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Review

Prosocial effects of oxytocin and clinical evidence for its therapeutic potential

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ABSTRACT

There has been unprecedented interest in the prosocial effects of the neuropeptide oxytocin in humans over the last decade. A range of studies has demonstrated correlations between basal oxytocin levels and the strength of social and bonding behaviors both in healthy individuals and in those suffering from psychiatric disorders. Mounting evidence suggests associations between polymorphisms in the oxytocin receptor gene and prosocial behaviors and there may also be important epigenetic effects. Many studies have now reported a plethora of prosocial effects of intranasal application of oxytocin, including the domains of trust, generosity, socially reinforced learning, and emotional empathy. The main focus of this review will be to summarize human preclinical work and particularly the rapidly growing number of clinical studies which have identified important links between oxytocin and a wide range of psychiatric disorders, and have now started to directly assess its therapeutic potential.

1. Introduction

The past decade has witnessed many advances in our understanding of the multifaceted role of the neuropeptide oxytocin (OXT) in the human social brain, building upon the findings reported over a period of 25 years in animal species such as rodents and sheep. From an evolutionary point of view OXT in one form or another (isotocin, mesotocin or oxytocin) is present in an extensive range of species from reptiles to primates, as one might expect if it plays a key role in the control of social and reproductive behaviors [116]. Both preclinical and clinical studies in humans have generated unprecedented interest in the therapeutic use of OXT in social and affective disorders and this review will summarize this body of work.

1.1. Key effects on social behavior in animals

In mammals OXT is synthesized from its precursor neurophysin-1 and is present as a small nine amino acid peptide [224] with one current known receptor (OXTR) which is a classic seven transmembrane domain polypeptide of the rhodopsin-type class 1 G-protein coupled receptor family [103]. Oxytocin is primarily synthesized in the magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus which project to the posterior pituitary and are responsible for its release into the peripheral venous bloodstream. There are, however, also parvocellular OXT-containing neurons in the PVN which rather than projecting to the pituitary project to a variety of brain regions including other hypothalamic regions, the cortex and limbic system. Originally it was thought that only these parvocellular OXT neurons were responsible for release of the peptide within the brain and this raised serious questions about the relevance of measuring its concentrations in the blood as an accurate reflection of brain release. However, subsequently it has been shown that dendritic release of OXT from the magnocellular neurons also contributes to brain release and particularly to concentrations found in the cerebrospinal fluid (CSF) [131]. Thus, there is a greater confidence in concluding that altered blood, saliva or urine concentrations of the peptide may reflect similar altered brain release although some caution must still be maintained here since release profiles in the brain do not always mirror those in the blood [5].

Initial findings in sheep that OXT was released within the brain as well as into the blood via the posterior pituitary while animals gave birth and suckled [98], followed by demonstrations that this brain release promoted both maternal responses and formation of attachment bonds with offspring [97], sparked off interest in the dual role of this peptide in promoting social bonds via its action within the brain as well as its peripheral hormonal actions in promoting uterine contractions and milk ejection. A large amount of work in voles, in particular, has also shown its key importance in promoting partner bonds following mating, and work in a variety of species has implicated the peptide in facilitating olfactory based social recognition memory and as a potent anxiolytic (see [168]).

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Table 1
Social bonds and emotions: OXT and social bonds.

Authors	Subjects	OXT Dose	Main Finding	Study Design
Buchheim et al. 2009 [23]	26 M	24 IU intranasally	OXT increased attachment in individuals having an insecure attachment phenotype	Double-blind, placebo-controlled, within-subjects design
Feldman et al. 2007 [55]	62F	no OXT treatment	OXT plasma levels in the early pregnancy and the postpartum periods were related to maternal bonding behaviors	Between-subjects design
Gonzaga et al. 2006 [69]	63 M, 63 F	no OXT treatment	Nonverbal display of romantic love was related to increased plasma OXT levels	Between-subjects design
Seltzer et al. 2010 [178]	61 F, 61 girls	no OXT treatment	Children receiving vocal and non-verbal contact with their mothers showed the highest plasma levels of OXT	Between-subjects design
Strathearn et al. 2009 [190]	30 F	no OXT treatment	Plasma OXT response to infant contact at 7 months was higher in mothers with secure attachment and correlated with brain activation in hypothalamus/ pituitary region	Between-subjects design
Taylor et al. 2010 [195]	32 M, 53 F	no OXT treatment	Increased plasma OXT was associated with distress in the pair-bond relationship for women, but not for men	Between-subjects design
Turner et al. 1999 [203]	25 F	no OXT treatment	Plasma OXT levels during sadness were correlated with lower anxiety in close relationships. Women in a couple relationship showed greater increases in OXT in response to positive emotion and higher basal levels of OXT were associated with greater interpersonal distress	Between-subjects design

Table 2
Social Bonds and emotions: OXT effects on trust, generosity and altruism in economic contexts.

Authors	Subjects	OXT Dose	Main Finding	Study Design
Baumgartner et al. 2008 [15]	49 M	24 IU intranasally	Subjects receiving OXT maintain their trusting behavior after betrayal, individuals receiving placebo respond to betrayal with a decrease in trust	Double-blind, placebo-controlled, between-subjects design
De Dreu et al. 2010 [35]	49 M	24 IU intranasally	OXT promotes in-group trust, cooperation and defense, but not offensive, aggression toward competing out-groups	Double-blind, placebo-controlled, between-subjects design
Declerck et al. 2010 [36]	119 M, 140 F	24 IU intranasally	OXT increased cooperative behavior when a social cue was present but not when a non-social cue was used	Double-blind, placebo-controlled, crossover-design
Israel et al. 2009 [93]	101 M, 102 F	no OXT treatment	OXTR alleles rs1042778, rs2268490, rs237887 were associated with altruism (dictator game and in a social values orientation task)	Between-subjects design
Kosfeld et al. 2005 [107]	128 M(TG[1]), 66 M(RG[2])	24 IU intranasally	OXT increased willingness to trust other people but did not increase trust towards impersonal things : "a project" for example	Double-blind, placebo-controlled, between-subjects design
Zak et al. 2004 [220]	82 M / F	no OXT treatment	Plasma OXT levels increased in response to a social signal of trust and were related to trustworthy behavior	Double-blind, placebo-controlled, between-subjects design
Zak et al. 2005 [221]	78 M, 78 F	no OXT treatment	Plasma OXT levels increased in a situation where there was a social intention of trust and were associated with trustworthiness/ trustworthy behavior	Double-blind, placebo-controlled, between-subjects design
Zak et al. 2007 [222]	68 M	40 IU intranasally	OXT increased generosity by 80% but had no effect on altruism	Double-blind, placebo-controlled, between-subjects design

[1] TG trust game.
[2] RG risk game.

Mice lacking functional expression of either OXT or OXTR (see [124]) show impaired social but not non-social recognition memory and have elevated levels of anxiety.

Work in animal species has established that OXT is a potent neuromodulator within the brain and many of its actions on social behavior appear to be produced via modulation of neurotransmitter signaling in a variety of different brain regions. It has also been established that there are OXT autoreceptors within the PVN whereby the peptide can act to potentiate its own release (see [96]). To date the brain distribution of the OXTR has only been extensively mapped in rodents [218] and sheep [21] and a major drawback as far as human-based research is concerned is that none of the current receptor ligands which have been successfully used in brain autoradiographic studies in rodents appear to work in the brains of sheep, monkeys or humans. It is possible to use in situ hybridization histochemistry, riboprobe (RNA probes) or polymerase chain reaction (PCR) methods to measure OXTR messenger RNA (mRNA), but so far they have only been employed to do this in rats [218] and sheep [21]. While there appear to be similar receptor distributions in rodents and sheep, and we can probably assume that it will be the same in monkeys and humans, the absence of a receptor-mapping study in humans remains an issue that definitely needs to be resolved. It also currently rules out the use of positron emission tomography (PET) approaches to study altered receptor expression in different experimental situations or in humans with specific polymorphisms in the OXTR which are associated with various psychiatric, social or affective disorders. This is particularly important in view of a key finding from studies in voles and other rodents showing that the pattern of OXTR expression is different in social compared with asocial species, most notably in terms of higher expression occurring in brain reward areas, such as the nucleus accumbens, and the frontal cortex in social species [124]. Differential levels of social bonding behavior within the same vole species have also been correlated with expression levels of OXTR in the nucleus accumbens [165]. It is assumed that these different patterns of OXTR expression are influenced by specific polymorphisms in the same was as they have been shown to be for the V1a vasopressin receptor [124] although this has yet to be confirmed. Epigenetic factors may also play an important role since the OXTR has been found to have a CpG island in its promoter and the methylation status of this can influence expression levels [102].

An important observation from brain OXTR mapping and OXT immunocytochemical studies in rodents and sheep is that cells expressing the receptor appear to be present in a wider range of

Table 3
Social bonds and emotions: OXT effects on trust and social interaction in other contexts.

Authors	Subjects	OXT Dose	Main Finding	Study Design
Alvares et al. 2010 [4]	37 M, 37 F	24 IU intranasally	OXT increased desire to play a cyberball game again with virtual partners after ostracism but had no effect on negative affective and attachment-related reactions after social rejection	Double-blind, placebo-controlled, between-subjects design
Guastella et al. 2008 [78]	69 M	24 IU intranasally	OXT lightly increased trustworthiness to happy faces	Double-blind, placebo-controlled, crossover-design
Mikolajczak et al. 2010 [144]	60 M	32 IU intranasally	OXT increased trust in a trust game but did not facilitate behavior when the partner was untrustworthy	Double-blind, placebo-controlled, between-subjects design
Mikolajczak et al. 2010 [145]	60 M	32 IU intranasally	OXT increased trust behavior where subjectś privacy was at stake	Double-blind, placebo-controlled, between-subjects design
Theodoridou et al. 2009 [196]	48 M, 48 F	24 IU intranasally	OXT increased facial trustworthiness and attractiveness in both sexes	Single blind, placebo-controlled, crossover design

Table 4
Social bonds and emotions: OXT effects on empathy.

Authors	Subjects	OXT Dose	Main Finding	Study Design
Barraza & Zak 2009 [12]	70 M, 75 F	no OXT treatment	OXT plasma levels increased viewing an emotional video and after empathic responses were experienced	Double-blind, placebo-controlled, between-subjects design
Bartz et al. 2010 [14]	27 M	24 IU intranasally	OXT improved cognitive empathy in less socially proficient individuals but not in good socially proficient individuals	Double-blind, placebo-controlled, between-subjects design
Domes et al. 2007 [45]	30 M	24 IU intranasally	OXT improved cognitive empathy measured by 'Reading the mind in the Eyes Test (RMET)	Double-blind, placebo-controlled, within-subjects design
Hurlemann et al. 2010 [92]	24 M	24 IU intranasally	OXT increased emotional but not cognitive empathy.	Double-blind, placebo-controlled, between-subjects design
Rodrigues et al. 2009 [163]	79 M, 113 F	no OXT treatment	OXTR allele rs53576 was associated with lower empathy abilities	Between-subjects design
Shamay-Tsoory et al. 2009 [180]	26 M, 33 F	24 IU intranasally	OXT increased envy ratings in unequal monetary gain conditions involving relative loss. OXT also increased the ratings of gloating in relative gain conditions but had no effect on emotional or general mood ratings	Double-blind, placebo-controlled, within-subjects design
Singer et al. 2008 [185]	20 M	32 IU intranasally	OXT reduced amygdala activation elicited by the anticipation and receipt of painful stimulation to their hand, no OXT effect increasing empathy when the participant observed their female partner receive painful stimulation	Double-blind, placebo-controlled, between-subjects design

brain regions than those found to express OXT-containing terminals. While this may reflect technical limitations it does seem possible that OXTR-expressing cells are present in regions where OXT itself is not released from nerve terminals. OXT-containing neurons and terminals in the PVN are very close to the third ventricle and OXT concentrations in the CSF during birth, for example, are actually as high, or even higher, than those found in peripheral blood. The half-life of OXT in CSF is also much longer than in blood (see [96]). This has led to the hypothesis that one of the key modes of action for OXT is paracrine whereby it enters the cerebroventricles following release from the PVN and is rapidly distributed via ventricular transport to act in a long-lasting and coordinated way on OXTRs across the brain. It could also ensure prolonged activation of the PVN parvocellular OXT neurons which are closest to the third ventricle through their autoreceptors. In this way OXT could act on its receptors over a period outlasting the key physiological events promoting its release, such as birth and sex, and contribute to the formation of subsequent social bonds. Indeed, in sheep high OXT concentrations in CSF are present for up to several hours after they give birth and the formation of resilient bonds with their offspring usually take 1–2 h [96].

1.2. Human preclinical and clinical findings

We will now review the large number of recent human preclinical and clinical studies reporting altered OXT release profiles, links between OXTR polymorphisms and social behavior or affective disorders and functional/therapeutic effects of intranasal OXT treatments. We will discuss the implications of these findings together with the key neural substrates where OXT may be acting and which of its neuromodulatory actions may be of most importance.

1.2.1. Administration routes for OXT in humans

Investigations into the potential functional effects of OXT in humans were initially hampered by the knowledge that animal-based work had revealed that following intravenous injections of the peptide only around 0.01% crossed the blood–brain barrier [98] and that the most convincing studies of functional effects had therefore used intracerebroventricular or intracerebral administration routes which could not easily be done in humans. However, work showing that a number of peptides enter the brain in high concentrations following an intranasal spray administration [20] has opened the way for a number of both preclinical and clinical studies investigating its functional and potential therapeutic effects. This mode of administration allows small molecules to enter the brain ventricular system quite rapidly since the blood–brain barrier at the base of the nose is relatively weak. However, the extensive vascularization in the nose means that substances also enter the peripheral blood in high concentrations and so potential side effects of such elevated peripheral OXT concentrations need to be considered. One possible way forward in the future to reduce such peripheral dosing effects may be to combine intranasal peptide treatments with routine vasoconstrictor drugs such as phenylephrine. Indeed, a study in rats has shown that by using this experimental strategy peripheral concentrations of peptides following intranasal administration can be significantly reduced without affecting those in CSF [40].

While no study has yet carried out a systematic evaluation of the dose–response and clearance of OXT from the CSF and blood

Table 5
Anxiolytic effects: OXT and social stress.

Authors	Subjects	OXT Dose	Main Finding	Study Design
Ditzen et al. 2009 [42]	23 M, 23 F	40 IU intranasally	OXT increased positive communication during couple conflict and reduced salivary cortisol level	Double-blind, placebo-controlled, between-subjects design
Heinrichs et al. 2003 [81]	37 M, 37 F	24 IU intranasally	OXT reduced salivary cortisol levels; lowest cortisol levels were observed when OXT was combined with social support and it had an anxiolytic effect	Double-blind, placebo-controlled, between-subjects design
Kubzansky et al. 2009 [111]	40 M, 40 F	24 IU intranasally	OXT reduced stress response (blood pressure, cardiovascular response), OXT plus social support reduced stress response even more but more in women than in men. The OXT effect was not affected by age	Double-blind, placebo-controlled, between-subjects design
Light et al. 2005 [122]	59 F	no OXT treatment	Increased plasma OXT and reduced blood pressure in post-menopausal women following hugs from their partners	Between-subjects design
Pierrehumbert et al. 2010 [156]	25 M, 26 F	no OXT treatment	Tendency towards significant positive correlation between OXT plasma level and perceived stress during a psychosocial stress task in adults exposed to traumatic experience during childhood or adolescence	Between-subjects design
Quirin et al. 2011 [160]	36 M	24 IU intranasally	OXT reduced cortisol response to stress in individuals with impaired emotional regulation abilities but not in those with high emotional regulation abilities	Double-blind, placebo-controlled, between-subjects design
Sanders et al. 1990 [169]	20 M, 20 F	no OXT treatment	OXT plasma levels increased after uncontrollable noise as a measure of psychological stress in high emotionality women but not in men	Between-subjects design
Taylor et al. 2006 [194]	73 F	no OXT treatment	Plasma OXT levels correlated with relationship stress and elevated cortisol	Between-subjects design
Tops et al. 2007 [201]	80 F	no OXT treatment	Positive correlation between OXT plasma levels and attachment scores and cortisol levels	Double-blind, placebo-controlled, within-subjects design (cortisol vs. placebo)

following intranasal treatment, a related peptide, arginine-vasopressin, which has also been reported to produce social effects, has been studied [20]. Vasopressin concentrations are increased in both CSF and blood over a period of at least 90 min following intranasal administration, which mirrors the OXT release profile seen in animals following events such as birth [98]. Most studies reporting intranasal effects of OXT have used doses of 24 IU [132] although the lowest dose of vasopressin used in the Born et al. [20] study was 40 IU. Assuming similar penetration of the blood–brain barrier by OXT as with vasopressin an extrapolation from the Born et al. [20] study would give an estimate of maximum CSF and plasma concentrations of OXT being in the region of 10 pg/ml (a 5–10-fold increase over basal concentrations), but this obviously needs to be experimentally confirmed.

2. Preclinical findings

Numerous preclinical studies have investigated the importance of OXT on a range of human social, cognitive and emotional behaviors and these are summarized in Tables 1–8.

2.1. Social bonds and emotions

A number of studies have focused on oxytocinergic modulation of the strength of social bonds and social emotions such as trust, generosity, altruism, and empathy. Many of the studies on social emotions have used paradigms incorporating a social context into monetary-based tasks although a number, particularly in relation to empathy, have used face stimuli or experimental situations depicting other individuals in different emotional contexts.

2.1.1. OXT and social bonds

Several studies have reported correlations between blood oxytocin levels and the strength of social bonds, particularly in the relation to mother–child [55] and romantic relationships [69]. A recent study has found that blood OXT concentrations can be elevated by vocal social communication between mothers and their daughters [178]. There are also a number of studies reporting altered blood OXT concentrations correlated with distressed pair-bonding relationships [195,203]. A functional magnetic resonance imaging (fMRI) study on 30 first-time new mothers found that when they viewed their own infant's smiling and crying faces the mothers with secure attachment (as assessed by an attachment

Table 6
OXT and amygdala responses to fear-evoking faces.

Authors	Subjects	OXT Dose	Main Finding	Study Design
Domes et al. 2007 [44]	13 M	24 IU intranasally	OXT reduced amygdala response to fearful, angry and happy faces	Double-blind, placebo-controlled, within-subjects design
Domes et al. 2010 [46]	16 F	24 IU intranasally	OXT enhanced activity in amygdala, fusiform gyrus and superior temporal gyrus in response to fearful but not to angry, happy or neutral facial expressions	Double-blind, placebo-controlled, within-subjects design
Gamer et al. 2010 [64]	46 M	24 IU intranasally	OXT treatment reduced activation of amygdala for fearful faces and enhanced activation to happy faces. OXT treatment increased gazes directed at eye region	Double-blind, placebo-controlled, crossover-design
Kirsch et al. 2005 [104]	15 M	27 IU intranasally	OXT reduced activation of the amygdala by fear-induced social stimuli and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear	Double-blind, placebo-controlled, crossover-design
Petrovic et al. 2008 [155]	30 M	32 IU intranasally	OXT reduced affective evaluations of conditioned faces and amygdala activity	Double-blind, placebo-controlled crossover design
Tost et al. 2010 [202]	103 M, 109 F	no OXT treatment	OXTR allele rs53576 was associated with reduced amygdala responses to emotional faces	Between-subjects design

interview) had greater activation of the ventral striatum and hypothalamus [190]. The increase in plasma OXT levels in response to infant contact at 7 months was also higher in secure mothers and positively correlated with neural activity in both regions. On the other hand insecure/dismissing mothers had greater activation of the insular cortex in response to their own infant's sad faces. These results suggest the same link between OXT and dopaminergic brain reward centers such as the ventral striatum as was identified in animal studies, although this has yet to be demonstrated directly in humans. One study has investigated the effects of a single dose of intranasal OXT in male subjects assessed for attachment security using the 'Adult Attachment Projective Picture System (AAP)' [23]. This found a significant increase in attachment security scores in individuals identified by the AAP as having an insecure attachment phenotype.

2.1.2. OXT effects on trust, generosity and altruism in neuroeconomic contexts

Several studies have utilized economic paradigms to demonstrate effects of OXT on increasing trust in others. Kosfeld et al. [107] investigated the effect of exogenous intranasal administration of 24 IU OXT on trustfulness. In an interactive trust game male subjects were given a sum of money and had to decide whether to transfer money to an account of a trustee and the sum was then trebled. The trustee then had the option to either share the earnings with the subject or keep all the money for himself. Trusting the other player could lead to richer payoffs for both individuals, but the investor risks that the trustee violated the trust. OXT increased people's willingness to trust each other, but did not modulate behavior when the subject was asked to transfer money into the account of 'a project' which clearly lacks an immediate social context. In related neuroeconomic experiments, Zak et al. [220,221] also found that OXT increases the feeling of trust. In their trust game paradigm an investor awarded a sum of money (between $1 and $10) to a trustee that was subsequently tripled by the experimenter. The trustee then had the option to return some portion of the money to the investor. In a control condition, the amount awarded to the trustee was decided by a random computer draw. Here, plasma OXT levels in the trustee were significantly higher in the experimental compared to the control condition. This suggests that the trustees' OXT levels were responsive to the intention of trust rather than to the receipt of money *per se*. The amount returned to the investor (a measure of trustworthiness) was significantly correlated with OXT levels for experimental but not control participants [221]. However, in a subsequent study Singer et al. [185] found no OXT effect in the same trust game. Baumgartner et al. [15] observed that OXT modulates social interactions after trust has been violated. After intranasal OXT or placebo

Table 7
Social recognition and learning and memory-related effects: OXT and face emotion recognition.

Authors	Subjects	OXT Dose	Main Finding	Study Design
DiSimplicio et al. 2009 [41]	29 M	24 IU intranasally	OXT treatment reduced misclassification of positive faces but had no effect on accuracy of facial expression recognition. No OXT effect on general memory for faces or on subjective rating of mood and anxiety	Double-blind, placebo-controlled, within-subjects design
Domes et al. 2007 [44]	30 M	24 IU intranasally	OXT treatment reduced activation of the amygdala by social stimuli, regardless of valence	Double-blind, placebo-controlled, within-subjects design
Evans et al. 2010 [50]	18 M	24 IU intranasally	OXT decreased aversion to angry faces	Double-blind, placebo-controlled, crossover-design
Fischer-Shofty et al. 2010 [57]	27 M	24 IU intranasally	OXT increased accuracy of recognition of fearful faces but had no effect on other emotions or on reaction time	Double-blind, placebo-controlled crossover design
Guastella et al. 2008 [77]	52 M	24 IU intranasally	OXT increased number of fixations and total gaze time toward the eye region of neutral human faces	Double-blind, placebo-controlled, crossover-design
Guastella et al. 2009 [74]	71 M, 33 F	24 IU intranasally	OXT had no effect on response time to angry or happy schematic faces or gaze time toward angry or happy schematic faces or on early perceptual detection of threat	Double-blind, placebo-controlled, crossover-design
Marsh et al. 2010 [136]	29 M, 21 F	24 IU intranasally	OXT enhanced recognition of positive faces in both sexes but had no effect on reaction times	Double-blind, placebo-controlled, between-subjects design
Savaskan et al. 2008 [171]	18 M, 18 F	20 IU intranasally	OXT attenuated accuracy of neutral and angry faces but had no effect on happy faces, no gender effect	Single-blind, placebo-controlled, crossover design

Table 8
Social recognition and learning and memory-related effects: OXT effects on storage and retrieval.

Authors	Subjects	OXT Dose	Main Finding	Study Design
Bruins et al. 1992 [22]	21 M	20 IU intranasally	OXT reduced initial and rate of memory storage but had no overall effect on short and long-term storage, delayed recall or recognition	Double-blind placebo-controlled, between-subjects design
Fehm-Wolfsdorf et al. 1984 [52]	20 M	10 IU intranasally	OXT had no effect on free recall after 1 week	Double-blind, placebo-controlled, between-subjects design
Fehm-Wolfsdorf et al. 1988 [51]	30 M	24 IU intranasally	OXT had no effect on learning or long-term recall	Double-blind, placebo-controlled, between-subjects design
Ferrier et al. 1980 [56]	4 M, 2F	15 IU for 3 days	OXT had no effect on free recall of four-letter nonsense words or recognition of pictures of faces	Double-blind, placebo-controlled, between-subjects design
Geenen et al. 1988 [65]	20 M	3780 mIU i.v.	OXT had no effect on immediate or delayed recall (after 20 min)	Double-blind, placebo-controlled, between-subjects design
Heinrichs et al. 2004 [82]	38 M	24 IU intranasally	OXT reduced recall performance and overall generation of associated target words but had no effect for neutral words	Double-blind, placebo-controlled, between-subjects design
Hurlemann et al. 2010 [92]	24 M	24 IU intranasally	OXT also enhanced learning using social (smiling and angry faces) but not non-social feedback.	Double-blind, placebo-controlled, between-subjects design
Kennett et al. 1982 [99]	12 F	not mentioned	OXT reduced delayed recall but had no effect on learning	Double-blind, placebo-controlled, between-subjects design
Rimmele et al. 2009 [162]	44 F	24 IU intranasally	OXT enhanced recognition memory for faces regardless of facial expression but not on either recollection or recognition	Double-blind, placebo-controlled, between-subjects design
Unkelbach et al. 2008 [205]	44 M	24 IU intranasally	OXT improved recognition and categorization speed for positive sex and relationship words but not for other word categories	Double-blind, placebo controlled between-subjects design

administration participants acted as investors in multiple rounds of a trust game with different trustees and an fMRI scan was carried out. In order to investigate the role of OXT following breaches of trust, the experiment was divided into a pre-feedback and post-feedback phase. In between the two phases, participants received feedback information indicating that roughly 50% of their decisions had resulted in poor investments—that is, their trust had been breached (trust game) or their gamble did not pay off (risk game). As expected, participants in the placebo group decreased their expression of trust (measured as amount of money invested) after discovering that their prior displays of trust had been violated; placebo-treated participants shared less in the trust game during the post-feedback phase compared with the pre-feedback phase. In contrast, participants treated with OXT maintained their prosocial behavior of sharing in the trust game, irrespective of breaches of trust. This behavioral difference in the post-feedback trust game was associated with less activation in amygdala, midbrain, and dorsal striatum in subjects treated with OXT. The authors suggested that OXT's effect on trust is modulated by neural systems mediating fear processing (amygdala and midbrain regions) and behavioral adaptations to feedback information (dorsal striatum). Importantly, these behavioral and neural differences were apparent during the trust game, but not during the risk game, further suggesting that the effect of OXT is exclusive to social risks. Similar to the trust game Zak et al. [222] investigated the effect of OXT on generosity using the ultimatum and dictator games. These two games are similar in nature in that an initial decision maker (DM1) is endowed with $10, to be split, in turn with a second player (DM2). In the simpler dictator game DM2 must accept any offer, whereas in the ultimatum game DM2 can reject offers below a pre-specified minimum. These rejections, though costly to DM2, punish DM1 since both players lose the money in this round. Therefore, in the ultimatum game, DM1's decision comes with an implicit awareness of DM2's capacity to judge and reject stingy offers, whereas in the dictator game, DM1's decision is not influenced by DM2's implicit expectations and emotional response. These differences allow experimenters to distinguish between the broader category of altruism (giving at a cost to oneself, as assayed in both games) and a subset of altruism called generosity (giving more than the receiver expects, as assayed only in the ultimatum game). In these games, generosity is defined as offers greater than the average of the minimal acceptable amount. OXT boosted generosity by 80% in the ultimatum game compared to placebo. By contrast, in the dictator game OXT had no effect on unilateral monetary transfers, thereby dissociating generosity from altruism effects. A recent study has also found a significant association between three single nucleotide polymorphism (SNP) alleles in the OXTR gene (rs1042778, rs2268490 and rs237887) and performance in the dictator game as well as in another related monetary paradigm, the social values orientation task [93].

Human altruism is shaped by parochialism – a preference for favoring the members of one's ethnic, racial or language group. De Dreu et al. [35] investigated the OXT effect on parochial altruism. Subjects were assigned into groups of three and told that another group of three would be playing at the same time. Each individual received €10 and had to select one from several options for distributing the money. Subjects receiving intranasal OXT treatment behaved more altruistically towards members of their own group, keeping less money for themselves and donating about twice as much to a pool that benefited all members of their own group. In the other experiment groups of three faced the possibility of a substantial financial loss to their group if the other group decided not to cooperate with their group by giving them money. While this threat did not influence individuals who received placebo, subjects who were administered OXT displayed more defensive aggression toward outsiders, pre-emptively punishing members of a competing out-group when their own group was in danger of suffering a financial loss. Another recently published investigation also highlights the pro-cooperative effects of OXT [36]. In this study, 259 participants took part in two economic games, the coordination game and the prisoner's dilemma game. In presence of social information (a brief face to face contact with the interacting party prior to the exchange) intranasal OXT treatment enhanced cooperative behavior whereas when no social information was given OXT treatment actually reduced it. The authors therefore suggested that social information may be required in order for OXT to facilitate both trust and cooperation.

2.1.3. OXT effects on trust and social interaction in other contexts

Intranasal OXT treatment has also been reported to increase trust when instead of money subjects' privacy (i.e. confidential information about them) was at stake [145]. Theodoridou et al. [196] found that both male and female participants judged neutral expression faces of either men or women as more trustworthy and attractive after OXT application. Guastella et al. [78] and Mikolajczak et al. [144] have reported that OXT-treated individuals tended to rate happy faces as more trustworthy than placebo-treated individuals. According to their findings, breaches of trust not only have a profound impact on social behavior, but could also act as a precursor to anxiety disorders such as social phobia. Future research we suggest should investigate how different types of feedback may modulate oxytocinergic effects. The interaction of betrayal, trust and OXT may be modulated by the valence of feedback (positive or negative), the response rate, the extent of betrayal, and social expectations of feedback (loved person vs. foe/contender). Recently, Alvares et al. [4] investigated whether OXT ameliorated the acute behavioral and affective consequences of social rejection by using a virtual ball tossing game. Two cartoon icons – representing two virtual players – toss the ball back and forth to each other and the subject. Subjects were either included or ostracized (thrown twice initially and then ignored). Ostracized subjects reported negative affective and attachment-related reactions, as well as a significant motivational change in increased desire to be involved in the game; these effects were not influenced by OXT. Intranasal OXT did, however, increase the subjects' desire to play again with the same players, suggesting that OXT enhanced desire for future social engagement following social inclusion.

2.1.4. OXT effects on empathy

A key prediction is that OXT should act as an empathogen in humans. In rodents for example, prosocial effects of the empathogenic drug, MDMA ('ecstasy') are blocked by an OXTR antagonist [197]. In one study, subjects viewing videos depicting humans in emotional circumstances have been found to show elevated OXT levels by an average of 47% over baseline compared to those who watched an emotionally neutral video, and the magnitude of change correlated positively with the degree of empathy experienced [12]. An increase in experienced empathy was also found to be associated with greater generosity in the ultimatum game [222]. Domes et al. [45] investigated whether OXT application could improve the ability to infer the mental state by interpreting subtle social cues. In the 'Reading the Mind in the Eyes Test (RMET)', images of the eye region of faces are presented, and participants are instructed to identify the emotion from this information. Intranasal OXT also improved performance on this task but only for the most difficult classifications. A recent study has also reported a significant association between an SNP allele in the OXTR (rs53576) and empathy as measured by performance on the RMET [163]. Intranasal OXT application has been found to improve accuracy in identifying emotions, but only in less socially proficient healthy individuals [14]. Social competence in this latter

study was measured with the 'Autism spectrum Quotient (AQ)', a self-report instrument predicting social-cognitive performance.

In the only study to directly assess the effects of intranasal OXT on both cognitive and emotional empathy in men, Hurlemann et al. [92] showed that while it strongly facilitated both direct (the intensity of feeling evoked for the person in the picture) and indirect (the intensity of arousal evoked by the picture) empathy, cognitive empathy (identifying the emotional state of the individual shown) was unaffected (Fig. 1). Here OXT had equivalent effects on positive and negative valence pictures and interestingly raised emotional empathy in men to levels usually seen in untreated women. The lack of effect of OXT on cognitive empathy found in this study appears to contradict the findings of Domes et al. [45] using the RMET task and Bartz et al. [14], although these latter two studies only found effects either when face expression discriminations were difficult or in subjects who scored low on social proficiency. The Hurlemann et al. [92] study also chose to use pictures of individuals in different scenes where cues from face expression, body posture and even context could all be used to interpret the emotion expressed, whereas the other studies used only visual cues from the eye region or faces. Thus, OXT may only improve cognitive empathy in subjects where this is impaired or when emotion cues are made difficult to interpret by restricting them to the eye region. Hurlemann et al. [92] also reported that monozygotic twin women with selective bilateral calcification damage to the amygdala as a result of congenital Urbach–Wiethe disease were impaired on emotional but not cognitive empathy components of the same task as given to men receiving placebo or OXT treatment. They concluded from this that OXT might be facilitating emotional empathy by acting on the amygdala. In this respect it is interesting that another study failed to find effects of OXT treatment on emotional empathy levels experienced by male subjects observing their female partner receiving a painful stimulation to a hand [185]. Arguably the lack of an OXT effect in this case might reflect a ceiling effect since the context is one where levels of emotional empathy would be expected to be very high in many subjects. However, empathy for experienced pain involves the insular cortex rather than the amygdala and the one OXT effect that was observed in the Singer et al. [185] study was a reduction in self-perceived pain in more selfish individuals which was associated with reduced amygdala activity.

In a study by Shamay-Tsoory et al. [180] subjects were required to play a game of chance with another person who either won more money (relative gain), lost more money (relative loss), or won and lost equal amounts of money (equal gain). They found that OXT-treated subjects reported more envy when another player gained more money than they did. Furthermore, OXT increased gloating when the individual gained more than the other player. While this could be interpreted as an OXT effect on increasing more negative social behaviors, Tops et al. [200] suggested an alternative interpretation whereby this effect might be explained as a potential consequence of the peptide increasing social engagement and perspective taking.

2.2. Anxiolytic effects

There is considerable potential therapeutic interest in the claimed anxiolytic properties of OXT and a number of preclinical studies have investigated this either in the context of ameliorating social stress or in reducing responses fear-evoking stimuli, particularly fearful or angry faces.

2.2.1. OXT and social stress

No general consensus has emerged regarding altered OXT release in response to stress. Sanders et al. [169] reported elevated plasma OXT levels in response to uncontrollable noise in women,

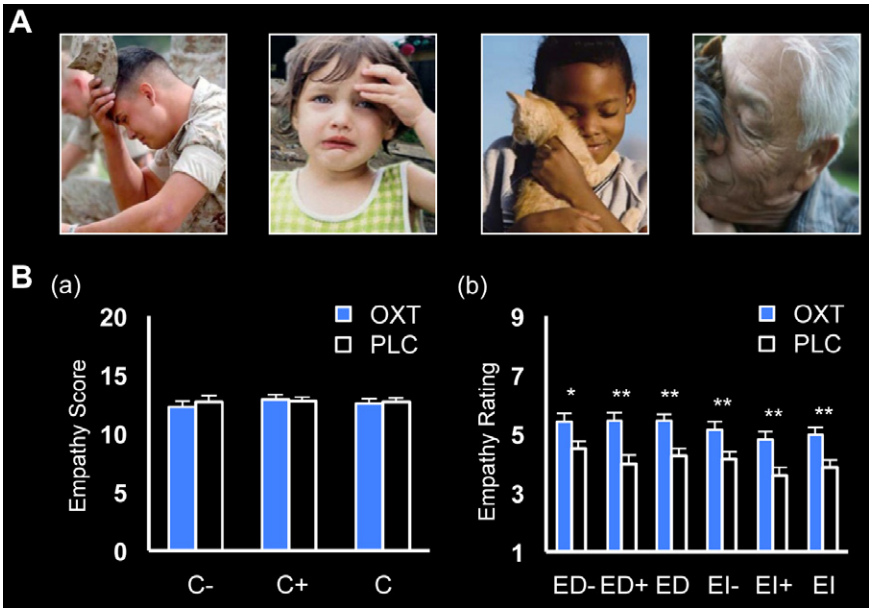

Fig. 1. Multifaceted Empathy Test (MET) administered by Hurlemann et al. [92]. A. Presented are four example pictures taken from the MET to test for negative (left two scenes) and positive (right two scenes) empathy valence. To assess cognitive empathy (C), participants were required to infer the mental state of the individual in each scene, and indicated the correct one from a list of four alternatives by push-button responses. For emotional empathy, participants were required to rate on a 1–9 intensity scale of how much they were feeling for the individual in each scene (ED) or how much they were aroused by each scene (EI). B. MET performance. (a) Cognitive empathy scores (C- = negative valence; C+ = positive valence; C = positive and negative combined) did not differ between male subjects treated with oxytocin (OXT, $n = 24$) and placebo controls (PLC; $n = 24$). (b) Emotional empathy ratings were increased across all categories [direct emotional empathy, negative valence (ED−), positive valence (ED+) and overall (ED); indirect emotional empathy, negative valence (EI−), positive valence (EI+) and overall (EI)] in male subjects treated with oxytocin (OXT, $n = 24$) compared to placebo (PLC, $n = 24$). These results document the empathogenic properties of oxytocin. Significant between-group differences: $^{**}p < 0.01$, $^{*}p < 0.05$.

but not in men. Taylor et al. [194] reported that plasma OXT levels were not associated with acute stress in post-menopausal women although they were elevated in individuals with chronic stress or gaps in social relationships.

In contrast, Pierrehumbert et al. [156] reported changes in plasma OXT concentrations during acute psychosocial stress induced by the 'Trier Social Stress Test (TSST)'. The TSST consists of a public speaking and mental arithmetic performance task in front of an audience. In this context OXT concentrations were negatively correlated with those of cortisol. Individuals with a life-threatening illness also displayed increased plasma OXT levels [156]. After oral cortisol application, Tops et al. [201] found increased plasma OXT levels in premenopausal women. Lastly, a study has reported increased plasma OXT and reduced blood pressure in post-menopausal women associated with hugs from their partners [122].

Four studies to date have used intranasal OXT in an attempt to demonstrate anxiolytic effects in healthy individuals. Heinrichs et al. [81] compared four groups, with the between-group factors OXT vs. placebo treatment and presence vs. absence of social support. Lowest cortisol levels together with increased calmness and decreased anxiety during the TSST were reported for individuals who were administered OXT plus social support, whereas the highest cortisol levels were measured in participants who had received neither OXT nor social support. In another study by Quirin et al. [160] the cortisol response was attenuated during the TSST following intranasal OXT treatment but only in individuals with impaired emotion regulation. Here emotion regulation was determined by the 'Action Control Scale (ACS)' [112] which measures self-control under demanding conditions. Kubanzansky et al. [111] reported that OXT treatment improves vagal control during the TSST and that a combination of OXT administration plus social support most effectively reduced cardiovascular and cortisol responses to psychosocial stress. The OXT effect on stress responses was stronger in women than in men, irrespective of age (25–65 years). Finally, intranasal OXT administration during couple conflict has been found to reduce salivary cortisol levels regardless of gender [42]. Furthermore, the authors reported increased duration of positive behaviors (including eye contact, interest, emotional self-disclosure, validation and caring) relative to negative behaviors (criticism, contempt, defense and domineering) during a conflict discussion measured by the 'Specific Affect Coding System (SPAFF)'. In summary, the majority of studies conducted so far support the view that intranasal OXT can reduce responses to social stress although the underlying mechanisms, and the specific interactions of OXT and cortisol, remain unclear.

2.2.2. OXT and amygdala responses to fear-evoking faces

It is well known that the human amygdala plays an important role in processing and controlling responses to fear-eliciting stimuli and a number of studies have investigated the potential for OXT treatment to reduce these. In several fMRI studies intranasal application of OXT has been reported to reduce amygdala responses to faces, particularly fearful ones [44,104]. Gamer et al. [64] reported attenuated activation in lateral and dorsal regions of the anterior amygdala for fearful faces but enhanced activity for happy expressions, an effect interpreted as a shift of the processing focus toward positive social stimuli. Intranasal OXT has also been found to decrease responses in anterior medial temporal and anterior cingulate cortices to faces that have been aversively conditioned by an electric shock [155]. Finally, the same OXTR SNP allele that was found to be associated with low empathy scores (rs53576) has now also been reported to be associated with reduced amygdala responses to emotional faces [202]. Results to date are therefore consistent with a potential anxiolytic action of OXT in reducing amygdala responses to fear-evoking faces as well as an enhanced response to faces expressing positive emotions.

2.3. Social recognition and learning and memory effects

Humans routinely make various trait judgments, based on first impressions. Although these judgments are not necessarily accurate, they critically affect social outcomes. For example, angry faces trigger automatic avoidance responses [135,199]. Given the prosocial effects of OXT and the consistent findings from animal studies that it facilitates odor-based social recognition and memory for individuals [168], a number of studies have investigated the effects of OXT treatment on recognition and memory for individuals and the emotions expressed by them, focusing on visual cues from faces. Both promnestic and amnestic properties of OXT have been investigated in social and non-social contexts.

2.3.1. OXT and face emotion recognition

Overall, findings have confirmed that OXT does facilitate accuracy in recognizing human facial expressions although the results are not consistent, particularly in terms of emotional valence. Marsh et al. [136] reported that OXT exclusively facilitated the recognition of happy faces in male and female volunteers, without beneficial effects on angry, disgusted, fearful, sad or surprised faces. Savaskan et al. [171] reported that the identification of angry and neutral expression faces but not of positive ones was increased in the OXT-treated group. In another study recognition of dynamic fearful faces was improved, while OXT had no effect on other facial emotions [57]. On the other hand DiSimplicio et al. [41] and Guastella et al. [74] found no OXT effect on subjects' ability to recognize emotions from faces although the misclassification of positive emotions as negative ones was decreased.

Intranasal OXT administration also diminished feelings of negativity toward faces conditioned with negative affective ratings, particularly in faces with direct gaze [155]. One explanation for the inconclusive results could relate to differences between the types of stimuli used. Guastella et al. [74] used schematic facial expressions, whereas most other studies employed photographs of static faces or movie clips of dynamic facial expressions of emotion. A greater ecological validity likely reflects a more realistic interpersonal situation and provides a more accurate picture of the human ability to recognize emotions conveyed by facial expressions. Furthermore, the experimental focus of the various studies differed. For example, Marsh et al. [136] examined the effect of OXT on each of the six basic emotions separately (angry, disgusted, fearful, happy, sad, and surprised), whereas Domes et al. [45] examined the ability to accurately discriminate between emotional facial expressions. Another explanation for the observed discrepancies could be the small sample size in all studies. Moreover, only three studies [45,74,136] included female participants.

Intranasal OXT has also been shown to increase the amount of time subjects gaze at the eye region of faces [64,77]. As the eye region is important for identifying face emotion expressions, this effect of OXT in increasing the time subjects spend looking at the eyes could provide a plausible explanation for improved face emotion recognition. Interestingly, Guastella et al. [74] found no OXT effect when schematic facial expressions were used, suggesting that genuine, realistic stimuli may provide more sensitive probes to assess the effects of OXT on face recognition.

2.3.2. OXT effects on learning and memory

In agreement with the animal literature a number of studies have shown that intranasal OXT facilitates social recognition memory in humans, although it is currently unclear as to whether it preferentially influences memory for faces with positive or negative face expressions, or both. Rimmele et al. [162] reported enhanced recognition memory for face identity in OXT-treated subjects, regardless of the facial emotion displayed. Savasken et al. [171] on the other hand found that OXT improved recognition

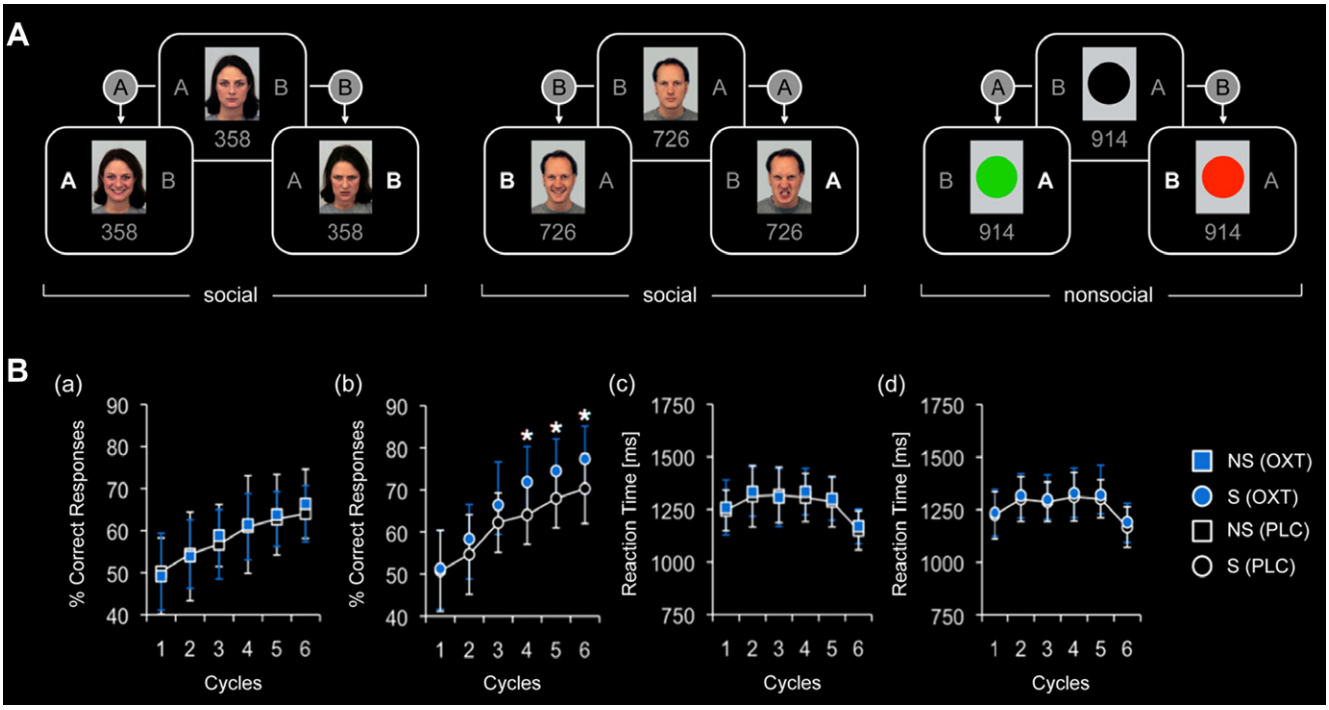

Fig. 2. Reinforcement associative learning task (RALT) administered by Hurlemann et al. [92] A. The RALT required subjects to make push-button responses to judge the arbitrary category membership 'A' or 'B' of 3-digit numerical items presented repeatedly on a computer screen, with visual feedback immediately following each item-category judgment [see 143]. Neutral faces changed to happy for correct responses or to angry for incorrect responses in the social condition (S); black circles changed to green for correct responses or to red for incorrect responses in the non-social condition (NS). Thus, knowledge of the correct or incorrect outcome of previous category judgments for a particular item served to enhance performance over subsequent trials. At the first cycle, subjects had no knowledge of the category membership and thus responded by guessing. B. RALT performance. (a) Percent correct responses for the non-social condition did not differ between male subjects treated with oxytocin (OXT, $n = 24$) or placebo (PLC, $n = 24$). (b) Oxytocin increased overall performance to 27 ± 8% above chance level in male subjects, compared to 20 ± 8% above chance for placebo controls in the social condition. This 7% performance gain in the social condition of the RALT documents the cognitive-enhancing potential of oxytocin. (c) Reaction times for the non-social condition did not differ between male subjects treated with oxytocin or placebo. (d) Reaction times for the social condition did not differ between male subjects treated with oxytocin or placebo. Significant between-group differences: $^{*}p < 0.05$.

Table 9
OXT and drugs of abuse: Alcohol.

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Coiro et al. 1991 [29]	24 M	0	no OXT treatment	↔	Found no alcohol effect on OXT plasma level	Between-subjects design
Coiro et al. 1992 [28]	16 F	0	no OXT treatment	↓	OXT release in response to breast stimulation was prevented by ethanol treatment (50 ml in 110 ml of whisky p.o.)	Placebo-controlled, between-subjects design
Marchesi et al. 1997 [134]	13 M	9 M	no OXT treatment	↓	Plasma OXT levels decreased in alcoholic patients regardless of the time of abstinence	Case-control study
Mennella and Pepino 2006 [140]	8 F	0	no OXT treatment	↓	Plasma OXT levels decreased after alcohol consumption (0,4 g alcohol/kg) in nulliparous women and were related to the feeling of drunkenness	Placebo-controlled, within-subjects design
Mennella et al. 2005 [141]	17 F	0	no OXT treatment	↑	Plasma OXT levels increased after alcohol consumption in lactating women (0,4 g alcohol/kg)	Placebo-controlled, within-subjects design
Sivukhina et al. 2006 [186]	26 M	22 M	no OXT treatment	–	OXT-immunoreactivity in neurons of the paraventricular nucleus increased whereas that in the supraoptic nucleus decreased in alcoholic patients compared to healthy controls	Case-control study

memory for the identity of neutral expression faces first viewed with either neutral or angry but not happy expressions. While Savasken et al. [171] did not find a memory-enhancing effect of OXT on face expression recognition *per se*, Guastella et al. [78] reported improved memory for happy but not for neutral or angry faces. In the Rimmele et al. [162] and Guastella et al. [78] studies OXT was administered during the learning phase of the task whereas Savasken et al. [171] gave it immediately after learning, suggesting that OXT may produce facilitatory effects on learning and consolidation.

In terms of other aspects of learning and memory, as in the animal literature, there is evidence that OXT may have both promnestic and amnestic effects. Several studies have used a variety of verbal learning paradigms and produced variable results, although

Table 10
OXT and drugs of abuse: Cocaine and opioids.

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Coiro et al. 1991 [30]	24 M (naloxone)	0	no OXT treatment	↑	The opioid antagonist naloxone enhanced the rise in OXT during insulin induced hypoglyemia.	Within-subjects design
Honer et al. 1986 [89]	Unknown	0	no OXT treatment	↔	Naloxone did not affect plasma OXT levels	Between-subjects design
Light et al. 2004 [123]	10 F (cocaine)	25 F	no OXT treatment	↓	Plasma OXT levels were decreased in women who had a history of cocaine exposure compared to mothers without cocaine use in the past	Case-control study
Lindow et al. 1992 [128]	9 F (morphine), 10 F (naloxone)	9 F	no OXT treatment	↓↔	Opioids inhibited maternal OXT release in the first stage of labor but naloxone did not affect plasma OXT levels	Between-subjects design
Lindow et al. 1993 [127]	10 F (morphine), 10 F (naloxone)	10 F	no OXT treatment	↔	Morphine and naloxone had no effect on plasma OXT levels	Between-subjects design
Lindow et al. 1998 [126]	12 F	10 F	no OXT treatment	↔	Fetal OXT production was not affected by the maternal administration of morphine in the first stage of labor.	Between-subjects design
Lindow et al. 1999 [125]	6 F (morphine), 6 F (naloxone)	5 F	no OXT treatment	↓↔	Morphine suppressed OXT release in breast-feeding women but naloxone had no effect on plasma OXT levels	Between-subjects design
Shibli et al. 2001 [181]	10 F (fentanyl)	10 F	no OXT treatment	↔	Opioid agonist fentanyl did not affect plasma OXT levels	Between-subjects design
Stocche et al. 2001 [187]	15 F (sufentanil)	15 F	no OXT treatment	↓	Opioid agonist sufentanil decreased plasma OXT levels in women during the first stage of labor	Between-subjects design

Table 11
OXT and drugs of abuse: Nicotine.

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Andersen et al. 1982 [8]	10 F	10 F	no OXT treatment	↔	Suckling-induced rise of plasma OXT did not differ in smoking and non-smoking women	Case-control study
Blackett et al. 1983 [18]	2 M	0	no OXT treatment	↔	No nicotine effect on plasma OXT levels in women during the final weeks of pregnancy	Between-subjects design
Chaudhury et al. 1960 [25]	not mentioned	not mentioned	no OXT treatment	↑	OXT release after nicotine exposure	Between-subjects design
Gaitan et al. 1964 [62]	29 F	0	no OXT treatment	↔	No nicotine effect on OXT level in women in the weeks of pregnancy	Placebo-controlled, between-subjects design
Seckl et al. 1988 [177]	6 M	0	no OXT treatment	↔	No smoking effect on plasma OXT levels. OXT levels increased after naloxone infusion plus smoking	Double-blind, placebo-controlled, between-subjects design

an additional complication in interpreting these findings is that OXT was sometimes given intravenously rather than intranasally, raising immediate questions concerning whether observed effects are directly centrally mediated. Bruins et al. [22] reported that intranasal OXT reduced initial storage (correctly remembered words after first presentation) and the rate of storage (number of trials to recall words at least once) for verbal material in healthy young men but had no effect on long-term storage (repeated retrieval without failures from the learning lists) or delayed recall (approximately 75 min later). OXT was found to decrease vigor in this task and this was suggested to contribute to the memory changes. Heinrichs et al. [82] also reported an amnestic effect for recall performance when OXT was administered in healthy young men. Using semantic word stimuli with reproduction-related vs. neutral meaning, OXT significantly impaired the overall number of associated target words with reproduction-related meaning. No difference between OXT and placebo was observed for neutral words. However, in another study OXT selectively promoted the recognition and categorization speed of positive sex- or relationship-related words [205]. OXT did not influence the decision and latencies for any other category (safety, threat, happiness, or sadness).

Other studies have reported no effects on learning or recall performance following intravenous or intranasal administration of OXT treatment in healthy female and male volunteers in [51,56,65,99].

Given the importance of OXT for social as opposed to non-social recognition memory a more appropriate approach in terms of potential effects on general memory function is to compare tasks where there is either a social or non-social feedback component [143]. Using this approach Hurlemann et al. [92] demonstrated that intranasal OXT did selectively facilitate learning in a task where three-digit numbers have to be assigned to one of two arbitrary categories over a number of learning cycles where social feedback is provided (smiling or angry faces). It had no effect, however, when non-social feedback was given using green or red lights (Fig. 2). Interestingly, patients with bilateral destruction of the amygdala due to Urbach–Wiethe disease do not show evidence for a social facilitation of learning in this same task, suggesting that OXT may be producing its effects on promoting learning where social feedback is used via the amygdala. This interpretation is supported by a further study showing that the beta-noradrenergic receptor antagonist, propranolol, which reduces amygdala responses to emotional faces, prevents social facilitation of learning in the RALT [145]. Hurlemann

Table 12
Autism spectrum disorders (ASD): OXT levels and influence of OXTR polymorphisms.

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Corbett et al. 2011 [31]	8 M	0	no OXT treatment	↔	Drama therapy to enhance social skills did not influence plasma OXT levels	Within-subjects design
Green et al. 2001 [71]	28 M	31 M	no OXT treatment	↓↑	Plasma OXT levels were decreased in ASD patients compared to healthy controls but OXT-precursor (OXT-X) levels were increased as was the ratio of OXT-X/OXT	Case-control study
Gregory et al. 2009 [72]	93 M, 26 F	0	no OXT treatment	↓	Epigenetic down-regulation of the OXTR gene in ASD	Genome-wide microarrays and comparative genomic hybridization
Jacob et al. 2007 [94]	45 M, 12 F	0	no OXT treatment	–	Association between OXTR allele rs2254298 but not rs53576 and ASD	Case-control study
Jansen et al. 2006 [95]	9 M, 1 F	13 M, 1 F	no OXT treatment	↑	Increased plasma OXT levels in ASD patients	Case-control study
Lerer et al. 2008 [119]	128 M, 24 F	133 parents	no OXT treatment	–	OXTR alleles (rs237897, rs13316193, rs237889, rs2254298, rs2268494 associated with ASD	Case-control study
Modahl et al. 1998 [148]	29 M	30 M	no OXT treatment	↓	Plasma OXT levels were reduced in autistic children compared to healthy controls	Case-control study
Wermter et al. 2010 [213]	95 M, 5 F	100 parents	no OXT treatment	-	OXTR allele rs2270465 associated with ASD	Case-control study
Wu et al. 2005 [216]	174 M, 21 F	195 parents	no OXT treatment	–	Association between OXTR alleles rs2254298, rs53576 and ASD	Case-control study

Table 13
Autism spectrum disorders (ASD): OXT treatment.

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Andari et al. 2010 [7]	11 M, 2 F	11 M, 2 F	24 IU intranasally	↓	Basal plasma OXT levels in autistic patients were reduced compared to healthy controls. OXT treatment increased time patients spent gazing at the eye region of faces; enhanced appropriate social behavior and affect and feelings of trust	Double-blind, placebo-controlled, within-subjects design
Fein et al. 1997 [54]	478 children	0	i.v. OXT administration during labor	–	No association between exogenous exposure of OXT to mothers during labor and ASD in their children	Between-subjects design
Gale et al. 2003 [63]	41 M	25 M	i.v. OXT administration during labor	-	No association between labor induction using OXT treatment and development of ASD	Case-control study
Guastella et al. 2010 [75]	8 M	8 M	24 IU intranasally	-	OXT treatment improved emotion recognition in autistic patients	Double-blind, placebo-controlled, cross-over design
Hollander et al. 2003 [87]	14 M, 1 F	0	10 IU i.v.	-	OXT treatment reduced repetitive behaviors in autistic patients	Double-blind, placebo-controlled, cross-over study
Hollander et al. 2007 [86]	14 M, 1 F	0	10 IU i.v.	-	OXT treatment enhanced processing and retention of social information in affective speech in autistic patients	Double-blind, placebo-controlled, cross-over design

et al. [92] therefore suggest, mainly on the basis of animal studies, that OXT may enhance learning in combination with positive prosocial components but aid forgetting when aversive or stressful stimuli are involved. The well-known fact that women appear to rapidly forget the pain of giving birth is also perhaps suggestive of the amnestic properties of OXT in aversive contexts, although this has still to be established experimentally. It may for example inhibit acquisition and/or consolidation of aversive experience during labor. Future research is urgently needed to disentangle OXT effects on various forms of memory as a function of the emotional salience of the learning material since this may be of particular significance in treatment of affective disorders such as post-traumatic stress disorder (PTSD).

3. Clinical findings

An increasing number of clinical studies are being published investigating potential therapeutic effects of intranasal OXT and associations between disorders and polymorphisms in the OXTR or altered epigenetic modulation of its expression. These studies are summarized in Tables 9–19, although it must be emphasized that many of them involve small numbers of patients and are simply correlative. Going forward it is important that future research involves sufficient patient numbers and employs experimental designs that rigorously test OXT's therapeutic potential.

3.1. Drugs of abuse

While OXT's primary mode of action is thought to promote reward associations with social behaviors such as bonding, there is no compelling current evidence that it produces any feelings of euphoria and is unlikely in itself to have any addictive properties *per se*. Indeed, human subjects given OXT intranasal spray do not report any conscious feelings of euphoria and are unable to determine accurately whether they have received OXT or placebo treatment [92,132]. However, there are some important links and interactions between OXT and substances of abuse.

3.1.1. OXT and alcohol dependence

Alcohol, which induces neurochemical changes in various brain regions, in particular on GABAergic, glutamatergic, cholinergic, serotonergic and catecholaminergic neuronal projection areas

Table 14
OXT and mood disorders.

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Bell et al. 2006 [17]	13 M, 23 F	0	no OXT treatment	-	Plasma OXT levels correlated with temperament dimension of reward dependence, novelty seeking and harm avoidance in patients with major depression	Between-subjects design
Cyranowski et al. 2008 [34]	7 F	17 M, 17 F	no OXT treatment	↑	Plasma OXT levels were increased in depressive patients compared to controls when they remembered a past experience of a strong feeling of love or infatuation	Case-control study
Devanand et al. 1998 [39]	18 M, 37 F	0	no OXT treatment	↔	No correlation between plasma OXT level and clinical response to ECT, but there was an inverse trend-level association between OXT levels and clinical response	Between subjecct design
Griffiths et al. 1989 [73]	1 F	0	no OXT treatment	↑↔	OXT levels increased immediately after ECT and returned to baseline 240 min after ECT in a pregnant women	Case report
Linkowski et al. 1984 [129]	5 M, 3 F	8 M, 4 F	no OXT treatment	↑	CSF neurophysin II levels were significantly higher in bipolar patients compared to controls	Case-control study
Linkowski et al. 1984 [129]	4 M, 4 F	8 M, 4 F	no OXT treatment	↔	CSF neurophysin II levels did not differ between unipolar patients and healthy controls	Case-control study
Meynen et al. 2007 [142]	9 M/F	9 M/F	no OXT treatment	↔	OXT brain mRNA expression did not differ between depressed patients and controls	Case-control study
Ozsoy et al. 2009 [153]	10 M, 30 F	12 M, 20 F	no OXT treatment	↓↔	Plasma OXT levels were decreased in female, but not male, unipolar and bipolar depressive patients compared to controls. Plasma OXT levels were not affected by antidepressive drug treatment or ECT	Case-control study
Parker et al. 2010 [154]	4 M, 7 F	7 M, 6 F	no OXT treatment	↑	Plasma OXT levels were elevated in depressed patients compared to controls	Case-control study
Pitts et al. 1995 [158]	10 M, 3 F	7 M, 6 F	no OXT treatment	↔	CSF OXT levels did not differ between depressed patients and controls	Case-control study
Purba et al. 1996 [159]	4 F	4 F	no OXT treatment	↑	OXT-expressing neurons in the PVN were increased in patients with major or bipolar depression compared to controls	Case-control study
Riddle et al. 1993 [161]	3 M, 7 F	0	no OXT treatment	↑	Plasma OXT levels after suprathreshold ECT stimulation were significantly greater than after threshold stimulation	Within-subjects design
Scantamburlo et al. 2007 [172]	4 M, 28 F	0	no OXT treatment	↓	Plasma OXT levels were negatively correlated with symptoms severity of depression and anxiety in depressive patients	Between-subjects design
Scott et al. 1986 [175]	6 M, 19 F	0	no OXT treatment	↑	Positive correlation between the OXT carrier molecule neurophysin and recovery from depression after ECT treatment	Within-subjects design
Scott et al. 1989 [176]	3 M, 16 F	0	no OXT treatment	↑	OXT-associated neurophysin after the first ECT was related to the extent of recovery from depression after ECT	Within-subjects design
van Londen et al. 1997 [209]	22 M, 30 F	17 M, 20 F	no OXT treatment	↔	Plasma OXT levels were not associated with neuropsychological performance in depressed patients	Case-control study
van Londen et al. 1998 [210]	14 M, 13 F	7 M, 15 F	no OXT treatment	↑	Plasma OXT levels were increased in depressive patients compared to controls	Case-control study
Warner et al. 1995 [212]	3 M, 4 F	0	no OXT treatment	↑	Plasma OXT levels increased at 5-minutes post-ECT seizure	Within-subject design
Whalley et al. 1982 [214]	5 F	2 F	no OXT treatment	↑	Plasma OXT levels increased 3 to 4 weeks before the onset of Mania	Case-control study
Zetsche et al. 1996 [223]	12 M/F	12 M/F	no OXT treatment	↓	Plasma OXT levels were reduced in depressed patients compared to controls	Case-control study

[150], is an effective inhibitor of OXT and has been used to prevent premature labor in women in the past [48]. Plasma OXT levels are also decreased in both breast-feeding and nulliparous women after acute alcohol consumption [28,140,141]. In non-alcoholic subjects peripheral OXT levels have been found to be related to feelings of drunkenness after alcohol consumption [140]. Coiro et al. [29] also found that pretreatment with ethanol completely abolished the OXT response to hypoglycemia in non-dependent young men. With alcohol-dependent patients on the other hand elevated plasma OXT levels have been reported even after periods of abstinence lasting from one to 28 days [134]. A post-mortem study in subjects with chronic alcohol abuse found reduced numbers of magnocellular hypothalamic neurons that produce OXT [186], in line with findings in rodents [183]. While further studies on links between alcoholism and impairments in the OXT system are required it seems likely that potential anti-social behaviors associated with chronic alcohol abuse may be linked to its effects on OXT.

Table 15
OXT and social anxiety disorder (SAD).

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Guastella et al. 2009 [76]	12 M	13 M	24 IU intranasally	-	OXT treatment enhanced mental representations after exposure therapy in patients with SAD	Double-blind, placebo-controlled, between-subjects design
Hoge et al. 2008 [85]	14 M, 10 F	11 M, 11 F	no OXT treatment	↔	Plasma OXT levels did not differ between patients with SAD and healthy controls and were positively correlated with symptom severity in subjects with SAD	Case-control study
Labuschagne et al. 2010 [113]	18 M	18 M	24 IU intranasally	-	OXT treatment attenuated the heightened amygdala reactivity to fearful faces in patients with generalized anxiety disorder	Double-blind, placebo-controlled, within-subject design

Table 16
OXT and obsessive-compulsive disorder (OCD).

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Altemus et al. 1999 [3]	7 M, 7 F	14 M, 12 F	no OXT treatment	↔	Normal CSF OXT levels in OCD compared to controls	Case-control study
Ansseau et al. 1987 [9]	1 M	0	8.4 to 16.8 IU intranasally over 4 weeks	-	OXT treatment improved OCD symptoms, but the patient developed psychotic symptoms, memory disturbances and decreased plasma sodium and osmolality	Case study, double-blind, placebo controlled (4 weeks OXT, 4 weeks placebo)
den Boer et al. 1992 [38]	3 M, 9 F	0	18 IU intranasally	-	OXT treatment did not affect OCD symptoms	Double-blind, placebo-controlled, between-subjects design
Epperson et al. 1996 [49]	4 M, 3 F	0	40 IU intranasally for 1 week, n=5: 160 IU/d, n=2: 320 IU/d	-	OXT treatment did not affect OCD symptoms	Double-blind, placebo-controlled, between-subjects design
Leckman et al. 1994 [114]	12 M, 17 F	19 M, 12 F	no OXT treatment	↑	CSF OXT levels were increased in patients with OCD and correlated with OCD severity	Case-control study
Salzberg and Swedo 1992 [167]	2 M, 1 F	0	8 IU intranasally		OXT treatment did not affect OCD symptoms	Double-blind, placebo-controlled, between-subjects design
Swedo et al. 1992 [193]	26 M, 17 F	0	no OXT treatment	↑	OXT CSF levels were positively correlated with depressive symptoms. The ratio of arginine vasopressin to OXT was negatively correlated with OCD and depressive symptoms	Between-subjects design

Table 17
OXT and post-traumatic stress disorder (PTSD) and borderline-personality disorder (BPD).

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Bartz et al. 2010 [14]	14 F	13 F	40 IU intranasally	–	OXT treatment decreased trust and cooperative behavior in patients with BPD	Double-blind, placebo-controlled, case-control study design
Pitman et al. 1993 [157]	43 M	0	20 IU OXT intranasally	–	OXT reduced physiological but not psychological responses in patients with PTSD	Double-blind, placebo-controlled, cross-over study
Simeon et al. 2011 [184]	10 F	11 F	40 IU intranasally	–	OXT treatment resulted in a significantly reduced dysphoric stress response in patients with BPD after the Trier Social Stress Task	Double-blind, placebo-controlled, within-subject design
Yatzkar and Klein 2010 [217]	18 M	0	Not mentioned	–	OXT reduced the severity of PTSD symptoms, improved mood and reduced thoughts about the traumatic event	Double-blind, placebo-controlled, cross-over study

3.1.2. OXT and empathogenic drugs

The drug, 3,4-methylendedioxymethamphetamine (MDMA) – commonly known as 'ecstasy' – is a widely used illegal drug that causes both empathogenic and anxiolytic effects. In agreement with animal studies plasma OXT concentrations have been reported to increase in the blood after MDMA consumption in humans [47,215]. Wolff et al. [215] argued that OXT effects could be related to changes in plasma and urine osmolality and hyponatraemia. However, research on rodents suggests that MDMA effects on OXT and prosocial behaviors may initially be mediated by the drug's action on the serotonin system. In rats the prosocial and OXT-releasing effects of MDMA are blocked by a 5-HT_{1A} receptor antagonist [197,198]. Another empathogenic drug, sodium-gamma-4-hydroxybutyric acid (GHB) has in the past been successfully used to promote uterine contractions during labor, once again suggestive of an effect on OXT release [66]. Further research is clearly needed to understand the potential underlying molecular mechanisms of MDMA- and GHB-induced prosocial behaviors in humans.

3.1.3. OXT and cocaine

Cocaine is also a stimulant drug that promotes feelings of well-being and hyperactivity. This drug targets dopaminergic systems in some of the same neural substrates as does OXT, notably the nucleus accumbens, amygdala and hippocampus. In line with animal studies cocaine use in pregnant mothers has been associated with poor maternal care and also with effects on social interactions and bonding in children born to cocaine addicts [191]. Animal-based studies have shown that OXT can interfere with cocaine's dopamine-dependent effects on increased activity and appears to reduce the utilization of dopamine in the nucleus accumbens by the drug [109].

Only one study has investigated the effect of cocaine abuse on the oxytocinergic system in humans. Mothers (at least one month but not more than 11 months postpartum) who used cocaine during pregnancy showed lower blood OXT levels than mothers who did not take cocaine [123]. Acute administration of cocaine in rodents has been reported to increase OXT release in the brain and this might possibly explain its initial prosocial effects [110]. Thus, while more research is required to establish the nature of cocaine and OXT interactions, the current emerging pattern is that although acute cocaine treatment initially increases OXT release, chronic use appears to reduce it, and possibly OXT's ability to release dopamine as well. The result of this is likely to be impaired maternal behavior and social bonding in the addict, and may also produce similar impairments in children born to addicts either due to cocaine exposure or poor quality maternal care, or both. Since OXT may interfere with cocaine's stimulation of dopamine release in the nucleus accumbens this also raises the possibility that it might be useful in the context of reducing cocaine dependency.

Table 18
OXT and schizophrenia: OXT levels and OXT treatment.

Authors	*n* (patients)	*n* (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Bakharev et al. 1984 [11]	27 M with OXT, 18 M without OXT	0	10 IU i.v. or intranasally daily over 7 days	–	OXT normalized mood and emotional status (asthenic or apathic states) compared to treatment with conventional neuroleptic agents. OXT weakly influenced neurosis like symptoms	Double-blind, placebo-controlled, between-subjects design
Beckmann et al. 1985 [16]	13 M	13 M, 2 F	no OXT treatment	↑	CSF OXT levels were increased in schizophrenic patients compared to healthy controls; CSF OXT levels increased after neuroleptic treatment (haloperidol) over 3 weeks	Between-subjects design (neuroleptic treatment vs. no neuroleptic treatment)
Bujanow 1972 [24]	not mentioned	not mentioned	10-15 IU i.v. or 20 to 25 IU once a day over 6 to 10 days	–	OXT enhanced therapeutic effects, no pathophysiological measures were mentioned	Case study
Feifel et al. 2010 [53]	19 M	0	1400 IU intranasally over 3 weeks	–	OXT reduced scores on the Positive and Negative Symptom Scale and Clinical global Impression-Improvement Scale.	Double-blind, placebo-controlled, within-subject design
Glovinsky et al. 1994 [67]	31 M, 9 F	10 M, 5 F	no OXT treatment	↔	CSF OXT levels did not differ between neuroleptic-treated schizophrenic patients, neuroleptic-withdrawn schizophrenic patients and healthy controls	Between-subjects design (neuroleptic treatment vs. no neuroleptic treatment vs. controls)
Goldman et al. 2008 [68]	4 M, 2 F	4 M, 3 F	no OXT treatment	↑	Plasma OXT levels were increased in polydipsic hyponatremic patients compared to healthy controls, polydipsic normonatremic or nonpolydipsic normonatremic schizophrenic patients. Higher plasma OXT levels were associated with greater accuracy of rating facial emotions but not of facial recognition. Plasma OXT levels were inversely correlated with anterior hippocampal volume	Between-subjects design
Keri et al. 2009 [100]	16 M, 34 F	16 M, 34 F	no OXT treatment	↑↔	Plasma OXT levels were significantly increased in schizophrenic patients compared to healthy controls and did not increase after trust-related interactions. No relationship was found between OXT levels and chlorpromazine-equivalent doses of antipsychotics	Case-control study
Legros et al. 1992 [117]	9 M	14 M	no OXT treatment	↑	Plasma OXT-neurophysin II levels were increased in schizophrenic patients compared to healthy controls and were significantly higher in the paranoid than in the non-paranoid schizophrenic group	Between-subjects design (schizophrenic patients vs. healthy controls)
Linkowski et al. 1984 [129]	9 M, 3 F	8 M, 4 F	no OXT treatment	↓	CSF OXT-neurophysin II levels were significantly lower in schizophrenic patients compared to controls	Case-control study
Rubin et al. 2010 [166]	37 M, 23 F	27 M, 31 F	no OXT treatment	↑↔	Higher plasma OXT levels were associated with prosocial behaviors (measured by PANNS prosocial factor) and with less severe positive symptoms and overall psychopathology in female patients, but not with negative symptoms. Plasma OXT levels were not associated with positive or negative symptoms in men	Case-control study

3.1.4. OXT and opioids

The animal literature has reported a number of interactions between opioids and OXT release and also that the peptide can improve tolerance of opioid withdrawal [96,108,110]. The efficacious effects of lithium in reducing symptoms of naloxone-precipitated withdrawal from morphine in mice have also been shown to involve an OXT-dependent mechanism [219]. The effect of opioids on the OXT system in humans has been investigated in women who are pregnant or in labor. In late pregnancy exogenous morphine administration had no effect on maternal plasma OXT levels [127] but during first stage of labor it reduced them [128]. OXT release was also inhibited by morphine in women during breast-feeding [125]. The opioid agonists fentanyl and sufentanil did not affect maternal blood OXT concentrations during pregnancy, but increased them during labor [181,187]. On the other hand, the opiate antagonist naloxone had no effect on blood OXT concentrations in women during late pregnancy or first-stage labor or in men [89,127,128]. Fetal production of OXT was reported to be unchanged after maternal application of morphine in first-stage labor [126]. Coiro et al. [29] have also found that the opioid antagonist naloxone enhanced the OXT rise during insulin-induced hypoglycemia in men. In summary, opioids seem to inhibit OXT release during labor and breast-feeding in women but not at other times, and not in men. The potential use of OXT to promote opioid tolerance and reduce withdrawal symptoms has yet to be investigated in humans.

3.1.5. OXT and other drugs of abuse

Interactions between OXT and benzodiazepines and cannabinoids in humans have yet to be investigated. However, as with opioids, a recent study in rats has shown that withdrawal symptoms arising from sudden precipitated cannabinoid abstinence in rats were reversed by lithium, via an OXT-dependent mechanism [33]. Specifically, lithium activates OXT-containing hypothalamic nuclei and its ability to prevent abstinence effects was reversed by co-administration of the OXT antagonist L-368,899. Moreover,

Table 19
OXT and eating disorders.

Authors	Disease	n (patients)	n (controls)	OXT Dose	OXT Level	Main Findings	Study Design
Chiodera et al. 1991 [27]	Anorexia nervosa	7 F	9 F	no OXT treatment	↔	Plasma OXT levels did not differ between anorexic patients and controls. No significant increase in OXT response to insulin-induced hypoglycemia and estrogen administration in underweight anorectic women but a slight increased OXT response in partial weight recovered anorexic patients	Between-subjects design and within-subject design
Chiodera et al. 1991 [27]	Bulimia nervosa	7 F	9 F	no OXT treatment	↔	Plasma OXT levels did not differ between bulimic patients and healthy controls	Case-control study
Demitrack et al. 1990 [37]	Bulimia nervosa	47 F	11 F	no OXT treatment	↔	CSF OXT levels did not differ between underweight bulimic patients, normal weight bulimic patients and healthy controls	Case-control study
Demitrack et al. 1990 [37]	Anorexia nervosa	5 F	11 F	no OXT treatment	–	CSF OXT levels were increased in underweight patients with anorexia nervosa compared to healthy controls	Case-control study
Frank et al. 2000 [59]	Bulimia nervosa	23 F	17 F	no OXT treatment	↑↔	CSF OXT levels did not differ between patients who recovered from bulimia nervosa but were increased in bulimic patients with a lifetime history of OCD and major depressive disorder. CSF OXT levels were not related to current depression or OCD symptoms in patients with bulimia nervosa	Case-control study
Frank et al. 2000 [59]	Anorexia nervosa	10 F	17 F	no OXT treatment	↔	CSF OXT levels did not differ between patients who recovered from binge/eating purging type anorexia nervosa compared to healthy controls	Case-control study

L-368,899 given in the absence of lithium worsened cannabinoid withdrawal syndrome. One study has reported increased OXT release in blood after nicotine exposure in men [25] although other studies have found no effect of intravenous or inhalational nicotine on OXT levels [8,18,62,177]. Also, breast feeding-induced rises in blood OXT concentrations did not differ between smoking and non-smoking women [8].

3.2. Autism spectrum disorders

Autism spectrum disorders (ASD) constitute a group of neurodevelopmental conditions defined by dysfunction in three core symptom domains: impairments of social communication and interaction, restricted and repetitive activities and interests, and social deficits. Social impairment involves a lack of eye contact, diminished social recognition of facial expressions and impaired daily interaction skills. In view of OXT's role in facilitating social responses and in face emotion recognition, there has been a particular focus on potential links to ASD. We will start by presenting work on the relationship between ASD and blood OXT levels, as well as with genetic and epigenetic variations in the OXTR. We will then review work reporting effects of either intravenous or intranasal OXT treatment on ASD symptoms.

3.2.1. Links between ASD, OXT release, receptor polymorphisms and epigenetic regulation

A number of studies have reported altered plasma OXT concentrations in individuals with ASD. Jansen et al. [95] found increased OXT levels in 10 adults with high-functioning ASD compared to 14 healthy controls although these were not correlated with impairment in social interaction or communication, or with stereotyped behavior. In contrast, reduced plasma OXT levels were reported in 29 autistic boys aged 6–11 years [148]. Also, while OXT levels increased with age in healthy children they did not do so in children with ASD. Green et al. [71] also observed decreased OXT and increased OXT-X precursor levels in children with ASD. The OXT-X/OXT ratio was increased in the group of autistic children. The authors suggested that autistic individuals processed the available prohormone incompletely compared with healthy subjects. Most recently Andari et al. [7] have also reported reduced plasma OXT levels in adults with high-functioning autism. One explanation for inconsistent study results could be the inclusion of different ASD subgroups. While Jansen et al. [95] and Andari et al. [7] studied subjects with high-functioning ASD, Modahl et al. [148] and Green et al. [71] studied children with various levels of intellectual function. Further research is needed to investigate whether OXT levels in children, adolescents and adults with ASD differ from each other.

There have been a number of studies reporting significant associations between a variety of SNP alleles in the OXTR and ASD [94,119,216]. One particular SNP in the third intron of OXTR has received the most attention (rs53576A). This has been found to be over-transmitted in some families with high-functioning ASD offspring [216] and may form a key component in haplotypes related to ASD [213]. As already discussed, this potential 'risk allele' has also been associated with empathy [163] maternal sensitivity [10], attachment behavior [32] positive affect [130] and reduced amygdala responses to emotional faces [202]. In Tost et al. [202], male carriers of rs53576A were found to have an increased amygdala volume, and other studies have reported increased amygdala volume in ASD [149,173]. More research is definitely needed, however, to investigate links between this and other polymorphisms in OXTR and ASD.

While it is known that the OXTR has a CpG island in its promoter, and that methylation levels can alter its expression in the peripheral organs [102], the possibility of epigenetic modification of OXTR in the brain has only recently been investigated and revealed a possible contribution of this in ASD. Gregory et al. [72] studying a family with ASD found one son with a genomic deletion in a region of the OXTR previously implicated in ASD. However, another ASD sibling did not have this deletion but instead exhibited epigenetic misregulation of OXTR through silencing by DNA methylation. A further analysis of ASD patients revealed increased DNA methylation of several OXTR CpG dinucleotides in both samples of peripheral blood cells and from the temporal cortex. There was a corresponding reduction in OXTR mRNA expression in the temporal cortex associated with the increased methylation. This study therefore is the first to reveal evidence for epigenetic down-regu-

lation of the OXTR in ASD and reveals a mechanism whereby adverse life events, such as early-life traumatic experience, might lead to significantly reduced OXTR expression in the brain.

3.2.2. Possible relationship between ASD and OXT treatment for the control of labor

Somewhat controversially it has been suggested that OXT administration to mothers during labor might contribute to the development of ASD and related syndromes in their children through the exogenous treatment of the mother acting to down-regulate OXT receptors in the fetal brain. Two barriers are commonly thought to prevent OXT from crossing from the mother's circulation to her infant during labor and potentially accessing the infanťs brain: the maternal-placenta barrier and the blood–brain barrier of the infant. However, Malek et al. [133] found that OXT can cross the human maternal placenta by diffusion and since the blood–brain barrier in the infant might not be as fully developed compared to adults it could be more permeable towards small lipid insoluble molecules like OXT [170]. Furthermore, stress during labor could result in the release of cytokines and promote oxidative stress which can make the blood–brain barrier more permeable than usual [6,151].

Hollander et al. [88] have argued that OXT administration to mothers during labor could therefore contribute to ASD in their children. In a retrospective approach the authors found that the mothers of patients with ASD had significantly higher rates of OXT application during labor (61%, 33 out of 54 patients) than those of healthy children (20–25%). However, two other studies have failed to support an association between exogenous exposure to OXT during labor and ASD [54,63]. Certainly if OXT does cross the maternal placenta, pass the blood–brain barrier of the infant and down-regulate OXTRs in the developing brain, then it remains a possibility that OXT administration during labor could under certain circumstances contribute to ASD. However, the etiology of ASD is multifactorial and still not fully understood. While OXT administration at labor may be one factor, further studies with larger sample sizes and information about dose and rate of OXT administration need to be carried out to investigate the correlation of OXT-induced labor and ASD more thoroughly.

3.2.3. Effects of OXT treatments on ASD symptoms

Guastella et al. [75] investigated the effect of intranasal OXT administration (24 IU) on emotion recognition for patients with ASD in a double-blind, randomized, placebo-controlled, cross-over study. OXT treatment improved emotion recognition as measured by the RMET in 16 male patients aged 12–19 years. Andari et al. [7] found that intranasal OXT administration (24 IU) in patients with ASD enhanced visual screening of faces and, in particular, of the socially informative eye region, as compared to placebo. In addition, Andari et al. [7] examined social interaction behavior by using a task in which the participant engaged in a multi-round ball-tossing game over a computer network with three fictitious partners who had different cooperative behavior styles. In this task healthy subjects quickly learn to return the ball more often to more co-operative partners who throw the ball back whereas ASD patients do not. Intranasal OXT treatment enhanced patients' ability to process socially relevant cues and throw the ball back more often to co-operative partners.

Two studies have used intravenous OXT treatment and reported positive effects in ASD patients. Given the fact that animal studies have shown that very little OXT given this way crosses the blood–brain barrier this raises some questions about the extent to which treatment effects are mediated by the peptide acting directly on its receptors in the brain. Hollander et al. [86] focused on auditory processing of social stimuli before and 30, 60, 120, 180, and 240 min over the course of an intravenous infusions of OXT (10 IU). 15 OXT-treated patients (age 19–56 years) showed increased retention of affective speech comprehension. Furthermore, the OXT-treated ASD patients appeared to retain the ability to accurately assign emotional significance to speech intonation. A previous study by the same group investigated the OXT effect on repetitive behavior in patients with ASD. In a double-blind, placebo-controlled, cross-over study, 15 adults with ASD received intravenous OXT infusion over a four-hour period. Repetitive behavior was measured by a four-point ordinal scale including need to know, repeating, ordering, need to tell/ask, self-injury and touching [87]. The severity and frequency of repetitive behaviors and the total number of different repetitive behaviors decreased after OXT administration compared to placebo. This reported reduction of repetitive behavior after OXT administration in patients with ASD is contrary to a positive correlation between OXT plasma levels and the frequency of repetitive behavior in patients with obsessive–compulsive disorder (OCD) where increased OXT levels are associated with greater frequency of repetitive behavior. Bartz and Hollander [13] argue that an OXT deficit is implicated in ASD, whereas too much OXT or an increased sensitivity to it is implicated in OCD.

In summary, while the studies presented here support the notion that OXT is an important component in the neurobiology of ASD, and that intranasal OXT treatment can produce beneficial effects on emotion recognition and responsiveness to social cues, more research is clearly required to help establish the precise nature and duration of beneficial effects and how it could be used most effectively in conjunction with other therapeutic approaches. OXT promotes social recognition and social interaction in patients with ASD and may reduce repetitive behavior. Going forward it will be important for high-quality clinical trials to be carried out and where detailed effects on specific ASD symptoms and on different ASD subgroups are characterized since clinical phenotypes of ASD vary widely. To date also no studies have included female ASD patients. Moreover, the efficiency and safety of long-term OXT treatment require further investigation since studies so far have only measured effects of single-dose treatments. Finally, combined treatment and brain-imaging studies will help our understanding of which neural substrates OXT might be acting on to produce therapeutic effects and may also identify key interactions between OXT and other neurotransmitter systems. Currently the animal literature suggests that dopamine, noradrenaline and serotonin could all be important in this respect.

3.3. Mood disorders

As already discussed preclinical studies have shown that OXT is released into systemic circulation in situations of psychosocial interaction, and involved in mechanisms of social bonding and social recognition. In view of disturbances in psychosocial relationships being a triggering factor for many affective disorders it has been suggested that the function and physiological regulation of the OXT system may be related to unipolar and bipolar depression.

3.3.1. OXT and depression

Results from studies measuring blood and CSF OXT levels in patients with depression have been inconsistent, showing reduced, unchanged or increased OXT levels compared to healthy controls. Ozsoy et al. [153] found that serum OXT levels were decreased both before and after treatment with antidepressant drugs or electroconvulsive therapy (ECT) in patients with major depression ($n = 29$) or bipolar depression ($n = 11$). There was neither a difference between patients with unipolar and bipolar depression nor between antidepressant drug treatments [six patients were treated with serotonin-reuptake inhibtors (SSRIs), 13 with the dual serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine, six with

tricyclic antidepressants] and ECT ($n = 15$). Frasch et al. [60] also observed decreased plasma OXT levels in 12 patients. Zetzsche et al. [223] found a reduced OXT secretion at night (between 22.00 h and 07.00 h) in patients with major depression. Scantamburlo et al. [172] reported a negative association between plasma OXT levels in depressed individuals and clinical scores of depression and anxiety. Other studies found no significant difference in OXT levels in plasma or CSF between depressed patients and controls [158,210]. Another study found no association between cognitive performance and plasma OXT levels in patients with affective disorder [210], however, it did not discriminate between diagnostic subsamples (bipolar depression, psychotic depression or nonpsychotic unipolar depression). In contrast, Parker et al. [154] reported significantly increased plasma OXT levels in seven female and four male patients with major depression compared to nine female and 10 male healthy controls. Here six of the patients continued their current psychiatric medication (antidepressants with or without concomitant anxiolytics) while four patients did not receive any medication. Depressed women show higher plasma OXT levels during the 'Guided Imagery Task (GIT)' in which participants are asked to imagine a past experience where they felt strong feelings of love or infatuation. There was a trend in depressed women toward higher OXT levels during a speech stress task in which participants had to defend themselves against a hypothetical shoplifting charge [34]. Bell et al. [17] noted that plasma OXT levels were correlated to the temperament dimension of reward dependence in 23 male and 37 female individuals with major depression.

The observed discrepancies between the above studies may be due to several confounding factors and heterogeneities: (i) Patient medication in the studies differed considerably and OXT concentrations may be influenced by the treatment with antidepressants in humans. For example, animal studies have demonstrated that SSRIs and venlafaxine elevate plasma OXT levels [152,206]. (ii) Patient samples were small and not homogeneous with respect to age range, diagnosis and treatment setting (inpatient and outpatient populations). Ozsoy et al. [153], for example, included patients with unipolar and bipolar depression. (iii) Gender distribution also differed across samples and there could be potential gender differences in OXT levels. Furthermore, in female participants oral contraceptives can increase OXT concentrations [189,207] and the latter also vary across the menstrual cycle [182,188,207]. Number of births, and lactation history can all affect OXT levels and should be taken into account as covariates in future studies.

Some studies have also reported altered numbers of OXT-expressing neurons or OXT mRNA expression in the brains of depressed patients post-mortem. Purba et al. [159] reported an increased number of OXT-expressing neurons in the PVN of patients with major depression or bipolar depression as compared to controls. An increase in OXT gene expression in the PVN of melancholic type depressed patients compared to non-melancholic type patients has been reported, although no difference in OXT mRNA was found when comparing the entire group of depressed patients to controls [142].

Studies have also investigated the correlation between plasma OXT levels and the clinical response to ECT although the results are controversial. Devanand et al. [39] reported only a weak negative association between the acute increment in OXT levels and clinical response in 55 patients with unipolar or bipolar depression, with or without psychotic symptoms. The number of ECT sessions averaged 9.4, and all patients were medication-free. In contrast, Scott et al. [175,176] found a positive correlation between the OXT carrier molecule neurophysin and recovery from depression after the first treatment across an ECT series. In the former study, outcome was assessed one week after the end of the treatment series, whereas in the latter study it was observed two months after the last ECT session. In one case report a 30-year-old woman with major depression underwent an ECT series beginning at 23 weeks of gestation. Her plasma OXT levels increased immediately and returned to baseline 240 min after ECT [73]. Because of the different study designs the investigations are difficult to compare to each other and results may be influenced by medication status, study population (bipolar vs. unipolar depression), and the treatment course of ECT.

It is also worth noting that reported successes in treatment of drug-resistant depression by vagal stimulation [70] may also partly involve the effect of such stimulation on brain OXT release. It is well established that vagal stimulation releases OXT and that signals from both the stomach during and uterus reach the brain via the vagus [189,204]. Indeed, in women with complete spinal cord section sexual orgasm, which is a potent releaser of OXT, can still be achieved following vaginal self-stimulation via the vagus [106]. In summary, there is clearly a need for further clarification of the biological basis of OXT in relation to mood disorders which may also help to elucidate their underlying pathophysiology. At this point in time, however, there is only correlative evidence for OXTs role as a potential therapeutic agent for mood disorders.

3.4. Anxiety and personality disorders

The anxiolytic properties of OXT found in preclinical studies, particularly in psychosocial contexts, have stimulated a number of clinical studies investigating its potential role in anxiety disorders such as social phobia and OCD. The anxiolytic effects of OXT together with its potential role in promoting amnesia for aversive or traumatic events have also led to some studies considering its role in PTSD. Lastly, a number of personality disorders also exhibit problems with social responses and trust although to date a role for OXT has only been investigated in borderline personality disorder (BPD).

3.4.1. OXT and social phobia

Social phobia or social anxiety disorder (SAD) is a disorder characterized by excessive fear of social interactions or performance. The patient is frightened to act in a way that will be embarrassing and because of this social situations are avoided. With a life-time prevalence of 12.1%, SAD is the third most common mental health disorder [101]. Little is known about the etiology of SAD although it appears to be influenced by neurobiological, temperamental, genetic, and environmental factors [121]. To date, few studies have investigated the role of OXT in SAD despite the fact that preclinical studies suggest an obvious potential for therapeutic use through reducing anxiety in social situations. Hoge et al. [85] found no significant differences in plasma OXT concentrations between a group of 24 patients with SAD (10 female, 14 male) compared to 22 healthy controls (11 female, 11 male) but within the SAD group, higher social anxiety symptom severity was associated with higher OXT levels, the sample size was small and the study did not control for medical treatment or gender. Another study has investigated the add-on effect of OXT in an OXT-augmented exposure-based cognitive behavior therapy (CBT) in 25 men with SAD. The patients received five weekly sessions of CBT. From week two to five, each patient self-administered either OXT (24 IU) or placebo intranasally before participating in the TSST. Guastella et al. [76] showed that administration of OXT in combination with exposure therapy improved mental representation of speech performance and speech appearance although this effect did not improve long-term outcome. The authors argued that this effect could be caused by OXT-enhanced cognitive processing of positive social stimuli. However, OXT did not alter SAD symptoms either in the short- or in the long-term.

To date only one neuroimaging study has investigated the effect of OXT on fear-related amygdala reactivity to threatening faces in patients with generalized SAD and found, as expected, that it reduced the amygdala hyper-reactivity in SAD patients to levels seen in controls [113]. In this study, however, OXT had no effect on reducing amygdala responses to faces in controls contrary to some preclinical studies described previously.

In summary, while there is a clear need for further clinical investigations there may well be a potential therapeutic role for OXT in SAD. While the lack of an overall beneficial effect in SAD patients self-administering OXT before CBT is disappointing, arguably the most important time to give OXT to SAD patients is prior to social interactions in the course of their everyday life both in an attempt to reduce anxiety but also to help reinforce the rewarding aspects of such social interactions.

3.4.2. OXT and obsessive–compulsive disorder

OCD is defined by the occurrence of either unwanted thoughts (obsessions), repetitive behaviors (compulsive rituals) or, most commonly, both. Patients recognize that the thoughts are a product of his or her mind. Compulsions are aimed at reducing distress or preventing some dreaded event. However, they are excessive or not realistically connected to what they are intended to prevent. The pathophysiological significance of OXT in OCD is still unclear. Leckman et al. [114,115] reported that OXT was elevated in the CSF of 29 adults with OCD compared to controls, whereas another study observed normal OXT levels in 14 patients with OCD [3]. In another study plasma OXT concentrations were positively correlated with depressive symptoms in 43 children with OCD [193]. The variable findings might be related to the following methodological differences: (i) Leckman et al. [114,115] included only male OCD patients whereas Altemus et al. [3] had similar numbers of male and female OCD patients and controls. In addition, Altemus et al. [3] did not explicitly mention stage of menstrual cycle or use of oral contraceptives in female participants. (ii) In the two studies lumbar punctures were performed at different times, either between 9.00 to 10.00 a.m. or at 12.30 p.m. There is, however, a circadian rhythm of OXT in human CSF with the peak occurring at midday [5]. (iii) OCD medications administered may also have influenced OXT levels and Leckman et al. [114,115] did not report detailed information about pharmacological treatment. Altemus et al. [3] included patients who were medication-free for at least five weeks before lumbar puncture. In summary, further studies are needed to clarify the role of OXT in the pathophysiology of OCD.

OCD most often begins in the late teens for males and the early twenties for females. Pregnancy is associated with an increased risk for onset or exacerbation of OCD [58]. During puberty, the third trimester of pregnancy and the early puerperium, OXT levels are elevated. It is possible that the increased OXT levels are correlated to the onset or worsening of OCD [138] but future research to identify a potential link between OCD and increased OXT levels during puberty, pregnancy or puerperium is required.

CBT and pharmacotherapy are regarded as the first-line treatments in OCD. Psychotherapy involves exposure and response prevention and this is generally considered to be the most effective treatment for OCD. 60% to 70% of patients respond to CBT, but in most cases, this is only a partial response (see also [1]). A clinical response is defined as a 35% reduction in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). However, in more than 12% of patients relapse after completion of CBT is described. Current pharmacological strategies encompass SSRIs or tricyclic antidepressants, in particular clomipramine although once again relapse rates after discontinuation of medication vary between 24% to 89% (see [1]). Based on the preclinical findings that OXT has an anxiolytic effect in humans [81,104], some studies have administered OXT to OCD patients, with mixed results. Pharmacological challenge studies with OXT intranasal spray have examined different OXT doses, periods of application and sample sizes. Den Boer and Westenberg [38] reported no effect on compulsive, depressive or anxiety symptoms in nine female and three male OCD patients. They administered one squeeze per nostril (22 IU) four times per day over six weeks. Additionally, two other patients received a threefold higher dosage with no advantage and only minimal side-effects. Salzburg and Swedo [167] found no OXT effect in one female and two male OCD patients after a single administration of OXT (8 IU). Epperson et al. [49], employing a randomized, double-blind, placebo-controlled, crossover design, administered seven OCD patients with 160 IU of OXT per day. After a preliminary analysis two patients were even given 320 IU of OXT per day. However, none of the patients showed a change in OCD symptoms. Ansseau et al. [9] reported one case of a patient whose symptoms improved in the first two weeks of treatment (8.4–16.8 IU OXT per day), but subsequently developed psychotic symptoms and memory disturbances.

In summary, to date no study has definitively shown potential therapeutic effects of OXT in relation to OCD although numbers of treated patients have been too small in many studies to yield conclusive findings. OCD patients may perhaps benefit from the anxiolytic properties of OXT if they are exposed to the fear-eliciting situation. As yet no study has attempted to combine CBT with OXT application in relation to OCD treatment and this could potentially be the best route to try. However, a combination of pharmacotherapy (e.g. SSRIs, tricyclic antidepressants) and OXT treatment might also be effective.

3.4.3. OXT and post-traumatic stress disorder

PTSD is an anxiety disorder that can develop in the aftermath of a harmful/life threatening event. Symptoms include the typical trias of hyper-arousal, avoidance behavior and re-experiencing of the trauma in the form of nightmares, flashbacks and intrusive thoughts, especially in situations reminiscent of the trauma. The risk of PTSD is increased by experience of early childhood trauma [105]. There is some evidence that increased blood OXT levels in mother-infant interactions are reduced in individuals raised in socially impoverished environments [61] and one study has reported that OXT concentrations in CSF were reduced in women exposed to early-childhood abuse [80].

In men who had experienced early separation from their parents intranasal OXT has also been reported to produce an attenuated suppression of cortisol [139]. PTSD patients also exhibit hypervigilance and enhanced startle responses, and in rats OXT treatment has been shown to reduce startle both in the presence and absence of a fear-conditioned stimulus [147]. In one of the first clinical studies using a single intranasal administration of OXT (20 IU) Pitman et al. [157] found that it reduced physiological but not psychological responses to combat imagery in Vietnam veterans suffering from PTSD. Whether more sustained periods of treatment where patients are able to self-administer OXT during flashbacks might also eventually reduce psychological as well as physiological symptoms and weaken the memory of original traumatic events needs further investigation.

There would also seem to be some potential in considering combining OXT treatment with extinction-based exposure therapy. A preliminary report has also found that intranasal OXT significantly lowered the level of anxiety, tension, restlessness and irritability in 18 PTSD patients as well as improving mood and reducing the intensity of recurrent thoughts about the trauma. Subjects apparently also reported increased desire for social interaction although there was only a small, but significant reduction in the severity of PTSD symptoms [217].

3.4.4. OXT and borderline-personality disorder

BPD is often associated with childhood trauma and neglect and unstable emotional and interpersonal relationships [120] including attachments that are unresolved or fearful [2]. As discussed above for PTSD there are a number of studies reporting altered OXT associated with early-childhood trauma. In particular, BPD is associated with excessive vigilance and enhanced reactivity to emotional and social stimuli [84]. Increased reactivity to emotional social stimuli is also evidenced by neuroimaging findings of enhanced amygdala reactivity to negative scenes [83] and facial expressions [146]. Furthermore, BPD patients often display a negativity bias particularly towards the perception of anger [43].

To date only two studies have investigated effects of intranasal OXT in BPD patients. One has reported that OXT treatment can actually make some symptoms worse. In this study BPD and control subjects played a social dilemma game with a partner. In the BPD patients OXT actually reduced trust and cooperative responses. This effect was particularly contributed to by those patients who were anxiously attached or rejection-sensitive [14]. The authors concluded from their results that OXT does not uniformly facilitate trust and prosocial behavior in humans and may impede it in individuals with chronic interpersonal insecurities. Indeed, the preclinical studies already discussed showing increased envy, jealousy [180] and parochial altruism [35] following intranasal OXT treatment are also suggestive that in some situations trust and prosocial feelings towards others can be decreased. However, in a second study on 14 BPD patients compared to 13 controls a 40 IU-intranasal OXT dose yielded effects in the TSST [184]. Specifically, the BPD patients showed greater attenuation of stress-induced dysphoria and a tendency towards a greater attenuation of the stress-induced cortisol increase. There was also a relationship found between emotional stress reactivity and childhood trauma alone or combined with self-esteem. The authors concluded that OXT may have a beneficial impact on emotional regulation in BPD.

In summary therefore potential relationships between impaired OXT function and BPD have been suggested, particularly in the context of early-life trauma or neglect, and potential therapeutic effects of OXT on emotional regulation have been demonstrated. However, one study carried out using a game playing paradigm has found reduced trust and co-operation. As with some other disorders, it will be important in future to consider potential therapeutic effects of intranasal OXT in relation to a patient's everyday social relationships.

3.5. Schizophrenia

Schizophrenia is a multifactorial, neurodevelopmental disorder caused by a combination of genetic and environmental risk factors. The symptoms of schizophrenia include positive (including delusions and hallucinations, typically regarded as manifestations of psychosis) and negative symptoms (including blunted affect, anhedonia, social withdrawal and lack of motivation) and cognitive impairment (especially in the domains of attention and declarative memory), which leads to many problems in social and occupational functioning and self-care. About 1% of the population is affected by schizophrenia, with similar rates across different countries, cultural groups, and sexes. Pharmacological treatments, which block dopamine D_2 receptors, are effective for delusions and hallucinations but less so for disabling cognitive and motivational impairments [79,179].

Recent studies have suggested that OXT abnormalities might contribute to the social deficits in schizophrenia (Review [19,164]), thus making the OXT system a promising therapeutic target for the treatment of schizophrenia. Several studies have measured central and peripheral OXT levels in patients with schizophrenia, but the link between the disorder and OXT levels remains inconclusive. Some authors found elevated plasma levels of OXT-neurophysin or elevated CSF OXT levels in schizophrenic patients [16,117]. Glovinsky et al. [67] reported no difference between individuals with and without schizophrenia, and Goldman et al. [68] found decreased plasma OXT in schizophrenic patients with polydipsic hyponatremia. There was no difference between polydipsic normonatremic and nonpolydipsic normonatremic schizophrenic patients and controls. After three weeks of haloperidol treatment, Goldman et al. [68] found no significant change in CSF OXT levels in schizophrenic patients. Additionally, CSF OXT levels correlated negatively with hippocampal volume in controls and patients with schizophrenia. Plasma OXT levels correlated with schizophrenic patients' accuracy in categorizing facial emotions [68]. In contrast to 50 controls, Keri et al. [100] did not find an OXT release in 50 patients with schizophrenia in response to trust-related interpersonal interactions. The authors suggested that a missing trust-related OXT increase might be driven by negative symptoms and social withdrawal. Initial promise for OXT as a treatment in patients with schizophrenia comes from two older clinical trials and one recently published study. In an open-label study, the investigators administered OXT either intravenously (daily dose of 10–15 IU) or intramuscularly (daily dose of 20–25 IU) over a period of 6–10 days [24]. Rapid therapeutic effects in patients with acute psychosis and weaker effects in chronic schizophrenic patients were described although the therapeutic advantage was not characterized in great detail. Bakharev et al. [11] found an improvement of negative symptoms in 27 men with schizophrenia who received 10 IU OXT over seven days compared to 13 men with schizophrenia who were treated with antipsychotic medication. Positive symptoms were influenced to a much lesser degree. In the most recently published study schizophrenic patients received three weeks of OXT and three weeks of placebo nasal spray in a random order (20 IU of OXT nasal spray were administered twice-daily in the first week and 40 IU twice-daily in the second and third week). OXT caused a reduction in all 'Positive and Negative Syndrome Scale (PANNS)' scores, although not until the final week of the treatment. The greatest effect of OXT treatment was observed in PANNS Negative [53]. The patients in the study were already being treated with antipsychotics and so OXT was able to provide beneficial effects on top of those produced by the antipsychotic drugs. An important finding in this study is that repeated intranasal doses of OXT are well tolerated. However, the fact that it took so long for the OXT treatment to have effects is a little surprising given the large number of studies that have reported rapid effects in other contexts. This may perhaps be due to the fact that patients were on antipsychotics, which antagonize the dopamine D_2 receptor, and it is known from animal studies that prosocial and bonding effects promoted by OXT are mediated via modulation of dopamine release acting on the D_2 receptor (see [124]). Possibly therefore effects might have been more rapid in the absence of antipsychotic treatment.

These initial results suggest clinical benefits of OXT treatment in patients with schizophrenia. However, further randomized controlled trials involving larger patient samples are necessary to confirm the therapeutic efficacy of OXT in schizophrenia. A key requirement for further research is addressing optimal timing and dosing and assessment of long-term outcomes. In addition, neuroimaging studies of the OXT-targeted brain regions could extend our understanding of the neural substrates where OXT treatment is acting.

3.6. Eating disorders

While often overlooked by comparison with its prosocial effects OXT also has anorexigenic actions, hence making it potentially important for the regulation of hunger and satiety [118,174,208].

Intravenous administration of OXT during fasting decreases levels of ghrelin in young, healthy men; ghrelin is a hormone that stimulates hunger and is increased before meals [211]. The glucocorticoid-induced increase of the hormone leptin that inhibits appetite is also inhibited by OXT in normal-weight, young men [26]. In light of these findings and animal-based research implicating the PVN as an important center for appetite control, a hypothesis that eating disorders are characterized by OXT dysregulation has been proposed. First, we will review the relationship between OXT levels and anorexia nervosa and bulimia nervosa and then discuss the association of OXT with adiposity. Finally we will review studies that have investigated OXT regulation in patients with Prader-Willi-Syndrome (PWS) which is associated with obesity.

Little is known about potential relations between OXT and anorexia nervosa or bulimia nervosa. Demitrack et al. [37] have reported low CSF OXT concentrations in five underweight anorectic women compared to healthy controls. However, Chiodera et al. [26] found no difference in plasma OXT levels in seven women with anorexia nervosa compared to nine healthy controls although underweight anorectic women did not respond to stimulation with estrogens or insulin-induced hypoglycemia. After partial weight recovery, there was a slight OXT increase in response to these stimuli. No differences in CSF or plasma OXT concentrations were found in normal- or under-weight bulimic women [26,37]. After recovery, OXT levels in the CSF did not differ in patients with anorexia nervosa or bulimia nervosa compared to controls [59]. The latter authors suggest that where OXT changes are found they may be secondary to malnutrition, weight loss and/or altered meal patterns. Two studies, however, have reported increased OXT plasma levels in women and men with adiposity [91,189]. Six months after a gastric banding operation OXT levels had decreased, but were still significantly elevated compared to a control group [189]. In contrast to normal-weight, young men, in obese individuals dexamethasone-induced increases in the appetite-inhibiting hormone leptin were not changed by OXT infusion [26].

Prader–Willi syndrome (PWS) is a rare imprinted gene disorder characterized by short stature, muscular hypotonia, hypogonadism, mental retardation, hyperphagia, and behavioral abnormalities such as compulsive behavior or anxiety. The etiology of excessive appetite and uncontrolled consumption of food is unknown. The available data regarding the correlation between OXT and hyperphagia in patients with PWS are inconsistent. It remains unclear whether OXT is involved in the hyperphagia seen in PWS patients. One study has reported reduced OXT cell numbers in the PVN of PWS patients [192]. However, both elevated [137] and normal [90,91] CSF OXT levels in individuals with PWS have been reported.

In summary, therefore, while there is evidence for the involvement of OXT in appetite control its role in appetite disorders is still unclear.

4. Synopsis and future directions

In this review we have summarized an increasingly large and complex literature reporting OXT release- or treatment-associated changes in a range of social and emotional behaviors both in normal healthy subjects and in individuals suffering from psychiatric disorders. Many studies have reported wide-ranging oxytocinergic modulation of social relationships, including bonding, attachment security, enhanced trust and empathy, inhibition of social stress and ameliorated responses to fear-evoking stimuli. However, OXT can also promote protection type behaviors which could result in increased intergroup conflict and aggression in some circumstances. Future studies will need to focus on disentangling OXT effects on different kinds of social and affiliative behaviors and establish the neural substrates where it acts to promote its effects. One of the most important tools in this respect will be the development of radioligands for the OXTR to allow PET studies which can elucidate both resting and dynamic OXTR changes in both preclinical and clinical contexts. To date mounting evidence suggests that the amygdala is a particularly important site for OXT action in reducing responses to negative social stimuli, such as fearful and angry faces and for enhancing them to positive social stimuli. It seems likely, too, that this region plays an important role in OXT-mediated effects on social recognition, emotional empathy and socially motivated learning. Given the importance of OXT modulation of noradrenergic and serotonergic function in animals for its social recognition and anxiolytic effects future research will need to investigate whether this is also true in humans and also whether combination treatments targeting both OXT and noradrenergic and/or serotonergic function will be more effective.

One of the key hypotheses concerning OXTs prosocial effects is that it increases the rewarding properties of social cues and interactions. While there is some support from fMRI studies that the ventral striatum is activated during exposure to social stimuli that evoke OXT release no studies have yet addressed the key question of whether OXT releases dopamine in this region and promotes rewarding effects via the D_2 receptor as in social voles [124]. Equally an important question is whether OXTR polymorphisms or epigenetic modification can significantly influence OXTR expression in the ventral striatum or other brain reward areas. In this context the important potential for therapeutic use of OXT treatment for addiction problems, particularly in terms of reducing drug withdrawal symptoms, has yet to be investigated in humans. Most studies attempting to establish direct behavioral effects of OXT in humans have employed a single intranasal administration of the peptide. None of these studies however have carried out a systematic evaluation of dose–response relationships and or of the dynamic changes in OXT which occur in the CSF and blood following intranasal administration. We also have yet to establish whether observed behavioral effects of intranasal OXT are limited to perhaps a few hours or can endure for a longer period. Potential receptor desensitization effects of repeated OXT treatments also need to be assessed.

Animal studies have shown us that social bonds formed after a rapid release of OXT in the brain following either birth or mating do so very quickly and are enduring, although the general consensus is that once bonds are formed OXT is not critical in maintaining them. What OXT appears to do is to make social cues both more memorable and rewarding. By acting as a neuroplasticity agent, OXT may help rewire neural systems, so that specific cues from individuals which whom bonds are formed are more likely to elicit recognition and pleasure in the future. Hopefully in a therapeutic context this may mean that durations of OXT treatment will not need to be prolonged since effects will be long-lasting, although clearly this is a very important question to address in future studies.

While to date no significant side effects on intranasal OXT have been reported, the fact that OXT can have effects on a large number of peripheral organs, particularly through contractile effects on smooth muscles, makes it important to target development of approaches where increases in peripheral OXT concentrations are minimized. Indeed, most studies have included only male subjects because of potential problems it might cause by promoting uterine contractions. A possible reason why peripheral treatments with OXT have in some cases been reported to cause behavioral effects may be through its peripheral muscular actions stimulating vagally mediated OXT release in the brain since the blood–brain barrier is very impermeable to it. One easy immediate approach to reducing peripheral OXT concentrations following intranasal treatment may be to combine it with routine vasoconstrictive agents such as phenylephrine.

While we have identified the many and obvious links between preclinical findings and clinical studies suggesting a promising therapeutic potential for OXT treatments in psychiatric disorders, there is still an important need for more large-scale controlled clinical studies. Preliminary evidence showing that OXT might have a therapeutic potential in ameliorating at least some psychiatric disorders is nevertheless already encouraging. Going forward, though, it will be important to recognize that while increasing OXT concentrations in the brain may be an effective 'kick-start' method for improving psychosocial problems in psychiatric patients, it may primarily act as an indirect 'facilitator' of behavior through modulation of classical neurotransmitter signaling. It is likely, therefore, that its most effective therapeutic use will be in combination with other drugs or nonpharmacological treatments, particularly those such as CBT, that considerably depend on the quality of social interaction between therapist and patient.

Conflicts of interest

The authors report no relevant biomedical financial interests or personal affiliations in connection with the content of this manuscript.

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References

[1] J.S. Abramowitz, S. Taylor, D. McKay, Obsessive–compulsive disorder, Lancet 374 (2009) 491–499.
[2] H.R. Agrawal, J. Gunderson, B.M. Holmes, K. Lyons-Ruth, Attachment studies with borderline patients: a review, Harv. Rev. Psychiat. 12 (2004) 94–104.
[3] M. Altemus, K.R. Jacobson, M. Debellis, M. Kling, T. Pigott, D.L. Murphy, P.W. Gold, Normal CSF oxytocin and NPY levels in OCD, Biol. Psychiat. 45 (1999) 931–933.
[4] G.A. Alvares, I.B. Hickie, A.J. Guastella, Acute effects of intranasal oxytocin on subjective and behavioral responses to social rejection, Exp. Clin. Psychopharmacol. 18 (2010) 316–321.
[5] J.A. Amico, R. Tenicela, J. Johnston, A.G. Robinson, A time-dependent peak of oxytocin exists in cerebrospinal fluid but not in plasma of humans, J. Clin. Endocrinol. Metab. 57 (1983) 947–951.
[6] D. Anagnostakis, J. Messaritakis, D. Damianos, H. Mandyla, Blood–brain barrier permeability in "healthy" infected and stressed neonates, J. Pediatr. 121 (1992) 291–294.
[7] E. Andari, J.R. Duhamel, T. Zalla, E. Herbrecht, M. Leboyer, A. Sirigu, Promoting social behavior with oxytocin in high-functioning autism spectrum disorders, Proc. Natl. Acad. Sci. USA 107 (2010) 4389–4394.
[8] A.N. Andersen, C. Lund-Andersen, J.F. Larsen, N.J. Christensen, J.J. Legros, F. Louis, H. Angelo, J. Molin, Suppressed prolactin but normal neurophysin levels in cigarette smoking breast-feeding women, Clin. Endocrinol. (Oxf.) 17 (1982) 363–368.
[9] M. Ansseau, J.J. Legros, C. Mormont, J.L. Cerfontaine, P. Papart, V. Geenen, F. Adam, G. Franck, Intranasal oxytocin in obsessive–compulsive disorder, Psychoneuroendocrinology 12 (1987) 231–236.
[10] M.J. Bakermans-Kranenburg, M.H. van Ijzendoorn, Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting, Soc. Cogn. Affect Neurosci. 3 (2008) 128–134.
[11] V.D. Bakharev, S.M. Tikhomirov, T.K. Lozhkina, Psychotropic properties of oxytocin, Probl. Endokrinol. (Mosk) 30 (1984) 37–41.
[12] J.A. Barraza, P.J. Zak, Empathy toward strangers triggers oxytocin release and subsequent generosity, Ann. NY Acad. Sci. 1167 (2009) 182–189.
[13] J.A. Bartz, E. Hollander, Oxytocin and experimental therapeutics in autism spectrum disorders, Prog. Brain Res. 170 (2008) 451–462.
[14] J.A. Bartz, J. Zaki, N. Bolger, E. Hollander, N.N. Ludwig, A. Kolevzon, K.N. Ochsner, Oxytocin selectively improves empathic accuracy, Psychol. Sci. 21 (2010) 1426–1428.
[15] T. Baumgartner, M. Heinrichs, A. Vonlanthen, U. Fischbacher, E. Fehr, Oxytocin shapes the neural circuitry of trust and trust adaptation in humans, Neuron 58 (2008) 639–650.
[16] H. Beckmann, R.E. Lang, W.F. Gattaz, Vasopressin–oxytocin in cerebrospinal fluid of schizophrenic patients and normal controls, Psychoneuroendocrinology 10 (1985) 187–191.
[17] C.J. Bell, H. Nicholson, R.T. Mulder, S.E. Luty, P.R. Joyce, Plasma oxytocin levels in depression and their correlation with the temperament dimension of reward dependence, J. Psychopharmacol. 20 (2006) 656–660.
[18] P.R. Blackett, S.M. Seif, D.H. Altmiller, A.G. Robinson, Familial central diabetes insipidus: vasopressin and nicotine stimulated neurophysin deficiency with subnormal oxytocin and estrogen stimulated neurophysin, Am. J. Med. Sci. 286 (1983) 42–46.
[19] E. Bora, M. Yucel, N.B. Allen, Neurobiology of human affiliative behaviour: implications for psychiatric disorders, Curr. Opin. Psychiat. 22 (2009) 320–325.
[20] J. Born, T. Lange, W. Kern, G.P. McGregor, U. Bickel, H.L. Fehm, Sniffing neuropeptides: a transnasal approach to the human brain, Nat. Neurosci. 5 (2002) 514–516.
[21] K.D. Broad, F. Levy, G. Evans, T. Kimura, E.B. Keverne, K.M. Kendrick, Previous maternal experience potentiates the effect of parturition on oxytocin receptor mRNA expression in the paraventricular nucleus, Eur. J. Neurosci. 11 (1999) 3725–3737.
[22] J. Bruins, R. Hijman, J.M. Van Ree, Effect of a single dose of des-glycinamide-[Arg8]vasopressin or oxytocin on cognitive processes in young healthy subjects, Peptides 13 (1992) 461–468.
[23] A. Buchheim, M. Heinrichs, C. George, D. Pokorny, E. Koops, P. Henningsen, M.F. O'Connor, H. Gundel, Oxytocin enhances the experience of attachment security, Psychoneuroendocrinology 34 (2009) 1417–1422.
[24] W. Bujanow, Hormones in the treatment of psychoses, Brit. Med. J. 4 (1972) 298.
[25] R.R. Chaudhury, G.F. Joplin, Preliminary observations on release of oxytocin and vasopressin in human subjects, J. Endocrinol. 21 (1960) 125–128.
[26] P. Chiodera, R. Volpi, L. Capretti, S. Cataldo, G. Speroni, V. Coiro, Effect of systemic oxytocin administration on dexamethasone-induced leptin secretion in normal and obese men, J. Clin. Endocrinol. Metab. 85 (2000) 3683–3686.
[27] P. Chiodera, R. Volpi, L. Capretti, C. Marchesi, L. d'Amato, A. De Ferri, L. Bianconi, V. Coiro, Effect of estrogen or insulin-induced hypoglycemia on plasma oxytocin levels in bulimia and anorexia nervosa, Metabolism 40 (1991) 1226–1230.
[28] V. Coiro, A. Alboni, D. Gramellini, C. Cigarini, L. Bianconi, D. Pignatti, R. Volpi, P. Chiodera, Inhibition by ethanol of the oxytocin response to breast stimulation in normal women and the role of endogenous opioids, Acta Endocrinol. (Copenh) 126 (1992) 213–216.
[29] V. Coiro, L. Capretti, C. Davoli, G. Speronij, L. Bianconi, U. Cavazzini, A. Marcato, C. Papadia, R. Volpi, P. Chioderat, Endogenous opioids modulate the oxytocin response to insulin-induced hypoglycaemia and partially mediate the inhibitory effect of ethanol in man, J. Neuroendocrinol. 3 (1991) 401–405.
[30] V. Coiro, P. Chiodera, Naloxone increases the angiotensin II stimulated rise of arginine vasopressin and oxytocin secretion in man, Neuroendocrinology 53 (1991) 209–213.
[31] B.A. Corbett, J.R. Gunther, D. Comins, J. Price, N. Ryan, D. Simon, C.W. Schupp, T. Rios, Brief report: theatre as therapy for children with autism spectrum disorder, Journal of Autism and Developmental Disorders 41 (2011) 505–511.
[32] B. Costa, S. Pini, P. Gabelloni, M. Abelli, L. Lari, A. Cardini, M. Muti, C. Gesi, S. Landi, S. Galderisi, A. Mucci, A. Lucacchini, G.B. Cassano, C. Martini, Oxytocin receptor polymorphisms and adult attachment style in patients with depression, Psychoneuroendocrinology 34 (2009) 1506–1514.
[33] S.S. Cui, R.C. Bowen, G.B. Gu, D.K. Hannesson, P.H. Yu, X. Zhang, Prevention of cannabinoid withdrawal syndrome by lithium: involvement of oxytocinergic neuronal activation, J. Neurosci. 21 (2001) 9867–9876.
[34] J.M. Cyranowski, T.L. Hofkens, E. Frank, H. Seltman, H.M. Cai, J.A. Amico, Evidence of dysregulated peripheral oxytocin release among depressed women, Psychosom. Med. 70 (2008) 967–975.
[35] C.K. De Dreu, L.L. Greer, M.J. Handgraaf, S. Shalvi, G.A. Van Kleef, M. Baas, F.S. Ten Velden, E. Van Dijk, S.W. Feith, The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans, Science 328 (2010) 1408–1411.
[36] C.H. Declerck, C. Boone, T. Kiyonari, Oxytocin and cooperation under conditions of uncertainty: the modulating role of incentives and social information, Horm. Behav. 57 (2010) 368–374.
[37] M.A. Demitrack, M.D. Lesem, S.J. Listwak, H.A. Brandt, D.C. Jimerson, P.W. Gold, CSF oxytocin in anorexia nervosa and bulimia nervosa: clinical and pathophysiologic considerations, Am. J. Psychiat. 147 (1990) 882–886.
[38] J.A. den Boer, H.G. Westenberg, Oxytocin in obsessive compulsive disorder, Peptides 13 (1992) 1083–1085.
[39] D.P. Devanand, S. Lisanby, E.S. Lo, L. Fitzsimons, T.B. Cooper, U. Halbreich, H.A. Sackeim, Effects of electroconvulsive therapy on plasma vasopressin and oxytocin, Biol. Psychiat. 44 (1998) 610–616.
[40] S.V. Dhuria, L.R. Hanson, W.H. Frey 2nd, Novel vasoconstrictor formulation to enhance intranasal targeting of neuropeptide therapeutics to the central nervous system, J. Pharmacol. Exp. Ther. 328 (2009) 312–320.
[41] M. Di Simplicio, R. Massey-Chase, P.J. Cowen, C.J. Harmer, Oxytocin enhances processing of positive versus negative emotional information in healthy male volunteers, J. Psychopharmacol. 23 (2009) 241–248.
[42] B. Ditzen, M. Schaer, B. Gabriel, G. Bodenmann, U. Ehlert, M. Heinrichs, Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict, Biol. Psychiat. 65 (2009) 728–731.

[43] G. Domes, D. Czieschnek, F. Weidler, C. Berger, K. Fast, S.C. Herpertz, Recognition of facial affect in borderline personality disorder, J. Pers. Disord. 22 (2008) 135–147.
[44] G. Domes, M. Heinrichs, J. Glascher, C. Buchel, D.F. Braus, S.C. Herpertz, Oxytocin attenuates amygdala responses to emotional faces regardless of valence, Biol. Psychiat. 62 (2007) 1187–1190.
[45] G. Domes, M. Heinrichs, A. Michel, C. Berger, S.C. Herpertz, Oxytocin improves "mind-reading" in humans, Biol. Psychiat. 61 (2007) 731–733.
[46] G. Domes, A. Lischke, C. Berger, A. Grossmann, K. Hauenstein, M. Heinrichs, S.C. Herpertz, Effects of intranasal oxytocin on emotional face processing in women, Psychoneuroendocrinology 35 (2010) 83–93.
[47] G.J. Dumont, F.C. Sweep, R. van der Steen, R. Hermsen, A.R. Donders, D.J. Touw, J.M. van Gerven, J.K. Buitelaar, R.J. Verkes, Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration, Soc. Neurosci. 4 (2009) 359–366.
[48] C.R. Edwards, Vasopressin and oxytocin in health and disease, Clin. Endocrinol. Metab. 6 (1977) 223–259.
[49] C.N. Epperson, C.J. McDougle, L.H. Price, Intranasal oxytocin in obsessive–compulsive disorder, Biol. Psychiat. 40 (1996) 547–549.
[50] S. Evans, S.S. Shergill, B.B. Averbeck, Oxytocin decreases aversion to angry faces in an associative learning task, Neuropsychopharmacology 35 (2010) 2502–2509.
[51] G. Fehm-Wolfsdorf, G. Bachholz, J. Born, K. Voigt, H.L. Fehm, Vasopressin but not oxytocin enhances cortical arousal: an integrative hypothesis on behavioral effects of neurohypophyseal hormones, Psychopharmacology (Berl) 94 (1988) 496–500.
[52] G. Fehm-Wolfsdorf, J. Born, K.H. Voigt, H.L. Fehm, Human memory and neurohypophyseal hormones: opposite effects of vasopressin and oxytocin, Psychoneuroendocrinology 9 (1984) 285–292.
[53] D. Feifel, K. Macdonald, A. Nguyen, P. Cobb, H. Warlan, B. Galangue, A. Minassian, O. Becker, J. Cooper, W. Perry, M. Lefebvre, J. Gonzales, A. Hadley, Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients, Biol. Psychiat. 68 (2010) 678–680.
[54] D. Fein, D. Allen, M. Dunn, C. Feinstein, L. Green, R. Morris, I. Rapin, L. Waterhouse, Pitocin induction and autism, Am. J. Psychiat. 154 (1997) 438–439.
[55] R. Feldman, A. Weller, O. Zagoory-Sharon, A. Levine, Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding, Psychol. Sci. 18 (2007) 965–970.
[56] B.M. Ferrier, D.J. Kennett, M.C. Devlin, Influence of oxytocin on human memory processes, Life Sci. 27 (1980) 2311–2317.
[57] M. Fischer-Shofty, S.G. Shamay-Tsoory, H. Harari, Y. Levkovitz, The effect of intranasal administration of oxytocin on fear recognition, Neuropsychologia 48 (2010) 179–184.
[58] A. Forray, M. Focseneanu, B. Pittman, C.J. McDougle, C.N. Epperson, Onset and exacerbation of obsessive-compulsive disorder in pregnancy and the postpartum period, J. Clin. Psychiat. 71 (2010) 1061–1068.
[59] G.K. Frank, W.H. Kaye, M. Altemus, C.G. Greeno, CSF oxytocin and vasopressin levels after recovery from bulimia nervosa and anorexia nervosa, bulimic subtype, Biol. Psychiat. 48 (2000) 315–318.
[60] A. Frasch, T. Zetzsche, A. Steiger, G.F. Jirikowski, Reduction of plasma oxytocin levels in patients suffering from major depression, Adv. Exp. Med. Biol. 395 (1995) 257–258.
[61] A.B. Fries, T.E. Ziegler, J.R. Kurian, S. Jacoris, S.D. Pollak, Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior, Proc. Natl. Acad. Sci. USA 102 (2005) 17237–17240.
[62] E. Gaitan, E. Cobo, M. Mizrachi, Evidence for the differential secretion of oxytocin and vasopressin in man, J. Clin. Invest. 43 (1964) 2310–2322.
[63] S. Gale, S. Ozonoff, J. Lainhart, Brief report: pitocin induction in autistic and nonautistic individuals, J. Autism. Dev. Disord. 33 (2003) 205–208.
[64] M. Gamer, B. Zurowski, C. Buchel, Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans, Proc. Natl. Acad. Sci. USA 107 (2010) 9400–9405.
[65] V. Geenen, F. Adam, V. Baro, H. Mantanus, M. Ansseau, M. Timsit-Berthier, J.J. Legros, Inhibitory influence of oxytocin infusion on contingent negative variation and some memory tasks in normal men, Psychoneuroendocrinology 13 (1988) 367–375.
[66] F.G. Geldenhuys, E.W. Sonnendecker, M.C. De Klrk, Experience with sodium-gamma-4-hydroxybutyric acid (gamma-OH) in obstetrics, J. Obstet. Gynaecol. Brit. Commonw. 75 (1968) 405–413.
[67] D. Glovinsky, K.T. Kalogeras, D.G. Kirch, R. Suddath, R.J. Wyatt, Cerebrospinal fluid oxytocin concentration in schizophrenic patients does not differ from control subjects and is not changed by neuroleptic medication, Schizophr. Res. 11 (1994) 273–276.
[68] M. Goldman, M. Marlow-O'Connor, I. Torres, C.S. Carter, Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits, Schizophr. Res. 98 (2008) 247–255.
[69] G.C. Gonzaga, R.A. Turner, D. Keltner, B. Campos, M. Altemus, Romantic love and sexual desire in close relationships, Emotion 6 (2006) 163–179.
[70] P.J. Goodnick, A.J. Rush, M.S. George, L.B. Marangell, H.A. Sackeim, Vagus nerve stimulation in depression, Exp. Opin. Pharmacother. 2 (2001) 1061–1063.
[71] L. Green, D. Fein, C. Modahl, C. Feinstein, L. Waterhouse, M. Morris, Oxytocin and autistic disorder: alterations in peptide forms, Biol. Psychiat. 50 (2001) 609–613.
[72] S.G. Gregory, J.J. Connelly, A.J. Towers, J. Johnson, D. Biscocho, C.A. Markunas, C. Lintas, R.K. Abramson, H.H. Wright, P. Ellis, C.F. Langford, G. Worley, G.R. Delong, S.K. Murphy, M.L. Cuccaro, A. Persico, M.A. Pericak-Vance, Genomic and epigenetic evidence for oxytocin receptor deficiency in autism, BMC Med. 7 (2009) 62.
[73] E.J. Griffiths, R.P. Lorenz, S. Baxter, N.S. Talon, Acute neurohumoral response to electroconvulsive therapy during pregnancy. A case report, J. Reprod. Med. 34 (1989) 907–911.
[74] A.J. Guastella, D.S. Carson, M.R. Dadds, P.B. Mitchell, R.E. Cox, Does oxytocin influence the early detection of angry and happy faces?, Psychoneuroendocrinology 34 (2009) 220–225
[75] A.J. Guastella, S.L. Einfeld, K.M. Gray, N.J. Rinehart, B.J. Tonge, T.J. Lambert, I.B. Hickie, Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders, Biol. Psychiat. 67 (2010) 692–694.
[76] A.J. Guastella, A.L. Howard, M.R. Dadds, P. Mitchell, D.S. Carson, A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder, Psychoneuroendocrinology 34 (2009) 917–923.
[77] A.J. Guastella, P.B. Mitchell, M.R. Dadds, Oxytocin increases gaze to the eye region of human faces, Biol. Psychiat. 63 (2008) 3–5.
[78] A.J. Guastella, P.B. Mitchell, F. Mathews, Oxytocin enhances the encoding of positive social memories in humans, Biol. Psychiat. 64 (2008) 256–258.
[79] P.D. Harvey, T.L. Patterson, L.S. Potter, K. Zhong, M. Brecher, Improvement in social competence with short-term atypical antipsychotic treatment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning, Am. J. Psychiat. 163 (2006) 1918–1925.
[80] C. Heim, L.J. Young, D.J. Newport, T. Mletzko, A.H. Miller, C.B. Nemeroff, Lower CSF oxytocin concentrations in women with a history of childhood abuse, Mol. Psychiat. 14 (2009) 954–958.
[81] M. Heinrichs, T. Baumgartner, C. Kirschbaum, U. Ehlert, Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress, Biol. Psychiat. 54 (2003) 1389–1398.
[82] M. Heinrichs, G. Meinlschmidt, W. Wippich, U. Ehlert, D.H. Hellhammer, Selective amnesic effects of oxytocin on human memory, Physiol. Behav. 83 (2004) 31–38.
[83] S. Herpertz, C. Albus, R. Kielmann, H. Hagemann-Patt, K. Lichtblau, K. Kohle, K. Mann, W. Senf, Comorbidity of diabetes mellitus and eating disorders: a follow-up study, J. Psychosom. Res. 51 (2001) 673–678.
[84] S. Herpertz, A. Gretzer, E.M. Steinmeyer, V. Muehlbauer, A. Schuerkens, H. Sass, Affective instability and impulsivity in personality disorder. Results of an experimental study, J. Affect. Disord. 44 (1997) 31–37.
[85] E.A. Hoge, M.H. Pollack, R.E. Kaufman, P.J. Zak, N.M. Simon, Oxytocin levels in social anxiety disorder, CNS Neurosci. Ther. 14 (2008) 165–170.
[86] E. Hollander, J. Bartz, W. Chaplin, A. Phillips, J. Sumner, L. Soorya, E. Anagnostou, S. Wasserman, Oxytocin increases retention of social cognition in autism, Biol. Psychiat. 61 (2007) 498–503.
[87] E. Hollander, S. Novotny, M. Hanratty, R. Yaffe, C.M. DeCaria, B.R. Aronowitz, S. Mosovich, Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders, Neuropsychopharmacology 28 (2003) 193–198.
[88] E.C. Hollander, C. Wong, C. DeCaria, G. Del Guidice-Asch, M.S. Buchsbaum, B. Aronowitz B, A dimensional approach to the autism spectrum, CNS Spectrum: Int. J. Neuropsych. Med 3 (1998) 22–39.
[89] W.G. Honer, C. Thompson, S.L. Lightman, T.D. Williams, S.A. Checkley, No effect of naloxone on plasma oxytocin in normal men, Psychoneuroendocrinology 11 (1986) 245–248.
[90] C. Hoybye, Endocrine and metabolic aspects of adult Prader–Willi syndrome with special emphasis on the effect of growth hormone treatment, Growth Horm. IGF Res. 14 (2004) 1–15.
[91] C. Hoybye, B. Barkeling, U. Espelund, M. Petersson, M. Thoren, Peptides associated with hyperphagia in adults with Prader–Willi syndrome before and during GH treatment, Growth Horm. IGF Res. 13 (2003) 322–327.
[92] R. Hurlemann, A. Patin, O.A. Onur, M.X. Cohen, T. Baumgartner, S. Metzler, I. Dziobek, J. Gallinat, M. Wagner, W. Maier, K.M. Kendrick, Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans, J. Neurosci. 30 (2010) 4999–5007.
[93] S. Israel, E. Lerer, I. Shalev, F. Uzefovsky, M. Riebold, E. Laiba, R. Bachner-Melman, A. Maril, G. Bornstein, A. Knafo, R.P. Ebstein, The oxytocin receptor (OXTR) contributes to prosocial fund allocations in the dictator game and the social value orientations task, PLoS One 4 (2009) e5535.
[94] S. Jacob, C.W. Brune, C.S. Carter, B.L. Leventhal, C. Lord, E.H. Cook Jr., Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism, Neurosci. Lett. 417 (2007) 6–9.
[95] L.M. Jansen, C.C. Gispen-de Wied, V.M. Wiegant, H.G. Westenberg, B.E. Lahuis, H. van Engeland, Autonomic and neuroendocrine responses to a psychosocial stressor in adults with autistic spectrum disorder, J. Autism. Dev. Disord. 36 (2006) 891–899.
[96] K.M. Kendrick, Oxytocin, motherhood and bonding, Exp. Physiol. 85 (2000) 111S–124S (Spec No).
[97] K.M. Kendrick, E.B. Keverne, B.A. Baldwin, Intracerebroventricular oxytocin stimulates maternal behaviour in the sheep, Neuroendocrinology 46 (1987) 56–61.
[98] K.M. Kendrick, E.B. Keverne, B.A. Baldwin, D.F. Sharman, Cerebrospinal fluid levels of acetylcholinesterase, monoamines and oxytocin during labour, parturition, vaginocervical stimulation, lamb separation and suckling in sheep, Neuroendocrinology 44 (1986) 149–156.

[99] D.J. Kennett, M.C. Devlin, B.M. Ferrier, Influence of oxytocin on human memory processes: validation by a control study, Life Sci. 31 (1982) 273–275.
[100] S. Keri, I. Kiss, O. Kelemen, Sharing secrets: oxytocin and trust in schizophrenia, Soc. Neurosci. 4 (2009) 287–293.
[101] R.C. Kessler, H. Birnbaum, O. Demler, I.R. Falloon, E. Gagnon, M. Guyer, M.J. Howes, K.S. Kendler, L. Shi, E. Walters, E.Q. Wu, The prevalence and correlates of nonaffective psychosis in the National Comorbidity Survey Replication (NCS-R), Biol. Psychiat. 58 (2005) 668–676.
[102] T. Kimura, F. Saji, K. Nishimori, K. Ogita, H. Nakamura, M. Koyama, Y. Murata, Molecular regulation of the oxytocin receptor in peripheral organs, J. Mol. Endocrinol. 30 (2003) 109–115.
[103] T. Kimura, O. Tanizawa, K. Mori, M.J. Brownstein, H. Okayama, Structure and expression of a human oxytocin receptor, Nature 356 (1992) 526–529.
[104] P. Kirsch, C. Esslinger, Q. Chen, D. Mier, S. Lis, S. Siddhanti, H. Gruppe, V.S. Mattay, B. Gallhofer, A. Meyer-Lindenberg, Oxytocin modulates neural circuitry for social cognition and fear in humans, J. Neurosci. 25 (2005) 11489–11493.
[105] K.C. Koenen, T.E. Moffitt, R. Poulton, J. Martin, A. Caspi, Early childhood factors associated with the development of post-traumatic stress disorder: results from a longitudinal birth cohort, Psychol. Med. 37 (2007) 181–192.
[106] B.R. Komisaruk, B. Whipple, A. Crawford, W.C. Liu, A. Kalnin, K. Mosier, Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the vagus nerves, Brain Res. 1024 (2004) 77–88.
[107] M. Kosfeld, M. Heinrichs, P.J. Zak, U. Fischbacher, E. Fehr, Oxytocin increases trust in humans, Nature 435 (2005) 673–676.
[108] G.L. Kovacs, Z. Borthaiser, G. Telegdy, Oxytocin reduces intravenous heroin self-administration in heroin-tolerant rats, Life Sci. 37 (1985) 17–26.
[109] G.L. Kovacs, Z. Sarnyai, E. Barbarczi, G. Szabo, G. Telegdy, The role of oxytocin–dopamine interactions in cocaine-induced locomotor hyperactivity, Neuropharmacology 29 (1990) 365–368.
[110] G.L. Kovacs, Z. Sarnyai, G. Szabo, Oxytocin and addiction: a review, Psychoneuroendocrinology 23 (1998) 945–962.
[111] L.D. Kubzansky, W.B. Mendes, A. Appleton, J. Block, G.K. Adler, Protocol for an experimental investigation of the roles of oxytocin and social support in neuroendocrine, cardiovascular, and subjective responses to stress across age and gender, BMC Public Health 9 (2009) 481.
[112] J. Kuhl, J. Beckmann, Volition and Personality: Action Versus State Orientation, Hogrefe & Huber, Göttingen, 1994. pp. 9–46.
[113] I. Labuschagne, K.L. Phan, A. Wood, M. Angstadt, P. Chua, M. Heinrichs, J.C. Stout, P.J. Nathan, Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder, Neuropsychopharmacology 35 (2010) 2403–2413.
[114] J.F. Leckman, W.K. Goodman, W.G. North, P.B. Chappell, L.H. Price, D.L. Pauls, G.M. Anderson, M.A. Riddle, C.J. McDougle, L.C. Barr, et al., The role of central oxytocin in obsessive compulsive disorder and related normal behavior, Psychoneuroendocrinology 19 (1994) 723–749.
[115] J.F. Leckman, W.K. Goodman, W.G. North, P.B. Chappell, L.H. Price, D.L. Pauls, G.M. Anderson, M.A. Riddle, M. McSwiggan-Hardin, C.J. McDougle, et al., Elevated cerebrospinal fluid levels of oxytocin in obsessive–compulsive disorder. Comparison with Tourette's syndrome and healthy controls, Arch. Gen. Psychiat. 51 (1994) 782–792.
[116] H.J. Lee, A.H. Macbeth, J.H. Pagani, W.S. Young 3rd, Oxytocin: the great facilitator of life, Prog. Neurobiol. 88 (2009) 127–151.
[117] J.J. Legros, C. Gazzotti, T. Carvelli, P. Franchimont, M. Timsit-Berthier, R. von Frenckell, M. Ansseau, Apomorphine stimulation of vasopressin- and oxytocin-neurophysins. Evidence for increased oxytocinergic and decreased vasopressinergic function in schizophrenics, Psychoneuroendocrinology 17 (1992) 611–617.
[118] G. Leng, T. Onaka, C. Caquineau, N. Sabatier, V.A. Tobin, Y. Takayanagi, Oxytocin and appetite, Prog. Brain Res. 170 (2008) 137–151.
[119] E. Lerer, S. Levi, S. Salomon, A. Darvasi, N. Yirmiya, R.P. Ebstein, Association between the oxytocin receptor (OXTR) gene and autism: relationship to Vineland adaptive behavior scales and cognition, Mol. Psychiat. 13 (2008) 980–988.
[120] K. Lieb, J.E. Rexhausen, K.G. Kahl, U. Schweiger, A. Philipsen, D.H. Hellhammer, M. Bohus, Increased diurnal salivary cortisol in women with borderline personality disorder, J. Psychiat. Res. 38 (2004) 559–565.
[121] R. Lieb, H.U. Wittchen, M. Hofler, M. Fuetsch, M.B. Stein, K.R. Merikangas, Parental psychopathology, parenting styles, and the risk of social phobia in offspring: a prospective-longitudinal community study, Arch. Gen. Psychiat. 57 (2000) 859–866.
[122] K.C. Light, K.M. Grewen, J.A. Amico, More frequent partner hugs and higher oxytocin levels are linked to lower blood pressure and heart rate in premenopausal women, Biol. Psychol. 69 (2005) 5–21.
[123] K.C. Light, K.M. Grewen, J.A. Amico, M. Boccia, K.A. Brownley, J.M. Johns, Deficits in plasma oxytocin responses and increased negative affect, stress, and blood pressure in mothers with cocaine exposure during pregnancy, Addict. Behav. 29 (2004) 1541–1564.
[124] M.M. Lim, L.J. Young, Neuropeptidergic regulation of affiliative behavior and social bonding in animals, Horm. Behav. 50 (2006) 506–517.
[125] S.W. Lindow, M.S. Hendricks, F.A. Nugent, T.T. Dunne, Z.M. van der Spuy, Morphine suppresses the oxytocin response in breast-feeding women, Gynecol. Obstet. Invest. 48 (1999) 33–37.
[126] S.W. Lindow, M.S. Hendricks, J.W. Thompson, Z.M. van der Spuy, Effects of morphine administration on the fetal production of oxytocin in labour, Clin. Sci. (Lond.) 95 (1998) 91–95.
[127] S.W. Lindow, Z.M. van der Spuy, M.S. Hendricks, F.A. Nugent, T.T. Dunne, The effect of morphine and naloxone administration on maternal oxytocin concentration in late pregnancy, Clin. Endocrinol. (Oxf.) 39 (1993) 671–675.
[128] S.W. Lindow, Z.M. van der Spuy, M.S. Hendricks, A.P. Rosselli, C. Lombard, G. Leng, The effect of morphine and naloxone administration on plasma oxytocin concentrations in the first stage of labour, Clin. Endocrinol. (Oxf.) 37 (1992) 349–353.
[129] P. Linkowski, V. Geenen, M. Kerkhofs, J. Mendlewicz, J.J. Legros, Cerebrospinal fluid neurophysins in affective illness and in schizophrenia, Eur Arch Psychiatry Neurol Sci 234 (1984) 162–165.
[130] M.J. Lucht, S. Barnow, C. Sonnenfeld, A. Rosenberger, H.J. Grabe, W. Schroeder, H. Volzke, H.J. Freyberger, F.H. Herrmann, H. Kroemer, D. Rosskopf, Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjects, Prog. Neuropsychopharmacol. Biol. Psychiat. 33 (2009) 860–866.
[131] M. Ludwig, G. Leng, Dendritic peptide release and peptide-dependent behaviours, Nat. Rev. Neurosci. 7 (2006) 126–136.
[132] E. Macdonald, M.R. Dadds, J.L. Brennan, K. Williams, F. Levy, A.J. Cauchi, A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research, Psychoneuroendocrinology (2011).
[133] A. Malek, E. Blann, D.R. Mattison, Human placental transport of oxytocin, J. Matern. Fetal Med. 5 (1996) 245–255.
[134] C. Marchesi, P. Chiodera, E. Brusamonti, R. Volpi, V. Coiro, Abnormal plasma oxytocin and beta-endorphin levels in alcoholics after short and long term abstinence, Prog. Neuropsychopharmacol. Biol. Psychiat. 21 (1997) 797–807.
[135] A.A. Marsh, N. Ambady, R.E. Kleck, The effects of fear and anger facial expressions on approach- and avoidance-related behaviors, Emotion 5 (2005) 119–124.
[136] A.A. Marsh, H.H. Yu, D.S. Pine, R.J. Blair, Oxytocin improves specific recognition of positive facial expressions, Psychopharmacology (Berlin) 209 (2010) 225–232.
[137] A. Martin, M. State, G.M. Anderson, W.M. Kaye, J.M. Hanchett, C.W. McConaha, W.G. North, J.F. Leckman, Cerebrospinal fluid levels of oxytocin in Prader–Willi syndrome: a preliminary report, Biol. Psychiat. 44 (1998) 1349–1352.
[138] C.J. McDougle, L.C. Barr, W.K. Goodman, L.H. Price, Possible role of neuropeptides in obsessive compulsive disorder, Psychoneuroendocrinology 24 (1999) 1–24.
[139] G. Meinlschmidt, C. Heim, Sensitivity to intranasal oxytocin in adult men with early parental separation, Biol. Psychiat. 61 (2007) 1109–1111.
[140] J.A. Mennella, M.Y. Pepino, Short-term effects of alcohol consumption on the hormonal milieu and mood states in nulliparous women, Alcohol 38 (2006) 29–36.
[141] J.A. Mennella, M.Y. Pepino, K.L. Teff, Acute alcohol consumption disrupts the hormonal milieu of lactating women, J. Clin. Endocrinol. Metab. 90 (2005) 1979–1985.
[142] G. Meynen, U.A. Unmehopa, M.A. Hofman, D.F. Swaab, W.J. Hoogendijk, Hypothalamic oxytocin mRNA expression and melancholic depression, Mol. Psychiat. 12 (2007) 118–119.
[143] Y. Mihov, S. Mayer, F. Musshoff, W. Maier, K.M. Kendrick, R. Hurlemann, Facilitation of learning by social-emotional feedback in humans is beta-noradrenergic-dependent, Neuropsychologia 48 (2010) 3168–3172.
[144] M. Mikolajczak, J.J. Gross, A. Lane, O. Corneille, P. de Timary, O. Luminet, Oxytocin makes people trusting, not gullible, Psychol. Sci. 21 (2010) 1072–1074.
[145] M. Mikolajczak, N. Pinon, A. Lane, P. de Timary, O. Luminet, Oxytocin not only increases trust when money is at stake, but also when confidential information is in the balance, Biol. Psychol. 85 (2010) 182–184.
[146] M.J. Minzenberg, J. Fan, A.S. New, C.Y. Tang, L.J. Siever, Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study, Psychiat. Res. 155 (2007) 231–243.
[147] G. Missig, L.W. Ayers, J. Schulkin, J.B. Rosen, Oxytocin reduces background anxiety in a fear-potentiated startle paradigm, Neuropsychopharmacology 35 (2010) 2607–2616.
[148] C. Modahl, L. Green, D. Fein, M. Morris, L. Waterhouse, C. Feinstein, H. Levin, Plasma oxytocin levels in autistic children, Biol. Psychiat. 43 (1998) 270–277.
[149] M.W. Mosconi, H. Cody-Hazlett, M.D. Poe, G. Gerig, R. Gimpel-Smith, J. Piven, Longitudinal study of amygdala volume and joint attention in 2- to 4-year-old children with autism, Arch. Gen. Psychiat. 66 (2009) 509–516.
[150] I. Nevo, M. Hamon, Neurotransmitter and neuromodulatory mechanisms involved in alcohol abuse and alcoholism, Neurochem. Int. 26 (1995) 305–336 (discussion 337–342).
[151] M.D. Noseworthy, T.M. Bray, Effect of oxidative stress on brain damage detected by MRI and in vivo 31P-NMR, Free Radical Biol. Med. 24 (1998) 942–951.
[152] E. Nowakowska, K. Kus, T. Bobkiewicz-Kozlowska, H. Hertmanowska, Role of neuropeptides in antidepressant and memory improving effects of venlafaxine, Pol. J. Pharmacol. 54 (2002) 605–613.
[153] S. Ozsoy, E. Esel, M. Kula, Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment, Psychiat. Res. 169 (2009) 249–252.

[154] K.J. Parker, H.A. Kenna, J.M. Zeitzer, J. Keller, C.M. Blasey, J.A. Amico, A.F. Schatzberg, Preliminary evidence that plasma oxytocin levels are elevated in major depression, Psychiat. Res. 178 (2010) 359–362.
[155] P. Petrovic, R. Kalisch, T. Singer, R.J. Dolan, Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity, J. Neurosci. 28 (2008) 6607–6615.
[156] B. Pierrehumbert, R. Torrisi, D. Laufer, O. Halfon, F. Ansermet, M. Beck Popovic, Oxytocin response to an experimental psychosocial challenge in adults exposed to traumatic experiences during childhood or adolescence, Neuroscience 166 (2010) 168–177.
[157] R.K. Pitman, S.P. Orr, N.B. Lasko, Effects of intranasal vasopressin and oxytocin on physiologic responding during personal combat imagery in Vietnam veterans with posttraumatic stress disorder, Psychiat. Res. 48 (1993) 107–117.
[158] A.F. Pitts, S.D. Samuelson, W.H. Meller, G. Bissette, C.B. Nemeroff, R.G. Kathol, Cerebrospinal fluid corticotropin-releasing hormone, vasopressin, and oxytocin concentrations in treated patients with major depression and controls, Biol. Psychiat. 38 (1995) 330–335.
[159] J.S. Purba, W.J. Hoogendijk, M.A. Hofman, D.F. Swaab, Increased number of vasopressin- and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression, Arch. Gen. Psychiat. 53 (1996) 137–143.
[160] M. Quirin, J. Kuhl, R. Dusing, Oxytocin buffers cortisol responses to stress in individuals with impaired emotion regulation abilities, Psychoneuroendocrinology 36 (2011) 898–904.
[161] W.J. Riddle, A.I. Scott, J. Bennie, S. Carroll, G. Fink, Current intensity and oxytocin release after electroconvulsive therapy, Biol Psychiatry 33 (1993) 839–841.
[162] U. Rimmele, K. Hediger, M. Heinrichs, P. Klaver, Oxytocin makes a face in memory familiar, J. Neurosci. 29 (2009) 38–42.
[163] S.M. Rodrigues, L.R. Saslow, N. Garcia, O.P. John, D. Keltner, Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans, Proc. Natl. Acad. Sci. USA 106 (2009) 21437–21441.
[164] A.J. Rosenfeld, J.A. Lieberman, L.F. Jarskog, Oxytocin, dopamine, and the amygdala: a neurofunctional model of social cognitive deficits in schizophrenia, Schizophr. Bull. (2010).
[165] H.E. Ross, S.M. Freeman, L.L. Spiegel, X. Ren, E.F. Terwilliger, L.J. Young, Variation in oxytocin receptor density in the nucleus accumbens has differential effects on affiliative behaviors in monogamous and polygamous voles, J. Neurosci. 29 (2009) 1312–1318.
[166] L.H. Rubin, C.S. Carter, L. Drogos, H. Pournajafi-Nazarloo, J.A. Sweeney, P.M. Maki, Peripheral oxytocin is associated with reduced symptom severity in schizophrenia, Schizophr Res 124 (2010) 13–21.
[167] A.D. Salzberg, S.E. Swedo, Oxytocin and vasopressin in obsessive–compulsive disorder, Am. J. Psychiat. 149 (1992) 713–714.
[168] G. Sanchez-Andrade, K.M. Kendrick, The main olfactory system and social learning in mammals, Behav. Brain Res. 200 (2009) 323–335.
[169] G. Sanders, J. Freilicher, S.L. Lightman, Psychological stress of exposure to uncontrollable noise increases plasma oxytocin in high emotionality women, Psychoneuroendocrinology 15 (1990) 47–58.
[170] N.R. Saunders, M.D. Habgood, K.M. Dziegielewska, Barrier mechanisms in the brain, II. Immature brain, Clin. Exp. Pharmacol. Physiol. 26 (1999) 85–91.
[171] E. Savaskan, R. Ehrhardt, A. Schulz, M. Walter, H. Schachinger, Post-learning intranasal oxytocin modulates human memory for facial identity, Psychoneuroendocrinology 33 (2008) 368–374.
[172] G. Scantamburlo, M. Hansenne, S. Fuchs, W. Pitchot, P. Marechal, C. Pequeux, M. Ansseau, J.J. Legros, Plasma oxytocin levels and anxiety in patients with major depression, Psychoneuroendocrinology 32 (2007) 407–410.
[173] C.M. Schumann, J. Hamstra, B.L. Goodlin-Jones, L.J. Lotspeich, H. Kwon, M.H. Buonocore, C.R. Lammers, A.L. Reiss, D.G. Amaral, The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages, J. Neurosci. 24 (2004) 6392–6401.
[174] M.W. Schwartz, S.C. Woods, D. Porte Jr., R.J. Seeley, D.G. Baskin, Central nervous system control of food intake, Nature 404 (2000) 661–671.
[175] A.I. Scott, L.J. Whalley, J. Bennie, G. Bowler, Oestrogen-stimulated neurophysin and outcome after electroconvulsive therapy, Lancet 1 (1986) 1411–1414.
[176] A.I. Scott, L.J. Whalley, J.J. Legros, Treatment outcome, seizure duration, and the neurophysin response to ECT, Biol. Psychiat. 25 (1989) 585–597.
[177] J.R. Seckl, M. Johnson, C. Shakespear, S.L. Lightman, Endogenous opioids inhibit oxytocin release during nicotine-stimulated secretion of vasopressin in man, Clin. Endocrinol. (Oxf.) 28 (1988) 509–514.
[178] L.J. Seltzer, T.E. Ziegler, S.D. Pollak, Social vocalizations can release oxytocin in humans, Proc. Biol. Sci. 277 (2010) 2661–2666.
[179] M.J. Sergi, Y. Rassovsky, C. Widmark, C. Reist, S. Erhart, D.L. Braff, S.R. Marder, M.F. Green, Social cognition in schizophrenia: relationships with neurocognition and negative symptoms, Schizophr. Res. 90 (2007) 316–324.
[180] S.G. Shamay-Tsoory, M. Fischer, J. Dvash, H. Harari, N. Perach-Bloom, Y. Levkovitz, Intranasal administration of oxytocin increases envy and schadenfreude (gloating), Biol. Psychiat. 66 (2009) 864–870.
[181] K.U. Shibli, A.R. Dhillon, J.A. Goode, C.L. Gilbert, J.W. Thompson, I.F. Russell, S.W. Lindow, Effect of intrathecal fentanyl on oxytocin secretion in pregnant women not in labour, Clin. Sci. (Lond.) 101 (2001) 415–419.
[182] L. Shukovski, D.L. Healy, J.K. Findlay, Circulating immunoreactive oxytocin during the human menstrual cycle comes from the pituitary and is estradiol dependent, J. Clin. Endocrinol. Metab. 68 (1989) 455–460.
[183] S.M. Silva, M.D. Madeira, C. Ruela, M.M. Paula-Barbosa, Prolonged alcohol intake leads to irreversible loss of vasopressin and oxytocin neurons in the paraventricular nucleus of the hypothalamus, Brain Res. 925 (2002) 76–88.
[184] D. Simeon, J. Bartz, H. Hamilton, S. Crystal, A. Braun, S. Ketay, E. Hollander, Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study, Psychoneuroendocrinology (2011).
[185] T. Singer, R. Snozzi, G. Bird, P. Petrovic, G. Silani, M. Heinrichs, R.J. Dolan, Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain, Emotion 8 (2008) 781–791.
[186] E.V. Sivukhina, A.A. Dolzhikov, E. Morozov Iu, G.F. Jirikowski, V. Grinevich, Effects of chronic alcoholic disease on magnocellular and parvocellular hypothalamic neurons in men, Horm. Metab. Res. 38 (2006) 382–390.
[187] R.M. Stocche, J.G. Klamt, J. Antunes-Rodrigues, L.V. Garcia, A.C. Moreira, Effects of intrathecal sufentanil on plasma oxytocin and cortisol concentrations in women during the first stage of labor, Reg. Anesth. Pain. Med. 26 (2001) 545–550.
[188] S. Stock, K. Bremme, K. Uvnas-Moberg, Plasma levels of oxytocin during the menstrual cycle, pregnancy and following treatment with HMG, Hum. Reprod. 6 (1991) 1056–1062.
[189] S. Stock, L. Granstrom, L. Backman, A.S. Matthiesen, K. Uvnas-Moberg, Elevated plasma levels of oxytocin in obese subjects before and after gastric banding, Int. J. Obes. 13 (1989) 213–222.
[190] L. Strathearn, P. Fonagy, J. Amico, P.R. Montague, Adult attachment predicts maternal brain and oxytocin response to infant cues, Neuropsychopharmacology 34 (2009) 2655–2666.
[191] L. Strathearn, L.C. Mayes, Cocaine addiction in mothers: potential effects on maternal care and infant development, Ann. NY Acad. Sci. 1187 (2010) 172–183.
[192] D.F. Swaab, J.S. Purba, M.A. Hofman, Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader–Willi syndrome: a study of five cases, J. Clin. Endocrinol. Metab. 80 (1995) 573–579.
[193] S.E. Swedo, H.L. Leonard, M.J. Kruesi, D.C. Rettew, S.J. Listwak, W. Berrettini, M. Stipetic, S. Hamburger, P.W. Gold, W.Z. Potter, et al., Cerebrospinal fluid neurochemistry in children and adolescents with obsessive–compulsive disorder, Arch. Gen. Psychiat. 49 (1992) 29–36.
[194] S.E. Taylor, G.C. Gonzaga, L.C. Klein, P. Hu, G.A. Greendale, T.E. Seeman, Relation of oxytocin to psychological stress responses and hypothalamic-pituitary-adrenocortical axis activity in older women, Psychosom. Med. 68 (2006) 238–245.
[195] S.E. Taylor, S. Saphire-Bernstein, T.E. Seeman, Are plasma oxytocin in women and plasma vasopressin in men biomarkers of distressed pair-bond relationships?, Psychol Sci. 21 (2010) 3–7.
[196] A. Theodoridou, A.C. Rowe, I.S. Penton-Voak, P.J. Rogers, Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness, Horm. Behav. 56 (2009) 128–132.
[197] M.R. Thompson, P.D. Callaghan, G.E. Hunt, J.L. Cornish, I.S. McGregor, A role for oxytocin and 5-HT(1A) receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine (“ecstasy”), Neuroscience 146 (2007) 509–514.
[198] M.R. Thompson, P.D. Callaghan, G.E. Hunt, I.S. McGregor, Reduced sensitivity to MDMA-induced facilitation of social behaviour in MDMA pre-exposed rats, Prog. Neuropsychopharmacol. Biol. Psychiat. 32 (2008) 1013–1021.
[199] A. Todorov, Evaluating faces on trustworthiness: an extension of systems for recognition of emotions signaling approach/avoidance behaviors, Ann. NY Acad. Sci. 1124 (2008) 208–224.
[200] M. Tops, Oxytocin: envy or engagement in others?, Biol Psychiat. 67 (2010) e5–6 (author reply e7).
[201] M. Tops, J.M. van Peer, J. Korf, A.A. Wijers, D.M. Tucker, Anxiety, cortisol, and attachment predict plasma oxytocin, Psychophysiology 44 (2007) 444–449.
[202] H. Tost, B. Kolachana, S. Hakimi, H. Lemaitre, B.A. Verchinski, V.S. Mattay, D.R. Weinberger, A. Meyer-Lindenberg, A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic–limbic structure and function, Proc. Natl. Acad. Sci. USA 107 (2010) 13936–13941.
[203] R.A. Turner, M. Altemus, T. Enos, B. Cooper, T. McGuinness, Preliminary research on plasma oxytocin in normal cycling women: investigating emotion and interpersonal distress, Psychiatry 62 (1999) 97–113.
[204] Y. Ueta, H. Kannan, T. Higuchi, H. Negoro, K. Yamaguchi, H. Yamashita, Activation of gastric afferents increases noradrenaline release in the paraventricular nucleus and plasma oxytocin level, J. Auton. Nerv. Syst. 78 (2000) 69–76.
[205] C. Unkelbach, A.J. Guastella, J.P. Forgas, Oxytocin selectively facilitates recognition of positive sex and relationship words, Psychol. Sci. 19 (2008) 1092–1094.
[206] K. Uvnas-Moberg, E. Bjokstrand, V. Hillegaart, S. Ahlenius, Oxytocin as a possible mediator of SSRI-induced antidepressant effects, Psychopharmacology (Berlin) 142 (1999) 95–101.
[207] K. Uvnas-Moberg, C. Sjogren, L. Westlin, P.O. Andersson, S. Stock, Plasma levels of gastrin, somatostatin, VIP, insulin and oxytocin during the menstrual cycle in women (with and without oral contraceptives), Acta. Obstet. Gyn. Scand 68 (1989) 165–169.
[208] E. Valassi, M. Scacchi, F. Cavagnini, Neuroendocrine control of food intake, Nutr. Metab. Cardiovasc. Dis. 18 (2008) 158–168.
[209] L. van Londen, J.G. Goekoop, G.M. van Kempen, A.C. Frankhuijzen-Sierevogel, V.M. Wiegant, E.A. van der Velde, D. De Wied, Plasma levels of arginine vasopressin elevated in patients with major depression, Neuropsychopharmacology 17 (1997) 284–292.
[210] L. Van Londen, J.G. Goekoop, A.H. Zwinderman, J.B. Lanser, V.M. Wiegant, D. De Wied, Neuropsychological performance and plasma cortisol, arginine

vasopressin and oxytocin in patients with major depression, Psychol. Med. 28 (1998) 275–284.
[211] G. Vila, M. Riedl, M. Resl, A.J. van der Lely, L.J. Hofland, M. Clodi, A. Luger, Systemic administration of oxytocin reduces basal and lipopolysaccharide-induced Ghrelin levels in healthy men, J. Endocrinol. 203 (2009) 175–179.
[212] G.N. Warner MD, C.A. Peabody, Oxytocin and prolactin release after electroconvulsive therapy: a pilot study, Current Therapeutic Research 56 (1995) 226–230.
[213] A.K. Wermter, I. Kamp-Becker, P. Hesse, G. Schulte-Korne, K. Strauch, H. Remschmidt, Evidence for the involvement of genetic variation in the oxytocin receptor gene (OXTR) in the etiology of autistic disorders on high-functioning level, Am. J. Med. Genet. B – Neuropsychiatr. Genet. 153B (2010) 629–639.
[214] L.J. Whalley, I.C. Robinson, G. Fink, Oxytocin and neurophysin in post-partum mania, Lancet 2 (1982) 387–388.
[215] K. Wolff, E.M. Tsapakis, A.R. Winstock, D. Hartley, D. Holt, M.L. Forsling, K.J. Aitchison, Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population, J. Psychopharmacol. 20 (2006) 400–410.
[216] S. Wu, M. Jia, Y. Ruan, J. Liu, Y. Guo, M. Shuang, X. Gong, Y. Zhang, X. Yang, D. Zhang, Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population, Biol. Psychiat. 58 (2005) 74–77.
[217] K.E. Yatzkar U., Intranasal oxytocin in patients with posttraumatic stress disorder: a single dose, pilot double blind crossover study, European Neuropsychopharmacology 20 (2010) S84 P.83.026.
[218] R. Yoshimura, H. Kiyama, T. Kimura, T. Araki, H. Maeno, O. Tanizawa, M. Tohyama, Localization of oxytocin receptor messenger ribonucleic acid in the rat brain, Endocrinology 133 (1993) 1239–1246.
[219] Z.D. You, J.H. Li, C.Y. Song, C.L. Lu, C. He, Oxytocin mediates the inhibitory action of acute lithium on the morphine dependence in rats, Neurosci. Res. 41 (2001) 143–150.
[220] P.J. Zak, R. Kurzban, W.T. Matzner, The neurobiology of trust, Ann. NY Acad. Sci. 1032 (2004) 224–227.
[221] P.J. Zak, R. Kurzban, W.T. Matzner, Oxytocin is associated with human trustworthiness, Horm. Behav. 48 (2005) 522–527.
[222] P.J. Zak, A.A. Stanton, S. Ahmadi, Oxytocin increases generosity in humans, PLoS One 2 (2007) e1128.
[223] A. Frasch, T. Zetsche, G. Jirikowski, H. Murck, A. Steiger, Nocturnal oxytocin secretion is reduced in major depression, Biol. Psychiat. 39 (1996) 290.
[224] E.A. Zimmerman, A.G. Robinson, M.K. Husain, M. Acosta, A.G. Frantz, W.H. Sawyer, Neurohypophysial peptides in the bovine hypothalamus: the relationship of neurophysin I to oxytocin, and neurophysin II to vasopressin in supraoptic and paraventricular regions, Endocrinology 95 (1974) 931–936.