Review

Biological Psychiatry

Dissecting the Role of Oxytocin in the Formation and Loss of Social Relationships

René Hurlemann and Dirk Scheele

ABSTRACT

Current concepts of human sociality highlight a fundamental role of the hypothalamic peptide oxytocin (OXT) in the formation and maintenance of social relationships. However, emerging evidence indicates that OXT does not invariably facilitate social bonding but also produces nonprosocial effects that may have evolved to promote offspring survival. From a mechanistic perspective, we hypothesize that OXT modulates interoceptive signals and self-referential processing, which may result in various social outcomes depending on context- and person-dependent variables such as early-life adversity. Based on this theoretical framework, we discuss translational implications for clinical trials and identify open questions for future research. Specifically, we propose that disrupted OXT signaling due to the loss of affectionate bonds may contribute to emotional disequilibrium and confer elevated risk for the onset of stress-related disorders.

Keywords: Attachment, Bond, Grief, Mental illness, Oxytocin, Social relationships

http://dx.doi.org/10.1016/j.biopsych.2015.05.013

A human ability to form and maintain interpersonal relationships, a product of evolutionary selective processes, is fundamental to mental health (1). For instance, social support by proximal others has been identified as a key resilience factor promoting successful coping with and adaptation to psychosocial stress (2). However, the underlying neurobiological mechanisms are not precisely understood. Current perspectives on the neurochemistry of human sociality suggest a central role of the peptide oxytocin (OXT) and its receptor (OXTR), which is expressed both in the brain and the periphery (3). As a peripherally acting hormone, OXT promotes parturition and lactation, whereas as a neuromodulator projected from the hypothalamus to brain areas implicated in social-emotional behavior, it helps create long-lasting social relationships ranging from infant-parent bonding in childhood to romantic relationships in adulthood. The loss of such affectionate bonds is associated with agonizing distress and elevated risk for the onset of multiple psychiatric disorders (4), suggesting that OXT signaling has a pivotal role in sustaining mental health.

OXYTOCIN AND SOCIAL ATTACHMENT IN NONHUMAN SPECIES

OXT has evolved over 700 million years and its homologs are present in various taxa from nonvertebrates to mammals (5), highlighting the ubiquitous role of the peptide in orchestrating social and reproductive behaviors. For example, genetically modified male nematodes (*Caenorhabditis elegans*) lacking an OXT-like molecule or the corresponding receptor perform poorly in mating (6). Further evidence supporting a key role of OXT-like peptides in pair-bond formation and offspring success comes from studies in monogamous zebra finches (*Taeniopygia guttata*) (7) and teleost fish (*Amatitlania nigrofasciata*) (8). The crucial influence of OXT on pair bonding has been best studied in two closely related species of vole, i.e., the monogamous prairie vole (*Microtus ochrogaster*) and the polygamous montane vole (*Microtus montanus*) (9,10). While the expression of OXT is similar among both species (11), brain distribution of the OXTR significantly differs between them, with high OXTR density in the prelimbic cortex and nucleus accumbens (NAcc) being crucial for the expression of monogamous behavior (12,13). However, accumulating evidence suggests that species differences in social relationships are not restricted to the OXT system per se but extend to other signaling pathways, including dopamine (DA) and arginine-vasopressin (AVP), and their reciprocal interactions (14,15). For example, heightened expression of AVP receptors (AVPRs) in the ventral forebrain of polygamous meadow voles (*Microtus pennsylvanicus*) elicits monogamous behavior (16). Current concepts hold that the AVP/OXT and DA systems closely interact in a site- and sex-specific manner to mediate partner preference formation, and similar cross-talk may also determine parenting styles (17). For instance, hypothalamic lesions block the initiation, but not the maintenance, of maternal behaviors in rats (18), suggesting that OXT may specifically facilitate the transition from avoidance of pups to caring for them (19,20). Recently, it was shown that OXT enables pup retrieval behavior in female mice by amplifying pup call responses in maternal auditory cortex (21). Furthermore, OXT has been implicated in maternal licking and grooming in rats (22), social affiliation of dogs toward their owners (23), and grooming of nonbond partners in chimpanzees, thus providing a cross-species mechanism that enables long-term

ISSN: 0006-3223

cooperative relationships between kin and nonkin mammals (24). Notably, the OXT system not only plays a pivotal role in the formation and maintenance of pair bonds but is also affected by their disruption. For example, social isolation through partner separation precipitates anxiety and depression-like behaviors in monogamous voles (25), which could be prevented by repeated subcutaneous injection of OXT (26). Furthermore, even short-term separation from their female partners induced profound grief reactions and heightened hypothalamic-pituitary-adrenal axis activity in male voles (27), suggesting that in highly social species, decreases in OXT signaling due to partner loss rapidly translate into stress-related disorders such as anxiety and depression.

OXYTOCIN AND INFANT-CAREGIVER ATTACHMENT

A plethora of studies in humans has focused on the potential validity of endogenous OXT concentrations as biomarkers for infant-caregiver attachment bonds and parenting styles. For instance, OXT plasma concentrations in the first trimester of pregnancy were shown to predict postpartum maternal attachment (28). Moreover, OXT plasma concentrations appear to correlate with the time devoted to affectionate parenting (such as soft hugs, caresses, or baby talk) in mothers and with stimulatory parenting (i.e., tossing the baby in the air or encouraging exploration and laughter) in fathers (29). Perhaps more informative than OXT concentrations at baseline is the rise in OXT levels during infant-caregiver interactions. The evidence suggests that the greater the amounts of OXT released in plasma during such interactions, the greater the mother's readiness for social reciprocity and flexible adaptation to the child's needs (30). Lower than normal cerebrospinal fluid (CSF) levels of OXT were measured in adult women with a history of childhood trauma and abuse (31), as well as in the urine of socially deprived children interacting with their mothers (32) [but see also (33)], indicating that early-life adversity has long-lasting impact on OXT signaling. However, the tempting idea that endogenous OXT concentrations specifically reflect and positively correlate with parenting contrasts with findings that OXT levels in urine tend to be higher in mothers interacting with unfamiliar children compared with their own children (34) and increase as a function of relationship anxiety and parenting stress (35).

A large body of evidence indicates a link between infant-caregiver attachment bonds and genetic variation in OXT pathways. For example, mothers with a silent G to A allele change in the OXTR gene (rs53576) show lower levels of sensitive parenting (36), and in a large twin sample, the same polymorphism was found to predict a mother's warmth toward her children (37). Additionally, there is evidence for an association between the A allele of OXTR (rs2254298) and attachment security in non-Caucasian infants (38). Indirect evidence for the relevance of rs2254298 also comes from a community study of women exhibiting higher or lower depression scores postpartum (39). Specifically, the rs2254298 GG homozygous genotype was overrepresented in depressed mothers and their families and was associated with lower OXT saliva concentrations. However, other studies have failed to establish a link between rs53576 or rs2254298 and attachment styles (40,41), and a recent study even identified a reverse association between genotype and positive parenting (i.e., that mothers with the GG genotype of rs53576 displayed lower levels of positive parenting) (42). It thus appears that genetic variation confers susceptibility for distinct attachment styles, but the extent to which a specific style is expressed in the behavioral phenotype is moderated by family environment (43,44).

Substantial evidence suggests that intranasal delivery of synthetic OXT (OXT^{IN}) is a useful means to dissect the peptide's contribution to infant-caregiver attachment. OXT^{IN} causes an increase in CSF levels of OXT (45), although we note that the exact transnasal route the peptide takes to reach the brain is still unclear and even a peripheral feedback mechanism enhancing endogenous release cannot be excluded. Recently, a single 24-IU dose of OXT^{IN} was found to be sufficient for inducing a significant increase in perceived attachment security in male adults previously classified as insecure (46). Furthermore, OXT^{IN} made fathers less hostile and motivated them to foster exploration behavior in their children (47). Interestingly, OXT^{IN} not only encouraged fathers to engage in stimulatory parenting but also increased the infant's salivary OXT concentrations in addition to changes in respiratory sinus arrhythmia response, an index of emotional reactivity, and social-emotional behavior (48). Together, these results suggest that heightened OXT levels may enhance social interactions between fathers and their children, perhaps by establishing closer proximity between them (49). Functional magnetic resonance imaging (fMRI) studies have sought to reveal the neural representations of parenting and its modulation by OXT^{IN}. For instance, OXT^{IN} in fathers was shown to alter globus pallidus responses to pictures of their own children (50). OXT^{IN} evoked greater responses in insula and inferior frontal gyrus, both of which are implicated in empathy (51) in women exposed to infant crying. OXT^{IN} also reduced amygdala responses to infant laughter (52). Notably, the effects of OXT^{IN} appear to be influenced by the attachment representations people possess. Less anxiously attached individuals remembered their mother as more caring and close after OXT^{IN}, but the opposite effect was observed for more anxiously attached individuals (53). In another study, OXT^{IN} decreased handgrip force in reaction to infant crying in female subjects without a childhood history of harsh parenting experiences (54). Together, these results challenge the popular notion that oxytocin has broad positive effects on social perception and instead suggest a strong dependency of OXT effects on person-dependent factors including early-life adversity.

OXYTOCIN AND ROMANTIC ATTACHMENT

During the early stages of romantic relationships, OXT plasma concentrations are elevated in new lovers compared with singles (55). OXT plasma levels are also increased in couples who exhibit higher interactive reciprocity and spend more time thinking of the partner and the relationship (55). In an instructed couple conflict scenario, participants showed more empathy if their partners had higher OXT plasma levels (56). In another study, OXT plasma levels were associated with more affectionate communication during a structured social support interaction task (57). In women, the expression of nonverbal affiliation cues was positively correlated with OXT plasma

release (58). In both sexes, greater self-reported levels of partner support and partner intimacy were related to higher OXT plasma concentrations (59,60). Early studies could not establish a relationship between interpersonal touch and OXT release (61–63), but more recent studies have detected a rise in OXT plasma levels after light touch or a massage (64–66). The impact of sexual activity on endogenous OXT release is informed by numerous studies showing increased OXT plasma concentrations after orgasm in humans (67–70) [but see also (71)].

Moreover, there are also reports documenting a positive correlation between OXT plasma concentrations and attachment anxiety (72) and interpersonal distress (61,73). As such, the tend and befriend model has been proposed (74,75), which states that gaps in positive social relationships are accompanied by elevations in OXT and that these increased OXT levels prompt affiliative efforts aimed at restoring positive social contact. Of note, the interpretation of peripheral OXT measurements is hampered by methodological issues (76) and the absence of a strong linear relationship between peripheral and central OXT concentrations (77). It is also still elusive whether peripheral or CSF measurements can reflect the subtle release of OXT from axons in a manner specific to a certain brain region (78). Associations between peripheral OXT levels and a specific type of social behavior may result from a positive feedback system such that one particular behavior elicits the release of endogenous OXT and vice versa. In addition, peripheral OXT may affect a diverse repertoire of social behaviors by modulating visceral target organs of the autonomic nervous system, many of which (e.g., the heart or digestive system) both locally synthesize OXT and express OXTRs (79).

OXTR gene variations (rs7632287) have also been associated with traits reflecting pair bonding, such as the quality of interactions with their romantic partners in women (80). Furthermore, a cumulative genetic risk for social dysfunctions was computed by summing up risk alleles on different polymorphisms, with high-risk individuals exhibiting difficulties in empathic communication in couple interactions (81).

Evidence for effects of OXT^{IN} on behaviors related to pair bonding is scarce. It has been shown, for example, that the peptide enhances positive communication in relation to negative behavior during couple conflicts and reduces cortisol saliva levels after the conflict (82). In women, OXT^{IN} also reduced salivary alpha-amylase, an index of sympathetic activity, whereas in men the peptide increased salivary alpha-amylase levels and emotional arousal during couple conflict (83). Interestingly, men under OXT were faster to detect the valence of positive stimuli conceptually associated with sexuality, bonding, and social relationships (84). Notably, OXT^{IN} further augmented epinephrine plasma responses to sexual activity in men (85) and increased the intensity of orgasm and contentment following sexual intercourse in heterosexual couples (86). By contrast, an early study using a 32-IU dose of OXT^{IN} failed to detect any behavioral or neural effects in 21 men who observed their female partner receiving painful stimulation (87).

Few studies have sought to explore a role of OXT^{IN} in partner preference. In one study, OXT^{IN} stimulated subjects to seek out information about an old partner but had no effect on the participant's choice for company (to work with or date) (88). In another study, OXT^{IN} motivated pair-bonded, but not single, men to keep a larger social distance from an unknown female experimenter (Figure 1) and inhibited approach toward attractive women depicted in photos (89). Previous fMRI studies have revealed that viewing the face of a romantic partner while recalling experiences with them activates reward-associated regions such as the ventral tegmental area (VTA) and NAcc (90,91). In healthy pair-bonded men, OXT^{IN} facilitated neural responses to the partner compared with unfamiliar women in the VTA and NAcc (Figure 2). On the behavioral level, these neural effects were paralleled by a more favorable attractiveness perception of the female partner (92). Interestingly, viewing pictures of a romantic partner also reduced self-reported thermal pain and greater analgesia was associated with increased activity in several reward-processing regions including the NAcc (93). To our knowledge, no study so far has tested whether partner-induced analgesia is related to OXT-mediated pain inhibition (94). Furthermore, by employing a mental imagery task, it has been shown that OXT^{IN} diminishes subjects' arousal judgments of and anterior cingulate cortex (ACC) responses to scenes describing sexual infidelity of the partner (95). Collectively, these data provide little support that OXT is involved in the formation of new pair bonds in humans but rather suggest that OXT may be more important for the maintenance of an already established pair bond. As such, this discrepancy compared with the role of OXT in prairie voles, where the peptide is necessary for the formation of new pair bonds (96), may be related to methodological differences in the assessment of pair bonding in rodents and humans or indicate a species-specific function of OXT.

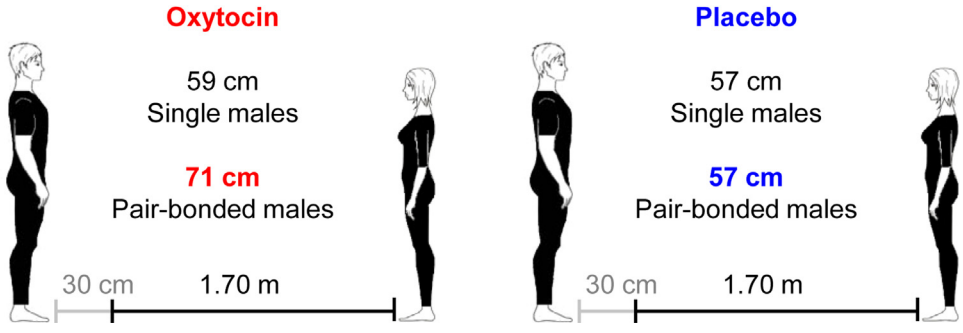

Figure 1. Oxytocin effects on the social distance between women and men. Male participants were asked to choose the ideal (most comfortable) distance to an attractive female experimenter. In the first half of the trials, the experimenter moved either toward (far, i.e., start distance of 2 m) or away from the subject (close, start distance of 30 cm), whereas in the second half, the male volunteer was the one approaching or withdrawing. Oxytocin increased the ideal distance that pair-bonded men maintained in relation to the unknown attractive woman across all conditions.

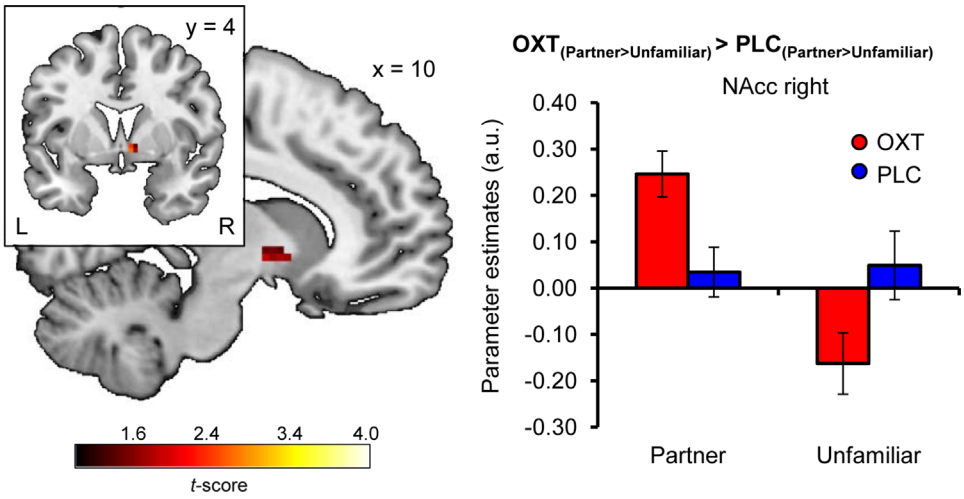

Figure 2. Oxytocin (OXT) effects on nucleus accumbens (NAcc) responses. The intranasal administration of OXT increased NAcc response to the female partner's face compared with a matched, unfamiliar woman. Error bars indicate the standard error of the mean. L, left hemisphere; PLC, placebo; R, right hemisphere.

It would stand to reason that OXT effects on pair bonding are mediated by DA, as the NAcc and VTA form two central hubs of the mesolimbic DA pathway. In a recent [^{11}C]raclopride positron emission tomography study, DA release was measured during a face-attraction rating task after OXT^{IN} administration (97). The authors could replicate the previous finding that OXT, in the absence of any partner stimuli, can enhance the perceived attractiveness of unfamiliar women (98), but this effect was not accompanied by an altered raclopride binding in the striatum. Instead, they observed increased binding in subregions of the right dorsomedial prefrontal gyrus and superior parietal gyrus under OXT. These data could mean that an OXT-DA interplay in the striatum is restricted to the domain of pair bonding or that OXT interacts with a different family of DA receptors or a completely different class of neurotransmitters. For instance, the rewarding properties of social interactions in mice require the coordinated activity of OXT and serotonin in the NAcc (99) and a recent [^{18}F]MPPF positron emission tomography study demonstrated that OXT^{IN} modulates serotonergic signaling in humans (100).

As of yet, no study has examined the behavioral and neural effects of OXT^{IN} on the processing of partner stimuli in women. In an fMRI study (101), OXT^{IN} did not alter amygdala responses, but it did selectively increase arousal ratings of infant stimuli in nulliparous, but not postpartum, women. In all women, OXT^{IN} administration resulted in greater VTA, but not NAcc, activation to infant and sexual images (102). A recent study also points to the importance of moderator variables for OXT effects on pair-bonding behavior (103). For instance, OXT^{IN} specifically increased the inclination for intimate partner violence in participants prone to physical aggression but not in participants with low aggressiveness traits. These data resonate well with the idea that OXT enhances an a priori existing predisposition, possibly by modulating self-referential processing and interoception.

A SELF-REFERENCE MODEL OF OXYTOCIN

Several theoretical frameworks have been proposed to explain the wide repertoire of social OXT effects (Table S1 in Supplement 1). On the one hand, OXT enhances the stress-and anxiety-buffering effect of social support from proximal others (104) and facilitates fear extinction by strengthening the control of regulatory prefrontal areas over amygdalar fear responses (105). On the other hand, in the absence of social support, OXT may increase the sensation of social stress, augment the impact of aversive information on defensive responses (i.e., the startle reflex), and induce a privileged recall of negative information by increasing neural responses in insular cortex (106,107). In an attempt to reconcile this conflicting evidence, it has been proposed that OXT exerts a lower-level general effect on general states and dispositions (108) and that the outcome of OXT administration is constrained by features of situations and/or individuals (109). In fact, OXT^{IN} effects are often moderated by the subject's gender (110,111) and context-dependent factors. One example for the latter is an fMRI study in which the subjective valence of interpersonal touch was experimentally manipulated (112). Specifically, OXT^{IN} was found to augment behavioral pleasantness ratings only in a positively framed social context. On the neural level, OXT^{IN} enhanced responses in a neural circuitry spanning the insula, precuneus, orbitofrontal cortex, and pregenual ACC. Interestingly, both the behavioral and neural effects were blunted in subjects with higher autistic-like traits. Modulatory influences of OXT^{IN} on neural reactivity of the insula, precuneus, and ACC have been observed across various cognitive and emotional domains in fMRI studies (95,107,111). Current concepts of human emotional awareness (113) highlight that the anterior insula cortex, which is often jointly activated with the ACC, contains representations that provide an emergent basis for subjective feelings from the body. The precuneus belongs to a widespread neurocircuitry of higher association cortical and subcortical areas and has been implicated in interoceptive awareness and consciousness (114). Thus, the observed pattern of results has been interpreted as indicating an OXT-induced self-referential processing bias that could explain the increased pleasantness in an already pleasant context and a diminished effect for participants with high autistic-like traits who experience social touch as less pleasant (115). This view was recently extended by the hypothesis that OXT's influence

on self-referential processing and interoception is also context-dependent (116). The authors predict that OXT augments interoceptive prediction errors through top-down modulation in the context of passive perception and that the peptide participates in interoceptive sensory attenuation in the context of self-generated action.

The idea that OXT influences self-referential processing and interoception is further supported by a recent study that indicates that OXT sharpens self-other perceptual boundaries (117). In a video-morphing task, OXT-treated participants exhibited a significantly shorter latency when discriminating between self and other. In two other studies (118,119), OXT^{IN} influenced participants' self-perception assessed by personality questionnaires and an adjective-sorting task. Specifically, subjects under OXT reported higher ratings of extraversion and openness to experiences and stronger positive attitudes toward themselves. At first glance, an OXT-induced self-referential processing bias seems hard to reconcile with the above mentioned bonding-related OXT effects and the fact that OXT has also been found to enhance other-regarding tendencies such as mind reading and emotional empathy (120,121). However, empathy and interoception are closely linked (122) and improved empathy may even be the by-product of sharpened interoceptive awareness. Furthermore, it is increasingly recognized that self-processing extends to incorporate significant others (123,124). By increasing self-referential processing in this way, OXT may be acting to promote in-group survival. Such a mechanism could help to explain why OXT promotes parochial altruism and ethnocentrism (125,126) and it may also account for the surprising observation that a pharmacologic augmentation of a first individual psychotherapy session via OXT caused more rather than less anxiety over the course of the session in patients with depression (127). Given this background, we conclude that one common denominator across diverse social OXT effects may be that the peptide induces a self-referential processing bias that can produce various social outcomes by enabling subjects to represent emotional experiences more consciously. Along these lines, the use of OXT as a pharmacologic augmentation of established treatments for psychiatric disorders not only contains the promise of an improved social functioning but may also aggravate an already distorted social perception. Clearly, future studies are warranted to selectively test the predictions of our preliminary model.

TRANSLATIONAL IMPLICATIONS AND NEW AVENUES FOR FUTURE RESEARCH

Intact social relationships can bring the elation of profound joy and they are an important resilience factor that can help to buffer the deteriorating consequences of stress preponderance. However, throughout life, humans are confronted with the breakup of relationships, which can be the source of sorrow and despair. In fact, acute grief after a relationship breakup (128,129) or the loss of an unborn child (130) is related to intense responses of the physical pain network encompassing the ACC and insula. Grief is a major risk factor for clinical depression (131), and in a substantial minority, the grief reaction does not abate but instead develops into complicated grief, which is associated with enduring functional impairments (132). Based on the strong overlap between human love and drug addiction, from initial encounter to withdrawal, it has been proposed that social attachment can be understood as a behavioral addiction, with OXT hijacking the brain reward system to promote bonding and affiliative behavior, and that treatments used to reduce drug cravings may also be effective in treating grief resulting from the loss of a loved one or a bad breakup (133). In two recent studies, OXT^{IN} was found to suppress stress-induced craving in cannabis-dependent individuals (134) and to block alcohol withdrawal (135). Against this background and given the strong body of evidence implicating OXT as a key modulator of human pair bonding reviewed above, future studies should probe OXT's potential to ameliorate withdrawal symptoms after a relationship breakup.

Another open question is related to the optimal treatment protocol. Considering the previous finding that OXT augments the antistress effects of social support (104), we expect that OXT should produce the most powerful effects as an adjunct to social interventions relying on the human attachment system. Previous clinical trials exploring the clinical potential of OXT have consistently shown that the OXT system is an enticing pharmacologic target for enhancing social cognition (136), but relatively few studies have focused on the bonding-related effects of OXT. A reduced capacity to form and maintain long-lasting social relationships is a hallmark of several conditions, including borderline personality disorder and autism and schizophrenia spectrum disorders; OXT could be a promising treatment option selectively targeting attachment dysfunctions. Based on our self-referential processing model, it also seems promising to combine OXT^{IN} with non-pharmacologic treatments of autism spectrum disorder such as real-time fMRI neurofeedback aimed at restoring control over anterior insula activity (137).

Furthermore, the effects of a single dose may deviate from that of a long-term OXT treatment, seeing as other antianxiety agents also produce anxiogenic effects after first-time dosage (138). In male voles, a long-term developmental treatment with low doses of OXT^{IN} resulted in a deficit in partner preference behavior (139), and in mice, chronic OXT treatment even induced an anxiogenic phenotype (140). In humans, OXT^{IN} treatment over 10 days in elderly subjects produced no significant effects on mood or the cardiovascular indices but yielded positive changes in psychological well-being and physical functioning (141). Similarly, the optimal dose for an OXT^{IN}-based intervention is still elusive. In voles, the propensity to display behaviors such as pair bonding is modulated in a dose-dependent manner (142), and in humans, 24-IU, but not 48-IU, of OXT^{IN} attenuates cortisol levels in response to physical stress (143). The selectivity of OXT for the OXTR relative to AVPRs is at least twentyfold (cf. Psychoactive Drug Screening Program K_i database), but AVPR cross-binding may occur and dominate resultant effects at higher doses. The majority of OXT studies in humans include a dose of 24-IU, but dose-response investigations are clearly necessary to establish individually tailored treatment regimens that consider additional factors such as gender, age, and weight.

In conclusion, the OXT system plays an integral role for human parenting and pair bonding, but future clinical trials are warranted to elucidate specific conditions and treatment parameters under which an OXT-induced self-referential processing bias may lead to the most beneficial clinical outcome.

ACKNOWLEDGMENTS AND DISCLOSURES

RH was supported by a Starting Independent Researcher Grant (NEMO–Neuromodulation of Emotion) jointly provided by the Ministry of Innovation, Science, Research & Technology of the German State of North Rhine-Westphalia and the University of Bonn.

We thank J. Horowitz for her comments on an early draft of this manuscript and Alexandra Patin for proofreading the manuscript.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry and Division of Medical Psychology, University of Bonn, Bonn, Germany.

Address correspondence to René Hurlemann, M.D., Ph.D., University of Bonn, Department of Psychiatry and Division of Medical Psychology, Bonn 53105, Germany; E-mail: renehurlemann@icloud.com.

Received Feb 13, 2015; revised May 19, 2015; accepted May 21, 2015.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2015.05.013.

REFERENCES

1. Insel TR, Young LJ (2001): The neurobiology of attachment. Nat Rev Neurosci 2:129–136.
2. Feder A, Nestler EJ, Charney DS (2009): Psychobiology and molecular genetics of resilience. Nat Rev Neurosci 10:446–457.
3. Boccia ML, Petrusz P, Suzuki K, Marson L, Pedersen CA (2013): Immunohistochemical localization of oxytocin receptors in human brain. Neuroscience 253:155–164.
4. Keyes KM, Pratt C, Galea S, McLaughlin KA, Koenen KC, Shear MK (2014): The burden of loss: Unexpected death of a loved one and psychiatric disorders across the life course in a national study. Am J Psychiatry 171:864–871.
5. Donaldson ZR, Young LJ (2008): Oxytocin, vasopressin, and the neurogenetics of sociality. Science 322:900–904.
6. Garrison JL, Macosko EZ, Bernstein S, Pokala N, Albrecht DR, Bargmann CI (2012): Oxytocin/vasopressin-related peptides have an ancient role in reproductive behavior. Science 338:540–543.
7. Klatt JD, Goodson JL (2013): Oxytocin-like receptors mediate pair bonding in a socially monogamous songbird. Proc Biol Sci 280: 20122396.
8. Oldfield RG, Hofmann HA (2011): Neuropeptide regulation of social behavior in a monogamous cichlid fish. Physiol Behav 102:296–303.
9. Young KA, Gobrogge KL, Liu Y, Wang Z (2011): The neurobiology of pair bonding: Insights from a socially monogamous rodent. Front Neuroendocrinol 32:53–69.
10. Young LJ, Wang Z (2004): The neurobiology of pair bonding. Nat Neurosci 7:1048–1054.
11. Wang Z, Zhou L, Hulihan TJ, Insel TR (1996): Immunoreactivity of central vasopressin and oxytocin pathways in microtine rodents: A quantitative comparative study. J Comp Neurol 366:726–737.
12. Shapiro LE, Insel TR (1992): Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Ann N Y Acad Sci 652:448–451.
13. Young LJ, Lim MM, Gingrich B, Insel TR (2001): Cellular mechanisms of social attachment. Horm Behav 40:133–138.
14. Aragona BJ, Liu Y, Yu YJ, Curtis JT, Detwiler JM, Insel TR, Wang Z (2006): Nucleus accumbens dopamine differentially mediates the formation and maintenance of monogamous pair bonds. Nat Neurosci 9:133–139.
15. Johnson ZV, Young LJ (2015): Neurobiological mechanisms of social attachment and pair bonding. Curr Opin Behav Sci 3:38–44.
16. Lim MM, Wang Z, Olazabal DE, Ren X, Terwilliger EF, Young LJ (2004): Enhanced partner preference in a promiscuous species by manipulating the expression of a single gene. Nature 429:754–757.
17. Bosch OJ, Neumann ID (2012): Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: From central release to sites of action. Horm Behav 61:293–303.
18. Insel TR, Harbaugh CR (1989): Lesions of the hypothalamic paraventricular nucleus disrupt the initiation of maternal behavior. Physiol Behav 45:1033–1041.
19. Insel TR (1997): A neurobiological basis of social attachment. Am J Psychiatry 154:726–735.
20. Rilling JK, Young LJ (2014): The biology of mammalian parenting and its effect on offspring social development. Science 345: 771–776.
21. Marlin BJ, Mitre M, D'Amour JA, Chao MV, Froemke RC (2015): Oxytocin enables maternal behaviour by balancing cortical inhibition. Nature 520:499–504.
22. Champagne F, Diorio J, Sharma S, Meaney MJ (2001): Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. Proc Natl Acad Sci U S A 98:12736–12741.
23. Nagasawa M, Mitsui S, En S, Ohtani N, Ohta M, Sakuma Y, *et al*. (2015): Social evolution. Oxytocin-gaze positive loop and the coevolution of human-dog bonds. Science 348:333–336.
24. Crockford C, Wittig RM, Langergraber K, Ziegler TE, Zuberbuhler K, Deschner T (2013): Urinary oxytocin and social bonding in related and unrelated wild chimpanzees. Proc Biol Sci 280:20122765.
25. Grippo AJ, Gerena D, Huang J, Kumar N, Shah M, Ughreja R, Carter CS (2007): Social isolation induces behavioral and neuroendocrine disturbances relevant to depression in female and male prairie voles. Psychoneuroendocrinology 32:966–980.
26. Grippo AJ, Pournajafi-Nazarloo H, Sanzenbacher L, Trahanas DM, McNeal N, Clarke DA, *et al*. (2012): Peripheral oxytocin administration buffers autonomic but not behavioral responses to environmental stressors in isolated prairie voles. Stress 15:149–161.
27. Bosch OJ, Nair HP, Ahern TH, Neumann ID, Young LJ (2009): The CRF system mediates increased passive stress-coping behavior following the loss of a bonded partner in a monogamous rodent. Neuropsychopharmacology 34:1406–1415.
28. Feldman R, Weller A, Zagoory-Sharon O, Levine A (2007): Evidence for a neuroendocrinological foundation of human affiliation: Plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. Psychol Sci 18:965–970.
29. Gordon I, Zagoory-Sharon O, Leckman JF, Feldman R (2010): Oxytocin and the development of parenting in humans. Biol Psychiatry 68:377–382.
30. Strathearn L, Iyengar U, Fonagy P, Kim S (2012): Maternal oxytocin response during mother-infant interaction: Associations with adult temperament. Horm Behav 61:429–435.
31. Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB (2009): Lower CSF oxytocin concentrations in women with a history of childhood abuse. Mol Psychiatry 14:954–958.
32. Wismer Fries AB, Ziegler TE, Kurian JR, Jacoris S, Pollak SD (2005): Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. Proc Natl Acad Sci U S A 102:17237–17240.
33. Young SN, Anderson GN (2010): Bioanalytical inaccuracy: A threat to the integrity and efficiency of research. J Psychiatry Neurosci 35:3–6.
34. Bick J, Dozier M (2010): Mothers' and children's concentrations of oxytocin following close, physical interactions with biological and non-biological children. Dev Psychobiol 52:100–107.
35. Feldman R, Gordon I, Zagoory-Sharon O (2011): Maternal and paternal plasma, salivary, and urinary oxytocin and parent-infant synchrony: Considering stress and affiliation components of human bonding. Dev Sci 14:752–761.
36. Bakermans-Kranenburg MJ, van Ijzendoorn MH (2008): Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. Soc Cogn Affect Neurosci 3:128–134.
37. Klahr AM, Klump K, Burt SA (2014): A constructive replication of the association between the oxytocin receptor genotype and parenting. J Fam Psychol 29:91–99.

38. Chen FS, Barth ME, Johnson SL, Gotlib IH, Johnson SC (2011): Oxytocin receptor (OXTR) polymorphisms and attachment in human infants. Front Psychol 2:200.
39. Apter-Levy Y, Feldman M, Vakart A, Ebstein RP, Feldman R (2013): Impact of maternal depression across the first 6 years of life on the child's mental health, social engagement, and empathy: The moderating role of oxytocin. Am J Psychiatry 170:1161–1168.
40. Mesquita AR, Soares I, Roisman GI, Ijzendoorn M, Bakermans-Kranenburg M, Luijk M, *et al*. (2013): Predicting children's attachment behaviors from the interaction between oxytocin and glucocorticoid receptors polymorphisms. Psychiatry Res 210:1322–1323.
41. Connelly JJ, Golding J, Gregory SP, Ring SM, Davis JM, Davey Smith G, *et al*. (2014): Personality, behavior and environmental features associated with OXTR genetic variants in British mothers. PloS One 9:e90465.
42. Michalska KJ, Decety J, Liu C, Chen Q, Martz ME, Jacob S, *et al*. (2014): Genetic imaging of the association of oxytocin receptor gene (OXTR) polymorphisms with positive maternal parenting. Front Behav Neurosci 8:21.
43. Bradley B, Davis TA, Wingo AP, Mercer KB, Ressler KJ (2013): Family environment and adult resilience: Contributions of positive parenting and the oxytocin receptor gene. Eur J Psychotraumatol 4.
44. Bradley B, Westen D, Mercer KB, Binder EB, Jovanovic T, Crain D, *et al*. (2011): Association between childhood maltreatment and adult emotional dysregulation in a low-income, urban, African American sample: Moderation by oxytocin receptor gene. Dev Psychopathol 23:439–452.
45. Striepens N, Kendrick KM, Hanking V, Landgraf R, Wullner U, Maier W, Hurlemann R (2013): Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. Sci Rep 3:3440.
46. Buchheim A, Heinrichs M, George C, Pokorny D, Koops E, Henningsen P, *et al*. (2009): Oxytocin enhances the experience of attachment security. Psychoneuroendocrinology 34:1417–1422.
47. Naber F, van Ijzendoorn MH, Deschamps P, van Engeland H, Bakermans-Kranenburg MJ (2010): Intranasal oxytocin increases fathers' observed responsiveness during play with their children: A double-blind within-subject experiment. Psychoneuroendocrinology 35:1583–1586.
48. Weisman O, Zagoory-Sharon O, Feldman R (2012): Oxytocin administration to parent enhances infant physiological and behavioral readiness for social engagement. Biol Psychiatry 72:982–989.
49. Weisman O, Delaherche E, Rondeau M, Chetouani M, Cohen D, Feldman R (2013): Oxytocin shapes parental motion during father-infant interaction. Biol Lett 9:20130828.
50. Wittfoth-Schardt D, Grunding J, Wittfoth M, Lanfermann H, Heinrichs M, Domes G, *et al*. (2012): Oxytocin modulates neural reactivity to children's faces as a function of social salience. Neuropsychopharmacology 37:1799–1807.
51. Riem MM, Bakermans-Kranenburg MJ, Pieper S, Tops M, Boksem MA, Vermeiren RR, *et al*. (2011): Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: A randomized controlled trial. Biol Psychiatry 70:291–297.
52. Riem MM, van IJzendoorn MH, Tops M, Boksem MA, Rombouts SA, Bakermans-Kranenburg MJ (2012): No laughing matter: Intranasal oxytocin administration changes functional brain connectivity during exposure to infant laughter. Neuropsychopharmacology 37: 1257–1266.
53. Bartz JA, Zaki J, Ochsner KN, Bolger N, Kolevzon A, Ludwig N, Lydon JE (2010): Effects of oxytocin on recollections of maternal care and closeness. Proc Natl Acad Sci U S A 107:21371–21375.
54. Bakermans-Kranenburg MJ, van Ijzendoorn MH, Riem MM, Tops M, Alink LR (2012): Oxytocin decreases handgrip force in reaction to infant crying in females without harsh parenting experiences. Soc Cogn Affect Neurosci 7:951–957.
55. Schneiderman I, Zagoory-Sharon O, Leckman JF, Feldman R (2012): Oxytocin during the initial stages of romantic attachment: Relations to couples' interactive reciprocity. Psychoneuroendocrinology 37: 1277–1285.
56. Schneiderman I, Kanat-Maymon Y, Zagoory-Sharon O, Feldman R (2014): Mutual influences between partners' hormones shape conflict dialog and relationship duration at the initiation of romantic love. Soc Neurosci 9:337–351.
57. Gouin JP, Carter CS, Pournajafi-Nazarloo H, Glaser R, Malarkey WB, Loving TJ, *et al*. (2010): Marital behavior, oxytocin, vasopressin, and wound healing. Psychoneuroendocrinology 35:1082–1090.
58. Gonzaga GC, Turner RA, Keltner D, Campos B, Altemus M (2006): Romantic love and sexual desire in close relationships. Emotion 6:163–179.
59. Grewen KM, Girdler SS, Amico J, Light KC (2005): Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. Psychosom Med 67:531–538.
60. Light KC, Grewen KM, Amico JA (2005): More frequent partner hugs and higher oxytocin levels are linked to lower blood pressure and heart rate in premenopausal women. Biol Psychol 69:5–21.
61. Turner RA, Altemus M, Enos T, Cooper B, McGuinness T (1999): Preliminary research on plasma oxytocin in normal cycling women: Investigating emotion and interpersonal distress. Psychiatry 62:97–113.
62. Wikstrom S, Gunnarsson T, Nordin C (2003): Tactile stimulus and neurohormonal response: A pilot study. Int J Neurosci 113:787–793.
63. Billhult A, Lindholm C, Gunnarsson R, Stener-Victorin E (2008): The effect of massage on cellular immunity, endocrine and psychological factors in women with breast cancer – a randomized controlled clinical trial. Auton Neurosci 140:88–95.
64. Rapaport MH, Schettler P, Bresee C (2010): A Preliminary study of the effects of a single session of Swedish massage on hypothalamic-pituitary-adrenal and immune function in normal individuals. J Altern Complement Med 16:1079–1088.
65. Morhenn VB, Park JW, Piper E, Zak PJ (2008): Monetary sacrifice among strangers is mediated by endogenous oxytocin release after physical contact. Evol Hum Behav 29:375–383.
66. Morhenn V, Beavin LE, Zak PJ (2012): Massage increases oxytocin and reduces adrenocorticotropin hormone in humans. Altern Ther Health Med 18:11–18.
67. Ogawa S, Kudo S, Kitsunai Y, Fukuchi S (1980): Increase in oxytocin secretion at ejaculation in male. Clin Endocrinol (Oxf) 13:95–97.
68. Carmichael MS, Warburton VL, Dixen J, Davidson JM (1994): Relationships among cardiovascular, muscular, and oxytocin responses during human sexual activity. Arch Sex Behav 23:59–79.
69. Murphy MR, Checkley SA, Seckl JR, Lightman SL (1990): Naloxone inhibits oxytocin release at orgasm in man. J Clin Endocrinol Metab 71:1056–1058.
70. Blaicher W, Gruber D, Bieglmayer C, Blaicher AM, Knogler W, Huber JC (1999): The role of oxytocin in relation to female sexual arousal. Gynecol Obstet Invest 47:125–126.
71. Kruger TH, Schiffer B, Eikermann M, Haake P, Gizewski E, Schedlowski M (2006): Serial neurochemical measurement of cerebrospinal fluid during the human sexual response cycle. Eur J Neurosci 24: 3445–3452.
72. Marazziti D, Dell'Osso B, Baroni S, Mungai F, Catena M, Rucci P, *et al*. (2006): A relationship between oxytocin and anxiety of romantic attachment. Clin Pract Epidemiol Ment Health 2:28.
73. Taylor SE, Gonzaga GC, Klein LC, Hu P, Greendale GA, Seeman TE (2006): Relation of oxytocin to psychological stress responses and hypothalamic-pituitary-adrenocortical axis activity in older women. Psychosom Med 68:238–245.
74. Taylor SE (2006): Tend and befriend: Biobehavioral bases of affiliation under stress. Curr Dir Psychol Sci 15:273–277.
75. Tabak BA, McCullough ME, Szeto A, Mendez AJ, McCabe PM (2011): Oxytocin indexes relational distress following interpersonal harms in women. Psychoneuroendocrinology 36:115–122.
76. McCullough ME, Churchland PS, Mendez AJ (2013): Problems with measuring peripheral oxytocin: Can the data on oxytocin and human behavior be trusted? Neurosci Biobehav Rev 37:1485–1492.
77. Kagerbauer SM, Martin J, Schuster T, Blobner M, Kochs EF, Landgraf R (2013): Plasma oxytocin and vasopressin do not predict

neuropeptide concentrations in human cerebrospinal fluid. J Neuroendocrinol 25:668–673.
78. Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, *et al*. (2012): Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73:553–566.
79. Gimpl G, Fahrenholz F (2001): The oxytocin receptor system: Structure, function, and regulation. Physiol Rev 81:629–683.
80. Walum H, Lichtenstein P, Neiderhiser JM, Reiss D, Ganiban JM, Spotts EL, *et al*. (2012): Variation in the oxytocin receptor gene is associated with pair-bonding and social behavior. Biol Psychiatry 71:419–426.
81. Schneiderman I, Kanat-Maymon Y, Ebstein RP, Feldman R (2013): Cumulative risk on the oxytocin receptor gene (OXTR) underpins empathic communication difficulties at the first stages of romantic love. Soc Cogn Affect Neurosci 9:1524–1529.
82. Ditzen B, Schaer M, Gabriel B, Bodenmann G, Ehlert U, Heinrichs M (2009): Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol Psychiatry 65: 728–731.
83. Ditzen B, Nater UM, Schaer M, La Marca R, Bodenmann G, Ehlert U, Heinrichs M (2012): Sex-specific effects of intranasal oxytocin on autonomic nervous system and emotional responses to couple conflict. Soc Cogn Affect Neurosci 8:897–902.
84. Unkelbach C, Guastella AJ, Forgas JP (2008): Oxytocin selectively facilitates recognition of positive sex and relationship words. Psychol Sci 19:1092–1094.
85. Burri A, Heinrichs M, Schedlowski M, Kruger TH (2008): The acute effects of intranasal oxytocin administration on endocrine and sexual function in males. Psychoneuroendocrinology 33:591–600.
86. Behnia B, Heinrichs M, Bergmann W, Jung S, Germann J, Schedlowski M, *et al*. (2014): Differential effects of intranasal oxytocin on sexual experiences and partner interactions in couples. Horm Behav 65:308–318.
87. Singer T, Snozzi R, Bird G, Petrovic P, Silani G, Heinrichs M, Dolan RJ (2008): Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain. Emotion 8: 781–791.
88. Liu JC, Guastella AJ, Dadds MR (2013): Exploring the role of intranasal oxytocin on the partner preference effect in humans. Psychoneuroendocrinology 38:587–591.
89. Scheele D, Striepens N, Güntürkün O, Deutschlander S, Maier W, Kendrick KM, Hurlemann R (2012): Oxytocin modulates social distance between males and females. J Neurosci 32:16074–16079.
90. Bartels A, Zeki S (2004): The neural correlates of maternal and romantic love. Neuroimage 21:1155–1166.
91. Acevedo BP, Aron A, Fisher HE, Brown LL (2012): Neural correlates of long-term intense romantic love. Soc Cogn Affect Neurosci 7: 145–159.
92. Scheele D, Wille A, Kendrick KM, Stoffel-Wagner B, Becker B, Güntürkün O, *et al*. (2013): Oxytocin enhances brain reward system responses in men viewing the face of their female partner. Proc Natl Acad Sci U S A 110:20308–20313.
93. Younger J, Aron A, Parke S, Chatterjee N, Mackey S (2010): Viewing pictures of a romantic partner reduces experimental pain: Involvement of neural reward systems. PloS One 5:e13309.
94. Zunhammer M, Geis S, Busch V, Greenlee MW, Eichhammer P (2015): Effects of intranasal oxytocin on thermal pain in healthy men: A randomized functional magnetic resonance imaging study. Psychosom Med 77:156–166.
95. Preckel K, Scheele D, Eckstein M, Maier W, Hurlemann R (2014): The influence of oxytocin on volitional and emotional ambivalence [published online ahead of print November 14]. Soc Cogn Affect Neurosci. http://dx.doi.org/10.1093/scan/nsu147.
96. Liu Y, Wang ZX (2003): Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. Neuroscience 121:537–544.
97. Striepens N, Matusch A, Kendrick KM, Mihov Y, Elmenhorst D, Becker B, *et al*. (2014): Oxytocin enhances attractiveness of unfamiliar female faces independent of the dopamine reward system. Psychoneuroendocrinology 39:74–87.
98. Theodoridou A, Rowe AC, Penton-Voak IS, Rogers PJ (2009): Oxytocin and social perception: Oxytocin increases perceived facial trustworthiness and attractiveness. Horm Behav 56:128–132.
99. Dolen G, Darvishzadeh A, Huang KW, Malenka RC (2013): Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. Nature 501:179–184.
100. Mottolese R, Redoute J, Costes N, Le Bars D, Sirigu A (2014): Switching brain serotonin with oxytocin. Proc Natl Acad Sci U S A 111:8637–8642.
101. Rupp HA, James TW, Ketterson ED, Sengelaub DR, Ditzen B, Heiman JR (2013): Lower sexual interest in postpartum women: Relationship to amygdala activation and intranasal oxytocin. Horm Behav 63:114–121.
102. Gregory R, Cheng H, Rupp HA, Sengelaub DR, Heiman JR (2015): Oxytocin increases VTA activation to infant and sexual stimuli in nulliparous and postpartum women. Horm Behav 69C:82–88.
103. DeWall CN, Gillath O, Pressman SD, Black LL, Bartz JA, Moskovitz J, *et al*. (2014): When the love hormone leads to violence: Oxytocin increases intimate partner violence inclinations among high trait aggressive people. Soc Psychol Personal Sci 5:691–697.
104. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U (2003): Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol Psychiatry 54:1389–1398.
105. Eckstein M, Becker B, Scheele D, Scholz C, Preckel K, Schlaepfer T, *et al*. (2014): Oxytocin facilitates the extinction of conditioned fear in humans [published online ahead of print October 30]. Biol Psychiatry. http://dx.doi.org/10.1016/j.biopsych.2014.10.015.
106. Striepens N, Scheele D, Kendrick KM, Becker B, Schafer L, Schwalba K, *et al*. (2012): Oxytocin facilitates protective responses to aversive social stimuli in males. Proc Natl Acad Sci U S A 109: 18144–18149.
107. Eckstein M, Scheele D, Weber K, Stoffel-Wagner B, Maier W, Hurlemann R (2014): Oxytocin facilitates the sensation of social stress. Hum Brain Mapp 35:4741–4750.
108. Churchland PS, Winkielman P (2012): Modulating social behavior with oxytocin: How does it work? What does it mean? Horm Behav 61:392–399.
109. Bartz JA, Zaki J, Bolger N, Ochsner KN (2011): Social effects of oxytocin in humans: Context and person matter. Trends Cogn Sci 15:301–309.
110. Preckel K, Scheele D, Kendrick KM, Maier W, Hurlemann R (2014): Oxytocin facilitates social approach behavior in women. Front Behav Neurosci 8:191.
111. Scheele D, Striepens N, Kendrick KM, Schwering C, Noelle J, Wille A, *et al*. (2014): Opposing effects of oxytocin on moral judgment in males and females. Hum Brain Mapp 35:6067–6076.
112. Scheele D, Kendrick KM, Khouri C, Kretzer E, Schlapfer TE, Stoffel-Wagner B, *et al*. (2014): An oxytocin-induced facilitation of neural and emotional responses to social touch correlates inversely with autism traits. Neuropsychopharmacology 39:2078–2085.
113. Craig AD (2009): How do you feel–now? The anterior insula and human awareness. Nat Rev Neurosci 10:59–70.
114. Lou HC, Luber B, Crupain M, Keenan JP, Nowak M, Kjaer TW, *et al*. (2004): Parietal cortex and representation of the mental Self. Proc Natl Acad Sci U S A 101:6827–6832.
115. Voos AC, Pelphrey KA, Kaiser MD (2013): Autistic traits are associated with diminished neural response to affective touch. Soc Cogn Affect Neurosci 8:378–386.
116. Quattrocki E, Friston K (2014): Autism, oxytocin and interoception. Neurosci Biobehav Rev 47:410–430.
117. Colonnello V, Chen FS, Panksepp J, Heinrichs M (2013): Oxytocin sharpens self-other perceptual boundary. Psychoneuroendocrinology 38:2996–3002.
118. Cardoso C, Ellenbogen MA, Linnen AM (2012): Acute intranasal oxytocin improves positive self-perceptions of personality. Psychopharmacology (Berl) 220:741–749.

119. Colonnello V, Heinrichs M (2014): Intranasal oxytocin enhances positive self-attribution in healthy men. J Psychosom Res 77: 415–419.
120. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC (2007): Oxytocin improves “mind-reading” in humans. Biol Psychiatry 61: 731–733.
121. Hurlemann R, Patin A, Onur OA, Cohen MX, Baumgartner T, Metzler S, *et al*. (2010): Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. J Neurosci 30:4999–5007.
122. Ernst J, Northoff G, Boker H, Seifritz E, Grimm S (2013): Interoceptive awareness enhances neural activity during empathy. Hum Brain Mapp 34:1615–1624.
123. Aron A, Fraley B (1999): Relationship closeness as including other in the self: Cognitive underpinnings and measures. Soc Cogn 17: 140–160.
124. Krienen FM, Tu PC, Buckner RL (2010): Clan mentality: Evidence that the medial prefrontal cortex responds to close others. J Neurosci 30: 13906–13915.
125. De Dreu CK, Greer LL, Handgraaf MJ, Shalvi S, Van Kleef GA, Baas M, *et al*. (2010): The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans. Science 328: 1408–1411.
126. De Dreu CK, Greer LL, Van Kleef GA, Shalvi S, Handgraaf MJ (2011): Oxytocin promotes human ethnocentrism. Proc Natl Acad Sci U S A 108:1262–1266.
127. Macdonald K, Macdonald TM, Brune M, Lamb K, Wilson MP, Golshan S, Feifel D (2013): Oxytocin and psychotherapy: A pilot study of its physiological, behavioral and subjective effects in males with depression. Psychoneuroendocrinology 38:2831–2843.
128. Najib A, Lorberbaum JP, Kose S, Bohning DE, George MS (2004): Regional brain activity in women grieving a romantic relationship breakup. Am J Psychiatry 161:2245–2256.
129. O’Connor MF, Wellisch DK, Stanton AL, Eisenberger NI, Irwin MR, Lieberman MD (2008): Craving love? Enduring grief activates brain’s reward center. Neuroimage 42:969–972.
130. Kersting A, Ohrmann P, Pedersen A, Kroker K, Samberg D, Bauer J, *et al*. (2009): Neural activation underlying acute grief in women after the loss of an unborn child. Am J Psychiatry 166:1402–1410.
131. Cole MG, Dendukuri N (2003): Risk factors for depression among elderly community subjects: A systematic review and meta-analysis. Am J Psychiatry 160:1147–1156.
132. Prigerson HG, Frank E, Kasl SV, Reynolds CF 3rd, Anderson B, Zubenko GS, *et al*. (1995): Complicated grief and bereavement-related depression as distinct disorders: Preliminary empirical validation in elderly bereaved spouses. Am J Psychiatry 152:22–30.
133. Burkett JP, Young LJ (2012): The behavioral, anatomical and pharmacological parallels between social attachment, love and addiction. Psychopharmacology (Berl) 224:1–26.
134. McRae-Clark AL, Baker NL, Maria MM, Brady KT (2013): Effect of oxytocin on craving and stress response in marijuana-dependent individuals: A pilot study. Psychopharmacology (Berl) 228:623–631.
135. Pedersen CA, Smedley KL, Leserman J, Jarskog LF, Rau SW, Kampov-Polevoi A, *et al*. (2013): Intranasal oxytocin blocks alcohol withdrawal in human subjects. Alcohol Clin Exp Res 37:484–489.
136. Shahrestani S, Kemp AH, Guastella AJ (2013): The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: A meta-analysis. Neuropsychopharmacology 38:1929–1936.
137. Caria A, de Falco S (2015): Anterior insular cortex regulation in autism spectrum disorders. Front Behav Neurosci 9:38.
138. Birkett MA, Shinday NM, Kessler EJ, Meyer JS, Ritchie S, Rowlett JK (2011): Acute anxiogenic-like effects of selective serotonin reuptake inhibitors are attenuated by the benzodiazepine diazepam in BALB/c mice. Pharmacol Biochem Behav 98:544–551.
139. Bales KL, Perkeybile AM, Conley OG, Lee MH, Guoynes CD, Downing GM, *et al*. (2013): Chronic intranasal oxytocin causes long-term impairments in partner preference formation in male prairie voles. Biol Psychiatry 74:180–188.
140. Huang H, Michetti C, Busnelli M, Manago F, Sannino S, Scheggia D, *et al*. (2014): Chronic and acute intranasal oxytocin produce divergent social effects in mice. Neuropsychopharmacology 39: 1102–1114.
141. Barraza JA, Grewal NS, Ropacki S, Perez P, Gonzalez A, Zak PJ (2013): Effects of a 10-day oxytocin trial in older adults on health and well-being. Exp Clin Psychopharmacol 21:85–92.
142. Bales KL, van Westerhuyzen JA, Lewis-Reese AD, Grotte ND, Lanter JA, Carter CS (2007): Oxytocin has dose-dependent developmental effects on pair-bonding and alloparental care in female prairie voles. Horm Behav 52:274–279.
143. Cardoso C, Ellenbogen MA, Orlando MA, Bacon SL, Joober R (2013): Intranasal oxytocin attenuates the cortisol response to physical stress: A dose-response study. Psychoneuroendocrinology 38:399–407.