An Allostatic Theory of Oxytocin

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Oxytocin has garnered considerable interest for its role in social behavior, as well as for the potential of intranasal administration to treat social difficulties. However, current theoretical models for the role of oxytocin in social behavior pay little consideration to its evolutionary and developmental history. This article aims to broaden our understanding of the role of oxytocin in social behavior by adopting an ethological approach through the lens of Nikolaas Tinbergen’s ‘four questions’ – how does oxytocin work; how does the role of oxytocin change during development; how does oxytocin enhance survival; and how did the oxytocin system evolve? We argue that oxytocin is most accurately described as an allostatic hormone that modulates both social and non-social behavior by maintaining stability through changing environments.

What Is the Role of Oxytocin in Human Behavior?
Oxytocin is an evolutionarily ancient [1] neuromodulator and hormone. It is primarily produced in the hypothalamus from which it is secreted both within the brain and into the circulatory system [2]. Oxytocin has captured the most interest of any neuromodulatory system [3] owing to its role in social behavior and cognition [4]. In light of reports that intranasally administered oxytocin improves social behavior and communication [5,6], it has been nominated as a potential therapeutic agent to help to remedy social impairments (see Glossary) [7], which are a key characteristic of several psychiatric disorders. However, more recent results have not matched early expectations regarding the effects of oxytocin on social behavior in psychiatric illnesses [8], and some studies report null effects (e.g., [9]). Historically, oxytocin has also been associated with terms such as the ‘moral molecule’ [10] and the ‘cuddle chemical’ [11]. These terms are now typically disregarded in the scientific literature [12], and oxytocin is generally considered to be a hormone that is involved in both prosocial and non-prosocial cognitive processes and behavior. However, this ‘social’ description has been disputed, and research demonstrates that oxytocin also modulates non-social cognition [13,14].

Poor replication rates in oxytocin research, paralleling many other areas of the behavioral sciences [15], have been largely attributed to methodological issues and poor understanding of the mechanisms of oxytocin action. Although efforts have been made to address these limitations – in terms of better understanding of intranasal oxytocin administration [16–18], identifying the dose–response of intranasal oxytocin [19–21], and improving study design [22,23] – the lack of an overarching theory that accounts for the function of oxytocin across a range of contexts has hindered conceptual replication and generalizability [24]. As mentioned above, it was originally hypothesized that oxytocin facilitates prosocial behavior. Although the original study [25] that popularized this theory has been the subject of fierce methodological critiques (e.g., [26]), the concept of a neuromodulator that influences positive, but not negative, social behavior is difficult to reconcile with the broader literature, such as the effect of oxytocin on maternal aggression [27]. Moreover, instead of being based on a broader theoretical framework that could be applicable to general human behavior (e.g., evolutionary theory), this theory was primarily based on a limited set of past results. Such an approach can hinder the abductive scientific process (i.e., drawing conclusions from an incomplete set of possible observations) and consequent conceptual replication has been disputed, and research demonstrates that oxytocin also modulates non-social cognition.

Highlights
Several studies on oxytocin could not be replicated, and this has been attributed to methodological limitations. Although this is an important issue, the impact of the lack of an overarching theory has yet to be recognized.

- Oxytocin is conventionally considered to be a social hormone, but more recent work suggests that it also modulates non-social cognition and behavior.
- Oxytocin facilitates the processing of social and non-social sensory cues that are crucial for survival.
- Oxytocin receptor location and oxytocin release patterns govern the diverse but coordinated actions of oxytocin on physiology and behavior.
- Oxytocin signaling changes across development to support the different environmental pressures at each developmental stage.

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Reconceptualizing the Role of Oxytocin Using an Ethological Approach

One example of a general framework that is emerging in the medical sciences is the use of an evolutionary perspective [28]. Although evolutionary perspectives can help to uncover why a phenotype evolved, they cannot easily answer how a phenotype operates. Answering these two interrelated ‘how’ and ‘why’ questions can help to uncover a rich synergistic understanding of oxytocin that would not be possible by answering each of these questions alone [29]. A classic ethological approach to generate a deeper understanding of phenotypes is Nikolaas Tinbergen’s ‘four questions’ framework [30]. These reciprocal questions are: (i) how did this phenotype evolve? (ii) How does this phenotype help survival? (iii) What is the physiological cause of this phenotype? (iv) How does this phenotype develop in the individual? The first two questions address evolutionary explanations whereas the second two address proximate explanations. Notably, these four questions consider not only the expression of a phenotype at a given moment but also the sequence of events that give rise to the phenotype. Tinbergen originally formulated these questions for behavioral phenotypes in animals; however, they have more recently been applied to several human characteristics, such as hormonal phenotypes [31], psychiatric conditions [32], and social behaviors [29].

In this article we review oxytocin through the lens of Tinbergen’s four questions. In light of the two proximate and two evolutionary explanations for the role of oxytocin in behavior and physiology, we argue that the role of oxytocin in behavior and cognition is best characterized as allostatic because it facilitates adaptation, consolidation, and stability through changing environments. Unlike Cannon’s original description of homeostasis [33], which refers to moment-to-moment post hoc physiological adjustments to the environment and static physiological set-points, allostatic accounts for anticipation of changes in the environment that helps to ensure the stability of the system – by integrating prior knowledge with current information to modulate behavior and adjust physiological set-points based on environmental demands (Box 1) [34].

Box 1. The Difference between Allostasis and Homeostasis

Allostasis and homeostasis both provide accounts for the regulation of physiological systems, but there are two crucial differences between Walter Cannon’s original homeostasis proposal [33] and allostatic [34]. First, allostatic suggests that organisms can anticipate future changes in the environment and make appropriate adjustments before they occur. Second, physiological set-points can be adjusted to better suit the environmental conditions within an allostatic system. To illustrate this we use energy metabolism as an example. A classical homeostatic system makes post hoc adjustments to return a system to a static set-point, such as eating in response to the detection of energy deficits so as to reach a predetermined metabolic activity level. By contrast, an allostatic system anticipates future environmental changes (e.g., by associating an environment with low energy opportunities) and adjusts metabolic activity via behavior and physiology to better cope with predicted change. Allostasis and homeostasis are not exclusive processes because they can operate complementarily [36]. Although predicting future conditions is efficient over the long term, prediction errors are certain to occur on occasion, especially when conditions rapidly change unpredictably. Thus, homeostasis is necessary to perform post hoc corrections to address prediction errors. However, the sensitivity of this correction is dependent on prior predictions.

Of course, descriptions of homeostasis have been updated since Walter Cannon’s original proposal to include anticipatory responses and adjustable set-points [34]. In light of more modern interpretations, it would be technically correct to use the term ‘homeostasis’ to describe a system that includes anticipatory responses and adjustable set-points; however, here we use the term ‘allostatic’ to avoid potential confusion between the classic and more recent interpretations of homeostasis.
model of oxytocin, which recognizes both its physiological and psychological actions, contains four key cognitive and behavioral allostatic components: oxytocin-mediated sensing, learning, prediction, and response (Figure 1). Oxytocin system impairments can influence any or all of these four cognitive and behavioral allostatic components, and this has implications for several psychiatric disorders.

How Did the Oxytocin System Evolve?
Identifying the physiological and behavioral effects of oxytocin that are highly conserved across species can help to clarify its purpose. Novel regulatory circuits develop from older circuits [35], and it therefore follows that unraveling the origins of a circuit can provide a better understanding of its present role. Thus, to help to decipher the role of oxytocin in human social behavior, it is instructive to characterize its evolutionary history (i.e., phylogeny). Oxytocin-like peptides are at least 600 million years old [36], and the precursor to mammalian oxytocin arose before vertebrates diverged from invertebrates [37]. Vasopressin shares its ancestry with this precursor, which is reflected by its structural similarity to oxytocin and the affinity of oxytocin for the V1A vasopressin receptor [38]. Oxytocin-like signaling influences behavioral responses to changing environments in organisms with relatively unsophisticated nervous systems that shared ancient common ancestors with humans. For instance, straightforward associative learning paradigms demonstrate that wild-type roundworms (Caenorhabditis elegans) can learn to associate particular environments with aversive properties. However, roundworms lacking an oxytocin homolog (nematocin) and its receptor fail to demonstrate the same degree of avoidance after

Figure 1. An Allostatic Model of Oxytocin. This account recognizes both the physiological and psychological actions of oxytocin. It contains four cognitive and behavioral components (green rectangles): oxytocin-mediated sensing, learning, prediction, and response. Two key physiological components are also represented in this model (yellow ellipses): vital physiological parameters and physiological adjustments. The oxytocin system facilitates the adjustment of sensing and response set-points, and also assists learning and prediction to better adapt to changing environments.
pre-exposure to the aversive stimulus [39]. This points to an error in the allostatic loop because mutant roundworms could not integrate current sensory information with prior knowledge owing to a deficit in associative learning. The role of oxytocin in adjusting to changes in environmental conditions, based on prior learning, seems to be conserved in humans [40].

Rapidly learning which behaviors best suit a new environment is integral to the success of an organism. This has been demonstrated in neurally unsophisticated invertebrate organisms such the roundworm, as described above [39], in which nematocin is expressed in sensory neurons that detect thermal or mechanical changes in the environment [39,41]. Oxytocin also influences memory and learning processes in a range of vertebrates [42,43]. For instance, compared to wild-type mice, oxytocin receptor (OXTR) knockout mice are deficient in reversal learning, which requires behavioral flexibility as well as the ability to learn new behavioral strategies so as to quickly adapt to changes in the environment [44]. In humans, intranasal oxytocin administration facilitates rapid adaptation to social fear signals, which has survival value in rapidly changing environments [45]. However, although the effects of oxytocin administration on memory and learning in humans have been less consistent than in animal research [42,46], these findings have been corroborated by analysis of oxytocin pathway gene expression in the human brain, which reported that regions with increased OXTR gene expression are associated with brain networks underlying learning processes [47], perhaps pointing to the need to improve intranasal administration methods. Behavioral flexibility is a crucial element of an allostatic system because it facilitates adaptive behavioral strategies to better suit a change in environmental conditions.

Oxytocin-like mediation of tissue contraction can be observed in invertebrates, such as earthworms (Eisenia fetida) and leeches (Whitmania pigra), where injection of an oxytocin-like peptide (anetocin) regulates the contraction of the earthworm gut and uterus homolog [48,49]. A similar physiological response has also been observed in sea squirts, where an oxytocin-like peptide was shown to influence osmoregulation via syphon contraction [50]. The role of oxytocin in osmoregulation is conserved in humans where it acts on oxytocin receptors in the cardiovascular system and the kidneys [51]. The effects of oxytocin on smooth muscle contraction are also conserved in humans, and oxytocin-mediated smooth muscle contractions play a role in human parturition, copulation, reproduction, gastric emptying, and cardiovascular regulation [2]. Therefore, although oxytocin seems to have first assisted basic tissue contraction, evolutionary pressures appear to have coopted the contractile effects of oxytocin for a broad range of physiological systems in mammals that underlie allostasis. Crucially, the effects of oxytocin on smooth muscle contraction seem to operate with adjustable set-points depending on situational demands (e.g., digestion, birth, lactation) [52–55], which is a key attribute of an allostatic system.

Long-range axonal projections from oxytocin and oxytocin-like neurons to other regions of the brain are only consistently found in complex vertebrates such as mammals [56] and reptiles [57]. Less complex basal vertebrates, that only show stereotypic reproductive behaviors, demonstrate unspecific central release into the cerebrospinal fluid (CSF) [58]. Together, this has led to speculation that long-range axonal projections to various brain regions, which facilitate the precise regulation of complex and sequential behaviors that are especially apparent in mammals, appeared more recently in our evolutionary history [59]. Altogether, the modulatory effects of oxytocin on complex mammalian social behaviors has come an extraordinarily long way from relatively basic functions such as the osmotic response in the sea squirt and gustatory learning in the roundworm. Despite this wide gamut of complexity, a common thread throughout the evolutionary history of oxytocin is its regulatory role. Our allostatic model proposes that the oxytocin system supports the processing of stimuli to promote survival and future acclimation to environmental shifts (Figure 1). Such stimuli are often, but not always, socially relevant. The
high conservation of the oxytocin system points to its important function in behavior and physiology. Although the oxytocin system plays a role in energy regulation via thermoregulation, appetite, and metabolic homeostasis [60], this system has also evolved to influence learning and behavior, which is an efficient means of regulating energy by anticipating and influencing the future via behavioral responses. To use a food foraging example, it is more efficient over the long run for an organism to predict locations with abundant food sources by integrating past experience than to use a trial-and-error strategy or a random selection process.

How Does the Oxytocin System Promote Reproduction and Survival?
Observational methods, such comparative analyses between species and understanding how the oxytocin system enhances reproduction and survival, can provide important clues to how the oxytocin system evolved in humans. In this section, we discuss how the role of oxytocin in improving prediction and shifting physiological set-points enhances present-day survival and reproduction.

Mating behaviors play an instrumental role in species propagation, and are therefore a prime candidate for the rapid selection of traits and the signaling systems that support them. There is evidence for an ancient role of the oxytocin system, and an oxytocin-like peptide (conopressin) in the great pond snail (*Lymnaea stagnalis*) plays a key role in stereotypic mating behaviors such as male copulation via gonadal contraction [61], mirroring the role of oxytocin in human ejaculation [62]. Similarly, nematocin in the roundworm modulates mating behaviors, including mate search and mate recognition [41]. The role of oxytocin on mating-related behaviors has been conserved in humans because oxytocin facilitates complex romantic bonds. For instance, intranasal oxytocin increases the perceived attractiveness of romantic female partners by heterosexual men [63], and modulates social distance between heterosexual males and females [64].

The most striking example of the role of oxytocin in offspring care is that oxytocin-knockout female mice cannot eject milk and feed their offspring [65]. Despite the well-known role of the oxytocin system in parturition, oxytocin-knockout mice can still give birth to viable young [66], suggesting that other systems work redundantly. Oxytocin has been shown to play an important role in mammalian mother–offspring behavior in several non-human species such as mice [67], prairie voles [68], and sheep [69]. In fact, the role of oxytocin in social behavior was first suggested in 1968 by Klopf and Klopf in relation to goat maternal behavior. The physiological role of oxytocin in parturition was well known at the time. However, in what was then an unorthodox idea, the Klopfers speculated that ‘this hormone [oxytocin], which apparently brings on the final uterine spasms which deliver the kid, is also implicated in the induction of maternal behavior’ ([70], p. 865). This prescient conclusion regarding the role of oxytocin in mammalian social behavior was confirmed by research decades later. At first glance, the ‘classic’ reproductive functions of oxytocin appear to be reflexive and homeostatic, rather than allostatic. However, the oxytocin system adapts to support the adjustment of physiological set-points (e.g., blood volume, natriuresis) to better cope with the situational demands of pregnancy, parturition, and lactation [71].

Oxytocin also plays an important role in appetite and feeding, which are crucial survival processes. For instance, antagonism of OXTR increases meal sizes in rodents [72], and OXTR knockout mice are heavier than wild-type mice [73]. Moreover, oxytocin is produced in the magnocellular neurons of the paraventricular nucleus of the hypothalamus, a region of the brain that is also involved in food intake regulation [74]. Oxytocin administration has been found to reduce food intake [75] and improve gastric motility [76] in humans, an effect that is most likely driven by oxytocin receptors located in gastrointestinal tract smooth muscle [77]. Although a relatively recent meta-analysis [78] concluded that oxytocin administration reduces feeding in
animals, there was no significant effect in humans, and this may reflect study heterogeneity or issues with intranasal oxytocin administration methods. Relatedly, a recent proposal using a life-history theory framework suggests that oxytocin is central to the allocation of limited resources, including energy [79].

The need to monitor the environment and adapt to changes is crucial for survival. Converging evidence suggests that oxytocin facilitates the processing of sensory cues such as temperature [80], hunger [81], pain [82,83], and thirst [81,84]. The altered processing of internal states are likely due to shifting of physiological set-points [82,83,85], which is an important element of allostatic systems [86]. For instance, increases in circulating oxytocin enhance tolerance to pain sensation in newborn mammals, which may be protective against stress dysregulation later in life. This analgesic effect may have translational value, and oxytocin treatment shortly after trauma in humans is protective against the later development of post-traumatic stress disorder [87]. Altogether, by mediating senses that contribute to learning, future prediction, and response processes (Figure 1), the oxytocin signaling system is well suited to facilitating survival.

How Does Oxytocin Exert Its Effects?

In mammals, oxytocin is predominately synthesized by magnocellular neurons in the supraoptic and paraventricular nuclei within the hypothalamus [88] (Figure 2). The supraoptic and paraventricular nuclei have magnocellular neuronal axons that project to the posterior pituitary, where oxytocin is stored for peripheral release to modulate the activity of several peripheral systems. Magnocellular long-range axonal neurons also project to several forebrain regions for central release, including the prefrontal cortex, arcuate nucleus, and hippocampus [89,90], to facilitate local delivery of oxytocin to several specific sites in the brain where it can modulate a diverse range of behaviors [88,89,91,92].

Given the relatively large amount of oxytocin that can be released dendritically [93], and the long half-life of oxytocin in the central nervous system (~20 minutes) [84] compared to the 2 minute half-life in blood, it is possible that centrally released oxytocin can diffuse to forebrain areas that are not directly reached by axonal projections [95–97]. Dendritically released oxytocin from the paraventricular nucleus has also been shown to travel to the sensory cortices either via diffusion or the CSF [98,99]. However, there has been more recent dispute regarding the effectiveness of diffusion via dendritic release for meaningful quantities of oxytocin delivery to sites that are distant from the hypothalamus and axonal projections [100]. This suggests that delivery to these distant sites might be largely carried out by axonal release via long-range projections. Oxytocin is also synthesized in parvocellular neurons of the paraventricular nucleus, with projections to the midbrain, spinal cord, dorsal vagal complex [92], and magnocellular neurons in the supraoptic nucleus [56]. Central release is mediated by both parvocellular and magnocellular neuronal axon release, where oxytocin can prime its own release [101], thus explaining the long-lasting behavioral effects of oxytocin.

The location of oxytocin receptors, the combination of axonal and dendritic oxytocin release, and the timing and coordination of oxytocin secretion contribute to the diverse, allostatic effects of oxytocin. Although the sites of oxytocin synthesis and axonal pathway destinations are similar across mammalian species, the sites of oxytocin receptor expression differ significantly [102]. The site of expression can evolve faster than axonal pathways – highlighting the role of extrasynaptic release – allowing relatively rapid behavioral acclimations to changes in the environment [103]. Only small variations in oxytocin receptor gene promoter elements are necessary to modify expression patterns, and this can facilitate rapid behavioral acclimations. The capacity to
independently regulate central and peripheral secretion \[104\], and to modulate peripheral effects simply by adjusting the release schedule of oxytocin (e.g., pulsatile secretion during lactation \[105\] versus continuous secretion for natriuresis \[106\]), as well as the widespread delivery of oxytocin in the brain and periphery, have important implications for the coordination of physiology and behavior. Diverse axonal projection destinations also help to regulate a diverse range of behaviors \[92\]. For instance, optogenetically mediated stimulation of hypothalamic neurons in rats induces specific oxytocin release in the central amygdala via axonal projections \[89\]. Recent human evidence derived from two post-mortem datasets indicates considerable diversity in the role of oxytocin in psychological processes, and there are associations between \(OXTR\) expression patterns in human brain and the brain circuits that underlie anticipatory, appetitive, and aversive mental states (Figure 3). Of >20 000 protein-coding genes, the expression pattern of \(OXTR\) was among the top 0.5% strongest correlations with these mental state patterns \[47\].

**How Does the Role of Oxytocin Change across Development?**

For our ancestors, each stage of development would have been associated with unique behavioral challenges related to survival and reproduction. For newborns and children, surviving the
The expression of an oxytocin-like peptide in early invertebrate development indicates that oxytocin signaling was early in the ontogenesis of this evolutionary ancient group of organisms. The central nervous system of sea squirt larvae, which is made up of only ~100 neurons, expresses oxytocin-like genes [107]. Oxytocin-related peptides are also expressed in the larval forms of roundworms [41] and red flour beetles (Tribolium castaneum), and the latter display increased expression compared to adults [108]. Oxytocin neuron development is highly conserved in vertebrates because they are generated early in embryonic development from the third ventricle prenatally in several mammalian and non-mammalian species including humans, rodents, fish, and chickens [109]. Oxytocin is first synthesized in the human brain prenatally and is detected at ~14 weeks of gestation [110], suggesting that this neuropeptide plays a role in fetal physiology and development. Unlike oxytocin receptor expression levels in the brain, which vary across the lifespan, the number of oxytocin neurons remains fairly similar from gestation to adulthood [109].

Research supports an analgesic and hypoxia-buffering role of oxytocin in early life during parturition [83,111], providing a possible explanation for fetal development of the oxytocin system – to
help to cope with stresses associated with childbirth. Relatedly, oxytocin may also assist with the expulsion of fluid from the lungs after birth [112], which assists in the fetal transition to independent respiration outside the womb. In terms of oxytocin release, the characteristic pulsatile release of oxytocin appears from birth in humans [113]. For newborns, oxytocin has been shown to trigger feeding behaviors, at least in mice [114]. In toddlers, evidence is emerging for the role of oxytocin in social behavior [115] and its stress-buffering effect [116], which has been more thoroughly investigated in adults. Scholars have identified specific ‘infant’, ‘pubertal’, and ‘adult’ patterns of oxytocin receptor expression in the brain across mammalian development, and both the infant and pubertal patterns are characterized by transient oxytocin receptor expression during these developmental periods [109,117,118]. These oxytocin binding patterns across development seem to vary between species [119], and this is consistent with species-specific evolutionary pressures.

Several lines of evidence indicate that environmental pressures on oxytocinergic signaling early in life impact on later physiology and behavior. Remarkably, it has been demonstrated that oxytocin facilitates cortical development in response to sensory experience in neonatal non-human mammals [98]. Specifically, it was shown that early-life sensory deprivation reduced oxytocin neuron firing in the paraventricular nuclei (PVN) as well as oxytocin release from the PVN, which is indicative of the crucial role of sensory experience in early life and that oxytocin signaling plays a role in this process. Moreover, oxytocin administration rescued the detrimental effects of sensory deprivation. In another example, nursery-reared rhesus monkeys demonstrate lower concentrations of oxytocin in CSF compared to mother-reared rhesus monkeys [120]. Oxytocin also plays an instrumental role in learning during development, for both social [121] and non-social cues [119], which impacts on future prediction of conditions and behavioral responses (Figure 1). Moreover, CSF levels of oxytocin in human neonates are positively associated with social engagement behaviors at 3 months of age [116], which is a critical early period for learning social communication. Although causation cannot be inferred from these results, subsequent work in macaque neonates demonstrated that oxytocin administration increases affiliative communicative gestures compared to placebo [122]. The highest levels of oxytocin binding in the prenatal and postnatal mouse around the period of parturition are also found in tissue regions that regulate physiological regulation and stress responses [123].

Why would evolution select particular biological systems to be especially sensitive to the environment, whereas others remain largely innate during critical periods of development? Systems that can be shaped by the environment require flexibility. Success for our ancestors was dependent on the ability to quickly adapt to changing environments, and this is thought to have been largely driven by cumulative learning from others [124]. The sensitivity of the oxytocin system to early-life stressors may be a tradeoff for its benefits on learning, prediction, and response. In other words, the extraordinary ability of humans to adapt to changing environments may come at the cost of psychiatric disorders that emerge when the biological systems that support learning, such as the oxytocin system, are impaired [125].

An Integrative Interpretation of the Role of Oxytocin via a Tinbergenian Approach

Answering Tinbergen’s four interrelated questions reveals a deep synergistic conception of behaviors and biological processes that is difficult to achieve by addressing each of these questions in isolation [126], namely, that the oxytocin system facilitates allostasis by anticipating change in the future and by adjusting physiological set-points to better cope with change (Figure 4, Key Figure). In terms of evolutionary explanations, several physiological and behavioral functions of oxytocin that support allostasis, particularly features that improve anticipation of future needs, are highly conserved across vertebrate and invertebrate species [39,40,44,45,50,51].
The oxytocin system also supports reproductive and survival functions by helping to adjust physiological set-points to better suit current needs. In terms of proximate explanations, the location of oxytocin receptors in the brain, and the combination of axonal and dendritic oxytocin release in the brain, support varied behaviors underlying sensation, reaction, learning, and prediction. In addition, the role of oxytocin in early-life learning and its changing function over the lifetime reflect how this neuropeptide supports flexible behaviors and shifting demands depending on the life-period.

Concluding Remarks
Close examination of the proximate and evolutionary explanations of the role of oxytocin suggests that it evolved as a hormone that promotes allostasis, which is the ability to maintain stability through change. This is consistent with the popularized role of oxytocin in social behavior because these behaviors can be used to maintain allostasis, and also recognizes the broader roles of oxytocin, beyond social behavior, in situations where survival and adaptation may be in conflict with prosocial responses. Although the concept of allostasis shares many similarities with homeostasis, allostasis recognizes that organisms can anticipate future challenges and adapt accordingly.

Outstanding Questions
What are the dose-dependent effects of intranasally administered oxytocin on allostatic processes? The commonly administered dose is 24 international units, but there is little evidence that this dose is the most efficacious.

Central oxytocin receptor (OXTR) patterns in human adults have been recently identified, helping to clarify the functional significance of oxytocin signaling. However, do OXTR expression patterns change across the lifespan? If so, what is the functional significance of these changes, and are they related to allostatic processes?

Where does intranasally administered oxytocin travel after administration? Preliminary evidence using a novel OXTR positron emission tomography tracer suggests that intranasally administered oxytocin in rodents reaches the olfactory bulb of rodents; however, an OXTR radiotracer has yet to be developed for human use. Identifying the destination of intranasally administered oxytocin can help to clarify its effects and confirm that intranasally administered oxytocin reaches the brain via a nose-to-brain route.

How does oxytocin signaling interact with other signaling systems to exert its effects on allostatic processes? For instance, OXTR is highly coexpressed with dopamine D2 and D5 receptors in the human brain. This suggests that dopamine signaling is likely to play an important role in oxytocin signaling via the reward of accurate allostatic prediction.

Despite the documented sex-specific roles of oxytocin across various domains (e.g., empathic accuracy, stress response, neural activity), the majority of oxytocin research has been conducted in males. Are the effects of oxytocin on allostatic processes sexually dimorphic? Do these sexually dimorphic effects change over the lifespan?
changes in the environment and respond accordingly through both physiological and behavioral strategies (Box 1 and Figure 1). Indeed, preliminary research has shown that intranasally administered oxytocin may improve the ability to anticipate the actions of others [128] and facilitate cooperative behavior [129], which could occur through improved theory of mind capability and neurobiological synchrony [130]. Although it has been proposed that oxytocin circuits contribute to learning and prediction-based impairments in autism [125], prior theories tend not to account for the non-social effects of oxytocin.

How does one neuropeptide influence such a diverse range of behaviors centered on the singular goal of allostasis? The unique properties of oxytocin signaling may answer this question. Oxytocin is a relatively unique messaging system in that it is almost exclusively produced in the hypothalamus but has a wide variety of actions both peripherally and centrally, which can occur simultaneously. Instead of evolving a new messenger system, evolution seems to have co-opted the ancestral oxytocin system by adjusting its release schedule and by engineering receptors that are sensitive to specific release schedules. Put another way, instead of developing a novel radiofrequency band for a new set of broadcasts, evolution uncovered a way to communicate using Morse code. Given that oxytocin exerts its effects both peripherally and centrally, this system is well placed to coordinate diverse physiological and psychological actions that center on specific goals [131]. Allostasis also requires the coordination of several parallel processes because allostatic systems need to anticipate future changes in environmental conditions and to make the required adjustments, which are often behavioral. Our allostatic model highlights the crucial role that oxytocin plays in learning and plasticity, which has implications for the treatment of social difficulty. Manipulation of the oxytocin system via intranasal administration could modulate the core features of learning, interoception, and prediction to improve social outcomes.

In this paper we propose that the primary role of oxytocin in behavior is to facilitate stability in changing environments, rooted in its evolutionary origins as a system to promote survival, and operationalized through circuits guiding learning, prediction, and response. At present, some aspects of our theoretical framework are speculative, particularly those drawn from a relatively small pool of human oxytocin studies whose outcomes are sometimes inconsistent. However, the main goal of our proposal is to stimulate these emerging lines of research. A greater research
focus is required on understanding the nuanced effects of oxytocin using various research approaches to investigate the diverse role that this messaging system has on different peripheral and central processes (see Outstanding Questions). Such work will extend our understanding of how this ancient neuropeptide modulates our response to both current and anticipated changes in the environment.

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