Oxytocin, Motivation and the Role of Dopamine

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Abstract

The hypothalamic neuropeptide oxytocin has drawn the attention of scientists for more than a century. The understanding of the function of oxytocin has expanded dramatically over the years from a simple peptide adept at inducing uterine contractions and milk ejection to a complex neuromodulator with a capacity to shape human social behavior. Decades of research have outlined oxytocin's ability to enhance intricate social activities ranging from pair bonding, sexual activity, affiliative preferences, and parental behaviors. The precise neural mechanisms underlying oxytocin's influence on such behaviors have just begun to be understood. Research suggests that oxytocin interacts closely with the neural pathways responsible for processing motivationally relevant stimuli. In particular, oxytocin appears to impact dopaminergic activity within the mesocorticolimbic dopamine system, which is crucial not only for reward and motivated behavior but also for the expression of affiliative behaviors. Though most of the work performed in this area has been done using animal models, several neuroimaging studies suggest similar relationships may be observed in humans. In order to introduce this topic further, this paper will review the recent evidence that oxytocin may exert some of its social-behavioral effects through its impact on motivational networks.

Keywords

oxytocin; motivation; dopamine; salience; valence

1. Introduction

This year marks the 60th anniversary since oxytocin was first synthesized and its structure established in the Nobel Prize winning work of Vincent du Vigneaud (du Vigneaud *et al*., 1953, 1954). Since that landmark work, scientists have grown to appreciate oxytocin as both a hormone contributing significantly to reproductive processes and as a complex neuromodulator capable of affecting a wide range of behaviors. While comprised of only nine amino acids, oxytocin is a highly influential neuropeptide known to significantly impact a variety of social and reproductive behaviors including pair bonding, as well as maternal, affiliative and sexual behaviors (see Burkett and Young, 2012, Campbell, 2010, Donaldson and Young, 2008, Lee *et al*., 2009, Meyer-Lindenberg *et al*., 2011).

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While historically considered a prosocial hormone, research suggests oxytocin promotes both positive (i.e. maternal behaviors, pair-bonding, altruism, trust) and negative social interactions (i.e. aggression, territoriality) depending on the context. Experimental manipulations of oxytocin indicate this neuropeptide enhances the salience of social cues as evidenced by greater attention devoted toward inspecting social cues, heightened cognitive processing of social information, and increased effort devoted to engaging social entities. Oxytocin may also be involved in shifting attributions of motivational value or valence towards social stimuli, resulting in alternative appetitive and aversive value assignments to certain social objects. For instance, oxytocin appears to be responsible for the aversive to appetitive shift in the appraisal of newborn pups in female rats. How precisely oxytocinergic activity shapes such processes is still being explored; however, multiple intersecting lines of research have revealed oxytocinergic modulation of activity within motivational networks, particularly within dopaminergic mesocorticolimbic circuits, may be involved.

This review will discuss how oxytocin may facilitate social behavior by increasing the salience of social stimuli and by shifting valence assessments of social objects through its effects on motivational networks. First, major pathways responsible for processing motivationally relevant stimuli will be reviewed, placing special emphasis on the influence of oxytocin and dopamine within pathways. This will be followed by a description of how particular components of social motivation are impacted by oxytocinergic and dopaminergic activity. Finally, a brief comment will be given on oxytocin's potential role as a mediator of salience and valence attribution for objects imbued with social value.

2. Anatomy of Motivation

Social interactions can be a source of joy or dread depending on the context. Key decisions must be made when encountering acquaintances and strangers; first, to determine whether they are friend or foe, then resolve whether any action is necessary and finally, if action is called for, settle on which action is appropriate (i.e. pursue, avoid, or attack). Such assessments are vital to survival and involve the engagement of motivational processes, which form an internal drive that pushes an organism to identify and engage motivationally relevant stimuli.

Motivation can be succinctly defined as "the set of processes through which organisms regulate the probability, proximity and availability of stimuli" (Salamone and Correa, 2012). Motivated behavior arises as a consequence of the collective activity of a network of interconnected regions that act to signal the significance of stimuli, assign motivational value and select appropriate action (Kalivas and Volkow, 2005, Figure 1). The ventral tegmental area (VTA) and its widespread projections to cortical and limbic regions form the foundation of the motivational circuitry. Dopaminergic neurons within VTA project to the nucleus accumbens, hippocampus, amygdala, ventral pallidum and various cortical areas including the prefrontal cortex to form the mesocorticolimbic pathway (Figure 1). The regions that make up this pathway share strong reciprocal connections and each respond to motivationally relevant stimuli. As there are large number of articles and reviews written regarding the roles each of these areas play in motivational behavior, this section of the review will serve to briefly summarize the overall anatomical organization of the major structures that make up the motivational system and highlight the key functions each region is generally believed to contribute to motivated behavior.

Prefrontal Cortex

The most anterior portion of the frontal cortex, this area consists of multiple subregions that contribute to a wide variety of activities spanning from cognition to motivation to decision making to emotion. The prefrontal cortex sends glutamatergic projections to many regions

within the mesocorticolimbic network including the nucleus accumbens, amygdala, hippocampus, and ventral pallidum and through these connections may provide top-down processing control to guide motivated behavior (Figure 1). As discussed in detail in an excellent review by Rushworth and colleagues, multiple subregions within the prefrontal cortex appear to directly contribute to the processing of rewards (Rushworth *et al*., 2011). The medial portions of the prefrontal cortex, including the ventromedial and medial orbitofrontal cortices, seem to carry representations of reward value. Similarly, the anterior cingulate cortex appears to encode the associations between a given action and a reward, for instance linking the amount of exerted effort necessary to receive a particular reward. On the other hand, the more lateral portions of the prefrontal cortex are hypothesized to be involved in the assignment of value to alternative rewards and comparing these values among different reward options (Rushworth *et al*., 2011).

Amygdala

This small structure in the medial temporal lobe has proposed roles in emotion, learning, memory as well as motivation (see reviews Baxter and Murray, 2002 and Murray and Wise, 2010). The amygdala receives and responds to sensory information from auditory, gustatory, visual, and olfactory domains (Zald and Pardo, 2002). Stimulation of the amygdala elicits recruitment of attention processes that boost processing of incoming sensory information and enhance vigilance (Davis and Whalen, 2001). Indeed, given the its connections with sensory domains as well as its glutamatergic projections to the nucleus accumbens and prefrontal cortex, the amygdala is well positioned to detect salient incoming stimuli and heighten arousal to aid in response. Early work revealed the amygdala responded primarily to cues related to fear, threat and danger and played a primary role in fear conditioning (e.g. Adolphs *et al*., 1995, LeDoux, 2000, Prather *et al*., 2001); however the amygdala appears to be reactive to positive salient events as well (Belova *et al*., 2008, Bermudez and Schultz, 2010a, b, Garavan *et al*., 2001, Hamann *et al*., 1999, 2002, Salinas *et al*., 1993, Santos *et al*., 2011). For instance, the amygdala is recruited during stimulus-reward learning (e.g. Baxter *et al*., 2000, Bermudez and Schultz, 2010a, Everitt *et al*., 2003, Everitt *et al*., 1991). Neuronal recordings in non-human primates indicate amygdalar neurons respond to cues predicting future reward and encode reward value and magnitude (Belova *et al*., 2008, Bermudez and Schultz, 2010a, b, Salinas *et al*., 1993).

Hippocampus

This structure located within the medial temporal lobe is a key neuroanatomical substrate in learning and memory. This region shares reciprocal connections with the prefrontal cortex, which plays important roles in cognition and memory (Barbas and Blatt, 1995, Laroche *et al*., 2000). Hippocampal damage results in memory impairments in declarative memory or, rather, memory for facts and events (Eichenbaum, 2004). The hippocampus is important for processing contextual information in memory such as where the reward was previously located (Eichenbaum, 2004, Luo *et al*., 2011) and is hypothesized to transmit this contextual information through its connections with the VTA and the nucleus accumbens to link context with reward (Ito *et al*., 2008, Luo *et al*., 2011). The hippocampus is also involved in novelty detection and hippocampal activation is necessary for salient novel stimuli to stimulate VTA activity (Floresco and Grace, 2003, Legault and Wise, 2001, Lisman and Grace, 2005, Lodge and Grace, 2006). Dopaminergic activity within the VTA is influenced by glutamatergic afferents originating from the hippocampus and projecting to medium spiny neurons in the nucleus accumbens (Floresco *et al*., 2001, Groenewegen *et al*., 1987).

Ventral Pallidum

Located within the basal ganglia, the ventral pallidum receives projections from a variety of neural structures including the amygdala, hippocampus and nucleus accumbens and sends projections to thalamic relays or to subcortical outputs (Zhang *et al*., 2012). The ventral pallidum also sends inhibitory γ –aminobutyric acid (GABA) projections to the VTA and nucleus accumbens. Reductions in GABAergic activity from the ventral pallidum results in increases in activity in dopamine neurons contained within the VTA that consequently increases extracellular dopamine within the nucleus accumbens (Floresco *et al*., 2003). Originally conceptualized as a region primarily handling the translation of limbic activity into motor behavior, current views suggest neurons within the ventral pallidum code for incentive salience as well as hedonic value (Smith *et al*., 2011).

Nucleus Accumbens

The nucleus accumbens, situated within the striatum, receives glutamatergic projections from the amygdala, hippocampus and prefrontal cortex and in turn sends GABAergic projections the VTA, substantia nigra and ventral pallidum (Haber and Knutson, 2009, Haber *et al*., 1990). This region is proposed to act in an integrative capacity assimilating goal directed information from the prefrontal cortex, environmental context from the hippocampus, and emotional significance from the amygdala to ultimately influence motor planning and action execution through its connections with the ventral pallidum and midbrain (Kalivas and Nakamura, 1999, Luo *et al*., 2011, Mogenson and Yang, 1991). Through these extensive reciprocal connections, the nucleus accumbens is in an ideal position to influence "the translation of will into action" (Goto and Grace, 2005, Kalivas and Nakamura, 1999, Mogenson and Yang, 1991). As will be discussed below, dopaminergic activity within the nucleus accumbens has been identified as a key neurochemical substrate in the attribution of salience.

Summary

Activity within and the interactions between the various brain regions that make up the mesocorticolimbic pathway contribute to the formation of motivated behavior. Innervated by ascending projections originating from the VTA, each region within the mesocorticolimbic pathway is hypothesized to play essential roles in the processing of motivationally relevant stimuli including salient social stimuli. As will be discussed, two neurochemicals acting in this pathway, dopamine and oxytocin, serve to shape social motivation and influence the expression of affiliative behaviors.

3. Role of Dopamine in Motivation

Dopamine was first implicated in "reward" processes in the 1950s in a series of experiments that explored electrical stimulation of the brain in rats. Olds and Milner noted that a rat that had been implanted with an electrode, within what was later identified to be the nucleus accumbens, preferentially spent time in the area where it had received electrical stimulation through the electrode the day prior (Olds and Milner, 1954). Further, when rats were trained to press a lever to electrically stimulate the electrodes themselves, they would press the lever repeatedly at astonishing rates reaching thousands of times per hour (Milner, 1989, Olds and Milner, 1954). Similar observations were then made in humans a short time later (Bishop *et al*., 1963). Shortly after Olds and Milner's observations, the presence of dopamine containing neurons within the VTA which projected to the nucleus accumbens would be established (Falck and Hillarp, 1959) and subsequent research would demonstrate that self-electrical stimulation could be dramatically reduced by applying dopaminergic antagonists or lesions to this area (Fibiger *et al*., 1987, Rolls *et al*., 1974). This work indicated a primary role for mesocorticolimbic dopamine in reward.

Dopamine acts on a family of related G protein-coupled receptors usually divided into two major classes: D1-like, consisting of D1 and D5 receptor subtypes, and D2-like, consisting of D2, D3 and D4 receptor subtypes (for a thorough review of dopaminergic signaling see Beaulieu and Gainetdinov, 2011). D1 receptors are enriched along the striatonigral 'direct' pathway whereas D2 receptors are observed along the striatopallidal 'indirect' pathway (Gerfen *et al.*, 1990). D1 receptors are differentiated from D2 receptors based on their ability to either stimulate (D1) or inhibit (D2) adenylyl cyclase activity. Activation of adenylyl cyclase results in cyclic adenosine monophosphate (cAMP) production, which can have significant effects on intracellular signaling. As such, activation of either D1 or D2 receptors can have opposing effects on neuronal activity. For instance, while D1 and D2 receptor subtypes are both involved in reward learning, they appear to have slightly different roles. D1 receptor activation in the direct pathway appears to be crucial in the acquisition phases of reward learning whereas D2 receptor deactivation in the indirect pathway seems to be necessary to switch to a new reward-seeking strategy (Yawata *et al.*, 2012).

Dopamine was originally posited to code for the pleasure derived from reward based on the results from electrical stimulation experiments and observations that when animals encountered either natural rewards (e.g. food, sex) or artificial rewards (e.g. drugs) dopamine release was stimulated and the firing rate of dopamine neurons in the mesocorticolimbic pathway increased (e.g. Corrigall *et al.*, 1992, Di Chiara and Imperato, 1988, Matsumoto and Hikosaka, 2009, Wise and Rompre, 1989). However, landmark work done by Wolfram Schultz and colleagues demonstrated that while dopamine neurons will indeed fire in response to unexpected rewards, they only show weak responses to fully anticipated rewards (Hollerman and Schultz, 1998, Schultz, 1998, Schultz *et al.*, 1998). Furthermore, large reductions or exaggerations in dopamine levels induced within the mesocorticolimbic system do not seem to alter hedonic reactions to natural rewards (Berridge *et al.*, 1989, Kaczmarek and Kiefer, 2000, Pecina *et al.*, 1997, Wyvell and Berridge, 2000). Instead, dopamine antagonists applied to the nucleus accumbens result in a reduction in the effort animals are willing to exert to obtain such rewards while leaving hedonic reactions to those rewards intact; or rather, a reduction in "wanting" as opposed to "liking" (Berridge and Robinson, 1998, Robinson *et al.*, 2005). Hence, dopaminergic manipulations appear to influence assignment of motivational value or salience, impacting the drive toward such rewards, rather than the pleasure derived from the reward itself (Berridge and Robinson, 1998, Bromberg-Martin *et al.*, 2010, Salamone, 2007). A further complication of the hedonic hypothesis of dopamine is that mesocorticolimbic dopaminergic fluctuations do not selectively interfere with behavioral responses towards appetitive stimuli but also affect aversive motivational processes as well. Dopamine neurons become engaged in response to negative, aversive and stressful stimuli (Abercrombie *et al.*, 1989, D'Angio *et al.*, 1987, Horvitz, 2000, Pezze and Feldon, 2004, Scott *et al.*, 2006) and dopamine depletions and antagonists applied within the mesocorticolimbic system impair active avoidance responses and block the development of place aversion (Salamone, 1994).

So, what does dopamine code for precisely? No consensus has emerged as of yet, however, current evidence suggests dopamine signaling carries multiple fragments of information. As recently reviewed by Bromberg-Martin and colleagues, it appears that while dopaminergic neurons generally encode an alerting signal for unexpected cues, distinct populations of dopamine neurons encode: 1) motivational value, whereby certain dopamine neurons are excited by appetitive stimuli, which promote approach, and inhibited by aversive stimuli, which promote withdrawal and 2) motivational salience, as other dopamine neurons show weak responses to neutral events but are excited by salient events (i.e. regardless of whether the event was appetitive or aversive in nature (Bromberg-Martin *et al.*, 2010). As such, modulation of dopamine neurotransmission in these circuits could lead to changes in either of these processes. As several lines of evidence suggest oxytocin modulates activity in

dopamine circuits, experimental data linking mesocorticolimbic dopamine activity and oxytocinergic functioning will be reviewed next.

4. Oxytocin interactions with motivational circuitry

4.1 Neurobiology of Oxytocin

Oxytocin is a circular nonapeptide synthesized primarily within paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. The posterior lobe of the pituitary contains axonal projections originating from the hypothalamus, which secrete oxytocin for release into circulation. Peripherally, oxytocin acts on reproductive physiologic processes to induce uterine contraction and stimulate milk ejection (Dale, 1906). Centrally, oxytocin neurons originating in the PVN also send projections to extrahypothalamic regions including the amygdala, hippocampus, nucleus accumbens and VTA (Figure 1) (Ross *et al.* 2009, Brinton *et al.*, 1984, Caffé *et al.*, 1989, Fliers *et al.*, 1986, Krémarik *et al.*, 1993, Loup *et al.*, 1991, Van Leeuwen *et al.*, 1985).

Oxytocin is released in response to psychological and physical stressors as well as in reaction to a variety of social stimuli (e.g. Jezova *et al.*, 1995, Lang *et al.*, 1983, Onaka, 2004, Robinson *et al.*, 2002, Wigger and Neumann, 2002). In addition to stimulation through direct projections, oxytocin can also be released somatodendritically to regulate its own activity (Moos *et al.*, 1984) and may travel through diffusion to activate extrahypothalamic areas containing oxytocin receptors (see review Stoop, 2012). Oxytocin binds primarily to its only oxytocin receptor (OXTR) although shows weak affinity towards vasopressin receptors. The OXTR belongs to the G-protein coupled seven transmembrane receptor (GPCR) superfamily and is centrally expressed in regions throughout the brain and spinal cord including within the hypothalamus, nucleus accumbens, amygdala and VTA (see review Stoop, 2012). OXTR are found in key areas within the mesocorticolimbic system and stimulation of OXTR within these regions, particularly within the VTA and nucleus accumbens, has been noted to influence motivated behavior, as will later be discussed. The distribution of oxytocin receptors in the brain is highly species dependent and has been shown to correspond to expression of social behaviors such as pair bonding (Insel and Young, 2001).

4.2 Oxytocin and Dopamine

Recent studies show activation of oxytocin neurons thought to target the VTA stimulates mesocorticolimbic dopaminergic neurons (Melis *et al.*, 2007, Melis *et al.*, 2009, Succu *et al.*, 2011, Succu *et al.*, 2008). Oxytocin receptors and corresponding messenger RNA have been localized within the VTA (Freund-Mercier *et al.*, 1987, Sofroniew, 1983, Vaccari *et al.*, 1998). Extensive work done by Melis, Argiolas and colleagues indicates that stimulation of dopamine receptors located on the cell bodies of oxytocinergic neurons within the PVN lead to penile erection in rats (e.g. Argiolas and Melis, 2004, Melis and Argiolas, 2003). Oxytocin injected into the VTA induces penile erections in rats and stimulates extracellular dopamine increases within the nucleus accumbens, which receives dopaminergic projections from the VTA (Melis *et al.*, 2007, Succu *et al.*, 2008). Application of an oxytocin receptor antagonist via intracerebroventricular (ICV) injection significantly diminishes dopamine agonist stimulated dopaminergic release in the nucleus accumbens and the pro-erectile effect of dopamine (Succu *et al.*, 2007).

Oxytocin stimulation of the amygdala and hippocampus can also lead to penile erection and increases in extracellular dopamine within the nucleus accumbens in rats (Melis *et al.*, 2009). This is suggested to occur due to activation of glutamatergic projections from the amygdala and hippocampus that act to stimulate mesolimbic dopamine neurons within the

VTA (Melis *et al*., 2009, Succu *et al*., 2011). More recent work has also demonstrated that oxytocin can also induce yawning when injected into the amygdala, hippocampus and VTA and this behavior occurs concurrently with increases in extracellular dopamine within the nucleus accumbens as well as the medial prefrontal cortex, which is blocked by ICV injections of oxytocin receptor antagonists (see review (Sanna *et al*., 2012). While oxytocin regulates dopamine release in extrahypothalamic regions, oxytocinergic neurons are susceptible to modulation by dopamine themselves as they also express dopamine receptors (Baskerville *et al*., 2009). Indeed, dopamine release in the nucleus accumbens has been demonstrated to produce stimulation of dopamine neurons within the PVN that can ultimately activate oxytocinergic neurons and induce penile erection (Melis *et al*., 2007, Melis *et al*., 2009, Succu *et al*., 2011, Succu *et al*., 2007).

5. Oxytocin, Dopamine and Social Salience

The location of oxytocin's receptors throughout the mesocorticolimbic dopamine system places oxytocin in an ideal position to influence a wide range of motivated behaviors. Several groups of researchers have posited that oxytocin's ability to influence behavioral responses to social stimuli is at least partially mediated by its capacity to increase the salience of social cues (Averbeck, 2010, Bartz *et al*., 2011, Burkett and Young, 2012, Gordon *et al*., 2011, Shamay-Tsoory *et al*., 2009). This fits well with the notion that dopamine plays primary roles in salience attribution and oxytocin is capable of affecting this activity.

5.1 Maternal Behavior

To put it awfully inadequately, infants are highly salient to their mothers. Over 80 years of rodent research has indicated that pups have high inherent value to parturient females. As this has been reviewed extensively elsewhere (e.g. Lonstein and Morrell, 2007, Trezza *et al*., 2011, Numan and Stolzenberg, 2009), this manuscript will highlight some of the observations that indicate dams are highly driven to maintain contact with pups and how this behavior can be modified through challenges to dopaminergic and oxytocinergic systems.

Lactating and recently parturient rodents will exert intense effort to gain access to pups while virgin female rats will tend to avoid or show aggression towards pups when first exposed to them (Fleming and Anderson, 1987, Fleming and Rosenblatt, 1974, Jakubowski and Terkel, 1985a, b, but note differences in laboratory mouse strains, Lonstein and De Vries, 2000, Noirot, 1972). Rats that have recently given birth and have been trained to press a bar in order to retrieve pups will press the bar continuously, hundreds of times over multiple hours in order to receive both their own pups as well as foster pups (see review Trezza *et al*., 2011). Dams also prefer to spend time in areas previously associated with pups (i.e. conditioned place preference) and exhibit preferences for cues associated with pups over those associated with drugs of abuse such as cocaine (Ferris *et al*., 2005, Mattson *et al*., 2001, Mattson *et al*., 2003). The neurobiological systems underlying such maternal drive are still being explored, however, a growing body of evidence suggests both dopaminergic and oxytocinergic systems play key roles in maternal behavior.

Maternal motivation, or the responsiveness of a mother towards her young, is influenced by activity within the mesocorticolimbic system (see Numan and Stolzenberg, 2009 for a comprehensive review). Lactating dams exhibit enhanced activity within the nucleus accumbens, striatum, prefrontal cortex, thalamus and VTA in response to suckling by pups (Febo *et al*., 2005, Ferris *et al*., 2005). Dopamine is released within the nucleus accumbens when a mother rat grooms or licks her offspring or after being reunited with her offspring after forced separation (Champagne *et al*., 2004, Hansen *et al*., 1993). Maternal rats exhibiting high levels of pup licking and grooming behavior tend to exhibit larger increases

in dopaminergic activity in the nucleus accumbens as a result of grooming their pups relative to their low licking and grooming counterparts (Shahrokh *et al*., 2010, Champagne *et al*., 2004). Such increases in extracellular dopamine activity observed in these mothers are positively associated with the time spent tending to their pups (Champagne *et al*., 2004). Artificially increasing extracellular dopamine levels within the nucleus accumbens through use of a dopamine reuptake inhibitor can enhance mother and pup interactions (Champagne *et al*., 2004) whereas applying dopaminergic antagonists or dopaminergic neurotoxins to the region interrupts such interactions (Hansen *et al*., 1993, Hansen *et al*., 1991a, Keer and Stern, 1999, Numan *et al*., 2005). Modulation of VTA activity can also influence maternal behaviors. For instance, pharmacological inactivation of the VTA abolishes the conditioned place preference for pups in postpartum females (Seip and Morrell, 2009). Inactivating the VTA by bupivacaine or by selectively destroying the dopamine neurons within the VTA can also reduce maternal behaviors such as pup retrieval and grooming (Seip and Morrell, 2009, Hansen *et al*., 1991b).

Oxytocinergic activity within the motivational system also serves as an important neurobiological substrate underlying maternal behavior. Mother rats displaying high levels of pup grooming behavior show an increased number oxytocinergic projections from the PVN to the VTA relative to rats exhibiting low levels of pup grooming behavior (Shahrokh *et al*., 2010). Similarly, oxytocin receptor levels within areas such as the medial preoptic area, nucleus accumbens, VTA and amygdala differ between rats displaying varying levels of maternal behavior, with increased maternal behavior being associated with higher oxytocin receptor concentrations (Francis *et al*., 2000, Shahrokh *et al*., 2010). Oxytocin has been theorized to play crucial roles both in the initiation of maternal behaviors and the modification of such behaviors once established (see Numan and Stolzenberg, 2009). Maternal behavior can be elicited through administration of oxytocin in virgin rats (Pedersen *et al*., 1982); whereas oxytocin antagonists applied within the VTA impair both pup retrieval and time spent in nursing postures over pups in parturient dams (Pedersen *et al*., 1994). Further, oxytocin receptor knockout postpartum mice show higher latencies to retrieve pups placed at the corners of the cage and spend less time in nursing postures (Takayanagi *et al*., 2005, but also see Nishimori *et al*., 1996). Interestingly, oxytocin also appears to influence an infant's behavior towards their mother. As mothers actively seek out their offspring, so do offspring seek out their mothers. Infant rats not only seek out their mothers but also show preferences with areas associated with maternal odors; preferences can be blocked through central administration of oxytocin antagonists (Nelson and Panksepp, 1996). Furthermore, oxytocin knockout pups also fail to show a preference for their mother over a novel lactating female and emit fewer ultrasonic vocalizations when separated from their mother (Winslow *et al*., 2000, Ross and Young, 2009).

It is of note that the actions of oxytocin and dopamine on maternal behavior do not appear to be entirely separate. For example, utilizing *in vivo* voltammetry, Shahrokh and colleagues demonstrated that oxytocin infusions into the VTA could enhance dopamine levels in the nucleus accumbens (Shahrokh *et al*., 2010). Furthermore, they observed that increases in dopaminergic concentrations in the nucleus accumbens induced by pup grooming among the maternal rats that demonstrate the highest levels of this behavior could be inhibited through administration of an oxytocin receptor antagonist into the VTA (Shahrokh *et al*., 2010).

Although less well studied in humans, bonding between mothers and children has also been associated with activity within mesocorticolimbic circuits. Functional magnetic resonance imaging (fMRI) paradigms have shown recruitment of the amygdala, ventral striatum, VTA/ substantia nigra as well as areas within the frontal cortex and insula in response to mothers seeing photographs of their own children versus other peoples children (Bartels and Zeki, 2004, Leibenluft *et al*., 2004, Strathearn *et al*., 2009, Strathearn *et al*., 2008, but see

Wittfoth-Schardt *et al*., 2012). Strathearn and colleagues demonstrated that new mothers classified as having a secure attachment style exhibited heightened BOLD activation within the orbitofrontal cortex, medial prefrontal cortex, ventral striatum and hypothalamus while viewing pictures of their own infants relative to mothers displaying insecure/dismissing attachment styles (Strathearn *et al*., 2009). Neural activity within hypothalamus was engaged in response to mothers viewing their own child's face versus an unknown child's face and this activity was significantly correlated with plasma oxytocin responses induced by physical interaction with their baby (Strathearn *et al*., 2009). Furthermore, oxytocin levels have been shown to predict the presentation of affectionate parental behaviors in humans (see Gordon *et al*., 2011). Plasma levels of oxytocin are positively related to the attention and affection mothers and fathers show their infant children (see Gordon *et al*., 2011). Other lines of research indicate mothers hearing crying sounds from an infant exhibit enhanced BOLD activation within the temporal lobe and amygdala (Riem *et al*., 2011). This amygdala activation is significantly attenuated following treatment by intranasal oxytocin and is suggested to reflect the stress-reducing effects of oxytocin that may help promote responsiveness to crying infants (Riem *et al*., 2011). Indeed, oxytocin, which is released during breast-feeding, has been demonstrated to lower reactivity of the hypothalamic pituitary adrenal (HPA) axis reducing levels of stress hormones including adrenocorticotropic hormone (ACTH) and cortisol, which may promote maternal care (see reviews by Heinrichs *et al*., 2009, Neumann and Landgraf, 2012, Uvnas-Moberg, 1997).

In sum, these data indicate infants are highly salient and mothers will devote a great deal of time and energy obtaining access to their offspring and show preferences for stimuli associated with them. These activities are associated with activity within multiple regions in the mesocorticolimbic pathway known to be critical in the processing of rewarding and motivationally salient stimuli. Interfering with oxytocinergic activity in these regions significantly modifies these maternal behaviors. In addition to promoting increased salience attribution towards offspring, oxytocin may also encourage a shift in valence assignment. For instance, for wild virgin rodents, pups can be treated as aversive stimuli, prompting attack. However, following parturition or treatment with oxytocin, pups are no longer regarded with disdain but rather as appetitive stimuli worth expending effort to obtain and care for.

5.2 Pair Bonding

Humans, unlike most mammals, are capable of forming long-lasting monogamous pair bonds. One other mammalian species that has been shown to form pair bonds are prairie voles (Insel and Young, 2001). These rodents have served as the primary animal model for studying the formation of pair bonds (Insel and Young, 2001). Unlike their montane counterparts, this species' male-female pairs will share a nest, defend their shared territory and both participate in parental care (Young *et al*., 1998). Males will display partner preferences for specific females following prolonged mating and exhibit aggression towards female strangers after extended cohabitation (Aragona *et al*., 2006). This review will highlight some of the major findings that relate to the involvement of dopamine and oxytocin in pair-bonding, but interested readers are encourage to consult one of the many excellent reviews available on this topic (e.g. Young *et al*., 2011).

Pair bond development is influenced by dopaminergic activity within the nucleus accumbens (Liu and Wang, 2003, Young *et al*., 1998). Dopamine neurotransmission is increased within the nucleus accumbens of prairie voles following mating and these increases are necessary for the formation of partner preference formation in males (Aragona *et al*., 2003). Pharmacologically blocking dopamine receptors by haloperidol prior to mating results in an elimination in partner preference by males (Aragona *et al*., 2003). In situations where

partner preferences would not necessarily be established, such as following short term cohabitation without mating, D2-receptor agonists applied to the nucleus accumbens shell can induce partner preferences (Aragona *et al.*, 2006). Activation of D1-like receptors on the other hand can block the formation of such pair bonds (Aragona *et al.*, 2006). The differential impact of D1 and D2 activation on partner preference formation appears to be due to the opposing intracellular changes induced by D1 and D2 receptor activation noted earlier (Aragona and Wang, 2007). Interestingly, D1-like receptor levels within the nucleus accumbens undergo changes following pair bonding in prairie vole males. Specifically, it appears that following the formation of a pair bond, D1-like receptor expression is increased in the nucleus accumbens in male prairie voles. Pair bonded males will then exhibit affiliative behavior towards their mates while expressing aggressive behavior towards strangers that can be blocked through antagonism of D1-like receptors within the nucleus accumbens (Aragona and Wang, 2009).

In addition to the nucleus accumbens, dopaminergic activity within other regions within the mesocorticolimbic network including the prefrontal cortex appear to be involved in the development of partner preferences. For instance, monogamous prairie voles exhibit lower concentrations of D1-like receptors and higher concentrations of D2-like receptors within the medial prefrontal cortex compared to their more promiscuous counterparts (Smeltzer *et al.*, 2006). Dopaminergic activity within the VTA may also contribute to pair bond formation as application of either GABAergic or glutamatergic antagonists within the VTA, both which presumably enhance dopamine release within the nucleus accumbens, can induce partner preferences in male prairie voles (Curtis and Wang, 2005). Altogether these data indicate dopaminergic activity plays an influential role in the formation of pair bonds.

Multiple lines of evidence indicate oxytocin is also key neurobiological substrate underlying the development of partner preferences (see review Young and Wang, 2004). The distribution of oxytocin receptors varies substantially between monogamous prairie voles and polygamous montane voles (Insel and Shapiro, 1992). Monogamous prairie voles show substantially higher oxytocin receptor concentrations within multiple areas including within the nucleus accumbens, amygdala, bed nucleus of the stria terminalis, and prefrontal cortex compared to the nonmonogamous montane voles (Insel and Shapiro, 1992). Indeed, the concentration of oxytocin receptors within the nucleus accumbens in female prairie voles is positively related to the speed at which they form partner preferences (Ross *et al.*, 2009). Altering oxytocin receptor expression in the nucleus accumbens using viral vector-mediated gene transfer can also affect partner preference formation in female prairie voles (Ross *et al.*, 2009). Partner preferences can also be shaped via pharmacological manipulations of oxytocin. For instance, ICV administration of oxytocin or injection of oxytocin directly into the nucleus accumbens can induce partner preferences in absence of mating (Cho *et al.*, 1999). Correspondingly, application of oxytocin receptor antagonists into either the nucleus accumbens or prefrontal cortex can block mating-induced partner preferences in female prairie voles (Young *et al.*, 2001).

As was noted during the previous section, oxytocin and dopamine do not act alone but rather appear to interact with one another to regulate the formation of pair bonds. For instance, it appears that both D2 receptors and oxytocin receptors must be stimulated in order to facilitate the formation of partner preferences (Liu and Wang, 2003). Injection of a D2-receptor antagonist into the nucleus accumbens of female prairie voles can prevent partner preference formation induced by oxytocin and oxytocin antagonists can block partner preference formation induced by D2-receptor agonist administration (Liu and Wang, 2003). In sum, these data suggest that both oxytocin and dopamine work together to influence partner preference formation in animals.

Although little work has been done in this area in humans, some neuroimaging data suggests motivational networks are engaged in response to romantic love. Aron and colleagues performed fMRI scanning on participants who described themselves as being intensely in love while they viewed pictures of their romantic partner or a familiar person (Aron *et al*., 2005). This study observed heightened activation within the VTA and caudate in response to viewing a romantic partner over viewing a familiar person (Aron *et al*., 2005). Similar studies have shown comparable networks are recruited in response to romantic love as they are recruited in response to maternal love including the prefrontal cortex and striatum (Bartels and Zeki, 2004). In regards to the influence of oxytocin on such attachments, Schneiderman and colleagues observed heightened plasma levels of oxytocin in new couples (Schneiderman *et al*., 2012). Higher plasma oxytocin levels were associated with higher levels of interaction between the couples and predicted which couples would remain together 6 months later (Schneiderman *et al*., 2012). One recent study explored whether oxytocin could induce partner preferences in humans (Liu *et al*., 2012). Female and male participants received oxytocin or placebo and were show video clips of a man and a woman. A day later the participant was shown pictures of an additional man and woman and was asked to decide which of the individuals they would like to learn more about and spend time with. Participants displayed an increased preference for people they had been introduced to immediately following administration of oxytocin, however, the choices made were not directed toward persons of the opposite gender. Since this study did not look exclusively at individuals who were single and was not framed in a strictly romantic context, more work is needed to determine the role of oxytocin in human partner preference formation. In short, these data and data obtained from animal work indicate systems normally engaged for the processing of motivationally relevant appetitive stimuli are also involved in the formation of pair bonds and can be regulated by oxytocin.

5.3 Aggression

5.3.1 Maternal Defensive Aggression—Intruders and other conspecifics are potentially dangerous threats to mothers and their pups and as such are highly salient social entities that require immediate attention in order to ensure safety. Mothers will aggressively attack intruders approaching their offspring (Rosenblatt *et al*., 1994). Maternal aggression peaks during lactation, suggesting oxytocin may regulate this behavior (see review Bosch and Neumann, 2012). The precise effect of oxytocin on maternal aggressive behavior still remains unclear. Oxytocin release occurs during maternal defensive aggression and the volume of release within the hypothalamus and amygdala is related to the amount of aggressive behavior displayed (Bosch *et al*., 2005). Higher concentration of oxytocin receptors within the lateral septum is associated with higher levels of aggression in rats (Caughey *et al*., 2011). Chronic ICV administration of oxytocin receptor antagonists can reduce maternal aggression in strains of rats exhibiting high anxiety and higher levels of defensive aggression (Bosch *et al*., 2005 but see Lubin *et al*., 2003). While these studies give the impression that increases in oxytocin activity are associated with higher levels of maternal aggression in these studies, others have reported the opposite (e.g. Giovenardi *et al*., 1998, Nephew *et al*., 2009). These differences in results appear to be due to differences between strains and differences in oxytocin administration protocols but further study is certainly warranted (Bosch and Neumann, 2012).

5.3.2 Selective Aggression—Pair bonding in prairie voles is characterized by the display of increased preferences of one's mate and aggressive behavior towards unfamiliar conspecifics (Aragona and Wang, 2009). Prior to pair bonding, male prairie voles show little aggression toward strangers, however, following successful pair bond formation, male prairie voles (and sometimes females) will actively attack strangers including sexually receptive females (Aragona *et al*., 2006, Gobrogge *et al*., 2007, Insel *et al*., 1995, Wang *et*

al., 1997, Winslow *et al.*, 1993). Thus, while pair bonding is associated with increased appetitive value being assigned to mates it is also characterized by aversive value assignment to once neutral conspecific strangers. This behavior is mediated by increased expression of D1 receptors within the nucleus accumbens, which occurs following extended exposure to the pair-bonded partner and is hypothesized to antagonize the formation of a second pair bond (Aragona *et al.*, 2006). Blockade of D1 receptors in these pair-bonded voles was observed to reduce aggressive behaviors towards unfamiliar females (Aragona *et al.*, 2006).

A human parallel to such mate selective behavior has been recently reported. Scheele and colleagues observed when heterosexual males in a relationship are treated with intranasal oxytocin, they preferred to keep attractive unfamiliar females at a greater distance relative to single men or men in relationships which had been treated with placebo (Scheele *et al.*, 2012). However, treatment with oxytocin had no effect on the social distance preferred when encountering unfamiliar males (Scheele *et al.*, 2012). So while there is significant evidence that oxytocin serves to enhance the salience of social cues, oxytocin, possibly through its influence on dopaminergic processes, also appears to influence shifts in valence attribution as well; resulting in the repelling of some social entities while drawing others closer.

5.4 Sexual Behavior

Engaging in sexual behavior is arguably the most fundamental form of primary reward. Sexual behavior can be divided into appetitive (the drive to perform) and consummatory (actual performance) components. This review will focus on the appetitive aspects of sexual behavior including those behaviors that serve to arouse action, bring mates together and prepare for a sexual encounter (see Everitt, 1990). Sexually receptive female rats are salient social entities to male rats. Male rats show preference for environments associated with the presence of females (Everitt, 1990). Studies examining extracellular dopamine within the nucleus accumbens observe enhanced dopamine concentrations when shown a sexually receptive female behind a screen (Damsma *et al.*, 1992, Pfaus *et al.*, 1990). Further, male rats will bar press to gain access to sexually receptive female rats (Everitt, 1990). Lesions to the amygdala reduce bar pressing behavior by males but do not affect copulatory behaviors (Everitt, 1990). This affect can be reversed through stimulation of dopaminergic activity within the nucleus accumbens (Everitt, 1990). D2 receptor antagonists infused into the nucleus accumbens increase the amount of time between mounts and intromissions, but not the rate of copulation; as such D2 antagonism is interpreted as reducing the appetitive but not consummatory aspects of sexual behavior (Everitt, 1990). Though establishing neurochemical distinctions between the appetitive and consummatory aspects of sexual behavior in females is more difficult, there is evidence to suggest that dopaminergic activity within the nucleus accumbens contributes to the experience of reward in females during mating (see Becker, 2009). Females display a preference for the pace at which copulation takes place during mating which appears to optimize the chances of pregnancy by engaging certain neuroendocrine processes (Adler, 1974, Erskine *et al.*, 1989, Gilman *et al.*, 1979, Jenkins and Becker, 2003b). Dopaminergic release within the nucleus accumbens only appears to occur when females copulate according to their pacing preferences (Becker *et al.*, 2001, Jenkins and Becker, 2003a, Mermelstein and Becker, 1995).

Oxytocin can enhance both male and female sexual behavior. Oxytocin is hypothesized to facilitate the appetitive value of sexual encounters and, as described in detail above, plays an important role in facilitating penile erection and is released in response to genital and breast stimulation (Carter, 1992, Melis and Argiolas, 2011). Oxytocin release and subsequent penile erection can be induced by stimulation of dopaminergic activity within the mesocorticolimbic system (Melis and Argiolas, 2011). Oxytocin administration reduces the

latency between intromission and ejaculation in male rats (Carter, 1992). In females, oxytocin influences the rodents display of lordosis, or an arching of the back and hindleg, in expectation of sexual behavior, which is a measure of female receptivity to a sexual encounter. Injections of oxytocin ICV increase lordosis duration and lordosis quotient (ratio of lordosis responses to male mounts, with increases in this ratio reflecting increases in female receptivity; Benelli *et al*., 1994). Reductions in both lordosis duration and quotient are noted following injection of an oxytocin antagonist (Benelli *et al*., 1994).

In humans, sexual arousal has been associated with increased neural activity within a number of regions within the motivational pathway including in the hypothalamus, striatum, amygdala insula, frontal cortex and cingulate (Arnow *et al*., 2002, Hamann *et al*., 2004, Karama *et al*., 2002, Park *et al*., 2001, Rauch *et al*., 1999, Redoute *et al*., 2000, Stoleru *et al*., 1999). Within the striatum, middle temporal cortex, cingulate, claustrum and in sensorimotor and pre motor areas, brain activity elicited by erotic visual stimulation has been shown to relate to sexual arousal as measured by penile turgidity (Arnow *et al*., 2002). Sexual arousal has also been shown to elicit slightly different responses in men and women, where men seem to recruit the amygdala and hypothalamus during the processing of sexually arousing stimuli compared to women (Hamann *et al*., 2004). However, both men and women exhibited significant activation within ventral striatal regions in response to sexually arousing images (Hamann *et al*., 2004).

Oxytocin has also been shown to play an important role in sexual behavior in humans. Oxytocin is released during sexual arousal and orgasm (Blaicher *et al*., 1999, Burri *et al*., 2008, Carmichael *et al*., 1987, but see Kruger *et al*., 2003, Murphy *et al*., 1987). Enhancement of oxytocin levels by intranasal administration prior to orgasm by masturbation results in increased catecholamine levels in the blood, heightened heart rate and increased perception of arousability (Burri *et al*., 2008). In sum, the data obtained from preclinical and human research studies indicate oxytocin, dopamine and regions within the motivational circuitry contribute to the appetitive aspects of sexual behavior and may regulate the degree of reward experienced during sexual encounters.

5.5 Other Social Interactions

The role of oxytocin mediating social interactions beyond those behaviors that occur between romantic partners or between parents and children has been explored by a number of groups (see reviews Bartz *et al*., 2011, Kemp and Guastella, 2011, McCall and Singer, 2012, Meyer-Lindenberg *et al*., 2011, Zink and Meyer-Lindenberg, 2012). Oxytocin can also influence social interactions between peers and strangers and appears to play essential roles in the identification and interpretation of social information. For instance, preclinical models have observed that oxytocin can affect social recognition (see Choleris *et al*., 2009, and Ross and Young, 2009 for review). Social recognition in rodents can be measured by noting the amount of time an individual spends investigating an unfamiliar entity over repeated exposures. Unfamiliar rodents, for instance, will spend a great deal of time sniffing one another at first but as time goes on the duration of these investigations will decrease as they become familiar with (i.e. recognize) one another. While oxytocin administration into the hippocampus or medial preoptic area of the hypothalamus enhances social recognition (i.e. reduced investigation time of a fellow rat encountered for the second time), ICV administration of oxytocin antagonists can result in social recognition deficits (Popik and van Ree, 1991, van Wimersma Greidanus and Maigret, 1996). Oxytocin knockout mice also exhibit social recognition impairments, however, these impairments can be reversed by oxytocin infusion into medial amygdala, indicating special involvement of the amygdala in this process (Choleris *et al*., 2003, Ferguson *et al*., 2001, Ferguson *et al*., 2000).

In humans, in addition playing a role in social recognition (see Kemp and Guastella 2011), oxytocin can also enhance behaviors that lead to increases in the collection of social information. For instance, oxytocin administration has been shown to orient attention toward faces, particularly the eye region (see Bartz *et al*., 2011, Kemp and Guastella, 2011). As such, increased attention to the eye region can increase awareness of social intent and can provide important information necessary to making decisions when social context is relevant. Concentrating on cues from the eye region of faces may lead to better inferences of mental state and increases emotional recognition; indeed, both skills are increased following oxytocin administration though valence appears to be an important mediator in determining oxytocin's effects (see Kemp and Guastella, 2011). Oxytocin also seems to bias perception in favor of attending to social objects like those displaying biological motion (Keri and Benedek, 2009). Furthermore, oxytocin administration has been shown to enhance memory for social but not non-social stimuli (Rimmele *et al*., 2009).

As mentioned above, the effect of oxytocin may be dependent on the valence of the social stimuli being processed. For instance, oxytocin improves the detection and classification of positive social and emotional stimuli but not for negative stimuli (see Kemp and Guastella, 2011). Memory and recognition for positive faces is improved relative to negative faces following oxytocin administration (see Kemp and Guastella, 2011, but see Savaskan *et al*., 2008). Domes and colleagues have recently reported oxytocin enhances eye gaze in happy and neutral stimuli but decreases in angry faces (Domes *et al*., 2012). Some research indicates oxytocin can improve an individual's ability to recognize fear but not necessarily other emotions (Fischer-Shofty *et al*., 2010) whereas other research seems to indicate oxytocin improves the recognition of happy faces over others (Marsh *et al*., 2010). Neuroimaging studies using an oxytocin intervention have found similarly mixed results (Zink and Meyer-Lindenberg, 2012). One possibility, which may explain some of the inconsistent results obtained in studies utilizing oxytocin interventions, may be due to interindividual differences in the effect of oxytocin, which could be related to intrinsic or genotypic differences (Bartz *et al*., 2011, Meyer-Lindenberg *et al*., 2011). Indeed, complex relationships between oxytocin genotype and sex have recently been reported with oxytocin gene polymorphisms predicting differential dopaminergic responses to a pain-stress challenge in a sex specific manner (Love *et al*., 2012).

Oxytocin effects also seem to be highly dependent on context. Oxytocin has also been shown to enhance a myriad of prosocial behaviors including promoting altruism, generosity, trust, and empathy (Bartz *et al*., 2011, Israel *et al*., 2012). However, such increases in positive social behavior are greatly dependent on the identity of the person whom this behavior is directed. De Dreu and colleagues reported that oxytocin administration was associated with increases in altruistic responses to members within the 'ingroup' but increases in aggressive behavior towards members within the 'outgroup' (De Dreu *et al*., 2012). These data seem to mirror some of the effects of oxytocin in animals. In rodents, for example, oxytocin increases positive social behaviors towards offspring and mates (i.e. in-group) but also increases aggression towards strangers and conspecifics (i.e. out-group).

Final Comment

Oxytocin clearly plays a central role in social behavior; however, researchers are still trying to grasp the main mechanism behind oxytocin's effects. First considered simply as a prosocial hormone, with recent data showing oxytocin can also increase elicited aggressive behaviors it now appears the effect of oxytocin is much more complex. Some have proposed oxytocin may act as a mediator of social salience, enhancing the processing of both positive and negative social stimuli thus promoting a wide range of positive and social behaviors. Support for this theory comes from the myriad of studies showing oxytocin administration

leads to increased attention and orientation towards social stimuli, enhanced memory for social stimuli over non-social stimuli, and improved social recognition. Oxytocin encourages social interactions between parents and children, partners, and peers. Indeed, animals treated with oxytocin will increase the amount of effort they are willing to exert to gain access to appetitive social agents, even at the expense of obtaining other forms of reward like food or drugs. Furthermore, the notion that oxytocin influences the attribution of motivational salience fits well with the demonstration of significant neurobiological interactions between oxytocinergic and dopaminergic systems.

However, some have pointed out this theory has difficulty explaining the occasional valence specific effects of oxytocin (Kemp and Guastella, 2011). For instance, oxytocin has been shown to enhance memory for happy faces relative to angry and neutral faces (Guastella *et al.*, 2008). Oxytocin administration has also been observed to improve recognition of positive facial expressions but not negative (Marsh *et al.*, 2010, but see Fischer-Shofty *et al.*, 2010). In addition, oxytocin suppresses amygdala activation for fearful faces but enhances activity for happy faces (Gamer *et al.*, 2010). As such, some researchers have taken to distinguishing oxytocin effects along a slightly different dimension, viewing oxytocin as an agent capable of encouraging approach related behaviors and discouraging withdrawal (Kemp and Guastella, 2011).

Another possibility is that through its interactions with the mesocorticolimbic dopamine system, oxytocin both enhances motivational salience attributions towards social stimuli and provokes shifts in motivational value. This theory arises out of observations of population specific motivational signals within dopaminergic neurons within the VTA (Bromberg-Martin *et al.*, 2010). As discussed above, signals within certain subpopulations of dopamine neurons are hypothesized to encode motivational salience while others carry signal relating to the motivational value (appetitive versus aversive; Bromberg-Martin *et al.*, 2010). Thus by modulating activity within this dopaminergic network, oxytocin may encourage alterations in both salience and valence assignment. If the salience of social cues increases as a result of oxytocinergic manipulation, one would expect an increase in the attention afforded towards social stimuli and a shift between inaction and action; however if processes involved in assignment of valence are also modified, one might expect more nuanced shifts in behavior, with increases in positive behavior towards certain entities and increases in negative behavior towards others. Behaviorally, oxytocin has been shown to facilitate shifts in valence attribution. For instance, in rodents, virgin rats' behavior towards pups can switch from aggressive or apathetic to affiliative through oxytocin administration (Pedersen *et al.*, 1982). Or in the case of pair-bonding, an appetitive to aversive shift is seen in male voles behavior towards unfamiliar sexually receptive females following successful pair bonding (Aragona and Wang, 2009). Recent studies in humans suggest oxytocin can have salience and valence independent effects. Gamer and colleagues found that oxytocin's effects on amygdala activity elicited by emotional faces was dependent on the valence of stimuli but the effects of oxytocin on enhancement of gaze shifts towards the eyes was valence independent (Gamer *et al.*, 2010).

Elucidating the role oxytocin plays in the processing of motivationally relevant information obtained from social stimuli is of substantial interest. Social interactions are exceedingly complex and require the evaluation of a variety of significant signals. More research is needed to ascertain how and if oxytocin modulates the degree to which social stimuli are considered relevant, determine whether these stimuli are aversive or appetitive, and what action should be taken (i.e. approach or withdrawal). Protocols that allow the differentiation between valence specific and salience specific effects may aid in our understanding of oxytocin effects on these processes.

Abbreviations

ICV	intracerebroventricular
VTA	ventral tegmental area
HPA axis	hypothalamic pituitary adrenal axis
ACTH	adrenocorticotropic hormone
cAMP	cyclic adenosine monophosphate

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Highlights

- Recent evidence suggests oxytocin acts to increase the salience of social stimuli.

- Oxytocin may affect social behaviors through its interaction with dopamine.

- Potential for oxytocin to shift assessments of value and salience via dopamine.

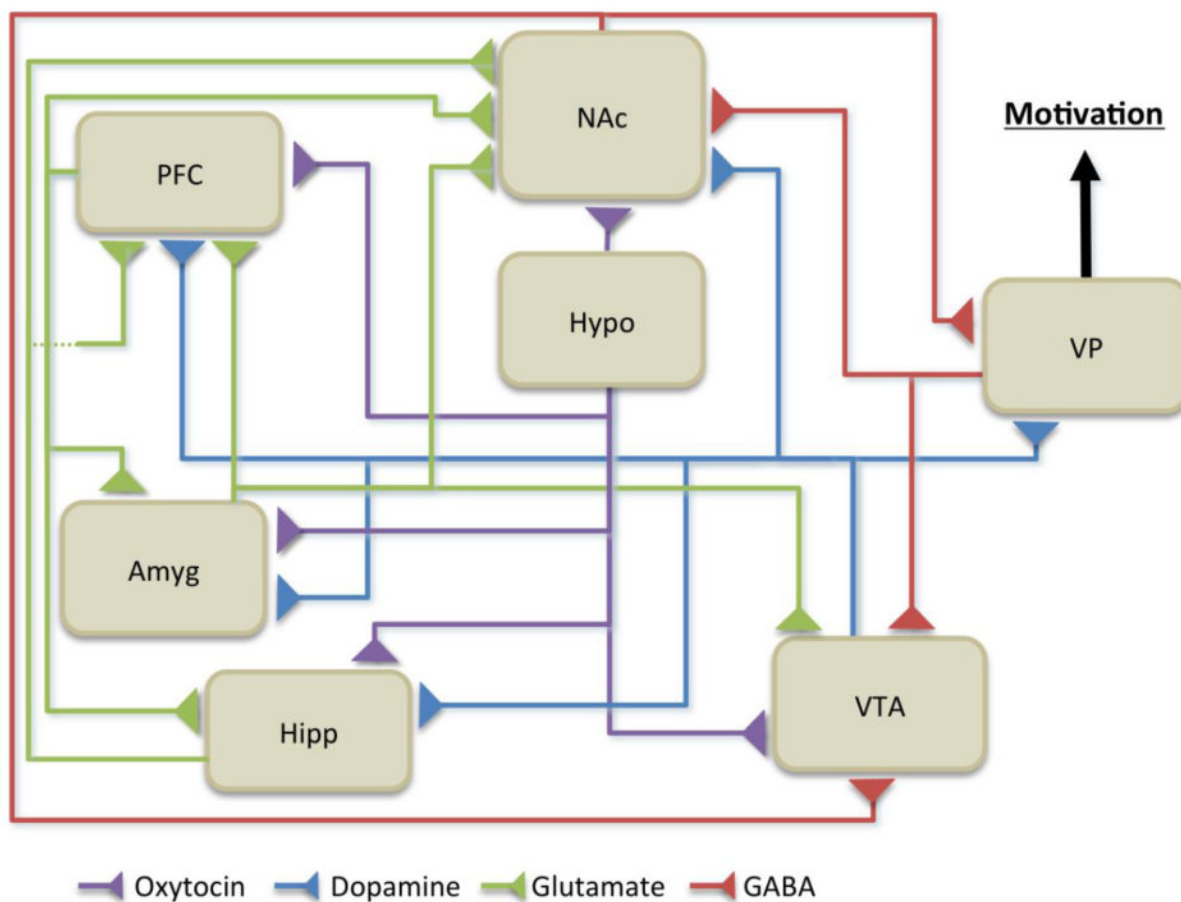- Interactions between oxytocin and dopamine will be reviewed

Figure 1. Simplified Schematic of Neuroanatomical Regions Contributing to Motivational Processes

Adapted from Kalivas and Nakamura, 1999, Blum *et al*., 2008 and Skuse *et al*., 2009. This simplified diagram outlines the major connections between regions that are believed to participate in the processing of social and motivationally relevant stimuli. Dopaminergic projections (blue) arising from the ventral tegmental area form the basis of the mesocorticolimbic pathway, which plays important roles in the development of motivated behaviors. The ventral pallidum is hypothesized to act as a major output region in this pathway ultimately connecting with motor systems to initiate motivated action. Dopaminergic activity within the mesocorticolimbic pathway can be modulated by oxytocin (purple) and the interaction between these two systems can influence a variety of social behaviors. Abbreviations: Amyg, amygdala; Hipp, hippocampus; Hypo, hypothalamus; NAc, nucleus accumbens; PFC, prefrontal cortex; VP, ventral palldium; VTA; ventral tegmental area.