 (IBM, New York, NY, USA). Quantitative behavioral data were compared using repeated measures ANOVAs and *t*-tests. Pearson's product-moment correlation was used for correlation analysis. Eta-squared and Cohen's *d* were calculated as measures of effect size. For qualitative variables Pearson's chi-squared tests were used. All reported *P*-values are two-tailed, if not otherwise noted, and *P*-values of $P < 0.05$ were considered significant.

Tables

Table S1. Demographics and neuropsychological performance Exp. 1

	OXT (n = 25) Mean (± SD)	PLC (n = 23) Mean (± SD)
Age (years)	25.04 (4.69)	24.13 (4.48)
Education (years)	16.64 (2.62)	16.18 (1.97)
Idealism (EPQ) [a]	61.68 (14.88)	63.59 (13.93)
Realism (EPQ) [a]	51.04 (14.59)	52.36 (12.23)
Positive affect (PANAS) [b]	19.96 (9.59)	22.61 (6.80)
Negative affect (PANAS) [b]	10.72 (1.14)	11.48 (2.47)
State Anxiety (STAI) [c]	43.84 (1.87)	44.65 (2.31)
Trait Anxiety (STAI) [c]	31.92 (7.91)	31.87 (10.9)
PAL [d]		
Total errors	20.88 (13.86)	18.26 (16.69)
Mean errors to success	1.56 (2.26)	1.61 (1.77)
SWM – 6 [e]		
Between errors	5.44 (8.16)	5.65 (8.13)
Strategy score	13.04 (3.43)	12.61 (3.63)

Notes. There were no significant differences between the OXT and PLC group (all *P*s > 0.05). Moral thoughts were measured by using Forsyth's [a] Ethics Position Questionnaire (EPQ). Anxiety and mood were assessed before the experiment with the [b] Positive and Negative Affective Schedule (PANAS) and the [c] State Trait Anxiety Inventory for State and Trait (STAI). [d] Paired Associate Learning (PAL) reports the number of errors made. [e] Social Working Memory (SWM) Strategy tests whether participants have

cognitive dysfunctions, which was not the case in either group. Abbreviations: OXT, oxytocin; PLC, placebo.

Table S2. Demographics and neuropsychological performance Exp. 2

	Mean (± SD) (n = 22)
Age (years)	26.73 (3.60)
Education (years)	17.32 (2.63)
RTI [a]	
Simple reaction time (ms)	298.26 (30.43)
Simple movement time (ms)	354.70 (61.16)
Five-choice movement time (ms)	316.37 (31.15)
Five-choice reaction time (ms)	365.02 (65.64)
PAL [b]	
Total errors	9.27 (6.51)
Mean errors to success	2.61 (1.91)
SWM – 8 [c]	
Between errors	9.68 (11.15)
Strategy score	14.18 (4.12)
Trait anxiety [d]	31.86 (8.60)
BDI [e]	3.32 (4.91)

Notes. Subjects' speed of response to a visual target, visual memory, and the ability to retain spatial information were measured with the [a] simple and reaction time task (RTI), the [b] paired associates learning task (PAL), and the [c] spatial working memory task (SWM), respectively. Anxiety symptoms were assessed by the [d] State Trait Anxiety Inventory and depressive symptoms by the self-report [e] BDI (Beck´s Depression Scale, Version II).

Table S3. Activation table for the GLM analysis in Exp. 1 under PLC

Region	Right/left	Cluster size (voxels)	*t-score*	*MNI-coordinates*		
				x	*y*	*z*
PLC: Moral > Non-Moral						
Medial frontal	L	1925	9.39	-27	26	52
Medial frontal	L		7.62	-3	53	28
Superior frontal	L		7.23	-6	44	49
Cingulate	L	428	6.62	0	-49	34
Precuneus*	L		5.54	-6	52	13
Angular gyrus*	L	139	7.69	-45	-58	25
Superior	R	121	6.15	57	-61	19
Angular gyrus*	R		4.77	54	-55	28
Middle	R		4.08	45	-73	13
Superior	L	21	5.44	-45	11	-32
Medial	R	39	5.20	6	-16	34
Inferior frontal	L	22	5.20	-42	26	-11
Fusiform gyrus	R	5	5.08	51	-13	-29
Insula	R	10	4.78	30	17	-14
Middle	L	15	4.63	-60	-1	-23
Inferior	R	39	4.55	63	-7	-20
Sub-gyral	R		3.82	48	-4	-23
Sub-gyral	R		3.79	45	-10	-17
Superior frontal	L	7	4.28	-24	59	4
Cuneus	R	42	4.27	12	-94	7
Calcarine	R		4.12	18	-91	-2
Superior	R	5	4.22	39	20	-38
Parahippocamp	R	3	4.20	24	-10	-29

Inferior frontal	R	7	4.14	33	29	-11
Superior	L	2	4.08	-39	20	-23
Middle	L	5	4.00	-21	-91	10
Middle	R	4	3.92	51	5	-32
Anterior	L	7	3.88	0	23	22
Calcarine	L	4	3.85	0	-88	10
Medial	R	1	3.32	45	-76	-2
Superior frontal	L	4	3.80	0	23	37
Inferior frontal	L	4	3.75	-48	23	13
Insula	L	1	3.73	-30	14	-11
Superior frontal	R	1	3.66	18	23	58
Inferior frontal	R	1	3.64	54	23	7
Medial	R	2	3.64	57	5	-26
Inferior parietal	L	2	3.60	-48	-58	40
Inferior	L	1	3.55	-54	-16	-26
PLC: Non-						
Cerebelum	R	1	4.60	33	53	-38
Postcentral	L	4	3.88	-45	-31	58
Postcentral	R	9	3.82	45	-40	61
Sub-gyral		1	3.66	42	-46	-5

Notes. Abbreviations: PLC, placebo; *Significant at $P < 0.05$ family wise error corrected.

Table S4. State measurement of anxiety, mood and attention

	OXT session (n = 22) Mean (± SD)	PLC session (n = 22) Mean (± SD)	*t*	*P*
State Anxiety (STAI)	31.95 (4.74)	31.45 (5.11)	0.43	0.67
State Anxiety (STAI)	32.95 (5.32)	32.14 (4.42)	0.95	0.35
Positive affect	28.68 (6.61)	28.41 (5.86)	0.28	0.78
Positive affect	27.77 (6.59)	28.14 (7.03)	-0.40	0.69
Negative affect	11.23 (1.57)	12.00 (3.45)	-1.07	0.30
Negative affect	11.55 (3.19)	11.09 (2.76)	0.66	0.52
D2 [c]	221.09	218.77	0.29	0.77

Notes. State anxiety before and after the experiment was assessed using the [a]STAI = State Trait Anxiety Inventory. Mood before and after the experiment was assessed using the [b] PANAS = Positive and Negative Affect Schedule. Attention performance after the experiment was assessed using the [c] D2 = Aufmerksamkeits- und Belastungstest. Abbreviations: OXT, oxytocin; PLC, placebo.

Table S5. Activation table for the GLM analysis in Exp. 2 under PLC

Region	Right/left	Cluster size (voxels)	*t-score*	*MNI-coordinates*		
				x	*y*	*Z*
PLC: Sexual > Neutral						
Medial frontal gyrus*	L	652	7.52	-8	50	14
Medial frontal gyrus*	L		5.95	-4	52	6
Cingulate gyrus*	L		5.52	-2	36	32
Anterior cingulate	R	70	6.13	4	36	8
Fusiform gyrus	L	13	5.71	-38	-50	-10
Inferior parietal	L	415	5.11	-60	-50	40
Middle temporal	L		5.09	-56	-50	4
Superior temporal	L		4.80	-60	-54	14
Middle cingulum	R/L	19	4.94	0	-18	40
Superior temporal	R	57	4.77	50	-48	14
Anterior cingulate	L	35	4.70	-2	38	-4
Medial frontal gyrus	R	58	4.57	12	38	44
Superior frontal gyrus	R		4.22	6	42	50
Middle temporal	L	116	4.51	-52	-74	20
Middle temporal	L		4.47	-40	-70	20
Middle temporal	L		4.38	-46	-80	26
Inferior frontal gyrus	R	19	4.44	42	26	6
Superior frontal gyrus	L	12	4.43	-2	22	58
Supramarginal gyrus	R	51	4.14	64	-48	24
Superior temporal	R		3.89	62	-50	14
Superior temporal	R	10	4.14	60	-60	20
Anterior cingulate	L	10	3.87	-2	20	22
Anterior cingulate	L		3.73	-4	26	28

PLC: Neutral >						
Inferior parietal	L	1922	6.55	-46	-40	58
Postcentral gyrus*	L		6.27	-52	-32	54
Posterior cingulate	L	951	6.32	-10	-46	4
Posterior cingulate	R		5.55	14	-50	4
Posterior cingulate	R		5.23	12	-56	12
Supramarginal gyrus*	R	212	5.50	64	-20	40
Postcentral gyrus*	R		4.65	52	-30	56
Supramarginal gyrus*	R		4.51	58	-16	28
Superior frontal gyrus	R	108	5.09	30	12	54
Middle frontal gyrus	R		4.02	32	4	58
Middle frontal gyrus	R		3.95	32	-6	58
Postcentral gyrus	R	12	4.60	40	-42	64
Pallidum	L	16	4.58	-24	-14	2
Middle cingulate	R	20	4.51	6	-38	34
Middle occipital gyrus	L	36	4.50	-28	-78	32
Superior occipital	L		3.57	-22	-78	38
Middle frontal gyrus	L	24	4.39	-28	12	60
Insula	L	12	4.06	-38	2	-6
Superior frontal gyrus	L	37	3.96	-18	2	60
Precentral gyrus	L	24	3.91	-32	-26	66
Precentral gyrus	L		3.79	-24	-26	64
Middle cingulate	L	10	3.88	-4	-28	36
Thalamus	L	12	3.84	-16	-30	-2
Middle frontal gyrus	L	42	3.82	-26	-6	64
Middle frontal gyrus	L		3.80	-26	-8	56
Middle frontal gyrus	L		3.12	-26	-12	48
Insula	L	10	3.71	-38	-16	0

Notes. The whole-brain analysis was thresholded at an uncorrected $P < 0.001$ with a cluster extent threshold of $k = 10$ voxels. *Significant at $P < 0.05$ family wise error corrected. Abbreviations: PLC, placebo.

Table S6. Relationship characteristics Exp. 2

Variable	Mean (± SD)
Relationship duration (months)	35.68 (25.33)
Age of partner (years)	24.64 (3.40)
Passionate Love Scale (PLS)[a]	6.44 (1.06)
Time (days) since the last time seen OXT[1]	1.73 (3.78)
Time (days) since the last time seen PLC[1]	1.38 (2.54)
Time (days) since the last intimate contact OXT[1]	4.45 (5.36)
Time (days) since the last intimate contact PLC[1]	3.38 (2.94)
Love style Eros[b]	6.86 (1.54)
Love style Ludus[b]	3.08 (0.98)
Love style Storge[b]	5.88 (1.19)
Love style Pragma[b]	4.49 (1.28)
Love style Mania[b]	4.05 (1.41)
Love style Agape[b]	6.95 (0.91)

Notes. Love in the relationship was measured with [a] the Passionate Love Scale (PLS) and different love styles were assessed using a German version of [b] Lee's Love Styles („Marburger Einstellungs-Inventar für Liebesstile (MEIL)"). Abbreviations: OXT, oxytocin; PLC, placebo; [1]There was no significant difference between the OXT and PLC sessions (all *P*s > 0.22).

References

Brickenkamp, R. & Zillmer, E. (1998). *The d2 Test of Attention*, Seattle, WA, Hogrefe & Huber Publishers.

Buss, D. M., Larsen, R. J., Westen, D. & Semmelroth, J. (1992). Sex-Differences in Jealousy - Evolution, Physiology, and Psychology. *Psychological Science, 3*, 251-255.

CANTABeclipse (2011). *Test Administration Guide*, Cambridge Cognition Limited.

Forsyth, D. R. (1980). A Taxonomy of Ethical Ideologies. *Journal of Personality and Social Psychology, 39*, 175-184.

Lee, J. A. (1988). Love styles. In: M. H. Barnes & R. J. Sternberg (eds). *The Psychology of love*, New Haven, Conn, Yale University Press. p. 38–67.

Sahakian, B. J. & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *Journal of the Royal Society of Medicine, 85*, 399-402.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 Suppl 20*, 22-33.

Spielberger, C. D., Gorsuch, R. L. & Lushene, R. E. (1970). *Manual for the State-Trait Anxiety Inventory*, Palo Alto, CA, Consulting Psychologists Press.

Takahashi, H., Matsuura, M., Yahata, N., Koeda, M., Suhara, T. & Okubo, Y. (2006). Men and women show distinct brain activations during imagery of sexual and emotional infidelity. *Neuroimage, 32*, 1299-1307.

Watson, D., Clark, L. A. & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology*, *54*, 1063-1070.

Chapter 5: General Discussion

This dissertation presents three studies that investigated intranasal OXT influence on social AA, the willingness to induce emotions and volitional and emotional ambivalence. One principal finding that all three presented studies have in common is that intranasal OXT promoted prosocial behavior. This should be said with caution, however, because, high psychopathic traits correlated positively with the willingness to induce fear (in the OXT group) in the second study. The second question, whether OXT only shows effects in *direct* interactions with conspecifics, is negated. OXT also reduced ambivalence in individuals who were faced with emotionally difficult situations. This is an important finding in regard to potential treatment applications. Regarding each study separately, we discovered that OXT facilitates social approach in women (Preckel, Scheele, Kendrick, Maier, & Hurlemann, 2014), while it is more complicated in men, in whom an interaction between OXT and relationship status has been revealed (Scheele et al., 2012). This sexual-dimorphic finding might be due to the differently evolved mating strategies which aim at maximizing evolutionary fitness in regard to asymmetric parenting investment (Buss, Larsen, Westen, & Semmelroth, 1992). In light of the different existing hypotheses and theories on OXT, the content of this study partly complements the approach/ withdrawal hypothesis, because we found an increased approach behavior towards positive social stimuli, while no OXT influence on the avoidance behavior in the AA task could be observed. The salience hypothesis cannot completely account for our findings either, because this hypothesis would have suggested an OXT effect on negative social stimuli which was not observed. The in-group/ out-group hypothesis cannot be applied for interpretations of study 1. The GAAO theory suggested that non-social

stimuli are most likely not influenced by OXT in many studies, because the non-social cues have a lower capacity to arouse. However, we selected social and non-social pictures for positive and negative valences from the IAPS database based on their previously obtained arousal ratings and did not find an OXT effect on non-social stimuli which speaks against the GAOO theory. The theory that OXT influences behavior in a context- and person- specific manner holds true according to this study. Consequently, we may suggest that OXT displays valence and social specific effects – acting on positive *social* stimuli.

The second study revealed OXT's ability to increase the willingness to induce positive emotions on the one hand, while it decreased the willingness to induce negative emotions on the other. Facilitated willingness to induce positive emotions can be interpreted in the context of the social approach/ withdrawal hypothesis, which posits that OXT might increase approach-related social behaviors and inhibit withdrawal-related social behaviors. The willingness to induce happy feelings in a conspecific can be regarded as approach-related social behavior, which was indeed up-regulated after OXT administration. The willingness to induce negative emotions, e.g. anger, likely repels people and can thus be interpreted as withdrawal-related social behavior, which was down-regulated by OXT. The salience hypothesis may also explain our results, because increased salience, induced through OXT, could result in better sensitivity of the social messages entailed in EES, thereby resulting in a different behavioral response. The in-group/ out-group hypothesis cannot be applied to this study. However, the findings by DeDreu suggest that aggressive behavior is increased towards out-group members after OXT administration. Our findings show a reduction of aggressive behavioral tendencies. This may imply that participants were either not imagining out-group persons while performing the task, or that OXT only increases aggression towards out-

group members when in-group members are present. This would be an interesting aspect to investigate in future studies. The GAAO theory is able to explain our finding, because OXT "facilitates the salience of personally relevant and emotionally evocative stimuli" (Harari-Dahan & Bernstein, 2014, p. 508), and the hypothesis does not point at a directionality of the OXT effect. However, our findings do not suffice to confirm the GAAO theory, because all EES included social interactions to the same extend, making them equally relevant. The context- and person-specific theory is thus sustained again, because even though the context in this study is equal for each participant, personality traits (cold-heartedness) revealed a positive correlation between psychopathic traits and the willingness to induce fear and anger, while a negative correlation occurred for the happy EES (in the OXT group). This finding is a clear indication for trait-dependent behavior after OXT administration.

The third study revealed that OXT alleviates volitional and emotional ambivalence. The first experiment is not easily integrated into the discussed OXT hypotheses, but an increase in affective salience might explain the accelerated RT to accepted dilemmas. The second experiment of study three may be interpreted in terms of the social-approach/ withdrawal hypothesis. The imagination of sexual or emotional partner infidelity may result in withdrawal from the partner as a consequence of jealousy or heartbreak. OXT reduced dACC activity and arousal ratings to the infidelity sentences, indicating down-regulation of social avoidance after imagining sexual infidelity. In this context, the salience hypothesis likely strengthened the secure feeling of the existing romantic relationship rather than the infidelity cues. A highly speculative suggestion can be made about the in-group/ out-group hypothesis in relation to this experiment: if the partner is seen as an in-group member (which can be assumed), then reduced arousal could indicate benevolent behavioral tendencies towards the partner in the

sense of forgiveness. It would have been interesting to include a component to measure the participant's behavior in a confrontation situation with the rival. A strong confirmation for the context-specificity of OXT would be increased aggressive behavior towards the rival, in combination with increased forgiving behavior towards the romantic partner. Even though this scenario could not have been tested in our study, the context- and person-specific theory explains the findings best. In the sexual infidelity condition, participants who received OXT showed reduced dACC activity and reduced arousal ratings. In the emotional infidelity condition the arousal ratings were also significantly reduced in the OXT group, but no group difference on neural activity was observed and the control condition did not yield any OXT effects.

In conclusion, the context- and person-specific OXT hypothesis can be used as an explanatory basis for all three studies and is the only theory that withstands the diverse range of findings after OXT administration. Indeed this hypothesis is elegantly designed, also in regard to the biological background of OXT. Future research is warranted to discover the biochemical underpinnings of the human OXT system in order to unravel the diverse findings and the relationship between gene variants, methylation patterns, personal experiences, attitudes and personality traits that apparently all modulate OXT's action on social-emotional behavior. Regarding OXT's prosocial effects, outlined in this dissertation, it appears that OXT might be a promising therapeutic agent for several psychiatric disorders. OXT promotes social approach to positive stimuli which could be beneficial for patients with social anxiety disorder. OXT also alleviated volitional and emotional ambivalence and ambivalence occurs in many psychiatric disorders such as schizophrenia, borderline personality disorder, and obsessive compulsive disorder. However, given OXT's nature of having diverse effects on

different individuals, more detailed information needs to be discovered before successful treatment applications can be developed.

References

Abu-Akel, A., & Shamay-Tsoory, S. (2011). Neuroanatomical and neurochemical bases of theory of mind. Neuropsychologia, 49(11), 2971-2984.

Acevedo, B. P., Aron, A., Fisher, H. E., & Brown, L. L. (2012). Neural correlates of long-term intense romantic love. Soc Cogn Affect Neurosci, 7(2), 145-159.

Acher, R., Chauvet, J., & Chauvet, M. T. (1995). Man and the chimaera. Selective versus neutral oxytocin

Adams, R., & David, A. S. (2007). Patterns of anterior cingulate activation in schizophrenia: a selective

Adolphs, R. (2009). The social brain: neural basis of social knowledge. Annu Rev Psychol, 60, 693-716.

Albers, H. E. (2014). Species, sex and individual differences in the vasotocin/vasopressin system: Relationship to neurochemical signaling in the social behavior neural network. Front Neuroendocrinol.

Ali, A., Deuri, S. P., Deuri, S. K., Jahan, M., Singh, A. R., & Verma, A. N. (2010). Perceived social support and life satisfaction in persons with somatization disorder. Ind Psychiatry J, 19(2), 115-118.

Altemus, M., Jacobson, K. R., Debellis, M., Kling, M., Pigott, T., Murphy, D. L., et al. (1999). Normal CSF oxytocin and NPY levels in OCD. Biological Psychiatry, 45, 931-933.

Alvergne, A., and Lummaa, V. (2010). Does the contraceptive pill alter mate choice in humans? Trends Ecol Evol 25, 171-179. doi: 10.1016/j.tree.2009.08.003.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci, 7(4), 268-277.

Anacker, A. M. J.;, & Beery, A. K. . (2013). Life in groups: The roles of oxytocin in mammalian sociality. Front Behav Neurosci. doi: 10.3389/fnbeh.2013.00185

Ansseau, M., Legros, J. J., Mormont, C., Cerfontaine, J. L., Papart, P., Geenen, V., et al. (1987). Intranasal oxytocin in obsessive-compulsive disorder. Psychoneuroendocrinology, 12, 231-236.

Antonius, D., Bruce, K. L., Moisa, B., Sinclair, S. J., Malaspina, D. & Tremeau, F. (2013). Familiarity preference in schizophrenia is associated with ambivalent attitudes towards others. Schizophrenia Research, 150, 229-234.

Aoki, Y., Yahata, N., Watanabe, T., Takano, Y., Kawakubo, Y., Kuwabara, H., Yamasue, H. (2014). Oxytocin improves behavioural and neural deficits in inferring others' social emotions in autism. Brain, 137(Pt 11), 3073-3086. doi: 10.1093/brain/awu231

Argiolas, A., & Gessa, G. L. (1991). Central functions of oxytocin. Neurosci Biobehav Rev, 15(2), 217-231.

Bales, K. L., & Carter, C. S. (2003). Sex differences and developmental effects of oxytocin on aggression and social behavior in prairie voles (Microtus ochrogaster). Horm Behav, 44(3), 178-184.

Bales, K. L., Pfeifer, L. A., & Carter, C. S. (2004). Sex differences and developmental effects of manipulations of oxytocin on alloparenting and anxiety in prairie voles. Dev Psychobiol, 44(2), 123-131.

Bar, M., Neta, M., & Linz, H. (2006). Very first impressions. Emotion, 6(2), 269-278.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes".

Bartz, J. A., Zaki, J., Bolger, N. & Ochsner, K. N. (2011). Social effects of oxytocin in humans: context and person matter. Trends in Cognitive Sciences, 15, 301-309.

Baumeister, R. F., & Leary, M. R. (1995). The Need to Belong - Desire for Interpersonal Attachments as a Fundamental Human-Motivation. Psychological Bulletin, 117(3), 497-529.

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U. & Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron, 58, 639-650.

Benoussaidh, A., Maurin, Y., & Rampin, O. (2004). Spinal effects of oxytocin on uterine motility in anesthetized rats. Am J Physiol Regul Integr Comp Physiol, 287(2), R446-453.

Bleuler, E. (1908). Die Prognose der Dementia praecox (Schizophreniegruppe). Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin, 65,436-464.

Bleuler, E. (1950). Dementia Praecox or the Group of Schizophrenias. New York: International Universities Press (Original work published 1911).

Boccia, M. L., Petrusz, P., Suzuki, K., Marson, L. & Pedersen, C. A. (2013). Immunohistochemical localization of oxytocin receptors in human brain. Neuroscience, 253, 155-164.

Bogen, T. M. (1998). The thematic apperception test the children's apperception test, and the senior apperception technique in clinical use, 6th edition. Contemporary Psychology, 43(5), 351-352.

Born, J., Lange, T., Kern, W., McGregor, G. P., Bickel, U., & Fehm, H. L. (2002). Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci, 5(6), 514-516.

Botvinick, M., Nystrom, L. E., Fissell, K., Carter, C. S. & Cohen, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature, 402, 179-181.

Bowler, C. M., Cushing, B. S., & Carter, C. S. (2002). Social factors regulate female-female aggression and affiliation in prairie voles. Physiology & Behavior, 76(4-5), 559-566.

Brailoiu, E., Dun, S. L., Brailoiu, G. C., Mizuo, K., Sklar, L. A., Oprea, T. I., et al. (2007). Distribution and characterization of estrogen receptor G protein-coupled receptor 30 in the rat central nervous system. J Endocrinol, 193(2), 311-321.

Breton, C., & Zingg, H. H. (1997). Expression and region-specific regulation of the oxytocin receptor gene in rat brain. Endocrinology, 138(5), 1857-1862.

Brett, M., Anton, J.-L., Valabregue, R. & Poline, J.-B. (2002) Region of interest analysis using an SPM toolbox. Presented al: 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan.

Brickenkamp, R. & Zillmer, E. (1998). The d2 Test of Attention, Seattle, WA, Hogrefe & Huber Publishers.

Burger, K., Fahrenholz, F., & Gimpl, G. (1999). Non-genomic effects of progesterone on the signaling function of G protein-coupled receptors. FEBS Lett, 464(1-2), 25-29.

Burri, A., Heinrichs, M., Schedlowski, M., & Kruger, T. H. (2008). The acute effects of intranasal oxytocin administration on endocrine and sexual function in males. Psychoneuroendocrinology, 33(5), 591-600.

Buss, D. M., Larsen, R. J., Westen, D., & Semmelroth, J. (1992). Sex Differences in Jealousy: Evolution, Physiology, and Psychology. Psycholgical Science, 3(4), 251-255.

Byun, H. M., Siegmund, K. D., Pan, F., Weisenberger, D. J., Kanel, G., Laird, P. W., et al. (2009). Epigenetic profiling of somatic tissues from human autopsy specimens identifies tissue- and individual-specific DNA methylation patterns. Hum Mol Genet, 18(24), 4808-4817.

Caffe, A. R., van Leeuwen, F. W., & Luiten, P. G. (1987). Vasopressin cells in the medial amygdala of the rat project to the lateral septum and ventral hippocampus. J Comp Neurol, 261(2), 237-252.

Caggiano, V., Fogassi, L., Rizzolatti, G., Thier, P., & Casile, A. (2009). Mirror neurons differentially encode the peripersonal and extrapersonal space of monkeys. Science, 324(5925), 403-406.

Caldwell, H. K., & Young, W. S., III. (2006). Oxytocin and Vasopressin: Genetics and Behavioral implications. In R. Lim (Ed.), Handbook of Neurochemistry and Molecular Neurobiology (Vol. 3, pp. 573-607). New York: Springer.

Caldwell, J. D., Walker, C. H., Pedersen, C. A., Barakat, A. S., & Mason, G. A. (1994). Estrogen increases affinity of oxytocin receptors in the medial preoptic area-anterior hypothalamus. Peptides, 15(6), 1079-1084.

Cannon, R., Lubar, J., Congedo, M., Thornton, K., Towler, K., & Hutchens, T. (2007). The effects of neurofeedback training in the cognitive division of the anterior cingulate gyrus. Int J Neurosci, 117(3), 337-357.

CANTABeclipse (2011). Test Administration Guide, Cambridge Cognition Limited.

Cardoso, C., Ellenbogen, M.A., and Linnen, A.M. (2012). Acute intranasal oxytocin improves positive self-perceptions of personality. Psychopharmacology (Berl) 220, 741-749. doi: 10.1007/s00213-011-2527-6.

Carson, D. S., Berquist, S. W., Trujillo, T. H., Garner, J. P., Hannah, S. L., Hyde, S. A., Parker, K. J. (2014). Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children. Mol Psychiatry. doi: 10.1038/mp.2014.132

Cattaneo, L., Sandrini, M., & Schwarzbach, J. (2010). State-dependent TMS reveals a hierarchical representation of observed acts in the temporal, parietal, and premotor cortices. Cereb Cortex, 20(9), 2252-2258.

Carter, C. S. (1992). Oxytocin and sexual behavior. Neurosci Biobehav Rev, 16(2), 131-144.

Carter, C. S. (1998). Neuroendocrine perspectives on social attachment and love.

Carter, C. S. (2014). Oxytocin Pathways and the Evolution of Human Behavior. Annual Review of Psychology, Vol 65, 65, 17-39.

Carter, C. S., Boone, E. M., Pournajafi-Nazarloo, H., & Bales, K. L. (2009). Consequences of early experiences

Carter, C. S., & Getz, L. L. (1993). Monogamy and the prairie vole. Sci Am, 268(6), 100-106.

Chen, F. S., Kumsta, R., von Dawans, B., Monakhov, M., Ebstein, R. P., & Heinrichs, M. (2011). Common oxytocin receptor gene (OXTR) polymorphism and social support interact to reduce stress in humans. Proc Natl Acad Sci U S A, 108(50), 19937-19942.

Chiodera, P., Salvarani, C., Bacchimodena, A., Spallanzani, R., Cigarini, C., Alboni, A., et al. (1991). Relationship between Plasma Profiles of Oxytocin and Adrenocorticotropic Hormone during Suckling or Breast Stimulation in Women. Hormone Research, 35(3-4), 119-123.

Choleris, E., Devidze, N., Kavaliers, M., and Pfaff, D.W. (2008). "Steroidal/neuropeptide interactions in hypothalamus and amygdala related to social anxiety," in Progress in Brain Research, eds. D.N. Inga & L. Rainer. Elsevier), 291-303.

Churchland, P.S., and Winkielman, P. (2012). Modulating social behavior with oxytocin: how does it work? What does it mean? Horm Behav 61, 392-399. doi: 10.1016/j.yhbeh.2011.12.003.

Cohen, S., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M., Jr. (1997). Social ties and susceptibility to the common cold. JAMA, 277(24), 1940-1944.

Coirini, H., Schumacher, M., Flanagan, L. M., & McEwen, B. S. (1991). Transport of estrogen-induced oxytocin receptors in the ventromedial hypothalamus. J Neurosci, 11(11), 3317-3324.

Colonnello, V., Chen, F. S., Panksepp, J., & Heinrichs, M. (2013). Oxytocin sharpens self-other perceptual boundary. Psychoneuroendocrinology, 38(12), 2996-3002. doi: 10.1016/j.psyneuen.2013.08.010

Cottet, M., Albizu, L., Perkovska, S., Jean-Alphonse, F., Rahmeh, R., Orcel, H., et al. (2010). Past, present and future of vasopressin and oxytocin receptor oligomers, prototypical GPCR models to study dimerization processes. Curr Opin Pharmacol, 10(1), 59-66.

Cushing, B.S., Martin, J.O., Young, L.J., and Carter, C.S. (2001). The effects of peptides on partner preference formation are predicted by habitat in prairie voles. Horm Behav 39, 48-58. doi: 10.1006/hbeh.2000.1633.

Dai, L., Carter, C. S., Ying, J., Bellugi, U., Pournajafi-Nazarloo, H., & Korenberg, J. R. (2012). Oxytocin and vasopressin are dysregulated in Williams Syndrome, a genetic disorder affecting social behavior. PLoS One, 7(6), e38513.

Dal Monte, O., Schintu, S., Pardini, M., Berti, A., Wassermann, E. M., Grafman, J., et al. (2014). The left inferior frontal gyrus is crucial for reading the mind in the eyes: Brain lesion evidence. Cortex, 58, 9-17.

Dalton, K. M., Nacewicz, B. M., Alexander, A. L., & Davidson, R. J. (2007). Gaze-fixation, brain activation, and amygdala volume in unaffected siblings of individuals with autism. Biol Psychiatry, 61(4), 512-520.

Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., & Damasio, A. R. (1994). The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science, 264(5162), 1102-1105.

Damiano, C. R., Aloi, J., Dunlap, K., Burrus, C. J., Mosner, M. G., Kozink, R., et al. (2014). Association between the oxytocin receptor (OXTR) gene and mesolimbic responses to rewards. Molecular Autism, 5(7), 1 - 12.

Davis, M. A. (1980). A multidimensional approach to individual differences in empathy. JSAS Catalog of Selected Documents in Psychology, 10(85).

De Dreu, C. K. (2012). Oxytocin modulates cooperation within and competition between groups: an integrative review and research agenda. Horm Behav, 61(3), 419-428.

De Vries, G. J., & Buijs, R. M. (1983). The origin of the vasopressinergic and oxytocinergic innervation of the rat brain with special reference to the lateral septum. Brain Res, 273(2), 307-317.

De Vries, G.J. (2008). "Sex differences in vasopressin and oxytocin innervation of the brain," in Progress in Brain Research, eds. D.N. Inga & L. Rainer. Elsevier), 17-27.

Decety, J., & Sommerville, J. A. (2003). Shared representations between self and other: A social cognitive neuroscience view. Trends Cogn Sci, 7(12), 527-533. doi: DOI 10.1016/j.tics.2003.10.004.

Delville, Y., Koh, E. T., & Ferris, C. F. (1994). Sexual differences in the magnocellular vasopressinergic system in golden hamsters. Brain Res Bull, 33(5), 535-540.

den Boer, J. A. & Westenberg, H. G. (1992). Oxytocin in obsessive compulsive disorder. Peptides, 13, 1083-1085.

DeVries, G. J., Buijs, R. M., Van Leeuwen, F. W., Caffe, A. R., & Swaab, D. F. (1985). The vasopressinergic innervation of the brain in normal and castrated rats. J Comp Neurol, 233(2), 236-254.

Dewsbury, D. A. (1987). The comparative psychology of monogamy. Nebr Symp Motiv, 35, 1-50.

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., & Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. Exp Brain Res, 91(1), 176-180.

Dimberg, U., & Thunberg, M. (1998). Rapid facial reactions to emotional facial expressions. Scand J Psychol, 39(1), 39-45.

Dinstein, I., Hasson, U., Rubin, N., & Heeger, D. J. (2007). Brain areas selective for both observed and executed movements. Journal of Neurophysiology, 98(3), 1415-1427.

Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U. & Heinrichs, M. (2009). Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biological Psychiatry, 65, 728-731.

Docherty, A. R., Sponheim, S. R. & Kerns, J. G. (2014). Further examination of ambivalence in relation to the schizophrenia spectrum. Schizophrenia Research, doi: 10.1016/j.schres.2014.06.015.

Domes, G., Lischke, A., Berger, C., Grossmann, A., Hauenstein, K., Heinrichs, M., et al. (2010). Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology, 35(1), 83-93.

Donaldson, Z. R., & Young, L. J. (2008). Oxytocin, vasopressin, and the neurogenetics of sociality. Science, 322(5903), 900-904.

Dubois-Dauphin, M., Barberis, C., & de Bilbao, F. (1996). Vasopressin receptors in the mouse (Mus musculus) brain: sex-related expression in the medial preoptic area and hypothalamus. Brain Res, 743(1-2), 32-39.

Dubois-Dauphin, M., Theler, J. M., Zaganidis, N., Dominik, W., Tribollet, E., Pevet, P., et al. (1991). Expression of vasopressin receptors in hamster hypothalamus is sexually dimorphic and dependent upon photoperiod. Proc Natl Acad Sci U S A, 88(24), 11163-11167.

Ebstein, R. P., Knafo, A., Mankuta, D., Chew, S. H., & Lai, P. S. (2012). The contributions of oxytocin and vasopressin pathway genes to human behavior. Horm Behav, 61(3), 359-379.

Eckstein, M., Scheele, D., Weber, K., Stoffel-Wagner, B., Maier, W. & Hurlemann, R. (2014). Oxytocin facilitates the sensation of social stress. Human Brain Mapping, 35, 4741-4750.

Eisenberger, N. I., Lieberman, M. D. & Williams, K. D. (2003). Does rejection hurt? An FMRI study of social exclusion. Science, 302, 290-292.

Emlen, S. T., & Oring, L. W. (1977). Ecology, sexual selection, and the evolution of mating systems. Science, 197(4300), 215-223.

Englander, Z. A., Haidt, J., & Morris, J. P. (2012). Neural basis of moral elevation demonstrated through inter-subject synchronization of cortical activity during free-viewing. PLoS One, 7(6), e39384.

Englert, C., Bertrams, A., and Dickhäuser, O. (2011). Entwicklung der Fünf-Item-Kurzskala STAI-SKD zur Messung von Zustandsangst. Zeitschrift für Gesundheitspsychologie 19, 173-180.

Epperson, C. N., McDougle, C. J. & Price, L. H. (1996). Intranasal oxytocin in obsessive-compulsive disorder. Biological Psychiatry, 40, 547-549.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci, 15(2), 85-93.

Etzel, J. A., Gazzola, V., & Keysers, C. (2008). Testing Simulation Theory with Cross-Modal Multivariate Classification of fMRI Data. Plos One, 3(11).

Evans, A. C., Marrett, S., Neelin, P., Collins, L., Worsley, K., Dai, W., et al. (1992). Anatomical mapping of functional activation in stereotactic coordinate space. Neuroimage, 1, 43-53.

Evans, J. J., Reid, R. A., Wakeman, S. A., Croft, L. B., & Benny, P. S. (2003). Evidence that oxytocin is a physiological component of LH regulation in non-pregnant women. Human Reproduction, 18(7), 1428-1431.

Evans, S., Shergill, S.S., and Averbeck, B.B. (2010). Oxytocin decreases aversion to angry faces in an associative learning task. Neuropsychopharmacology 35, 2502-2509. doi: 10.1038/npp.2010.110.

Fan, Y., Duncan, N. W., de Greck, M., & Northoff, G. (2011). Is there a core neural network in empathy? An fmri based quantitative meta-analysis. Neurosci Biobehav Rev, 35(3), 903-911. doi: 10.1016/j.neubiorev.2010.10.009.

Feldman, R. (2012). Oxytocin and social affiliation in humans. Horm Behav 61, 380-391. doi: 10.1016/j.yhbeh.2012.01.008.

Feldman, R., Gordon, I., Schneiderman, I., Weisman, O., & Zagoory-Sharon, O. (2010). Natural variations inmaternal and paternal care are associated with systematic changes in oxytocin following parent–infant contact. Psychoneuroendocrinology, 35(8), 1133 – 1141.

Feldman, R., Zagoory-Sharon, O., Weisman, O., Schneiderman, I., Gordon, I., Maoz, R., et al. (2012). Sensitive Parenting Is Associated with Plasma Oxytocin and Polymorphisms in the OXTR and CD38 Genes. Biol Psychiatry, 72(3), 175 – 181.

Fisher, H. E., Aron, A., & Brown, L. L. (2006). Romantic love: a mammalian brain system for mate choice. Philos Trans R Soc Lond B Biol Sci, 361(1476), 2173-2186.

Fleming, A. S., Corter, C., Stallings, J., & Steiner, M. (2002). Testosterone and prolactin are associated with emotional responses to infant cries in new fathers. Horm Behav, 42(4), 399-413.

Forsyth, D. R. (1980). A taxonomy of ethical ideologies. Journal of Personality and Social Psychology, 39(1), 175-184. doi: Doi 10.1037//0022-3514.39.1.175

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. Brain, 119 (Pt 2), 593-609.

Gamer, M., & Buchel, C. (2012). Oxytocin specifically enhances valence-dependent parasympathetic responses. Psychoneuroendocrinology, 37(1), 87-93.

Garrison, J. L., Macosko, E. Z., Bernstein, S., Pokala, N., Albrecht, D. R., & Bargmann, C. I. (2012). Oxytocin/vasopressin-related peptides have an ancient role in reproductive behavior. Science, 338(6106), 540-543. doi: 10.1126/science.1226201

Gazzola, V., Aziz-Zadeh, L., & Keysers, C. (2006). Empathy and the somatotopic auditory mirror system in humans. Curr Biol, 16(18), 1824-1829.

Gazzola, V., Rizzolatti, G., Wicker, B., & Keysers, C. (2007). The anthropomorphic brain: the mirror neuron system responds to human and robotic actions. Neuroimage, 35(4), 1674-1684.

Gerin, W., Milner, D., Chawla, S., & Pickering, T. G. (1995). Social Support as a Moderator of Cardiovascular Reactivity in Women - a Test of the Direct Effects and Buffering Hypotheses. Psychosomatic Medicine, 57(1), 16-22.

Getz, L. L., & Carter, C. S. (1996). Prairie-vole partnerships. American Scientist, 84, 56 - 62.

Getz, L. L., & Hofmann, J. E. (1986). Social organization in free-living prairie voles, Microtus orchrogaster. Behav Ecol Sociobiol, 18, 275 - 282.

Gillath, O., Shaver, P. R., Baek, J. M., & Chun, D. S. (2008). Genetic correlates of adult attachment style. Pers Soc Psychol Bull, 34(10), 1396-1405.

Gimpl, G., & Fahrenholz, F. (2001). The oxytocin receptor system: structure, function, and regulation. Physiol Rev, 81(2), 629-683.

Gimpl, G., Burger, K., Politowska, E., Ciarkowski, J., & Fahrenholz, F. (2000). Oxytocin receptors and cholesterol: interaction and regulation. Exp Physiol, 85 Spec No, 41S-49S.

Goodson, J. L. (2013). Deconstructing sociality, social evolution and relevant nonapeptide functions. Psychoneuroendocrinology, 38(4), 465-478. doi: 10.1016/j.psyneuen.2012.12.005

Goodson, J. L., Evans, A. K., & Wang, Y. (2006). Neuropeptide binding reflects convergent and divergent evolution in species-typical group sizes. Horm Behav, 50(2), 223-236.

Gossen, A., Hahn, A., Westphal, L., Prinz, S., Schultz, R. T., Grunder, G., et al. (2012). Oxytocin plasma concentrations after single intranasal

oxytocin administration - a study in healthy men. Neuropeptides, 46(5), 211-215.

Gouin, J. P., Carter, C. S., Pournajafi-Nazarloo, H., Glaser, R., Malarkey, W. B., Loving, T. J., et al. (2010). Marital behavior, oxytocin, vasopressin, and wound healing. Psychoneuroendocrinology, 35(7), 1082-1090.

Graff-Radford, J., Whitwell, J. L., Geda, Y. E. & Josephs, K. A. (2012). Clinical and imaging features of Othello's syndrome. European Journal of Neurology, 19, 38-46.

Gramer, M. & Supp, N. (2014). Social support and prolonged cardiovascular reactivity: The moderating influence of relationship quality and type of support. Biologcial Psychology, 101, 1-8.

Grazzini, E., Guillon, G., Mouillac, B., & Zingg, H. H. (1998). Inhibition of oxytocin receptor function by direct binding of progesterone. Nature, 392(6675), 509-512.

Grecucci, A., Giorgetta, C., Bonini, N., & Sanfey, A. G. (2013). Reappraising social emotions: the role of inferior frontal gyrus, temporo-parietal junction and insula in interpersonal emotion regulation. Front Hum Neurosci, 7, 523.

Greene, J. D., Nystrom, L. E., Engell, A. D., Darley, J. M. & Cohen, J. D. (2004). The neural bases of cognitive conflict and control in moral judgment. Neuron, 44, 389-400.

Greene, J. D., Sommerville, R. B., Nystrom, L. E., Darley, J. M. & Cohen, J. D. (2001). An fMRI investigation of emotional engagement in moral judgment. Science, 293, 2105-2108.

Gregory, S. G., Connelly, J. J., Towers, A. J., Johnson, J., Biscocho, D., Markunas, C. A., et al. (2009). Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. BMC Med, 7, 62.

Grillon, C., Krimsky, M., Charney, D.R., Vytal, K., Ernst, M., and Cornwell, B. (2013). Oxytocin increases anxiety to unpredictable threat. Mol Psychiatry 18, 958-960. doi: 10.1038/mp.2012.156.

Guastella, A. J., & MacLeod, C. (2012). A critical review of the influence of oxytocin nasal spray on social cognition in humans: evidence and future directions. Horm Behav, 61(3), 410-418.

Gumley, A., Braehler, C. & Macbeth, A. (2014). A meta-analysis and theoretical critique of oxytocin and psychosis: prospects for attachment and compassion in promoting recovery. British Journal of Clinical Psychology, 53, 42-61.

Hackam, D. G. (2007). Translating animal research into clinical benefit - Poor methodological standards in animal studies mean that positive results may not translate to the clinical domain. British Medical Journal, 334(7586), 163-164.

Hall, E. R. (1981). The Mammals of North America. New York: John Wiley.

Hamilton, A. F., & Grafton, S. T. (2008). Action outcomes are represented in human inferior frontoparietal cortex. Cereb Cortex, 18(5), 1160-1168.

Harari-Dahan, O., & Bernstein, A. (2014). A general approach - avoidance hypothesis of Oxytocin: Accounting for social and non-social effects of oxytocin. Neurosci Biobehav Rev, 47C, 506-519.

Hardin, R. (2002). Managing Trust. In K. S. Cook, R. Hardin & M. Levi (Eds.), Trust and Trustworthiness. New York: Russell Sage Foundation.

Harris, L. T., McClure, S. M., van den Bos, W., Cohen, J. D., & Fiske, S. T. (2007). Regions of the MPFC differentially tuned to social and nonsocial affective evaluation. Cogn Affect Behav Neurosci, 7(4), 309-316.

Harrison, B. J., Pujol, J., Soriano-Mas, C., Hernandez-Ribas, R., Lopez-Sola, M., Ortiz, H., et al. (2012). Neural correlates of moral sensitivity in obsessive-compulsive disorder. Arch Gen Psychiatry, 69(7), 741-749.

Haslam, S. A., Jetten, J., Postmes, T., & Haslam, C. (2009). Social Identity, Health and Well-Being: An Emerging Agenda for Applied Psychology. Applied Psychology-an International Review-Psychologie Appliquee-Revue Internationale, 58(1), 1-23.

Hatfield, E., Cacioppo, J. L., & Rapson, R. L. (1993). Emotional contagion. Current Directions in Psychological Sciences, 2, 96-99.

Heekeren, H. R., Wartenburger, I., Schmidt, H., Prehn, K., Schwintowski, H. P. & Villringer, A. (2005). Influence of bodily harm on neural correlates of semantic and moral decision-making. Neuroimage, 24, 887-897.

Heinrichs, M., Baumgartner, T., Kirschbaum, C. & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biological Psychiatry, 54, 1389-1398.

Heinrichs, N., Hahlweg, K., Fiegenbaum, W., Frank, M., Schröder, B., and Witzleben (Van), I. (2002). Validität und Reliabilität der Social Interaction Anxiety Scale (SIAS) und der Social Phobia Scale (SPS). Verhaltenstherapie, 26-35.

Hermans, E. J., Bos, P. A., Ossewaarde, L., Ramsey, N. F., Fernandez, G., & van Honk, J. (2010). Effects of exogenous testosterone on the ventral striatal BOLD response during reward anticipation in healthy women. Neuroimage, 52(1), 277-283.

Hietanen, J. K., Surakka, V., & Linnankoski, I. (1998). Facial electromyographic responses to vocal affect expressions. Psychophysiology, 35(5), 530-536.

Hofer, M. A. (1987). Early social relationships: a psychobiologist's view. Child Dev, 58(3), 633-647.

Hoffman, J. (1964). Bodily Changes in Pain, Hunger, Fear and Rage - Cannon,W. Contemporary Psychology, 9(11), 454-454.

Holmes, C. J., Hoge, R., Collins, L., Woods, R., Toga, A. W. & Evans, A. C. (1998). Enhancement of MR images using registration for signal averaging. Journal of Computer Assisted Tomography, 22, 324-333.

Holt-Lunstad, J. & Clark, B. D. (2014). Social stressors and cardiovascular response: Influence of ambivalent relationships and behavioral ambivalence. International Journal of Psychophysiology, 93, 381-389.

Hou, C., Liu, J., Wang, K., Li, L., Liang, M., He, Z., et al. (2007). Brain responses to symptom provocation and trauma-related short-term memory recall in coal mining accident survivors with acute severe PTSD. Brain Res, 1144, 165-174.

Hrdy, S. B. (2009). Mothers and Others: The Evolutionary Origins of Mutual Understanding: Harvard University Press.

Humble, M. B., Uvnas-Moberg, K., Engstrom, I. & Bejerot, S. (2013). Plasma oxytocin changes and anti-obsessive response during serotonin reuptake inhibitor treatment: a placebo controlled study. BMC Psychiatry, 13, 344.

Hurlemann, R., Patin, A., Onur, O.A., Cohen, M.X., Baumgartner, T., Metzler, S., Dziobek, I., Gallinat, J., Wagner, M., Maier, W., and Kendrick, K.M. (2010). Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. J Neurosci 30, 4999-5007. doi: 10.1523/JNEUROSCI.5538-09.2010.

Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J. C., & Rizzolatti, G. (2005). Grasping the intentions of others with one's own mirror neuron system. PLoS Biol, 3(3), e79.

Insel, T. R., Young, L., Witt, D. M., & Crews, D. (1993). Gonadal steroids have paradoxical effects on brain oxytocin receptors. J Neuroendocrinol, 5(6), 619 – 628.

Insel, T.R., and Hulihan, T.J. (1995). A gender-specific mechanism for pair bonding: oxytocin and partner preference formation in monogamous voles. Behav Neurosci 109, 782-789.

Ishunina, T. A., & Swaab, D. F. (1999). Vasopressin and oxytocin neurons of the human supraoptic and paraventricular nucleus: size changes in relation to age and sex. J Clin Endocrinol Metab, 84(12), 4637-4644.

Jabbi, M., Swart, M., & Keysers, C. (2007). Empathy for positive and negative emotions in the gustatory cortex. Neuroimage, 34(4), 1744-1753. doi: DOI 10.1016/j.neuroimage.2006.10.032

Jack, A., Connelly, J. J., & Morris, J. P. (2012). DNA methylation of the oxytocin receptor gene predicts neural response to ambiguous social stimuli. Front Hum Neurosci, 6, 280.

Jackson, P. L., Meltzoff, A. N., & Decety, J. (2005). How do we perceive the pain of others? A window into the neural processes involved in empathy. Neuroimage, 24(3), 771-779. doi: DOI 10.1016/j.neuroimage.2004.09.006

Jezova, D., Jurankova, E., Mosnarova, A., Kriska, M., & Skultetyova, I. (1996). Neuroendocrine response during stress with relation to gender differences. Acta Neurobiol Exp (Wars), 56(3), 779-785.

Johnson, A.E., Coirini, H., Insel, T.R., and Mcewen, B.S. (1991). The regulation of oxytocin receptor binding in the ventromedial

hypothalamic nucleus by testosterone and its metabolites. Endocrinology 128, 891-896. doi: 10.1210/endo-128-2-891.

Kagerbauer, S. M., Martin, J., Schuster, T., Blobner, M., Kochs, E. F., & Landgraf, R. (2013b). Plasma oxytocin and vasopressin do not predictneuropeptide concentrationsinhuman cerebrospinal fluid. Journal of Neuroendocrinology, 25, 668-673.

Kaminsky, Z., Tochigi, M., Jia, P., Pal, M., Mill, J., Kwan, A., et al. (2012). A multi-tissue analysis identifies HLA complex group 9 gene methylation differences in bipolar disorder. Mol Psychiatry, 17(7), 728-740.

Kanske, P., & Kotz, S. A. (2011). Emotion speeds up conflict resolution: a new role for the ventral anterior cingulate cortex? Cereb Cortex, 21(4), 911-919.

Karama, S., Lecours, A. R., Leroux, J. M., Bourgouin, P., Beaudoin, G., Joubert, S., et al. (2002). Areas of brain activation in males and females during viewing of erotic film excerpts. Hum Brain Mapp, 16(1), 1-13.

Karelina, K., & DeVries, A. C. (2011). Modeling social influences on human health. Psychosom Med, 73(1), 67-74.

Kelly, J. R., & Barsade, S. G. (2001). Mood and emotions in small groups and work teams. Organizational Behavior and Human Decision Processes, 86(1), 99-130. doi: 10.1006/obhd.2001.2974

Kelly, M. J., & Ronnekleiv, O. K. (2008). Membrane-initiated estrogen signaling in hypothalamic neurons. Mol Cell Endocrinol, 290(1-2), 14-23.

Kemp, A. H., & Guastella, A. J. (2011). The Role of Oxytocin in Human Affect: A Novel Hypothesis. Current Directions in Psychological Science, 20(4), 222-231.

Kemp, A.H., and Guastella, A.J. (2011). The Role of Oxytocin in Human Affect: A Novel Hypothesis. Current Directions in Psychological Science 20, 222-231. doi: 10.1177/0963721411417547.

Kennedy, D.P., Glascher, J., Tyszka, J.M., and Adolphs, R. (2009). Personal space regulation by the human amygdala. Nat Neurosci 12, 1226-1227. doi: 10.1038/nn.2381.

Keri, S., and Benedek, G. (2009). Oxytocin enhances the perception of biological motion in humans. Cogn Affect Behav Neurosci 9, 237-241. doi: 10.3758/CABN.9.3.237.

Keysers, C., & Gazzola, V. (2007). Integrating simulation and theory of mind: from self to social cognition. Trends Cogn Sci, 11(5), 194-196.

Keysers, C., Kaas, J. H., & Gazzola, V. (2010). Somatosensation in social perception. Nat Rev Neurosci, 11(6), 417-428. doi: 10.1038/nrn2833

Kilner, J. M., & Frith, C. D. (2008). Action observation: inferring intentions without mirror neurons. Curr Biol, 18(1), R32-33.

Kim, Y. R., Kim, C. H., Cardi, V., Eom, J. S., Seong, Y., & Treasure, J. (2014). Intranasal oxytocin attenuates attentional bias for eating and fat shape stimuli in patients with anorexia nervosa. Psychoneuroendocrinology, 44, 133-142.

Kingham, M. & Gordon, H. (2004). Aspects of morbid jealousy. Advances in Psychiatric Treatment, 10, 207-215.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., Gruppe, H., Mattay, V.S., Gallhofer, B., and Meyer-Lindenberg, A. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. J Neurosci 25, 11489-11493. doi: 10.1523/JNEUROSCI.3984-05.2005.

Klumpp, H., Post, D., Angstadt, M., Fitzgerald, D. A., & Phan, K. L. (2013). Anterior cingulate cortex and insula response during indirect and direct processing of emotional faces in generalized social anxiety disorder. Biol Mood Anxiety Disord, 3, 7.

Knobloch, H. S., & Grinevich, V. (2014). Evolution of oxytocin pathways in the brain of vertebrates. Front Behav Neurosci, 8, 31. doi: 10.3389/fnbeh.2014.00031

Koenigs, M., Young, L., Adolphs, R., Tranel, D., Cushman, F., Hauser, M., et al. (2007). Damage to the prefrontal cortex increases utilitarian moral judgements. Nature, 446, 908-911.

Kog, E., Vertommen, H., and Vandereycken, W. (1987). Minuchin's psychosomatic family model revised: A concept-validation study using a multitrait-multimethod approach. Famliy Process 26, 235-252.

Kohler, E., Keysers, C., Umilta, M. A., Fogassi, L., Gallese, V., & Rizzolatti, G. (2002). Hearing sounds, understanding actions: action representation in mirror neurons. Science, 297(5582), 846-848.

Kok, B. E., & Fredrickson, B. L. (2010). Upward spirals of the heart: Autonomic flexibility, as indexed by vagal tone, reciprocally and prospectively predicts positive emotions and social connectedness. Biological Psychology, 85(3), 432-436.

Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., and Fehr, E. (2005). Oxytocin increases trust in humans. Nature 435, 673-676. doi: 10.1038/nature03701.

Kramer, K. M., Choe, C., Carter, C. S., & Cushing, B. S. (2006). Developmental effects of oxytocin on neural activation and neuropeptide release in response to social stimuli. Horm Behav, 49(2), 206-214.

Krohne, H.-W., Egloff, B., Kohlmann, C.W., and Tausch, A. (1996). Untersuchung mit einer deutschen Form der Positive and Negative Affect Schedule (PANAS). Diagnostica 42, 139-156.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., Fox, P. T. (2000). Automated talairach atlas labels for functional brain mapping. [Research Support, U.S. Gov't, P.H.S.]. Hum Brain Mapp, 10(3), 120-131.

Landgraf, R. (1985). Plasma Oxytocin Concentrations in Man after Different Routes of Administration of Synthetic Oxytocin. Exp Clin Endocrinol Diabetes, 85(2), 245 - 248.

Landgraf, R., & Neumann, I. D. (2004). Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. Frontiers in Neuroendocrinology, 25(3-4), 150-176.

Lane, A., Luminet, O., Rime, B., Gross, J. J., de Timary, P., & Mikolajczak, M. (2013). Oxytocin increases willingness to socially share one's emotions. Int J Psychol, 48(4), 676-681. doi: 10.1080/00207594.2012.677540

Lang, P.J., Bradley, M.M., and Cuthbert, B.N. (2005). International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-6. Gainesville, FL: University of Florida.

Lawrence, E. J., Shaw, P., Giampietro, V. P., Surguladze, S., Brammer, M. J., & David, A. S. (2006). The role of 'shared representations' in social perception and empathy: An fmri study. Neuroimage, 29(4), 1173-1184. doi: 10.1016/j.neuroimage.2005.09.001

Leckman, J. F., Goodman, W. K., North, W. G., Chappell, P. B., Price, L. H., Pauls, D. L., et al. (1994). Elevated cerebrospinal fluid levels of oxytocin in obsessive-compulsive disorder. Comparison with

Tourette's syndrome and healthy controls. Archives of General Psychiatry, 51, 782-792.

Lee, J. A. (1988). Love styles. In: M. H. Barnes & R. J. Sternberg (eds). The Psychology of love, New Haven, Conn, Yale University Press. p. 38–67.

Leggitt, J. S., & Gibbs, R. W. (2000). Emotional reactions to verbal irony. Discourse Processes, 29(1), 1-24. doi: 10.1207/S15326950dp2901_1

Levy, K.N., and Kelly, K.M. (2010). Sex Differences in Jealousy: A Contribution From Attachment Theory. Psycholgical Science 21, 168-173. doi: 10.1177/0956797609357708

Lischke, A., Gamer, M., Berger, C., Grossmann, A., Hauenstein, K., Heinrichs, M., Herpertz, S.C., and Domes, G. (2012). Oxytocin increases amygdala reactivity to threatening scenes in females. Psychoneuroendocrinology 37, 1431-1438. doi: 10.1016/j.psyneuen.2012.01.011.

Liscum, L., & Munn, N. J. (1999). Intracellular cholesterol transport. Biochim Biophys Acta, 1438(1), 19-37.

Liu, J.C.J., Guastella, A.J., and Dadds, M.R. (2012). Effects of oxytocin on human social approach measured using intimacy equilibriums. Horm Behav 62, 585–591.

Loth, E., Poline, J. B., Thyreau, B., Jia, T., Tao, C., Lourdusamy, A., et al. (2014). Oxytocin Receptor Genotype Modulates Ventral Striatal Activity to Social Cues and Response to Stressful Life Events. Biological Psychiatry, 76, 367-376.

Loup, F., Tribollet, E., Dubois-Dauphin, M., and Dreifuss, J.J. (1991). Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. Brain Res 555, 220-232.

Lucht, M. J., Barnow, S., Sonnenfeld, C., Rosenberger, A., Grabe, H. J., Schroeder, W., et al. (2009). Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjects. Prog Neuropsychopharmacol Biol Psychiatry, 33(5), 860-866.

Ludwig, M., Tobin, V. A., Callahan, M. F., Papadaki, E., Becker, A., Engelmann, M., & Leng, G. (2013). Intranasal application of vasopressin fails to elicit changes in brain immediate early gene expression, neural activity and behavioural performance of rats. [Research Support, N.I.H., Extramural

Lundstrom, J.N., and Jones-Gotman, M. (2009). Romantic love modulates women's identification of men's body odors. Horm Behav 55, 280-284. doi: 10.1016/j.yhbeh.2008.11.009.

MacDonald, K., & Feifel, D. (2012). Dramatic improvement in sexual function induced by intranasal oxytocin. J Sex Med, 9(5), 1407-1410.

Madeira, M. D., Sousa, N., Cadete-Leite, A., Lieberman, A. R., & Paula-Barbosa, M. M. (1993). The supraoptic nucleus of the adult rat hypothalamus displays marked sexual dimorphism which is dependent on body weight. Neuroscience, 52(3), 497-513.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A. & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage, 19, 1233-1239.

Malekpour, M. (2007). Effects of attachment on early and later development. British Journal of Developmental Disabilities, 53(105), 81-95.

Maney, D. L., Goode, C. T., Lange, H. S., Sanford, S. E., & Solomon, B. L. (2008). Estradiol modulates neural responses to song in a seasonal songbird. J Comp Neurol, 511(2), 173-186.

Marsh, A. A., & Cardinale, E. M. (2012). When psychopathy impairs moral judgments: Neural responses during judgments about causing fear. Soc Cogn Affect Neurosci, 9(1), 3-11. doi: doi: 10.1093/scan/nss097

Mateo, J. M. (2009). Maternal Influences on Development, Social Relationships, and Survival Behaviors. In Maternal effects in mammals. University of Chicago Press: Chicago.

Mattick, R.P., and Clarke, J.C. (1998). Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. Behav Res Ther 36, 455-470.

McCarthy, M. M. (1995). Estrogen modulation of oxytocin and its relation to behavior. Adv Exp Med Biol, 395, 235-245.

Mcguire, B., & Novak, M. (1984). A Comparison of Maternal-Behavior in the Meadow Vole (Microtus-Pennsylvanicus), Prairie Vole (Microtus-Ochrogaster) and Pine Vole (Microtus-Pinetorum). Animal Behaviour, 32(Nov), 1132-1141.

McGuire, B., Gretz, L. L., Hofmann, J. E., Pizzuto, T., & Frase, B. (1993). Natal dispersal and philopatry in prairie voles (Microtus ochrogaster) in relation to population density, season, and natal social environment. Behav Ecol Sociobiol, 32, 293 - 302.

McKiernan, K. A., D'Angelo, B. R., Kaufman, J. N., & Binder, J. R. (2006). Interrupting the "stream of consciousness": An fmri investigation. Neuroimage, 29(4), 1185-1191. doi: 10.1016/j.neuroimage.2005.09.030

Metherall, J. E., Waugh, K., & Li, H. (1996). Progesterone inhibits cholesterol biosynthesis in cultured cells. Accumulation of cholesterol precursors. J Biol Chem, 271(5), 2627-2633.

Naber, F. B., Poslawsky, I. E., van Ijzendoorn, M. H., van Engeland, H., & Bakermans-Kranenburg, M. J. (2013). Brief report: oxytocin

enhances paternal sensitivity to a child with autism: a double-blind within-subject experiment with intranasally administered oxytocin. J Autism Dev Disord, 43(1), 224-229.

Neumann, I. D., Maloumby, R., Beiderbeck, D. I., Lukas, M., & Landgraf, R. (2013). Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice. Psychoneuroendocrinology, 38(10), 1985-1993.

Newman, S. W. (1999). The medial extended amygdala in male reproductive behavior. A node in the mammalian social behavior network. Ann N Y Acad Sci, 877, 242-257.

Niedenthal, P. M. (2007). Embodying emotion. Science, 316(5827), 1002-1005. doi: 10.1126/science.1136930

Nohlen, H. U., van Harreveld, F., Rotteveel, M., Lelieveld, G. J. & Crone, E. A. (2014). Evaluating ambivalence: social-cognitive and affective brain regions associated with ambivalent decision-making. Social Cognitive and Affective Neuroscience, 9, 924-931.

Nomura, M., Iidaka, T., Kakehi, K., Tsukiura, T., Hasegawa, T., Maeda, Y., et al. (2003). Frontal lobe networks for effective processing of ambiguously expressed emotions in humans. Neurosci Lett, 348(2), 113-116.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain--a meta-analysis of imaging studies on the self. [Meta-Analysis

Nunes, S., Fite, J. E., Patera, K. J., & French, J. A. (2001). Interactions among paternal behavior, steroid hormones, and parental experience in male marmosets (Callithrix kuhlii). Horm Behav, 39(1), 70 - 82.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. Trends Cogn Sci, 9(5), 242-249.

Oliveras, D., & Novak, M. (1986). A Comparison of Paternal Behavior in the Meadow Vole Microtus-Pennsylvanicus, the Pine Vole Microtus-Pinetorum and the Prairie Vole Microtus-Ochrogaster. Animal Behaviour, 34, 519-526.

Onoda, K., Okamoto, Y., Toki, S., Ueda, K., Shishida, K., Kinoshita, A., et al. (2008). Anterior cingulate cortex modulates preparatory activation during certain anticipation of negative picture. Neuropsychologia, 46(1), 102-110.

Opialla, S., Lutz, J., Scherpiet, S., Hittmeyer, A., Jancke, L., Rufer, M., et al. (2014). Neural circuits of emotion regulation: a comparison of mindfulness-based and cognitive reappraisal strategies. Eur Arch Psychiatry Clin Neurosci.

Otake, K., Shimai, S., Tanaka-Matsumi, J., Otsui, K., & Fredrickson, B. L. (2006). Happy people become happier through kindness: A counting kindnesses intervention. Journal of Happiness Studies, 7, 361 - 375. doi: 10.1007/s10902-005-3650-z

Ozbay, F., Johnson, D. C., Dimoulas, E., Morgan, C. A., Charney, D., & Southwick, S. (2007). Social support and resilience to stress: from neurobiology to clinical practice. Psychiatry (Edgmont), 4(5), 35-40.

Patchev, V. K., Schlosser, S. F., Hassan, A. H., & Almeida, O. F. (1993). Oxytocin binding sites in rat limbic and hypothalamic structures: site-specific modulation by adrenal and gonadal steroids. Neuroscience, 57(3), 537-543.

Patisaul, H.B., Scordalakes, E.M., Young, L.J., and Rissman, E.F. (2003). Oxytocin, but not oxytocin receptor, is rRegulated by oestrogen receptor beta in the female mouse hypothalamus. J Neuroendocrinol 15, 787-793. doi: 10.1046/j.1365-2826.2003.01061.x.

Pepping, G. J., & Timmermans, E. J. (2012). Oxytocin and the biopsychology of performance in team sports. ScientificWorldJournal, 2012, 567363.

Perel, P., Roberts, I., Sena, E., Wheble, P., Briscoe, C., Sandercock, P., et al. (2007). Comparison of treatment effects between animal experiments and clinical trials: systematic review. British Medical Journal, 334(7586), 197-200.

Perry, A., Bentin, S., Shalev, I., Israel, S., Uzefovsky, F., Bar-On, D., and Ebstein, R.P. (2010). Intranasal oxytocin modulates EEG mu/alpha and beta rhythms during perception of biological motion. Psychoneuroendocrinology 35, 1446-1453. doi: 10.1016/j.psyneuen.2010.04.011.

Petrovic, P., Kalisch, R., Singer, T. & Dolan, R. J. (2008). Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. Journal of Neuroscience, 28, 6607-6615.

Preckel, K., Scheele, D., Eckstein, M., Maier, W., & Hurlemann, R. (2014). The influence of oxytocin on volitional and emotional ambivalence. Soc Cogn Affect Neurosci, in press.

Preckel, K., Scheele, D., Kendrick, K. M., Maier, W., & Hurlemann, R. (2014). Oxytocin facilitates social approach behavior in women. Frontiers in Behavioral Neuroscience, 8.

Prehn, K., Kazzer, P., Lischke, A., Heinrichs, M., Herpertz, S. C., & Domes, G. (2013). Effects of intranasal oxytocin on pupil dilation indicate increased salience of socioaffective stimuli. Psychophysiology, 50(6), 528-537. doi: Doi 10.1111/Psyp.12042

Prudom, S. L., Broz, C. A., Schultz-Darken, N., Ferris, C. T., Snowdon, C., & Ziegler, T. E. (2008). Exposure to infant scent lowers serum testosterone in father common marmosets (Callithrix jacchus). Biol Lett, 4(6), 603-605.

Radke, S., Roelofs, K., and De Bruijn, E.R. (2013). Acting on anger: social anxiety modulates approach-avoidance tendencies after oxytocin administration. Psychol Sci 24(8), 1573-1578. doi: 10.1177/0956797612472682.

Rakic, P. (2009). Evolution of the neocortex: a perspective from developmental biology. Nat Rev Neurosci, 10(10), 724-735.

Renfro, K.J., and Hoffmann, H. (2013). The relationship between oral contraceptive use and sensitivity to olfactory stimuli. Horm Behav 63, 491-496. doi: 10.1016/j.yhbeh.2013.01.001.

Research Support, Non-U.S. Gov't]. Biol Psychiatry, 65(9), 728-731. doi: 10.1016/j.biopsych.2008.10.011

Research Support, Non-U.S. Gov't]. J Neuroendocrinol, 25(7), 655-667. doi: 10.1111/jne.12046

Research Support, Non-U.S. Gov't]. Neuroimage, 31(1), 440-457. doi: 10.1016/j.neuroimage.2005.12.002

Research Support, Non-U.S. Gov't]. Neuroimage, 62(1), 493-499. doi: 10.1016/j.neuroimage.2012.05.012

Research Support, Non-U.S. Gov't]. Psychoneuroendocrinology, 38(8), 1418-1425. doi: 10.1016/j.psyneuen.2012.12.023

Riem, M. M., Bakermans-Kranenburg, M. J., Huffmeijer, R., & van Ijzendoorn, M. H. (2013). Does intranasal oxytocin promote prosocial behavior to an excluded fellow player? A randomized-controlled trial with Cyberball. Psychoneuroendocrinology, 38(8), 1418-1425.

Riem, M. M., Bakermans-Kranenburg, M. J., Pieper, S., Tops, M., Boksem, M. A., Vermeiren, R. R., et al. (2011). Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: a randomized controlled trial. Biol Psychiatry, 70(3), 291-297.

Rilling, J. K., Demarco, A. C., Hackett, P. D., Chen, X., Gautam, P., Stair, S., et al. (2014). Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. Psychoneuroendocrinology, 39.

Rilling, J. K., DeMarco, A. C., Hackett, P. D., Thompson, R., Ditzen, B., Patel, R., et al. (2012). Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in men. Psychoneuroendocrinology, 37(4), 447-461.

Rilling, J.K., Demarco, A.C., Hackett, P.D., Chen, X., Gautam, P., Stair, S., Haroon, E., Thompson, R., Ditzen, B., Patel, R., and Pagnoni, G. (2014). Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. Psychoneuroendocrinology. doi: 10.1016/j.psyneuen.2013.09.022.

Rizzolatti, G., & Sinigaglia, C. (2010). The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. Nat Rev Neurosci, 11(4), 264-274.

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. Brain Res Cogn Brain Res, 3(2), 131-141.

Rizzolatti, G., Fadiga, L., Matelli, M., Bettinardi, V., Paulesu, E., Perani, D., et al. (1996). Localization of grasp representation in humans by PET: 1. Observation versus execution. Exp Brain Res, 111(2), 246 - 252.

Rizzolatti, G., Fogassi, L., & Gallese, V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci, 2(9), 661-670.

Rodrigues, S. M., Saslow, L. R., Garcia, N., John, O. P., & Keltner, D. (2009). Oxytocin receptor genetic variation relates to empathy and

stress reactivity in humans. Proc Natl Acad Sci U S A, 106(50), 21437-21441.

Roelofs, K., Minelli, A., Mars, R.B., Van Peer, J.M., and Toni, I. (2009). On the neural control of social emotional behavior. Social Cognitive and Affective Neuroscience 4, 50-58. doi: 10.1093/scan/nsn036.

Rosen, G. J., De Vries, G. J., Villalba, C., Weldele, M. L., Place, N. J., Coscia, E. M., et al. (2006). Distribution of vasopressin in the forebrain of spotted hyenas. J Comp Neurol, 498(1), 80-92.

Ross, H.E., Freeman, S.M., Spiegel, L.L., Ren, X., Terwilliger, E.F., and Young, L.J. (2009). Variation in oxytocin receptor density in the nucleus accumbens has differential effects on affiliative behaviors in monogamous and polygamous voles. J Neurosci 29, 1312-1318. doi: 10.1523/JNEUROSCI.5039-08.2009.

Rota, G., Sitaram, R., Veit, R., Erb, M., Weiskopf, N., Dogil, G., et al. (2009). Self-Regulation of Regional Cortical Activity Using Real-Time fMRI: The Right Inferior Frontal Gyrus and Linguistic Processing. Human Brain Mapping, 30(5), 1605-1614.

Rupp, H.A., James, T.W., Ketterson, E.D., Sengelaub, D.R., Ditzen, B., and Heiman, J.R. (2014). Amygdala response to negative images in postpartum vs nulliparous women and intranasal oxytocin. Soc Cogn Affect Neurosci 9, 48-54. doi: 10.1093/scan/nss100.

Saarela, M. V., Hlushchuk, Y., Williams, A. C., Schurmann, M., Kalso, E., & Hari, R. (2007). The compassionate brain: Humans detect intensity of pain from another's face. Cereb Cortex, 17(1), 230-237. doi: 10.1093/cercor/bhj141

Sahakian, B. J. & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: discussion paper. Journal of the Royal Society of Medicine, 85, 399-402.

Salonia, A., Nappi, R.E., Pontillo, M., Daverio, R., Smeraldi, A., Briganti, A., Fabbri, F., Zanni, G., Rigatti, P., and Montorsi, F. (2005). Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. Horm Behav 47, 164-169. doi: 10.1016/j.yhbeh.2004.10.002.

Saphire-Bernstein, S., Way, B. M., Kim, H. S., Sherman, D. K., & Taylor, S. E. (2011). Oxytocin receptor gene (OXTR) is related to psychological resources. Proc Natl Acad Sci U S A, 108(37), 15118-15122.

Sato, W., Kubota, Y., & Toichi, M. (2014). Enhanced subliminal emotional responses to dynamic facial expressions. Front Psychol, 5, 994.

Schächtele, B. (2009). "Buchstaben-Zahlen-Folgen (BZF). Untertest aus dem Wechsler-Intelligenztest. für Erwachsene (WIE)," in Handbuch neuropsychologischer Testverfahren. Band 1: Aufmerksamkeit, Gedächtnis, exekutive Funktionen, eds. D. Schelling, R. Drechsler, D. Heinemann & W. Sturm. (Göttingen: Hogrefe), 804-809.

Scheele, D., Kendrick, K. M., Khouri, C., Kretzer, E., Schlapfer, T. E., Stoffel-Wagner, B., et al. (2014). An Oxytocin-Induced Facilitation of Neural and Emotional Responses to Social Touch Correlates Inversely with Autism Traits. Neuropsychopharmacology, 39, 2078-2085.

Scheele, D., Striepens, N., Güntürkün, O., Deutschländer, S., Maier, W., Kendrick, K.M., and Hurlemann, R. (2012). Oxytocin Modulates Social Distance between Males and Females. J Neurosci 14, 16074-16079. doi: 10.1523/JNEUROSCI.2755-12.2012.

Scheele, D., Striepens, N., Kendrick, K. M., Schwering, C., Noelle, J., Wille, A., et al. (2014b). Opposing effects of oxytocin on moral judgment in males and females. Human Brain Mapping, doi: 10.1002/hbm.22605.

Scheele, D., Wille, A., Kendrick, K.M., Stoffel-Wagner, B., Becker, B., Güntürkün, O., Maier, W., and Hurlemann, R. (2013). Oxytocin enhances brain reward system responses in men viewing the face of their female partner. PNAS 110, 20308 - 20313. doi: 10.1073/pnas.1314190110.

Schnell, K., Dietrich, T., Schnitker, R., Daumann, J., & Herpertz, S. C. (2007). Processing of autobiographical memory retrieval cues in borderline personality disorder. J Affect Disord, 97(1-3), 253-259.

Seema, K. N., & Begum, K. (2008). Childrearing Practices Among Kurubas and Soliga Tribes From South India. Stud. Tribes Tribals, 6(1), 59 -62.

Shamay-Tsoory, S. G., Fischer, M., Dvash, J., Harari, H., Perach-Bloom, N., & Levkovitz, Y. (2009). Intranasal administration of oxytocin increases envy and schadenfreude (gloating). Biol Psychiatry, 66(9), 864-870.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amoriam, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., and Dunbar, G. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. J Clin Psychiatry 59, 22 - 33.

Shenhav, A. & Greene, J. D. (2010). Moral judgments recruit domain-general valuation mechanisms to integrate representations of probability and magnitude. Neuron, 67, 667-677.

Shimamura, A. P. (2000). The role of the prefrontal cortex in dynamic filtering. Psychobiology, 28(2), 207-218.

Shukovski, L., Healy, D. L., & Findlay, J. K. (1989). Circulating immunoreactive oxytocin during the human menstrual cycle comes

from the pituitary and is estradiol dependent. J Clin Endocrinol Metab, 68(2), 455-460.

Simpson, J. R., Jr., Snyder, A. Z., Gusnard, D. A., & Raichle, M. E. (2001). Emotion-induced changes in human medial prefrontal cortex: I. During cognitive task performance. Proc Natl Acad Sci U S A, 98(2), 683-687.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Firth, C.D. (2004). Empathy for pain involves the affective but not sensory components of pain. Science, 303(5661), 1157-1162.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). Manual for the state-trait anxiety inventory. Palo Alto, CA: Consulting Psychologists Press.

Stankova, T., Eichhammer, P., Langguth, B., and Sand, P.G. (2012). Sexually dimorphic effects of oxytocin receptor gene (OXTR) variants on Harm Avoidance. Biology of Sex Differences 17, 1-5. doi: 10.1186/2042-6410-3-17.

Striepens, N., Kendrick, K.M., Hanking, V., Landgraf, R., Wullner, U., Maier, W., and Hurlemann, R. (2013). Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. Sci Rep 3, 3440. doi: 10.1038/srep03440.

Striepens, N., Matusch, A., Kendrick, K.M., Mihov, Y., Elmenhorst, D., Becker, B., Lang, M., Coenen, H.H., Maier, W., Hurlemann, R., and Bauer, A. (2014). Oxytocin enhances attractiveness of unfamiliar female faces independent of the dopamine reward system. Psychoneuroendocrinology 39, 74-87. doi: 10.1016/j.psyneuen.2013.09.026.

Striepens, N., Scheele, D., Kendrick, K.M., Becker, B., Schafer, L., Schwalba, K., Reul, J., Maier, W., and Hurlemann, R. (2012).

Oxytocin facilitates protective responses to aversive social stimuli in males. Proc Natl Acad Sci U S A 109, 18144-18149. doi: 10.1073/pnas.1208852109.

Szeto, A., McCabe, P. M., Nation, D. A., Tabak, B. A., Rossetti, M. A., McCullough, M. E., et al. (2011). Evaluation of enzyme immunoassay and radioimmunoassay methods for the measurement of plasma oxytocin. Psychosom Med, 73(5), 393-400.

Takahashi, H., Matsuura, M., Yahata, N., Koeda, M., Suhara, T. & Okubo, Y. (2006). Men and women show distinct brain activations during imagery of sexual and emotional infidelity. Neuroimage, 32(3), 1299-1307.

Taylor, G. J., Bagby, R. M., Ryan, D. P., Parker, J. D., Doody, K. F., & Keefe, P. (1988). Criterion validity of the toronto alexithymia scale. Psychosomatic Medicine, 50(5), 500-509.

Taylor, P. V., Veenema, A. H., Paul, M. J., Bredewold, R., Isaacs, S., & de Vries, G. J. (2012). Sexually dimorphic effects of a prenatal immune challenge on social play and vasopressin expression in juvenile rats. Biol Sex Differ, 3(1), 15.

Taylor, S. E., Gonzaga, G. C., Klein, L. C., Hu, P., Greendale, G. A., & Seeman, T. E. (2006). Relation of oxytocin to psychological stress responses and hypothalamic-pituitary-adrenocortical axis activity in older women. Psychosom Med, 68(2), 238-245.

Taylor, S. E., Klein, L. C., Lewis, B. P., Gruenewald, T. L., Gurung, R. A. R., & Updegraff, J. A. (2000). Biobehavioral Responses to Stress in Females: Tend-and-Befriend, Not Fight-or-Flight. Psychological Review, 107(3), 411 - 429.

Taylor, S. E., Saphire-Bernstein, S., & Seeman, T. E. (2010). Are plasma oxytocin in women and plasma vasopressin in men biomarkers of distressed pair-bond relationships? Psychol Sci, 21(1), 3-7.

Theodoridou, A., Penton-Voak, I.S., and Rowe, A.C. (2013). A direct examination of the effect of intranasal administration of oxytocin on approach-avoidance motor responses to emotional stimuli. PLoS One 8, e58113. doi: 10.1371/journal.pone.0058113.

Theodoridou, A., Rowe, A. C., Penton-Voak, I. S., & Rogers, P. J. (2009). Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. Horm Behav, 56(1), 128-132.

Thomas, J. A., & Birney, E. C. (1979). Parental Care and Mating System of the Prairie Vole, Microtus-Ochrogaster. Behavioral Ecology and Sociobiology, 5(2), 171-186.

Tops, M., van Ijzendoorn, M. H., Riem, M. M., Boksem, M. A., & Bakermans-Kranenburg, M. J. (2011). Oxytocin receptor gene associated with the efficiency of social auditory processing. Front Psychiatry, 2, 60.

Tost, H., Kolachana, B., Hakimi, S., Lemaitre, H., Verchinski, B. A., Mattay, V. S., et al. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. Proc Natl Acad Sci U S A, 107(31), 13936-13941.

Tremeau, F., Antonius, D., Cacioppo, J. T., Ziwich, R., Jalbrzikowski, M., Saccente, E., et al. (2009). In support of Bleuler: objective evidence for increased affective ambivalence in schizophrenia based upon evocative testing. Schizophrenia Research, 107, 223-231.

Tribollet, E., Audigiers, S., Dubois, D. M., & Dreifuss, J. J. (1990). Gonadal steroids regulate oxytocin receptors but not vasopressin receptors in the brain of male and female rats. Brain Res, 511(1), 129 – 140.

Uchino, B. N., Holt-Lunstad, J., Uno, D. & Flinders, J. B. (2001). Heterogeneity in the social networks of young and older adults: prediction of mental health and cardiovascular reactivity during acute stress. Journal of Behavioral Medicine, 24(4), 361-382.

Uchino, B. N., Smith, T. W. & Berg, C. A. (2014). Spousal relationship quality and cardiovascular risk: dyadic perceptions of relationship ambivalence are associated with coronary-artery calcification. Psychological Science, 25, 1037-1042.

Uddin, L. Q., Molnar-Szakacs, I., Zaidel, E., & Iacoboni, M. (2006). rTMS to the right inferior parietal lobule disrupts self-other discrimination. [Research Support, N.I.H., Extramural]

van Harreveld, F., Rutjens, B. T., Rotteveel, M., Nordgren, L. F. & van der Pligt, J. (2009). Ambivalence and decisional conflict as a cause of psychological discomfort: Feeling tense before jumping off the fence. Journal of Experimental Social Psychology, 45(1), 167-173.

Van Kesteren, R. E., Smit, A. B., De Lange, R. P., Kits, K. S., Van Golen, F. A., Van Der Schors, R. C., et al. (1995). Structural and functional evolution of the vasopressin/oxytocin superfamily: vasopressin-related conopressin is the only member present in Lymnaea, and is involved in the control of sexual behavior. J Neurosci, 15(9), 5989-5998.

Varnava, A., Mccarthy, M., and Beaumont, J.G. (2002). Line bisection in normal adults: direction of attentional bias for near and far space. Neuropsychologia 40(8), 1372-1378. doi: 10.1016/S0028-3932(01)00204-4.

Veening, J. G., de Jong, T., & Barendregt, H. P. (2010). Oxytocin-messages via the cerebrospinal fluid: Behavioral effects; a review. Physiology & Behavior, 101(2), 193-210.

Wang, Z. X., Hulihan, T. J., & Insel, T. R. (1997). Sexual and social experience is associated with different patterns of behavior and neural activation in male prairie voles. Brain Research, 767(2), 321-332.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The panas scales. J Pers Soc Psychol, 54(6), 1063-1070.

Weisman, O., Zagoory-Sharon, O., and Feldman, R. (2012). Oxytocin administration to parent enhances infant physiological and behavioral readiness for social engagement. Biol Psychiatry 72(12), 982-989. doi: 10.1016/j.biopsych.2012.06.011.

Wild, B., Erb, M., & Bartels, M. (2001). Are emotions contagious? Evoked emotions while viewing emotionally expressive faces: Quality, quantity, time course and gender differences. Psychiatry Res, 102(2), 109-124.

Williams, J. R., Catania, K. C., & Carter, C. S. (1992). Development of partner preferences in female prairie voles (Microtus ochrogaster): the role of social and sexual experience. Horm Behav, 26(3), 339-349.

Williams, J. R., Insel, T. R., Harbaugh, C. R., & Carter, C. S. (1994). Oxytocin administered centrally facilitates formation of a partner preference in female prairie voles (Microtus ochrogaster). J Neuroendocrinol, 6(3), 247-250.

Wingfield, J. C., Hegner, R. E., Dufty, J. A. M., & Ball, G. F. (1990). The “challenge hypothesis”: theoretical implications for patterns of

testosterone secretion, mating systems, and breeding strategies. American Naturalist, 136(6), 829 – 846.

Winslow, J. T., Hastings, N., Carter, C. S., Harbaugh, C. R., & Insel, T. R. (1993). A role for central vasopressin in pair bonding in monogamous prairie voles. Nature, 365(6446), 545-548.

Witt, D. M., Carter, C. S., & Walton, D. M. (1990). Central and peripheral effects of oxytocin administration in prairie voles (Microtus ochrogaster). Pharmacol Biochem Behav, 37(1), 63-69.

Yamamoto, Y., Cushing, B. S., Kramer, K. M., Epperson, P. D., Hoffman, G. E., & Carter, C. S. (2004). Neonatal manipulations of oxytocin alter expression of oxytocin and vasopressin immunoreactive cells in the paraventricular nucleus of the hypothalamus in a gender-specific manner. Neuroscience, 125(4), 947-955.

Young, L.J., Wang, Z., Donaldson, R., and Rissman, E.F. (1998). Estrogen receptor alpha is essential for induction of oxytocin receptor by estrogen. Neuroreport 9, 933-936.

Zaki, J., Davis, J. I., & Ochsner, K. N. (2012). Overlapping activity in anterior insula during interoception and emotional experience. [Research Support, N.I.H., Extramural]

Zaki, J., Ochsner, K. N., Hanelin, J., Wager, T. D., & Mackey, S. C. (2007). Different circuits for different pain: patterns of functional connectivity reveal distinct networks for processing pain in self and others. Soc Neurosci, 2(3-4), 276-291.

Zhong, S., Monakhov, M., Mok, H.P., Tong, T., Lai, P.S., Chew, S.H., and Ebstein, R.P. (2012). U-shaped relation between plasma oxytocin levels and behavior in the trust game. PLoS One 7, e51095. doi: 10.1371/journal.pone.0051095.

Appendices

Appendix A: List of Abbreviations

AA	approach and avoidance
aal	automatic anatomic labeling
ACC	anterior cingulate cortex
ANOVA	analysis of variance
AVP	vasopressin
BBB	blood-brain barrier
BDI	Beck's Depression Inventory
BZF	Letter-Number-Sequence
CANTAB	Cambridge Neurophsychological Test
CSF	cerebrospinal fluid
dACC	dorsal anterior cingulate cortex
EC	eye contact
EES	emotion evocative statement
EPI	echoplanar imaging
EPQ	Ethic Position Questionnaire
ER	estrogen receptor
Exp.	Experiment
FFF	flight-fright-fight
fMRI	functional magnetic resonance imaging
FoV	field of view
FWE	family-wise error
IAPS	International Affective Picture System
IPL	inferior parietal lobe
IU	international Unit
LCD	liquid crystal display

M.I.N.I.	Mini-International Neuropsychiatric Interview
MEIL	Marburg Attitude Scales to Love Styles
MNI	Montreal Neurological Institute
NPI	neurophysin I
NPII	neurophysin II
OCD	obsessive-compulsive disorder
OFC	orbitofrontal cortex
OXT	oxytocin
OXTR	oxytocin receptor
PAL	paired associates learning task
PANAS	Positive and Negative Affect Schedule
PLC	placebo
PLS	Passionate Love Scale
PM	person moving
PVN	paraventricular nucleus
ROI	region of interest
RT	reaction time
RTI	reaction time task
SBBN	Social behavior brain network
SEM	standard error of the mean
SIAS	Social Interaction Anxiety Scale
SNP	single nucleotide polymorphism
SON	supraoptic nucleus
SP	starting position
SPS	Social Phobia Scale
SWM	spatial working memory task
T	testosterone

TD	Talairach Daemon
TE	echo time
TPJ	temporoparietal junction
TR	repetition time
WFU	Wake Forest University

Appendix B: Explanation to the contributions of the co-authors

Manuscript 1: Oxytocin facilitates social approach behavior in women

Planning and conceptual design: Katrin Preckel, Dirk Scheele (postdoctoral researcher) and René Hurlemann (team leader)

Experimental guidance, experimental execution and organization: Katrin Preckel

Programming: Paul Jung (student assistant)

Analysis: Katrin Preckel

Figure creation: Katrin Preckel

Writing the manuscript: Katrin Preckel, Dirk Scheele and René Hurlemann

Manuscript 2: Oxytocin increases the willingness to induce happy emotions and decrease the willingness to induce negative emotions

Planning and conceptual design: Katrin Preckel and René Hurlemann (team leader)

Experimental guidance, experimental execution and organization: Katrin Preckel, Monika Eckstein (another PhD – student), Dirk Scheele (postdoctoral researcher) who helped me with the fMRI measurements, because there need to be two people present at all times

Programming: Paul Jung (student assistant)

Analysis: Katrin Preckel

Figure creation: Katrin Preckel

Writing the manuscript: Katrin Preckel, Ben Becker (a postdoctoral researcher) and René Hurlemann

Manuscript 3: The influence of oxytocin on volitional and emotional ambivalence

Planning and conceptual design: Experiment 1: Katrin Preckel and René Hurlemann, Experiment 2: Dirk Scheele and René Hurlemann

Experimental guidance, experimental execution and organization: Katrin Preckel, Monika Eckstein (another PhD – student) and Dirk Scheele (postdoctoral researcher) who helped me with the fMRI measurements, because there need to be two people present at all times

Programming: Paul Jung (student assistant)

*Analysis:*Experiment 1: Katrin Preckel, Experiment 2: Dirk Scheele

Figure creation: Experiment 1: Katrin Preckel, Experiment 2: Dirk Scheele

Writing the manuscript: Katrin Preckel, Dirk Scheele and René Hurlemann

The two experiments were initially designed to be published in different articles.

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