

# An integrated framework for the role of oxytocin in multistage social decision-making

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Interest in the effects of oxytocin on social behavior has persisted even as an overarching theory describing these effects has remained largely elusive. Some of the earliest studies on the effects of oxytocin on social decision-making indicated that oxytocin might enhance prosocial actions directed toward others. This led to development of the prosocial hypothesis, which stipulates that oxytocin specifically enhances prosocial choices. However, further work indicated that oxytocin administration could elicit antisocial behaviors as well in certain social situations, highlighting the importance of context-dependent effects. At least two prominent hypotheses have been used to explain these seemingly contradictory findings. The social salience hypothesis indicates that the effects of oxytocin can be conceptualized as a general increase in the salience of social stimuli in the environment. Distinctly, the approach/withdrawal hypothesis stipulates that oxytocin enhances approach behaviors and decreases withdrawal behaviors. These phenomenologically motivated hypotheses regarding the effects of oxytocin on social behavior have created controversies in the field. In this review, we present a multistage framework of social decision-making designed to unify these disparate theories in a process common to all social decisions. We conceptualize this process as involving multiple distinct computational steps, including sensory input, sensory perception, valuation, decision formulation, and behavioral output. Iteratively, these steps generate social behaviors, and oxytocin could be acting on any of these steps to exert its effects. In support of this framework, we examine both behavioral and neural evidence across rodents, non-human primates, and humans, determining at what point in our multistage framework oxytocin could be eliciting its socially relevant effects. Finally, we postulate based on our framework that the prosocial, social salience, and approach/withdrawal hypotheses may not be mutually exclusive and could explain the influence of oxytocin on social behavior to different extents depending on context.

## KEYWORDS

approach/withdrawal hypothesis, multistage framework, oxytocin, prosocial hypothesis, social behavior, social salience hypothesis

## 1 | INTRODUCTION

Substantial research interest into the effect of oxytocin (OT) on social behavior persists across a variety of organisms, including rodents, non-human primates, and humans, among others. Early in this line of research, it appeared as though OT administered to humans promoted positive and prosocial behaviors (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) as well as attention to certain facial areas, particularly the eyes (Guastella, Mitchell, & Dadds, 2008). However, further studies across humans (De Dreu et al., 2010; Shamay-Tsoory et al., 2009) and non-human primates (Chang, Barter, Ebitz, Watson, & Platt, 2012; Ebitz, Watson, & Platt, 2013; Landman, Sharma, Sur, & Desimone, 2014) indicated that the effects of OT are far more complicated and less categorically defined than originally thought and also include the enhancement of negative social emotions, suppression of attentional allocation to images containing negatively valenced social information, and context-specific self-regarding actions (Bartz, Zaki, Bolger, & Ochsner, 2011). The observed diversity in the effects of OT has led to divergent phenomenologically motivated hypotheses as to the impact of OT on social cognition. These include the prosocial hypothesis (Macdonald & Macdonald, 2010; Meyer-Lindenberg, 2008), which states that OT increases positive social behaviors such as trust and altruism, the social salience hypothesis (Shamay-Tsoory & Abu-Akel, 2016), which states that OT instead seems to enhance the salience of social cues more broadly, and the approach/withdrawal hypothesis (Harari-Dahan & Bernstein, 2014; Kemp & Guastella, 2010, 2011), which states that OT increases approach behaviors and decreases withdrawal behaviors.

While these hypotheses have been useful in conceptualizing some of the seemingly contradictory effects of OT both within and across species, more emphasis is needed on building a comprehensive framework and on fully integrating how these disparate hypotheses may relate to each other. Such a framework could be useful in providing a more unified theory concerning the effects of OT on social behavior and could help elucidate the effects that OT may have at different stages of social decisions. Additionally, a particularly useful framework should be based not only on the observed behavioral effects of OT in humans, but also on work across humans and other mammalian animal models that attempts to elucidate the effect that OT has on the central nervous system (CNS) in a way that is not possible in studies of human participants. Such studies can drive further mechanistic insight into the effect of OT on social behavior.

In this review, we will put forth a unifying framework encompassing the similarities and meaningful differences between the various theories of the effects of OT on social cognition. In order to do this, we will focus on the effects that OT could have at various computational stages involved universally during social decision-making. These stages include sensory input, sensory perception, valuation, decision formulation, and behavioral output. Each existing theory concerning the effect of OT on social cognition implies that OT should exert its effects over only one specific processing stage. In contrast, this framework allows placement of each theory in a continuous, unified context, in which OT can exert its modulation over multiple processing stages. For

example, while the salience hypothesis stipulates that OT should have its effects primarily during the sensory perception stage of social cognition, our framework acknowledges that OT could have its effect during multiple stages in the decision-making process, possibly integrating seemingly divergent hypotheses. After further exploring the implications of each theory in this multistage framework, we will weigh the plausibility of each according to mechanistic research regarding the effects of OT within the CNS across multiple organisms including rodents, non-human primates, and humans.

## 2 | EXISTING HYPOTHESES

### 2.1 | Prosocial hypothesis

Perhaps the earliest conceptualization of the effects of OT on social cognition stems from work done in both rodent models and humans that indicated an increase in prosocial behavior following OT administration. For example, extensive work in rodents has indicated the effects of OT not only on parturition and milk letdown (Gimpl & Fahrenholz, 2001), but also in pair bonding and maternal nurturing in both rats (Lim & Young, 2006) and monogamous prairie voles (Cho, DeVries, Williams, & Carter, 1999; Williams, Carter, & Insel, 1992). In rodents, the effects of OT at OT receptors (OXTRs) can be manipulated by injecting either OT or OT antagonists into the rodent brain. When OT is injected systemically into the ventricles of the brain, virgin female rats show nest building and grooming behaviors not typical of nulliparous rats (Pedersen, Ascher, & Monroe, 1982), while systemic injection of OT antagonists into the ventricles of the brain delays the onset of maternal behaviors following parturition (Fahrbach, Morrell, & Pfaff, 1985). Together, this early evidence from rodent models is consistent with the notion that OT promotes prosocial behaviors that are strongly associated with reproductive fitness.

Further research involving the administration of intranasal, exogenous OT to humans seemed to indicate that the prosocial effects of OT might reach even further than positive modulations of pair bonding and maternal behavior (that is, beyond the means to achieve reproductive fitness). Early findings in the human literature indicated nearly universal prosocial effects following OT administration, including positive effects on trust (Kosfeld et al., 2005), emotion recognition (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), and altruism (Zak, Stanton, & Ahmadi, 2007). Thus, early findings regarding the effects of OT on social behavior are largely consistent with the theory that OT increases multiple forms of prosocial behavior across species.

### 2.2 | Social salience hypothesis

Although early findings appear to suggest that OT elicits prosocial behaviors, it has become clear that the effects of OT are often noticeably context dependent. For example, the positive effects of OT on trust (Kosfeld et al., 2005) are abolished when the other individual appears untrustworthy (Mikolajczak, Pinon, Lane, de Timary, & Luminet, 2010) or is unknown (Declerck, Boone, & Kiyonari, 2010).

An even stronger argument against the prosocial hypothesis of OT comes from findings that OT often shows negative effects on certain social behaviors. For example, further studies into the effects of OT in humans indicate that OT can increase feelings of envy and schadenfreude during competitive gameplay (Shamay-Tsoory et al., 2009), elicit defensive behaviors toward out-group members (De Dreu et al., 2010), decrease trust and cooperation in borderline personality disorder (Bartz, Simeon, et al., 2011), and facilitate protective responses to aversive social stimuli (Striepens et al., 2012). Furthermore, although OT promotes pair bonding in female prairie voles, female voles treated with OT early in development show aggression and mate-guarding behaviors as well as reduced social behaviors (Bales & Carter, 2003). Supporting these assertions concerning context dependency, exogenous OT infused into the amygdala of golden hamsters has been shown to increase maternal aggression (Ferris et al., 1992), and OT release has been found to correlate with maternal aggression behavior in lactating rats under a maternal defense test, although these effects of OT have not been reported in virgin female rodents (Bosch, Meddle, Beiderbeck, Douglas, & Neumann, 2005).

In order to resolve these complex findings, researchers have theorized that instead of universally enhancing prosocial behaviors, OT may facilitate recognition of and attention to social cues in the environment, regardless of whether they are positive or negative in valence. This is commonly referred to as the social salience hypothesis of OT. Importantly, not all canonical effects of OT are considered explicitly prosocial and may be equally related to attentional mechanisms. While not explicitly at odds with the prosocial hypothesis, OT has been found to increase looking to the eye region of faces and encourage gaze following in rhesus macaques (Dal Monte et al., 2017; Dal Monte, Noble, Costa, & Averbach, 2014; Putnam, Roman, Zimmerman, & Gothard, 2016) and humans (Guastella et al., 2008), indicating that OT could be acting on neural circuits involved in social attention.

Recent work in rodents has also supported the social salience hypothesis, as OT has been found to enhance social recognition by modulating early olfactory processing in adult rats (Oettl et al., 2016) and facilitating maternal behavior by balancing the magnitude and timing of excitation and inhibition specifically in left auditory cortex in female rats (Marlin, Mitre, D'Amour, Chao, & Froemke, 2015) (but see (Guastella, Carson, Dadds, Mitchell, & Cox, 2009), which suggests that OT does not impact early perceptual processing of visual social stimuli in humans). Together, these findings suggest a role of OT not so much in facilitating prosocial behavior, but in more broadly facilitating the perception and recognition of behaviorally important sensory inputs, like stimuli with social importance, in the surrounding environment that promote the need for behavioral adjustment.

Still, research across humans and non-human primates has largely reported that the effects of OT are dependent on the value of social stimuli, arguing against a pure form of the salience explanation that is not signed with respect to value. First, numerous studies have indicated that OT specifically enhances attention to the eyes and often reduces attention to areas such as the mouth (Dal Monte et al., 2014, 2017; Guastella et al., 2008), which is at odds with the notion that OT

increases broad salience of social cues and seems to suggest that OT selectively orients attention to informative, and therefore valuable, social cues. Additionally, although OT was found to increase gaze to the eye region in humans irrespective of the emotion depicted (Gamer, Zurowski, & Buchel, 2010), OT had divergent effects on amygdala activity to faces depicting different emotions in the same study (Gamer et al., 2010). Other similar studies have further complicated these findings. In a study that found that OT increased protective responses to aversive social stimuli in males, while amygdala activation was reduced following intranasal OT administration, OT also facilitated left insula responses as well as functional coupling between the left amygdala, left insula, and left inferior frontal gyrus (Striepens et al., 2012), suggesting that the effects of OT may have a more concerted effect on neural circuitry rather than a simple decrease in amygdala activation. Other work in humans indicated behavioral differences that depend on valence, including a specific increase in the recognition of positive sex and relationship words (Unkelbach, Guastella, & Forgas, 2008), a specific increase in the recognition of positive facial expressions (Marsh, Yu, Pine, & Blair, 2010), and a specific decrease in aversion to angry faces during an associative learning task (Evans, Shergill, & Averbach, 2010).

Research from non-human primates corresponds to these findings, as OT has been found to blunt the emergence of a vigilance state when dominant faces are presented, attenuate attention to negative facial expressions, and increase performance in a reward-guided saccade task when distracting threat or fear faces are concurrently presented (Ebitz et al., 2013; Landman et al., 2014; Parr, Modi, Siebert, & Young, 2013). Work in rhesus macaques has also indicated that a systemic increase of OT selectively increases gaze to a conspecific only in the context of prosocial actions (Chang et al., 2012). These findings are not entirely unanimous, however, as OT has also been observed to increase the ability to recognize fear but not other emotions in humans (Fischer-Shofty, Shamay-Tsoory, Harari, & Levkovitz, 2010). Still, these findings have indicated the possibility of a modified form of the salience hypothesis, in which OT increases the salience of positive social cues and decreases the salience of negative social cues (Averbach, 2010). However, this modified hypothesis alone does not explain why OT would drive negative social emotions and behaviors in humans in certain experimental contexts (De Dreu et al., 2010; Shamay-Tsoory et al., 2009).

### 2.3 | Social approach/withdrawal hypothesis

While much of the previous behavioral and physiological literature across species can be interpreted using the social salience theory of OT, certain neural and behavioral findings complicate this interpretation and may instead support the social approach/withdrawal hypothesis. For example, attenuation of the amygdala hemodynamic response in humans across multiple paradigms, including the trust game (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008) and the viewing of emotional faces (Domes, Heinrichs, Glascher, et al., 2007; Gamer et al., 2010; Kirsch et al., 2005), cannot immediately be reconciled with the social salience hypothesis. Under the salience

hypothesis, one might expect the amygdala, a region often conceived as being involved in social perception and cognition, to instead exhibit increased activation after OT administration to enhance sensitivity to social stimuli.

Further biological evidence involving the interaction of OT and cortisol would seem to support the social approach/withdrawal hypothesis as well. When OT was administered to participants before psychosocial stress, a combination of OT and social support resulted in the lowest cortisol concentrations and the most decreased stress ratings, and OT even in the absence of social support trended toward attenuating cortisol levels (Heinrichs, Baumgartner, Kirschbaum, & Ehler, 2003). As stress is heavily associated with withdrawal behaviors, this reduction in both stress ratings and cortisol levels is consistent with the approach/withdrawal hypothesis. Correspondingly, OT has been observed to improve self-appraisals and speech performance in participants with social anxiety disorder, which the authors of the study suggest could indicate a reduction of threat-associated cognitive-processing biases (Guastella, Howard, Dadds, Mitchell, & Carson, 2009). Finally, as mentioned in the previous section, work across humans and non-human primates indicates that the effects of OT are likely valence-specific (Chang et al., 2012; Ebitz et al., 2013; Evans et al., 2010; Landman et al., 2014; Marsh et al., 2010; Unkelbach et al., 2008). Thus, this research largely suggests that OT may generally increase approach behaviors and decrease withdrawal behaviors, possibly based on the value of social stimulus or context.

The appeal of this hypothesis has even led to more hardline versions, including those which state that the effects of OT are not inherently social in nature but instead more broadly involved in enhancing approach-related behaviors (Harari-Dahan & Bernstein, 2014). However, this version of the hypothesis is not consistent with all past studies, including those that suggest that OT enhances memory for faces but not nonsocial objects (Rimmele, Hediger, Heinrichs, & Klaver, 2009) and affects arousal ratings for pictures of humans but not animals (Norman et al., 2011). In addition, even the more specific social approach/withdrawal hypothesis cannot fully explain the inverse findings observed in borderline personality disorder, in which OT is actually found to decrease trust and cooperation (Bartz, Simeon, et al., 2011).

### 3 | OT IN THE CONTEXT OF MULTISTAGE SOCIAL DECISION-MAKING

To integrate these divergent hypotheses concerning the effects of OT on social cognition and behavior, we will turn to a unifying framework taking into account all steps that must be completed for a socially motivated and oriented behavior to occur (Figure 1). First, the organism, whether it is a rodent, monkey, or human, must sense and perceive a social stimulus in its environment. We sort these processes into the two earliest steps, *sensory input* and *sensory perception*. Next, the organism must generate a set of possible behavioral choices and assign a value to each of these options. Notably, this process must exist both in deliberate decision-making paradigms, including those utilizing

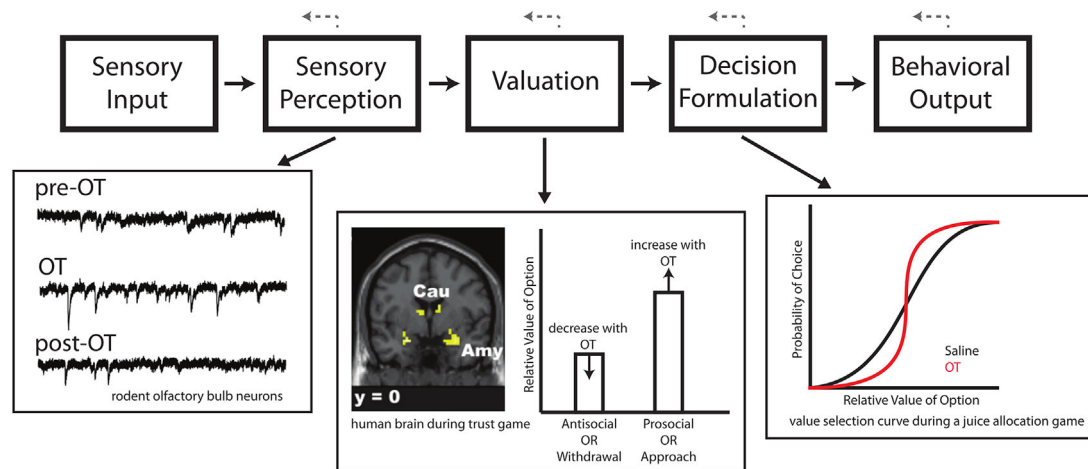
approaches from behavioral economics, as well as more unconstrained paradigms, including picture or movie viewing of a conspecific. We refer to these processes as *valuation*. The next step should be to take the entire set of behavioral options and their associated values and choose one option based on these values by a logical action-selection method. We consider this *the decision formulation step* in the generation of social behavior. Finally, the organism must perform the selected action, which we define as *the behavioral output step*. It is important to note that each of these stages could feed back to one or more previous stages to subsequently impact the next set of computations.

Importantly, OT could be acting on or gating any of these sequential processes in order to influence the final behavioral output when an organism is placed in a social situation. It is our intuition that the three aforementioned hypotheses of the effects of OT on social cognition would affect largely different stages along the pathway from sensory input to behavioral output, rather than only acting on one specific phase of processing. Examining each step in the process in the context of these hypotheses could therefore be informative in conceptualizing the implications of each theory under a unified framework.

#### 3.1 | Effects of OT on social perception

If OT were to have a facilitating effect at the social perception stage of decision-making, this would be most consistent with the social salience hypothesis, rather than the prosocial or approach/withdrawal hypotheses. Behavioral examination of early social processing of faces has yielded complicated results in human participants. Certain studies explicitly characterizing the effects of OT in early visual processing find no effect on variables including response time, accuracy of identifying angry versus happy faces, and gaze toward angry or happy faces (Guastella, Carson, et al., 2009). However, other studies in humans using attentional capture techniques do strongly suggest the modulation of early perceptual processing by OT (Ellenbogen, Linnen, Grumet, Cardoso, & Joobar, 2012), and similar studies in monkeys have also indicated the effects of OT in perceptual processing, although these studies generally find that OT diminishes the salience of distracting social stimuli in these distractor-based paradigms (Ebitz et al., 2013; Landman et al., 2014). A recent study further indicated that facial recognition ability in male infant macaques correlates with OT levels in cerebrospinal fluid later in life (Madrid et al., 2017).

Still, examining neural representation of the earliest stages of social perception in the CNS is exceedingly difficult in humans, given the temporal and spatial limitations of the typical methods available in human research. However, recent work in rodents has started to reveal the intricacies of the effect of OT in social contexts during sensory processing at a neural level. Pairing either systemic OT injection or optogenetically enhanced endogenous OT release from paraventricular oxytonergic neurons with pup calls in virgin female mice can elicit retrieval behaviors (Marlin et al., 2015). Utilizing a combination of molecular and electrophysiological techniques, it was determined that OXTR expression (Figure 2a) as well as neural responses to pup calls



**FIGURE 1** The effects of OT as conceptualized via a multistage model of social decision-making. The top row of the schematic shows all necessary steps that must take place during social decision-making, including sensory input, sensory perception, valuation, decision formulation, and behavioral output. The dotted arrows illustrate that each of these stages could feed back to one or more previous stages to subsequently impact the next set of computations. Below are panels depicting the potential behavioral or neural effects of OT on sensory perception, valuation, and decision formulation steps in the social decision-making process. The panel to the left shows the effect of OT on olfactory bulb neurons in rodents, indicating a potential role for OT in amplifying sensory perception of social odors. This panel shows a voltage-clamp trace, with a higher amount of excitatory postsynaptic potentials observed in olfactory neurons during optogenetically stimulated release of OT from the paraventricular nucleus of the hypothalamus. Taken with permission from (Oettl et al., 2016). The middle panel displays the results of an fMRI study showing that OT may shift the value of certain social behaviors, as is depicted by the schematic bar graph. The brain image shows the observed results when humans play a trust game, indicating a modulation of activation in the caudate (Cau) and amygdala (Amy) by OT. Adapted with permission from (Baumgartner et al., 2008). The panel to the right shows a theoretical choice probability curve. As the values on the x-axis increase, the relative value of a certain option increases, such that the y-axis then describes the probability of choosing this option. OT, relative to a saline control, may decrease noise during decision formulation, thus leading to a steeper curve (i.e., an increase in sensitivity to the relative value). This curve applies to any two-choice economic task, including a social juice allocation task developed for rhesus macaques (Chang, Winecoff, & Platt, 2011; Chang et al., 2012)

were lateralized to the left auditory cortex and involved precise temporal coordination between inhibitory and excitatory responses in these auditory neurons (Marlin et al., 2015). This neural signature was present in dams but not virgin females, although they could be elicited in virgin females with either topical OT application or with optogenetic stimulation of OT terminals in left auditory cortex (Marlin et al., 2015).

Additionally, further work in rats indicated that optogenetically enhanced OT release from paraventricular oxytonergic neurons increased social exploration and same-sex recognition of conspecifics (Oettl et al., 2016). This effect was mediated at the level of the olfactory bulb and involved an enhancement of inhibitory interneuron activity, lowering the signal-to-noise ratio of neurons involved in olfactory sensation (Oettl et al., 2016). Notably, deletion of OXTRs in these olfactory areas impaired social recognition but left odor detection and identification intact in non-social contexts (Oettl et al., 2016). These two studies provide strong support that OT ultimately influences social behavior by acting at the levels of both auditory and olfactory sensory perception in rodents, most consistent with the social salience hypothesis.

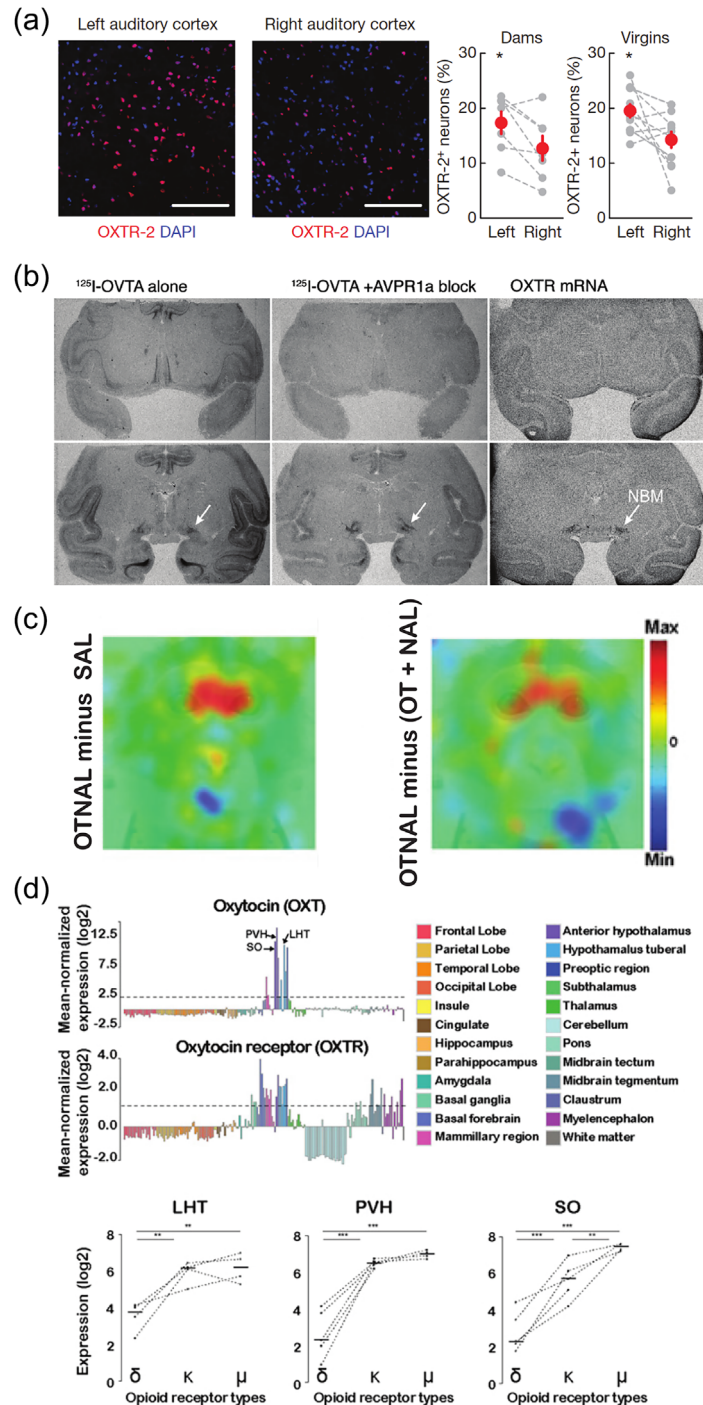
### 3.2 | Effects of OT on valuation

OT may regulate social behavior by modulating the valuation stage of decision-making. OT modulation at this stage may be more in line with

the prosocial or approach/withdrawal hypotheses than with the social saliency hypothesis, as both approach and withdrawal would require a more volitional shift due to the valuation of behavioral options in a given social situation. For example, in the prosocial hypothesis, one might expect a general increase in valuation of prosocial as opposed to antisocial behavioral options. The mechanisms that potentially underlie the approach/withdrawal hypothesis are largely similar and may involve an enhancement of value for approach-related behaviors and a decrease in value for withdrawal-related behaviors.

Given the relatively slower time course of these volitional processes compared to the aforementioned sensory processes, probing this stage in social behavior formulation at the neural level is more amenable to fMRI in human participants. Based on the prosocial and approach/withdrawal hypotheses, it is reasonable to predict that reward-related regions in the brain during social processing may be modulated by OT administration. This neural activation, whether it is an increase or a decrease compared to an appropriate saline control, could underlie a discrepancy in the valuation of potential social behaviors, driving the effects of OT at the behavioral level. Indeed, multiple studies have observed a decrease in amygdala activation with OT administration during socially relevant tasks (Baumgartner et al., 2008; Domes, Heinrichs, Glascher, et al., 2007; Gamer et al., 2010; Kirsch et al., 2005). Importantly, according to the social salience hypothesis and the conception that OT may affect





**FIGURE 2** The anatomical distribution of OT-releasing neurons and OXTRs across rodents, non-human primates, and humans. (a) A fluorescent micrograph displaying a left-lateralized bias for OXTR-2 positive neurons in the auditory cortex in both dams and virgin mice. Taken with permission from (Marlin et al., 2015). (b) OXTR autoradiography and in situ hybridization showing OXTR localization to the nucleus basalis of Meynert (NBM) in the rhesus macaque. Note the high degree of specificity in OXTR expression in the NBM relative to other areas. Taken with permission from (Freeman et al., 2014). (c) On the left, gaze patterns in rhesus macaques viewing a live conspecific after OT and naloxone (OTNAL) combined treatment relative to saline (SAL). On the right, the effects of OTNAL relative to the added effects of individually administered OT and naloxone (OT + NAL). Results show that the effects of OT and NAL administered together cannot be explained by the added effects of separate OT and NAL administration. Taken with permission from (Dal Monte et al., 2017). (d) Top plots show the distribution of oxytocin (OXT) and oxytocin receptor (OXTR) microarray gene expression patterns in the human brain, based on the Allen Human Brain Atlas (Hawrylycz et al., 2012). Bottom plots show the enrichment of  $\mu$ - and  $\kappa$ -opioid receptors in areas high in OXT expression, including the lateral hypothalamus (LHT), paraventricular nucleus of the hypothalamus (PVH), and the supraoptic nucleus (SO), demonstrating the overlap between OXTR and opioid receptors primarily in OT-releasing sites. Taken with permission from (Dal Monte et al., 2017)

the sensory perception stage of social decision-making, one would likely expect an increase in amygdala activation. However, a decrease in amygdala activation indicates instead that OT seems to generally inhibit an area widely thought to be involved in fear, social avoidance, and phobia (Davis, 1992; Ohman, 2005), more consistent with the notion that OT is modulating the relative valuation of approach and withdrawal behaviors.

### 3.3 | Effect of OT on decision formulation

Finally, it is possible that OT may have its effects at the stage in which values are compared in order to ultimately influence behavior. OT may not in fact have an effect on how an organism assigns value to a set of potential actions when in a social context, but instead on how the organism uses these values to inform its decision. This is not necessarily embedded in the prosocial or approach/withdrawal hypotheses of OT *per se*, as these hypotheses suggest a modulation of the value of certain actions in triggering either approach or withdrawal behavior. Instead, if OT were to influence the decision formulation stage itself, which occurs after and is influenced by the valuation stage, OT may enhance socially appropriate actions regardless of whether they are prosocial or antisocial, or whether they are approach-related or withdrawal-related.

If OT were to impact social decision-making at the decision formulation stage, one should be able to observe effects whereby actions of opposite valences are both enhanced by OT in the same paradigm. In other words, if OT increases the signal-to-noise ratio, or accuracy, with which an organism utilizes its set of values to inform its social behaviors, this could constitute an increase in either prosocial or antisocial, or additionally in either approach-related or withdrawal-related, behaviors depending on what the organism determines is appropriate in a given social context. This pattern of results has been observed in pairs of rhesus macaques during a specific version of the social reward allocation task (Chang et al., 2012). In this behavioral paradigm, monkeys chose to reward themselves, a conspecific, or neither monkey (Chang et al., 2012). This paradigm led to a self-regarding preference (choosing to reward themselves over the conspecific) as well as an other-regarding preference (choosing to reward the conspecific over neither) depending on context (Chang et al., 2012). When OT was administered systemically, both the baseline other-regarding and self-regarding preferences were bolstered, such that monkeys preferred more strongly to reward the conspecific as opposed to no one and also to reward themselves as opposed to the conspecific (Chang et al., 2012). This set of findings could be consistent with modulation during the decision formulation step of social decision-making (i.e., reflecting an enhancement of pre-existing preferences).

Interestingly, however, when OT was focally infused into the basolateral amygdala (BLA) in a similar task with a slightly different set of choices, it weakly, albeit significantly, increased baseline preference to deliver juice to the conspecific over neither, but also decreased the baseline preferences to withhold reward from the conspecific when choosing between sharing and not sharing the reward (Chang et al., 2015). This contrast supports the notion that the effects of OT are different

depending on where it is acting on the social decision-making continuum. That is, OT effects within BLA may be involved in the valuation stage described above, rather than the decision formulation stage.

### 3.4 | Further implications of a unified framework

Importantly, our multistage framework of OT indicates that not all the current OT hypotheses are mutually exclusive. In particular, it is entirely possible that OT could be modulating multiple steps in the decision-making process, possibly even concurrently. OT may also modulate different stages depending on the social context or even on individual differences in developmental experiences between animals (Bales & Perkeybile, 2012), likely mediating some of the inconsistencies observed in the effects of OT on social behavior (Bartz, Zaki, et al., 2011). Thus, on a common continuum of events that occur during social decision-making, OT could simultaneously have an effect on the perception of social stimuli, the salience of social stimuli, as well as the propensity to approach or avoid said stimuli.

## 4 | EFFECTS OF OT ON THE MAMMALIAN BRAIN

In attempting to discern between the multiple theories of the effects of OT on social cognition, it is useful to consider work that focuses not only on behavioral results, but also attempts to provide mechanistic insight into the effects of OT in the CNS. Similar to strictly behavioral studies concerning OT, these studies cut across rodents, non-human primates, and humans using a variety of molecular, electrophysiological, and neuroimaging techniques. We will now review these studies in the context of our multistage framework in order to determine whether insight can be gleaned into which step of the social decision-making process is impacted most significantly by OT. For simplification, we will split the arguments into two possibilities, one for sensory perception and one for valuation and decision formulation.

### 4.1 | The argument for effects on sensory perception

A large body of research from animal models indicates the modulatory influence of OT on sensory systems. Even in the non-social domain, OT seems to have robust analgesic effects on pain perception in animal models, although results are less consistent in human participants (Boll, Almeida de Minas, Raftogianni, Herpertz, & Grinevich, 2017). Additionally, we have already addressed two rodent papers that use a combination of molecular, optogenetic, and electrophysiological techniques to show the impact of OT on auditory (Marlin et al., 2015) and olfactory (Oetl et al., 2016) cortices during social behavior. These would support the theory that OT is impacting the perception-related stages of social decision-making.

Potentially surprising work concerning the neuroanatomical distribution of OXTRs in the rhesus macaque also seems to strongly support a role of OT in fundamental sensory processes (Freeman, Inoue, Smith, Goodman, & Young, 2014). While previous studies were

unable to differentiate between OXTRs and vasopressin 1a receptors (AVPR1As), the authors of this study utilized a competitive binding autoradiography protocol that allowed them to specifically localize OXTRs (Freeman et al., 2014). Using this technique in combination with *in situ* hybridization, the authors report that OXTR expression at cell bodies is much more restricted than AVPR1A expression and is primarily limited to the nucleus basalis of Meynert (NBM), pedunculo-pontine tegmental nucleus, superficial gray layer of the superior colliculus, trapezoid body, and ventromedial hypothalamus (Figure 2b). One caveat is that these techniques are not optimized for detecting OXTRs in presynaptic terminals at the projected sites (Freeman et al., 2014). This is an important consideration, especially in the context of the widespread cholinergic connections from the NBM to other brain areas. Notably, the NBM projects to the amygdala and is additionally the single major source of cholinergic innervation to the entire cortex (Everitt & Robbins, 1997; Mesulam, Mufson, Levey, & Wainer, 1983). If OXTRs were indeed expressed at the presynaptic terminals of cholinergic NBM neurons, this would provide a mechanism for OT modulation of cholinergic inputs at sites across the cerebral cortex as well as the amygdala. Interestingly, the collection of areas conclusively determined to express OXTRs at cell bodies are primarily involved in sensory processes, including modulation of visual attention, integration of multiple streams of sensory information, and reorientation to visual stimuli. If OT is predominantly exerting its effects through OXTRs in the primate brain as opposed to also acting on vasopressin receptors, this provides strong evidence of a potential role at the level of sensory perception and integration. Even more strikingly, while OXTRs tend to be concentrated in areas involved in olfactory processing in rodents, OXTRs are consistently found in areas relating to visual processing and attention across multiple species of non-human primates (Freeman & Young, 2016), providing further evidence for a role of OT in the sensory processing of socially relevant stimuli.

## 4.2 | The argument for effects on valuation and decision formulation

While some mechanistic evidence points to the potential effects of OT on sensory pathways, many studies indicate a powerful interaction between OT and dopaminergic as well as serotonergic reward pathways. Some of the most canonical work in OT has involved the comparison of monogamous and non-monogamous voles. Specifically, this line of research has largely indicated that differences in OT and vasopressin signaling in reward-related neural structures ultimately underlies differences in the propensity of pair-bonding between different species of vole (Carter, Grippio, Pournajafi-Nazarloo, Ruscio, & Porges, 2008; Donaldson & Young, 2008; Insel, Winslow, Wang, & Young, 1998; Young & Wang, 2004). Additionally, infusion of either OT antagonists or dopamine antagonists into the nucleus accumbens of female prairie voles was found to disrupt expression of partner preferences (Liu & Wang, 2003).

More recent work in Syrian hamsters and mice has additionally indicated the role of OT in reward-related neural circuitry. In Syrian hamsters, activation of OXTRs, but not vasopressin receptors, in the

ventral tegmental area were found to be necessary for reward-like properties of social interactions (Song, Borland, Larkin, O'Malley, & Albers, 2016). In mice, neurons in the paraventricular nucleus of the hypothalamus have been found to project to the ventral tegmental nucleus, releasing OT specifically during instances of social interaction (Hung et al., 2017). Intriguingly, the authors of this study were able to demonstrate with causal manipulations that direct stimulation of oxytocinergic neurons in the paraventricular nucleus increased prosocial behavior, while inhibition of oxytocinergic terminals in the ventral tegmental area decreased social interaction (Hung et al., 2017). Other work in mice has also indicated the importance of OT projections to the nucleus accumbens, with OT modulating the activity of medium spiny neurons at this structure (Dolen, Darvishzadeh, Huang, & Malenka, 2013). Furthermore, the authors of this study were able to determine the required interaction of the OT and serotonin systems both within the accumbens core and at the dorsal raphe nucleus to mediate social reward processing in mice (Dolen et al., 2013). The importance of the interaction between OT and serotonin has also been observed using positron emission tomography (PET) in human participants, with relevance for the treatment of autism spectrum disorder (ASD). Specifically, OT has been found to modulate serotonin binding potential in healthy participants, although this effect is absent when OT is administered to ASD patients (Lefevre et al., 2017). Taken together, these studies indicate an interaction between OT and reward-related dopaminergic and serotonergic neural circuitry for regulating social behavior. That is, these studies likely support an effect on the valuation or decision formulation stages, as the OT system appears to be involved in neural circuitry thought to be involved in value-based decision-making.

Work using intranasal administration in combination with fMRI in humans likewise suggests effects in brain regions more canonically thought to be involved with valuation rather than sensory perception. As was already mentioned, some of the most verified findings on the effects of OT in the human brain involve a reduction in amygdala activation (Baumgartner et al., 2008; Domes, Heinrichs, Glascher, et al., 2007; Gamer et al., 2010; Kirsch et al., 2005). This is perhaps more consistent with the value-related hypotheses of OT effects on social decision-making, as it is unclear how a decrease in amygdala activation could be related to an increase in the salience of social stimuli. Several other studies also indicate modulation of brain regions thought to be even more directly related to reward processing. One study found that OT diminished a decrease in trust behavior following breaches of trust in an economic game (Baumgartner et al., 2008). In addition to a decrease in activity in the amygdala, the study also found modulation of activity in the midbrain and dorsal striatum (Baumgartner et al., 2008), areas directly related to value updating when new information is acquired.

Later studies broadly replicated these results, finding that OT significantly enhanced ventral tegmental area activation, another area involved in value processing, during a social incentive delay task (Groppe et al., 2013). OT was also found to increase ratings of a partner's face in men, potentially mediated by an increase in activation of both the ventral tegmental area and nucleus accumbens with intranasal OT administration (Scheele et al., 2013). Studies concerning



oxytocin and maternal attachment also indicate a potential effect of OT on value-related neural areas. For example, while OT decreased amygdala activation in response to infant laughter in women, functional connectivity between the amygdala and reward-related regions, including orbitofrontal cortex and the anterior cingulate, was increased (Riem et al., 2012). Maternal attachment has also been observed to predict brain and OT responses, as mothers with secure attachment show increased activation of the value-related ventral striatum as well as the oxytocin-releasing hypothalamus/pituitary region when viewing the faces of their infants compared to insecure/dismissing mothers (Strathearn, Fonagy, Amico, & Montague, 2009). Peripheral OT responses to infant contact were also higher in secure attachment mothers and correlated with activation in both regions (Strathearn et al., 2009).

Interestingly, the effects of OT on value-related areas may be divergent in men and women, as a line of research ultimately including a sample size of over 300 participants determined that OT increases activation in the ventral striatum in men but decreases activation in the same region in women during the canonical prisoner's dilemma game (Feng et al., 2015; Rilling et al., 2012, 2014). Finally, work involving patients with ASD also implicates OT in value-related neural circuitry. In children with ASD, OT was found to increase activation of numerous brain areas involved in valuation, including the ventral striatum and orbitofrontal cortex, during a task necessitating social judgments (Gordon et al., 2013). Together with the aforementioned rodent studies, these results would seem to indicate effects of OT on either the valuation or decision formulation stages of our multistage framework, more consistent with the prosocial and approach/withdrawal hypotheses than with the salience hypothesis of OT.

#### 4.3 | The effects of OT in the context of integrated valuation and attention processes

Our framework for interpreting the effects of OT on social decision-making underscores the interactive nature of various stages in the process. A recent study provides a good example that supports shared, non-mutually-exclusive mechanisms of OT action across multiple stages. Using a novel gaze interaction paradigm in rhesus macaques (Dal Monte, Piva, Morris, & Chang, 2016), the authors of this study explored the potential interaction between the OT and opioid systems in boosting social attention (Dal Monte et al., 2017). This study determined a supralinear effect of combined OT with opioid antagonism on social attention, such that the combination of intranasal administration of OT and the opioid blocker naloxone enhanced interactive social attention to a conspecific more than the added effects of either drug alone (Figure 2c). Corresponding to these findings, the major OT-releasing sites in the human brain were found to display enriched expression of  $\kappa$ - and  $\mu$ -opioid receptors (Figure 2d), further indicating a potential interaction between these two systems (Dal Monte et al., 2017). This could have important implications in strengthening the effects of OT in its potential use as a treatment for the social deficits associated with multiple neuropsychiatric disorders.

In the context of the social salience and approach/withdrawal hypotheses, however, it is difficult to determine which hypothesis is supported by these findings. The opioid system is implicated primarily in value processing, which would seem to support the more value-related approach/withdrawal hypothesis. Still, the behavior evaluated in this study is intrinsically related to sensory perception and salience. It is therefore important to note that processes relating to valuation are also likely to impact salience and attention, and vice versa. This has likely been part of what has caused confusion in this field, as theories have been driven by the assumption that the current hypotheses are mutually exclusive. However, in the context of our multistage framework, it becomes clear that these hypotheses concern different steps in a common process that recursively operates in order to underlie dynamic, real-time social behaviors. Thus, a unified theory, rather than mutually distinct hypotheses, might be optimal in conceptualizing the effects of OT on social decision-making.

## 5 | CONCLUDING REMARKS

Non-human primates present a uniquely well-suited animal model to further explore the effects of OT on social behavior. While work in rodents has continued to provide us with a granular view of the microcircuitry involved in mechanistically driving the effects of OT, these approaches can fail to capture certain aspects of the OT system unique to human and non-human primates. Concurrently, while intranasal administration of OT to human participants has provided us with direct demonstration of behavioral effects in humans and continues to be a popular mode of research, the range of techniques available to probe the neural mechanisms underlying behavioral effects in humans remain sparse. Work using non-human primates presents an important intermediate option between these two cases, whereby invasive techniques can be used to examine neural circuitry in an animal model that naturally exhibits complex social behaviors often resembling those of humans. Future research in this model could therefore be particularly insightful in examining the neurobiology underlying OT and high-level social cognition.

Conceptualizing the effects of OT on social behavior at computationally unique steps in a multistage process also illuminates the possibility that OT may act on individual steps, or simultaneously on multiple steps, depending on context and individual differences. Mechanistic findings regarding the action of OT at the level of the CNS span both sensory and reward areas, potentially implicating OT in multiple processing steps required during typical social behaviors. For example, OT has been found to function in excitatory/inhibitory balance in the auditory cortex of rodents during pup calls (Marlin et al., 2015). Still, other studies have implicated OT in the modulation of predominantly reward-related regions, such as the nucleus accumbens and ventral tegmental area, during economic paradigms that involve taking others into account when making decisions (Baumgartner et al., 2008; Groppe et al., 2013; Scheele et al., 2013). Such findings suggest that the prosocial, social salience, and approach/withdrawal hypotheses may not be mutually exclusive. Rather, OT may act on various

stages of the social decision-making process. This assertion could explain much of the controversy in this field of study and suggests the need for future experiments to further explore the role of individual differences as well as experimental demand or context in determining at which stage OT has the strongest effects in guiding social behavior.

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## CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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