1 **Title:** Antisocial oxytocin: complex effects on social behavior

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3 **Author names and affiliations:** Annaliese K. Beery^{a*}

4 ^a*Department of Psychology, Department of Biology, Neuroscience Program, Smith College,*
5 *Northampton, MA, USA*

6
7 ***Corresponding author:**

8 Annaliese K. Beery

9 Smith College, Clark Science Center

10 44 College Lane

11 Northampton, MA 01063

12 Phone: (413) 585-3918

13 Fax: (413) 585-3786

14 Email: abeery@smith.edu

15
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21 **Abstract**

22 Research on the role of oxytocin and other neuropeptides in vertebrate social behavior is a
23 quintessential example of integrative biology — spanning species, scientific disciplines, and
24 levels of analysis to address mechanisms of behavior. Oxytocin is involved in a wide variety of
25 processes related to social behavior, including social recognition, affiliation, and maternal
26 behavior. While there is a great deal of well-placed emphasis on the prosocial effects of
27 oxytocin, antisocial effects related to decreased or deterred social interaction have also been
28 documented. Studies from the human literature reveal increased outgroup discrimination and
29 reduced affiliative behavior in certain individuals following oxytocin administration. Animal
30 studies shed further light on the role of oxytocin in fear conditioning, stranger avoidance, and
31 aggression. In some cases, prosocial behavior towards one individual or group may come at the
32 expense of prosociality towards another. From this growing literature we learn that the antisocial
33 effects of oxytocin are an integral aspect of its effects on social behavior.
34

Introduction

The role of oxytocin (OT) in social processes ranging from maternal behavior to mate affiliation is well established, leading to its popular designation as the “love” or “cuddle” hormone. There is growing appreciation, however, that OT also plays a role in a different side of social behavior[1–8]: in animals, OT has been associated with aggression, social selectivity, and fear. In humans, OT has been linked to dishonesty, ethnocentrism, social stress, envy, and reduced cooperation among other outcomes (table 1). These antisocial behaviors and emotions—characterized by avoidance, aggression, or reduced prosocial behavior—are nonetheless important features of the behavioral repertoires of social individuals.

Oxytocin is a 9-amino-acid peptide hormone that acts in the brain and in the periphery. In mammals, these peripheral functions include muscle contractions related to reproduction, such as orgasm, milk ejection for lactation, and uterine contractions leading to birth[9]. Astonishingly, oxytocin and related nonapeptides play a role in reproductive functions across the animal kingdom[10,11], for example: modulating ejaculation and egg deposition in snails, movements characteristic of mating in leeches, and sex-specific mating behaviors in the roundworm *C. elegans*[12–14]. These reproduction-related functions of oxytocin and related peptides evolutionarily preceded their roles in the central regulation of complex behaviors[15], many of which also relate to reproduction, including maternal behavior and formation of mating partnerships. Despite the remarkable consistency with which oxytocin-like peptides play important roles in reproductive and social functions across the animal kingdom, it is important to note that oxytocin has a host of additional effects, including regulation of heart rate and blood pressure, motor activity, water balance, pain sensitivity, and opiate tolerance. On the behavioral front, OT also contributes to stress and anxiety-related behaviors, feeding, grooming, and learning and memory[9]. Thus oxytocin cannot be defined by any one of its functions[16].

With this diversity of roles in mind, we should adopt a multidimensional view of oxytocin[2,5], including behaviors traditionally considered to be within the antisocial realm of social behavior. This review addresses the complexity of oxytocin and the behaviors it affects, and presents the body of research findings on antisocial effects of oxytocin to date. These antisocial effects of oxytocin are often complementary to prosocial effects, occurring in the same individuals, and triggered by the same events.

The human literature on antisocial effects of oxytocin has been reviewed elsewhere[2–4,7], and is synthesized in table 1. Many of these studies indicate that pro- and antisocial effects of oxytocin vary with individual and social context. This review surveys the complexity of studying oxytocin and social behavior in humans and other animals, with further discussion of the roles of oxytocin in decreased social contact, aggression, and fear in non-human mammals.

Complexity of Studying Social Behavior

Scientists often refer to the neurobiology of social behavior as if it were a single process, but social behaviors are diverse, and similar behaviors in different species may be mediated in different ways, necessitating caution in generalization. Neurobiological investigations of social behavior typically focus on specific measures such as social preference, motivation, and recognition. These behaviors are important aspects of the lives of social species, but are part of larger, species-specific social repertoires. For example, affiliation towards other individuals is common to social species, but may vary in intensity and social targets across different social systems. The study of oxytocin and social behavior has benefitted greatly from studies of prairie voles (*Microtus ochrogaster*), in which closely bonded breeding pairs form the core of social units that include alloparental offspring[17]. Other social groups form in the absence of monogamy, especially same-sex groups of mothers and non-dispersed female offspring (e.g. elephants, horses, lions, prairie dogs, and some human societies)[18]. Yet other social groups lack kinship; when the benefits of sociality are high, unrelated individuals may come together either in loose aggregations, or to form specific social groups. Thus, individual behavioral variables such as social approach or contact may depend on very different motivations and sensory processes within these different social structures. Even species that share traits such as monogamy or alloparental behavior may not rely on a consistent set of underlying mechanisms to exhibit that behavior[19,20]. Deciphering which similar social phenotypes are mediated by similar or different underlying mechanisms will be an important challenge for future studies.

Complexity of Studying Oxytocin

In addition to the inherent complexity of oxytocin's diverse effects, studies of the functions of oxytocin face additional challenges. Peripheral oxytocin is only moderately correlated with brain oxytocin, and peripheral measurement of oxytocin is sensitive to assay type, presence or

absence of an extraction step, and sample type (e.g. blood, urine, saliva)[21]. There is some concern that enzyme immunoassays sample more than oxytocin, and that measures of unextracted samples are unreliable[21,22]. Even if peripheral measures can be obtained reliably, it is currently unclear how we should expect OT to change with social adversity. For example, CSF OT is lower in response to some adverse social circumstances — e.g. in women with a history of childhood abuse[23] and in nursery-reared versus mother-reared rhesus monkeys[24]. However, plasma OT is higher in women experiencing low-quality relationships or relationship distress[25]. This complexity undermines our ability to assign simple interpretations to differing OT levels, and is reminiscent of similar difficulty in interpreting circulating glucocorticoid levels, which may be increased or depressed with stress exposure and stress-related disorders[26–28].

Some pitfalls of measurement studies can be circumvented by administration studies. These are more able to reveal causality, but have their own limitations. Oxytocin is believed not to cross the blood-brain barrier under normal circumstances[9]. Thus it is unclear how to interpret effects associated with peripherally injected oxytocin — although more recent evidence suggests that supraphysiological OT doses do increase CSF OT[29]. Recent studies have finally demonstrated that intranasally administered OT elevates CSF OT[29–31], although questions still remain about mechanisms of transport, effectiveness, and study power[32–34]. Manipulations that increase OT in the CSF, including intracerebroventricular (*icv*) infusion, still do not mimic normal biological delivery, as endogenous oxytocin is projected from hypothalamic nuclei to specific regions within the brain[15]. Thus, any non-site specific administration may have a host of effects not present in the unmanipulated brain[35]. Finally, oxytocin and vasopressin receptors are promiscuous for each others' ligand, and OT may exert effects through vasopressin receptors, especially at high doses[35].

Additional difficulties arise in the translation of findings from one species to others. There are many species differences in location of oxytocin receptors (OTRs) within the brain (figure 1), and these differences are widely believed to be linked to species-specific variation in oxytocin-related behaviors, from monogamy to group-living[36–38]. For example, oxytocin acting in the nucleus accumbens plays an important role in maintaining opposite-sex pairbonds in female prairie voles, and artificial induction of OTRs in this region in mice promotes partner preferences. However the full story must be more complex, as enhanced expression of OTRs in

this region in meadow voles (*Microtus pennsylvanicus*) does not lead to pair bonds[39], and monogamous California mice (*Peromyscus californicus*) do not have pronounced OTR binding in this region[40]. This pattern also does not account for social behavior between peers: while some group-living rodents such as naked mole-rats have OTRs in the nucleus accumbens, others such as social tuco-tucos appear to lack them entirely[37]. Thus translation from one species to another, or from one social behavior to another must be treated with caution. Sex differences and individual differences in OT signaling must also be considered[41].

Antisocial OT

In rodents and in primates, OT has been associated with reductions in social contact, increases in territorial and maternal aggression, and altered fear, in addition to known prosocial effects.

Social contact and huddling

In female prairie voles, oxytocin administration facilitates formation of a preference for a partner male over an unfamiliar stranger[42]— classically considered a prosocial effect. This enhanced huddling with a partner is not in addition to stranger huddling, but in place of it; another way to interpret this social selectivity is that social behavior towards unfamiliar individuals is reduced, potentially parallel to human findings related to in-group and out-group dynamics [43,44]. In some cases, decreased affiliation towards unfamiliar individuals becomes overt aggression (see mate-guarding in *Aggression* section below)—thought to be an important antisocial aspect of affiliation towards a mate.

OT has been widely reported to increase social contact and investigation, but some studies have documented *reduced* social contact following oxytocin administration, particularly with unfamiliar individuals. For example, marmosets are spontaneously prosocial, especially towards opposite-sex strangers, but less so when treated with marmoset-specific Pro⁸-OT[45]. In female California mice, intranasal oxytocin decreased social interaction with an unfamiliar female, at a magnitude similar to the effect of prior social defeat[46]. In capuchin monkeys, intranasal oxytocin administration decreased congregating behavior between individuals, and was associated with reduced food sharing[47].

The impact of OT on social contact and preference varies with timing and/or duration of

administration. For example, Bales *et al.* [48] found that short-term administration of OT in prairie voles led to *enhanced* social contact between male cage-mates, while chronic administration was followed by *impairment* of partner preference formation in males. In this instance, reduced partner preference took the form of a preference for huddling with the novel stranger, with no overall difference in huddling time.

The effects of oxytocin on partner preferences are also brain region-specific — *i.e. oxytocin can act in some regions to enhance partner preferences, while impairing them in others. In meadow voles, females form preferences for familiar peers in short, winter-like day lengths when they cohabit in groups*[49–51]. The brains of short-day meadow voles exhibit increased oxytocin receptor density in multiple brain regions (relative to the brains of less socially tolerant long-day voles) suggesting a potential mechanism for one component of this seasonal transition [52,53]. Within the lateral septum, however, higher oxytocin receptor density is associated with reduced social huddling [53]. And while infusion of oxytocin to the cerebrospinal fluid of short day females enhances preference for familiar cagemates over strangers[53], injection of oxytocin into the lateral septum eliminates such preferences, without affecting total huddling time (Anacker, Christensen and Beery, unpublished; Anacker *et al.* Soc Behav Neurosci Abstract P119, 2015). The lateral septum may be an important region for effects of oxytocin on social selectivity, among other behaviors (see box 1: A focus on septal oxytocin).

Aggression

Oxytocin has been associated with aggression in multiple contexts, including “mate-guarding”, maternal aggression for protection of young, and territory defense.

In prairie voles, mated males and females exhibit aggression towards unfamiliar opposite-sex individuals, both in the field and in the lab[54]. Female prairie voles also become more aggressive towards other females following extended (8d) cohabitation with a male, or during pregnancy[55]. The transition to enhanced stranger aggression *may protect the relationship with the mate, linking aggression to affiliation. Stranger aggression appears to* relate to dopamine receptor regulation[56] and other neurochemical processes, but also to be influenced by oxytocin. Females treated with oxytocin within a day of birth (relative to controls and oxytocin receptor antagonist (OTA) treated individuals) exhibit enhanced aggression and reduced social huddling following only brief (1h) cohabitation with a male—a duration normally insufficient to

189 induce such changes[57].

190 Many studies have demonstrated effects of oxytocin on maternal aggression, which **once**
191 **again links affiliation (towards pups) with aggression (towards others)**, and illustrates the
192 context-specificity of oxytocin's effects on social behavior. Specifically, oxytocin inhibits pup-
193 directed aggression while enhancing aggression towards adult intruders (reviewed in [58]). Early
194 experiments in mice found that suppression of oxytocin expression also reduced maternal
195 aggression[59]. Female golden hamster dams given repeated injections of oxytocin to the central
196 amygdala exhibited greater aggression towards a male intruder, with greater contact time and
197 more bites[60]. Substantial research on maternal aggression has been conducted in rats
198 selectively bred for high or low anxiety behaviors (HAB, LAB), with concurrent differences in
199 aggression (HAB rats exhibit more aggression)[61]. Chronic *icv* administration of oxytocin
200 enhances maternal aggression in LAB dams, while chronic OTA infusion reduced aggression in
201 HAB dams, suggesting that endogenous OT plays a role in such aggression[59]. Oxytocin acting
202 in the central amygdala may play an important role in processing both positively and negatively
203 valenced social cues[2]. Microdialysis measures of OT in the CeA revealed increased release
204 during a maternal defense test in rats, with correlations between amount of OT release and
205 aggression. Local bilateral increase of OT via retrodialysis increased aggression in HAB
206 dams[61]. These studies suggest that oxytocin is an important contributor to maternal aggression,
207 although some studies also find that OT attenuates maternal aggression in rats[62,63]. These
208 differences may be due to differences in rat strain, timing of drug administration, or duration of
209 treatment. Oxytocin is also likely to contribute to maternal aggression through its actions in other
210 brain regions (reviewed in [59]).

211 Oxytocin also appears to be involved in territorial aggression in males. *Icv* oxytocin
212 enhanced aggression in squirrel monkeys among dominant males, while increasing scent
213 marking in subordinates[64]. Oxytocin signaling appears important for mouse aggression in the
214 resident-intruder paradigm, as selective knockout of OTRs in neurons of the raphe nucleus
215 induced a deficit in male aggressive behavior without influencing maternal aggression[65].
216 Natural variation in aggressive behavior in male wild-type Groningen rats is associated with
217 higher oxytocin receptor density, with more OTR binding in the BNST and CeA of more
218 aggressive males—although more aggressive males also expressed less transcript for OT in the
219 hypothalamus than less aggressive males[66].

In non-mammals, oxytocin-like peptides may also play a role in aggression. In territorial finches, peripheral OTA administration reduces aggressive behavior, although this may not be linked to central effects at oxytocin-like mesotocin receptors[67].

Fear

Both fear-enhancing and fear-reducing effects of OT have been documented. This seeming contradiction appears to be partly explained by different effects in specific brain regions, or even specific populations of neurons within a brain region. In the amygdala, OT signaling and acute OT administration have been linked to reduced fear and anxiety through many studies in rats and mice as well as in humans[8,68–72]. Even in this region, dose and duration of OT impact whether anxiety is reduced or enhanced, potentially through negative feedback regulation of OT receptor density[73]. Fear-enhancing effects of oxytocin have been documented in the lateral septum (box 1), where OTRs have been linked to greater fear after negative social encounters, putatively through enhanced memory of such encounters[74,75] (however, see [76]). The role of vasopressin within the lateral septum has also been well studied for its links to aggression and territoriality[77], and a subset of effects of oxytocin in the lateral septum may occur through actions at the vasopressin receptor[78]. As oxytocin signaling in the lateral septum begins to be better understood, we may encounter more ways in which OT in this region is particularly important for social selectivity and social memory.

Conclusions

As research on oxytocin has proliferated, it has become clear that its effects vary with factors including dose, timing, brain region of action, subject sex, social context, and prior experience. From this complexity, emerging patterns inform us about the pivotal role oxytocin plays in many aspects of social behavior, including antisocial behaviors. Apparently opposing findings should become clarified as we understand more about these factors — for example, long-term administration may have opposite effects from acute administration because of downregulation of receptors and other habituation pathways.

Antisocial functions of oxytocin—such as aggression—may facilitate prosocial behavior towards other individuals such as in-group members or reproductive partners, although it is not necessary to have such pairings in all cases[79]. While these outcomes have been present from

the early days of research on OT and social behavior, new research findings have increased awareness of the extent and importance of these functions, and made them part of oxytocin's "story".

Research on the roles of oxytocin in social behaviors provides an excellent example of the progress that can be made by integrating across species, levels of analysis, and types of questions to understand complex behaviors[80]. There is much more work to be done, and comparative studies of species that vary in social traits will improve our understanding of which aspects of oxytocin signaling and function are shared across or are unique to individual species, aiding in appropriate translation of findings[37,81].

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Table 1 appears below so that the references will be correctly autonumbered after the text citations. The identical table is also attached as a separate file.

	Study summary	Subjects	Reference
Envy and In- vs out-group	Envy and gloating increased following loss and gain tasks.	M+F	Shamay-Tsoory et al. 2009 [82]
	OT increased racial in-group bias in neural responses; correlation with positive implicit attitudes toward racial in-group.	M	Sheng et al. 2013 [83]
	OT increased in-group favoritism and sometimes out-group derogation.	M	De Dreu et al. 2011 [84]
	OT associated with group-benefitting (but not self-benefitting) lies when gains at stake.	M	Shalvi & De Dreu 2014 [44]
	OT promotes in-group trust and cooperation, and defensive but not offensive out-group aggression.	M	De Dreu et al. 2010 [85]
Stress	Increase in perceived social stress despite no cort response after OT.	M	Eckstein et al. 2014 [86]
	Increased defensive response to unpredictable (but not predictable) shocks following OT versus AVP, control administration.		Grillon et al. 2013 [87]
	OT potentiates startle response to negative stimuli, biases subsequent memory toward the negative.	M	Striepens et al. 2012 [88]
	Plasma OT positively correlated with gaps in social relationships, less positive relationships, and cort levels.	F	Taylor et al. 2006 [89]
Context	OT enhances cooperation when social information present, decreases cooperation when absent.	M+F	Declerck et al. 2010 [90]
	OT enhances cooperation after prior contact with game partner; increases self-interested behavior in anonymous conditions (but not in participants with prosocial value orientations).	M+F	Declerck et al. 2014 [91]
Individual differences	OT increased interpersonal violence inclinations in those prone to physical aggression only.	M+F	DeWall et al. 2014 [92]
	Males in relationships but not single males maintained more space between themselves and attractive females following OT exposure.	M	Scheele et al. 2012 [93]
	Anxiously and securely attached individuals remember mothers as less or more caring (respectively) following OT.	M	Bartz et al. 2010 [94]
	Only anxiously attached demonstrate selective decreases in agency following OT.	M	Bartz et al. 2015 [95]
Sex differences	Increased anger and math performance in women following OT and social stress; less negative affect and greater vagal rebound in men.	M+F	Kubzansky et al. 2012 [96]
	Amygdalar activity decreases in males, increases in females in response to faces following OT.	M+F	Domes et al. 2007, 2010 [97,98]
	OT promotes altered neural responses; self interest in males, altruism in females.	M+F	Scheele et al. 2014 [99]
	Plasma OT elevated with relationship distress in women but not men.	M+F	Taylor et al. 2010 [25]
	Less evidence of trust repair in females than men following OT, particularly in high trait forgiveness females.	M+F	Yao et al. 2014 [100]
Mental illness	Decreased trust and cooperation in anxiously attached, rejection sensitive borderline personality disorder participants.	M+F	Bartz et al. 2011 [101]
	High psychopathic characteristics and traits associated with socially deviant lifestyle correlated with increased urinary OT.	M	Mitchell et al. 2013 [102]
	Serum OT positively associated with positive symptom severity in schizophrenia.	M+F	Rubin et al. 2014 [103]
	Higher plasma OT related to increased schizotypal traits.	F	Tseng et al. 2014 [104]

FIGURE LEGENDS

Table 1. Overview of human studies illustrating the role of oxytocin in negatively valenced social behaviors and emotions, often in a person- or context-specific manner. Note: this is not an exhaustive list, and not all replication studies find these effects – see [111].

Figure 1. Oxytocin receptor distributions across a sampling of rodent species illustrates consistency and variation. Broad distribution of OTRs throughout the forebrain is consistent with OT involvement in a wide variety of socially relevant processes. Sites of major OT production and distribution are largely conserved, while OTR distribution is quite variable. Most species exhibit OTR binding in regions such as the LS, BNST, VMH, and various nuclei of the amygdala, but only a few species exhibit binding in regions such as the CPu and hippocampus. This heterogeneity underscores the importance of exercising caution when extrapolating between species. Data are based on tables and images from autoradiographic receptor binding assays in prior syntheses[105,106] and additional papers[107–109] and represent data from 1-16 individuals; areas marked as “no binding” may have low level binding within the apparent background. Binomial nomenclature is provided when the common name of the species is not unique. Abbreviations: OB (olfactory bulb), AON (anterior olfactory nucleus), PFC (prefrontal cortex), Cing (cingulate cortex), CPu (caudoputamen), NAcc (nucleus accumbens), DEN (dorsal endopiriform nucleus), LS (lateral septum), BNST (bed nucleus of the stria terminalis), MPOA (medial preoptic area), PVN (paraventricular nucleus), SON (supraoptic nucleus), CA1-3 (cornu ammonis 1-3 of the hippocampus), DG (dentate gyrus), Thal (thalamus), CeA (central nucleus of the amygdala), CoA/MeA (cortical or medial amygdala), BLA (basolateral amygdala). Anatomical placements are approximate, as brain regions from multiple sagittal planes have been projected onto a single plane, and different species may exhibit binding in different subregions of these structures (e.g. thalamic nuclei, or dorsal or ventral LS). The sagittal section was adapted from the mouse brain atlas of Paxinos and Franklin[110].

Figure 2. Oxytocin signaling in the lateral septum. Left panel: a coronal section with dense oxytocin receptor binding in the lateral septum. Right panel: oxytocin fibers in the ventral lateral septum. Images are of receptor autoradiography and immunohistochemistry, respectively, in brain tissue from female meadow voles.

Box 1: A focus on septal oxytocin

Oxytocin in the lateral septum has been implicated in several studies finding negative or antisocial effects of OT. OT is released into the lateral septum[59], and while OT is generally anxiolytic, septal oxytocin receptors have been associated with enhanced fear following social defeat in mice[68, but see 70]. More OTRs in this region are correlated with decreased alloparental care in prairie voles and reduced social huddling in meadow voles[53,112], and injection of OT into the lateral septum disrupts same-sex partner preferences (unpublished data). Of note, species differ markedly in the density of OTRs in this region (figure 1). The lateral septum is part of neural circuits involved in social recognition, territoriality, and other social behavioral processes, and may be a region in which OT influences social selectivity and social learning.

[Figure 2 and caption should be placed here]

Figure 1

Figure 2