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Convergence of oxytocin and dopamine signalling in neuronal circuits: Insights into the neurobiology of social interactions across species

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ABSTRACT

Social behaviour is essential for animal survival, and the hypothalamic neuropeptide oxytocin (OXT) critically impacts bonding, parenting, and decision-making. Dopamine (DA), is released by ventral tegmental area (VTA) dopaminergic neurons, regulating social cues in the mesolimbic system. Despite extensive exploration of OXT and DA roles in social behaviour independently, limited studies investigate their interplay. This narrative review integrates insights from human and animal studies, particularly rodents, emphasising recent research on pharmacological manipulations of OXT or DA systems in social behaviour. Additionally, we review studies correlating social behaviour with blood/cerebral OXT and DA levels. Behavioural facets include sociability, cooperation, pair bonding and parental care. In addition, we provide insights into OXT-DA interplay in animal models of social stress, autism, and schizophrenia. Emphasis is placed on the complex relationship between the OXT and DA systems and their collective influence on social behaviour across physiological and pathological conditions. Understanding OXT and DA imbalance is fundamental for unravelling the neurobiological underpinnings of social interaction and reward processing deficits observed in psychiatric conditions.

1. Introduction

Social behaviour is an essential component of an animal's life. It plays a significant role in the formation and maintenance of social relationships, reproductive success, and overall survival within a social group (Kappeler, 2022). Among the multiple neurobiological systems that may be involved in regulating social behaviour, oxytocin (OXT) and dopamine (DA) have been identified as key components. The importance of social behaviour for an individual's fitness and survival emphasises the necessity of comprehending the complex neuronal mechanisms governing social behaviour.

Certain brain regions such as the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus have been identified as essential components concerning social behaviour (Wang et al., 2022). These regions are the primary producers of OXT, which is released into both the blood and the brain in response to reproductive stimuli (e.g. birth, suckling, sex) as well as social interaction and stressors (Landgraf and Neumann, 2004). The nonapeptide OXT is often referred to as the "social neuropeptide", and is recognised for its involvement in fostering social attachments, maternal care, and affiliative interactions (Lee et al., 2009). Its actions are primarily mediated by OXT receptors (OXTR), which are G-protein-coupled receptors (GPCR) extensively expressed throughout the body and the brain, including areas involved in social cognition, emotional processing, and reward (Jurek and Neumann, 2018). Various social behaviours are shaped by OXT, such as social approach, bonding, parenting, and decision-making in social contexts (Menon and Neumann, 2023). In this context, over the last decades, several lines of research focused on investigating the neuronal mechanisms of this neuropeptide and its role in regulating social behaviour. The main goal is to develop appropriate therapies and new tools for manipulating the OXT system, potentially leading to treatments for brain disorders associated with disrupted social interactions.

Dopaminergic neurons, arising from both the ventral tegmental area (VTA) and substantia nigra (SN), have attracted significant scientific interest regarding social behaviour, particularly VTA-DA neurons, owing to their central role in modulating the pleasurable and aversive aspects of social interactions (Gunaydin et al., 2014; Ilango et al., 2014; Merrer et al., 2024; Solié et al., 2022). VTA-DA neurons play a central role in governing processes related to learning and the formation of memories associated with hedonic and motivational rewards (Rossato et al., 2009; Salamone and Correa, 2012; Wise, 2004). SNc-DA neurons play a pivotal role in motor function, goal-directed behaviour and

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reward (Ilango et al., 2014; Kim et al., 2015). This area of study has a rich history, with a primary focus on addiction research, particularly concerning the treatment of substance use disorders. However, it is important to recognize that the influence of dopaminergic neurons extends well beyond the context of addiction and encompasses a broad spectrum of cognitive and emotional processes. Dopaminergic neuron actions are mediated by GPCRs, which range from D1 to D5 (Sibley et al., 1993). These receptors can be categorised into two subgroups: D1-type receptors (including D1 and D5), which stimulate neuronal activity and are associated with reward-related reactions, and D2-type receptors (comprising D2, D3 and D4), which inhibit neuronal activity and reward-related responses (Beaulieu and Gainetdinov, 2011).

Dopaminergic neurons of the VTA, which extend their projections to the nucleus accumbens (NAc), play a pivotal role in regulating both social cues and reward processing in both humans and rodents (Bariselli et al., 2018; Gunaydin et al., 2014, 2014; Kawamichi et al., 2016). Specifically, research has demonstrated that VTA dopaminergic neurons become activated in rodents engaged in conspecific interactions, and increased activity in these neurons promotes social reinforcement learning (Bariselli et al., 2018; Dölen et al., 2013; Solié et al., 2022). This establishes the foundation for considering DA as a positive modulator of social behaviour and a potential target for addressing social-related disorders.

In this review, we aim to integrate insights derived from studies involving humans and animals exploring the interconnected relationship between OXT and DA and their collective influence on social behaviour across various animal species. We first provide a succinct overview of the interaction between the OXT and DA systems in the brain. Subsequently, we delve into studies that investigate the impact of pharmacological manipulations of the OXT and DA systems on social behaviour. Additionally, we spotlight research exploring the correlation between social behaviour and fluctuations in blood/cerebral levels of OXT and DA. Given the extensive literature available, our analysis centres on studies that investigated non-reproductive social interactions such as sociability and cooperation, alongside reproductive social interactions including pair bonding and parental care. Furthermore, we include a few studies that offered insights into the interplay between OXT and DA in animal models of social stress, as well as in conditions such as autism spectrum disorder (ASD) and schizophrenia. We establish connections between findings from human research and specific investigations conducted in animals, particularly rodents. Moreover, we underscore selected studies examining the potential of intranasal OXT as a therapeutic approach for alleviating maladaptive social behaviour associated with conditions like ASD. This review seeks to elucidate the complex connections between OXT and DA, exploring their combined impact on social behaviour across both typical physiological conditions and pathological states.

2. Reciprocal interplay between oxytocin and dopamine systems in the brain

Over the last 15 years, various studies have shown that OXT may enhance awareness of social behaviour, possibly through its interaction with the mesolimbic dopaminergic system. Anatomically, there is a close relationship between OXT and DA pathways in the brain (Baskerville and Douglas, 2010). The PVN, one of the main sources of OXT in the brain, innervate high DA-containing regions like the VTA, NAc, amygdala (AMY), and prefrontal cortex (PFC) (Melis et al., 2007; Roeling et al., 1993; Succu et al., 2008). Additionally, the PVN and the SON express DA receptors and receive dopaminergic innervations, possibly from the VTA (Buijs et al., 1984; Decavel et al., 1987; He et al., 2021; Rivkees and Lachowicz, 1997). In addition, the VTA, NAc, and AMY express both OXTR and DA receptors (Baskerville et al., 2009; Buijs et al., 1984; Roeling et al., 1993). Optogenetic activation or increased expression of tyrosine hydroxylase (TH, the rate-limiting enzyme in catecholamine biosynthesis) in the anteroventral periventricular nucleus (AVPV) of the mouse hypothalamus, led to elevated circulating OXT levels, while the ablation of AVPV TH+ neurons resulted in decreased OXT levels (Scott et al., 2015). Although direct neuroanatomical evidence of OXT's modulation of dopaminergic neurons in the VTA is limited, earlier research has shown that in the NAc, OXT fibres originating from the PVN are closely juxtaposed with dopaminergic innervation that arises from the VTA (He et al., 2021; Melis et al., 2007; Succu et al., 2008). Furthermore, OXT exerts precise control over DA neurons (Xiao et al., 2017). OXT signalling has distinct effects on DA neurons in different brain regions. In slice recording experiments, the OXT application increased firing rates in VTA-DA neurons but decreased firing rates in lateral substantia nigra pars compacta (SNc)-DA neurons. Optogenetic stimulation of OXT fibres also showed opposing effects, enhancing VTA-DA neuron activity while reducing activity in lateral SNc-DA neurons. The enhancement of VTA-DA neuron firing by light stimulation was blocked by an OXT receptor antagonist, indicating direct modulation by OXT. However, the antagonist alone could not prevent light-induced inhibition of SNc-DA neurons. This inhibition was found to be mediated indirectly via local GABA neurons, as it was reduced in the presence of GABA receptor antagonists. Thus, the dual effect of OXT on DA neurons in both the VTA and SNc highlights the complexity of OXT's regulation of the brain's reward systems. Although OXT may influence VTA and SNc DA activity to enhance socially rewarding interactions at the expense of exploration, further research is needed to explore the potential implications for reward-related behaviour. It is theoretically possible that SNc-DA neurons may encode information valence in a manner akin to VTA-DA neurons.

3. Oxytocin and dopamine systems in social behaviour

3.1. Oxytocin and dopamine systems in sociability

Social behaviour is governed by OXT in both humans and animals (Bosch and Young, 2018; Menon and Neumann, 2023; Neumann, 2008). One hypothesis posits that OXT enhances the relevance of both positive and negative social cues through distinct neuronal circuits, which can account for why OXT has both anxiolytic and anxiogenic effects (Shamay-Tsoory and Abu-Akel, 2016; Steinman et al., 2019). Importantly, OXT appears to affect social interactions and avoidance tendencies by altering the perceived significance of socially meaningful cues (Menon and Neumann, 2023; Shamay-Tsoory and Abu-Akel, 2016). Notably, the interaction between OXT and DA is increasingly acknowledged as a potential mechanism shaping social behaviour (Triana-Del Rio et al., 2022).

For example, a study by Groppe et al. (2013) illustrates how intranasal OXT treatment can modulate the recognition of social cues and activate reward-related brain regions, such as the VTA, using functional magnetic resonance imaging (fMRI). In this study, the authors investigated the effects of intranasal OXT treatment on the processing of social cues related to social reward (friendly face) or social punishment (angry face) in humans. Intranasal OXT administration has demonstrated the ability to elevate the central levels of this peptide, not only in the cerebrospinal fluid but also in specific brain regions (Neumann et al., 2013). Using a social incentive learning task, the authors found that women with high sociability (i.e., high scores in the Temperament and Character Inventory "cooperativeness") demonstrated enhanced recognition of both rewarding and punishing cues when compared with women with low sociability tendencies (i.e., low "cooperativeness" scores) (Groppe et al., 2013). The administration of intranasal OXT had contrasting effects on these two groups, enhancing the recognition of social cues in low-sociable participants while diminishing it in high-sociable ones. Furthermore, it is noteworthy that following OXT administration, the VTA exhibited increased activation specifically in response to rewarding and aversive cues, but not in response to neutral cues. This suggests that OXT may influence the brain's reward circuitry, which includes DA pathways, to assign salience to socially relevant cues.

A notable limitation is the inability to directly measure DA levels due to constraints associated with invasive techniques. While activation of the VTA is often associated with changes in DA release, it is not the sole determinant. Further research is essential to achieve a comprehensive understanding of DA dynamics in human studies, allowing for more conclusive insights into the interaction between OXT and DA in shaping social behaviour and perceptions of social significance.

Similar to observations from Groppe et al. (2013), another fMRI study showed a decrease in AMY activation following intranasal OXT was observed in response to both fearful expressions and happy facial expressions (Domes et al., 2007). This suggests that OXT may exert a modulatory effect on the AMY responses to facial expressions, irrespective of their emotional valence (positive or negative). This modulation may signify a reduction in uncertainty regarding the predictive value of social stimuli, thus facilitating social approach behaviour. Similar results have recently been observed in mice (Ferretti et al., 2019). In this study, the authors explored how the OXT system influenced the mice's ability to discern between unfamiliar conspecifics exhibiting negative (after fear conditioning) or positive (after relief from water deprivation) emotional states. The study revealed the essential role of OXT projections from the PVN to the central AMY in discerning fear or relief states, highlighting their significance over other brain regions like the NAc, PFC, and hippocampus. While no direct link with DA has been established considering the significant role of DA in reward processing and motivation, the influence of OXT on AMY activity may indirectly impact DA pathways involved in social reward processing and emotional regulation. The VTA-AMY pathway has been relatively understudied in the context of social behaviour compared with the well-established VTA-DA projections to the NAc and PFC. Consequently, its functional role remains largely unknown.

The interconnected relationship between OXT and DA in the VTA is a critical factor in modulating sociability and reward generated by social interactions in rodents. In one study, the authors manipulated PVN-OXT neurons with optogenetics and employed selective OXTR knockout (KO) in VTA-DA neurons, illustrating the essential role of OXT in enhancing sociability and social-conditioned place preference in adult mice with C57Bl/6 background (Hung et al., 2017). Specifically, optogenetic stimulation of PVN-OXT neurons or their VTA terminals enhanced sociability and facilitated social-conditioned place preference, whereas optogenetic inhibition of the same terminals reduced sociability and eliminated social-conditioned place preference. Furthermore, the administration of an OXTR agonist to brain slices increased the spontaneous spiking of VTA-DA neurons, an effect that could be reversed by applying an OXTR antagonist. Further experiments indicate that OXT increases the excitation-to-inhibition balance in DA neurons originating from the VTA and projecting to the medial shell of the NAc. This suggests that OXT release in the VTA during social interactions enhances the excitability of these DA neurons, leading to increased DA release in the NAc, thereby reinforcing social interactions.

3.2. Oxytocin and dopamine systems in cooperation

Cooperation and social bonding among individuals are facilitated by OXT (Patin et al., 2018; Yang et al., 2021). To illustrate, a recent fMRI study by Rilling et al. (2018) examined the impact of intranasal OXT treatment on brain activity during cooperative interactions in humans using a dyadic social interaction task. This task, also referred to as the Prisoner's dilemma game, is a renowned model in game theory that portrays the conflict between individual self-interest and collaborative cooperation. In women displaying positive social interactions (cooperation), intranasal OXT treatment was associated with decreased activation of the insula, orbitofrontal cortex, lateral septum and NAc, which are areas that receive mesolimbic DA projections. Conversely, no effects of intranasal OXT treatment were observed in women when they were not cooperating. However, intranasal OXT treatment had no discernible impact on brain activity in men when they were cooperating. In addition, reduced AMY and VTA activation after a non-cooperative outcome was found in this group (Rilling et al., 2018). Thus, OXT administration can modulate brain activity during cooperative interactions, particularly in regions receiving mesolimbic DA projections. These effects appear to be influenced by sex and the specific context of social interactions. These findings suggest that OXT may have evolved distinct, sex-specific functions, impacting neuronal and behavioural processes in a manner that is tailored to individual characteristics and social scenarios. This insight holds promise for the development of personalised medicine approaches that consider the unique responses of individuals to OXT-based interventions. In a prior fMRI investigation, Rilling et al. (2004) explored the activation of the DA system when predicting a social partner's response to altruistic actions. In participants engaged in one-shot Prisoner's Dilemma games, brain regions that receive dopaminergic projections, the ventromedial PFC and ventral striatum, showed an increased activation to reciprocated altruism and a decreased activation to unreciprocated altruism (Rilling et al., 2004). These findings suggest that DA conveys reward prediction error information (Schultz, 1998), shaping our judgments about individuals likely to reciprocate.

Drawing parallels between this human study and research conducted in rodents, a study examined cooperation in Long–Evans rats using a modified version of the Prisoner's dilemma game conducted in an operant chamber (Wood et al., 2016). In this experimental setup, pairs of rats were placed in the chamber, divided by a metal screen, with each side equipped with a retractable lever and a pellet dispenser. During each trial, the rats had the option to cooperate (by pressing a lever) or defect (by withholding a response), without prior knowledge of their partner's choice. The game had varying outcomes: cooperation resulted in three food pellets for each side, unilateral defection provided five pellets to the defector only, and when neither rat cooperated, no pellets were dispensed. The results revealed that rats adjusted their operant behaviour based on the requirements for cooperation (lever pressing or withholding response) and their hunger levels (hungry or fed ad libitum). Notably, an intraperitoneal OXT injection significantly influenced the trial outcomes, leading to a decrease in defection and an increase in cooperation (Donovan et al., 2020), a pattern similar to what has been observed in humans (Rilling et al., 2018).

While the parallels between human and rodent studies are intriguing, it is important to note that the translation of findings from rodents to humans can be challenging due to species differences. Furthermore, without direct measurement of the DA system, it remains unclear whether OXT and DA interact to influence cooperation in humans and rats. Therefore, further research using animal models and incorporating measures of both OXT and DA systems would be necessary to elucidate their interaction and its effects on cooperative behaviour as well as the reward-related neuronal circuitry.

3.3. Oxytocin and dopamine systems in pair-bonding

The OXT system plays a significant role in promoting social affiliation, attachment, and partner preference across species (Blumenthal and Young, 2023; Bosch and Young, 2018). Intranasal OXT administration has been investigated in the context of partner preference, revealing that it can enhance the attractiveness of the heterosexual men's partner and activate DA brain regions like the NAc and VTA (Scheele et al., 2013). This suggests that OXT might play a role in fostering romantic bonds by increasing the perceived attractiveness and reward value of the partner compared with unfamiliar individuals, potentially involving interactions with the DA system. Comparable outcomes were observed in female prairie voles, where OXT administration into the prelimbic cortex facilitated the formation of mating-induced partner preference, subsequently leading to heightened DA release in the NAc (Young et al., 2014). The precise mechanisms by which OXT infusion in the prelimbic cortex could alter DA release were not addressed in the paper. It is possible that VTA-DA terminals within the NAc express glutamatergic

receptors, and that glutamate release from the PFC modulates accumbal DA release. Supporting this hypothesis, the release of DA by glutamate has been demonstrated in vitro in rat slices (Clow and Jhamandas, 1989) and synaptosomes(Desce et al., 1992), and much evidence has been provided which supports the role of the glutamatergic corticostriatal neurons in the presynaptic regulation of DA release (Galli et al., 1991; Krebs et al., 1989; Saul'skaya, 1997).

Supporting the notion that OXT-DA interactions might contribute to the OXT-induced effects on social bonding (Young et al., 2014), the systemic administration of a dopaminergic antagonist effectively blocked the partner preference induced by OXT in female prairie voles (Liu and Wang, 2003). Furthermore, following the administration of a DA reuptake inhibitor, male and female prairie voles exhibited a loss of partner preference, accompanied by a subsequent reduction in oxytocinergic immunoreactive cells in the PVN (Hostetler et al., 2016).

Limited information exists regarding the involvement of the OXT system in social affiliation beyond rodents. A particular study investigated gene expression correlations of OXT and DA concerning social variation in coral reef butterflyfishes (*f. Chaetodontidae*) (Nowicki et al., 2020). The gene expression correlates of social variation were assessed within and between different species and sexes, comparing pair-bonding individuals with solitary ones and high-affiliation species with those less affiliative. The study found that individual differences in sociality were associated with OXTR and D1R expression in the dorsal portion of the ventral telencephalon, the mammalian homologue of the NAc. However, there were no major changes in OXTR as well as D1 receptor (D1R) and D2 receptor (D2R) expression in the VTA. In the context of pair bonding in adult zebra finches (*Taeniopygia guttata*), known for monogamous pairs and courtship behaviour, a study evaluated song preference in pair-bonded and unpaired females (Day et al., 2019). Paired females preferred their partner's song, while unpaired females showed no preference. Subcutaneous injection of a D2R agonist, but not a D1R agonist, induced a significant preference for the partner's song in unpaired females, suggesting D2R activation is sufficient for song preference. Another recent study assessed activation patterns in the social behaviour network (O'Connell and Hofmann, 2012) during social singing contexts in adult male zebra finches, revealing upregulation of the mRNA expression of the neuronal activation marker *Egr1* in various brain areas including the PVN (Anderson et al., 2023). The investigation did not directly assess VTA activity dependent on social context. However, the bidirectional connection between PVN and VTA, as already demonstrated in zebra finches, raises questions about the role of PVN OXT neurons projecting to VTA during social singing. Collectively, these studies (Anderson et al., 2023; Day et al., 2019; Nowicki et al., 2020) emphasize the significance of the interplay between OXT and DA and their combined impact on pair bonding, extending beyond the context of humans and rodents. Additionally, comprehending the specific and shared patterns with mammals would aid in unravelling the molecular evolution of social behaviour.

The influence of intranasal OXT administration was examined in response to scenes with positive (erotic) or aversive (fearful) valence in a fMRI study conducted on young adult men (Sauer et al., 2019). While no significant behavioural changes were noted after the treatment, OXT was found to enhance the activation of brain regions associated with reward processing, such as the VTA and NAc, in response to erotic scenes. These findings are in line with previous data showing that OXT mediated VTA activation to socially rewarding cues (Groppe et al., 2013) as well as with another study showing increased VTA activation to sexual images by intranasal OXT in women (Gregory et al., 2015). They also align with the notion that erotic stimuli typically evoke approach behaviour, which is thought to be mirrored by activation in the DA reward system.

3.4. Oxytocin and dopamine systems in parental care

Given that OXT has broader implications beyond pair bonding, intranasal OXT's effects were also examined concerning maternal and paternal bonding with their offspring (Neumann, 2009; Yoshihara et al., 2018). In a fMRI study conducted by Li et al., (2017), it was shown that intranasal OXT has a significant impact on brain activation in fathers when exposed to images of their children. Remarkably, OXT enhanced the brain's response to viewing pictures of their children, notably in regions such as the anterior cingulate cortex, known for parental caregiving, the visual cortex, possibly associated with task attention, and in the caudate nucleus, implicated in reward processing. Intriguingly, the caudate nucleus receives projections from midbrain DA and is part of the nigrostriatal DA system, which, like the mesolimbic DA system, plays a role in reward and motivation (Ikemoto et al., 2015). These findings suggest that OXT may enhance the reward or salience of visual stimuli related to one's child through its interaction with the DA system.

Building upon these insights into OXT's role in parental bonding and neuronal processing related to parental behaviour (Li et al., 2017), similar findings were replicated in mandarin voles regarding the involvement of OXT neurons in regulating paternal care (He et al., 2021). Specifically, chemogenetic activation of OXT neurons projecting from the PVN to the VTA increased fathers' interest in their pups, leading to extended licking behaviour. Conversely, inhibiting these neurons resulted in reduced pup-licking by the fathers. Both the activation and inhibition of OXT neurons were accompanied by increased and decreased DA release in the NAc, respectively, providing further evidence for the interaction between OXT and the DA reward system in shaping social behaviour (He et al., 2021).

Providing additional support for this hypothesis, one study investigated the impact of a dopaminergic reuptake inhibitor on adult male mandarin voles, which resulted in a reduction in paternal care behaviour (Wang et al., 2014). This behaviour change was accompanied by a decrease in oxytocinergic immunoreactive cells in the PVN, further establishing a connection between OXT and DA in regulating paternal care.

While we discussed various studies on pharmacological OXT treatments, it is important to consider research on blood/cerebral variations in OXT levels in response to various social stimuli. For example, one combined functional MRI-PET scanner study investigated plasma OXT and cerebral DA responses in mothers watching videos of their children compared with unfamiliar children to understand social affiliation and maternal bonding (Atzil et al., 2017). They specifically explored synchronous maternal behaviour (i.e., "mothers who were sensitive to their infant's cues for social engagement and who adjusted their behaviour to meet those needs"). The findings showed a significant positive correlation between synchronized maternal behaviour and heightened D2-type dopamine receptor response to the infant, tracked by changes in [11C] raclopride binding in many brain areas including the NAc. These behavioural findings were supported by stronger intrinsic connectivity within the medial AMY network, encompassing the NAc, the AMY and the medial PFC, all involved in prosocial behaviour regulation. In addition, plasma OXT positively correlated with vocalisation synchrony (i.e., when the mother engages in motherese [high-pitched speech and sing-song vocalization] while the infant responds with cooing, giggling, or laughing). In response to the own infant, plasma OXT also tended to positively correlate with DA responses in the NAc, indexed by changes in [11C]raclopride binding potential. In conclusion, this study underscores the involvement of OXT and DA in maternal behaviour, aligning with findings from animal studies. For example, a study on C57BL/6 N maternal mice revealed that pup vocalizations activate OXT neurons in the PVN through the posterior intralaminar thalamus, part of the non-lemniscal auditory pathway implicated in maternal and social behaviour (Valtcheva et al., 2023). This activation results in increased firing of PVN-OXT neurons and central OXT release in areas controlling pup retrieval, especially triggering OXT release in the VTA. Furthermore, investigations in Sprague-Dawley rats demonstrated that intra-NAc OXT injections or OXTR antagonist injections altered the onset of maternal behaviour (D'Cunha et al., 2011), while systemically

administered DA reuptake inhibitors stimulated maternal behaviour and reduced maternal aggression (Johns et al., 2005). In Long-Evans rats, an intra-VTA infusion of OXT increased DA release in the NAc of virgin females, whereas an OXTR antagonist significantly decreased DA release in the NAc of lactating females, suggesting an effect of OXT on DA neurons of the VTA (Shahrokh et al., 2010).

In addition to pharmacological studies of OXT and investigations into blood or cerebral OXT levels, we have also sought studies that explore the intricate interplay between genetic variations and environmental factors. Variations in OXT-related genes like OXTR, as well as DA-related genes, particularly single nucleotide polymorphisms (SNPs), have been linked to social-emotional dysregulation, including aspects of social cognition, empathy, and aggression (Grinevich et al., 2016; Pavlov et al., 2012). However, there are few studies concurrently examining SNPs in both OXT and DA-related genes and their collective impact on social-emotional behaviour. In one study, specific genetic variations in OXTR or catechol-O-methyltransferase (COMT), involved in DA breakdown, were associated with decreased sociality (Koyama et al., 2022). In the other study, variations in the DA beta-hydroxylase (DBH) gene, which influences DA signalling, interacted with childhood parenting experiences to affect maternal behaviour and compassion levels (Dobewall et al., 2021). However, limited evidence exists regarding SNPs' structural and functional consequences in OXTR, COMT, or DBH genes. Further research is needed to comprehensively understand how genetic variations in OXT and DA-related genes can impact social behaviour through OXT and DA signalling alterations.

4. Oxytocin and dopamine systems in maladaptive social behaviour

As highlighted in the introduction, OXT and DA are central to regulating various aspects of normal social behaviour. Emerging evidence also suggests their involvement in maladaptive social behaviour. Studies indicate that OXT influences processes implicated in disorders characterized by social deficits, such as major depressive disorder, posttraumatic stress disorder, ADS, and schizophrenia (Cochran et al., 2013; Sippel et al., 2017). Conversely, dysregulation of the DA system is linked to these disorders (Grace, 2016). To bridge this gap, we present a review of selected studies exploring OXT and DA interactions in social deficit disorders.

4.1. Social stress models

Examining animal models of social stress has provided valuable insights into the interplay of OXT and DA in social behaviour (Duque--Wilckens et al., 2020; Lukas et al., 2011). A recent study found that chronic psychosocial stress, specifically social isolation during adolescence, led to increased social interaction but impaired social recognition in adult male mice compared with those housed in groups (Musardo et al., 2022). These behavioural changes were associated with heightened activity and quantity of OXT neurons in the PVN. Additionally, electrophysiological recordings showed increased excitability in PVN neurons projecting to the VTA. By suppressing PVN-OXT neurons using chemogenetics, social interaction and VTA-DA neuron excitability were normalized in isolated mice. These findings suggest a pivotal role of altered PVN-OXT neuron activity in mediating the effects of adolescent social isolation on adult social behaviour. Other studies used social defeat stress (SDS), considered a severe stressor based on social hierarchy and dominance. In this paradigm, a rodent (defined as an intruder) is introduced to the cage of an aggressive, dominant rodent (defined as the resident) in repeated sessions that can last days or weeks (Hammels et al., 2015). Long-term SDS is associated with cognitive impairment, social deficits, anxiety- and depressive-like behaviours. In rodents, where high sociability is typical, OXT promotes pro-social behaviour and counteracts social avoidance. This is evidenced by experiments where intracerebroventricular (i.c.v.) administration of an OXTR antagonist in naive male Wistar rats or C57BL/6 mice decreased their preference for social interaction (Lukas et al., 2011). Moreover, following a single episode of social defeat, male rats exhibited social avoidance, but their innate social preference could be reinstated by i.c.v. infusion of synthetic OXT (Lukas et al., 2011). In female California mice, SDS resulted in reduced social approach and increased social vigilance along with increased *Oxt* mRNA levels and co-localization of OXT with c-fos (a marker of cellular activity) in the bed nucleus of the stria terminalis (BNST) (Duque-Wilckens et al., 2020). Interestingly, knocking down OXT in the BNST prevented the SDS-induced increase in social vigilance and decrease in social approach, while OXT infusion into the BNST induced social vigilance in both stress-naïve female and male California mice, highlighting the significant role of OXT in modulating social vigilance. Dopaminergic neurons of the VTA also play a complex role in the development of susceptibility to SDS in mice and rats. Changes in DA activity have been observed in male Long-Evans socially defeated rats, with increased DA release in regions like the NAc and PFC (Tidey and Miczek, 1996). Additionally, research has shown increased firing rates of VTA-DA neurons during aggressive confrontations in male Sprague-Dawley rats (Anstrom et al., 2009) and in C57BL/6 male mice susceptible to SDS (i.e., showing social avoidance) (Cao et al., 2010). Optogenetic studies have shown that inhibiting the DA VTA-NAc pathway promotes stress resilience while inhibiting the DA VTA-mPFC projections increases stress susceptibility in C57BL/6 male mice (Chaudhury et al., 2013). Chronic optogenetic activation of VTA-DA neurons in susceptible mice can restore their firing rate to normal levels, reverse social avoidance, and shift them from susceptibility to resilience, underscoring the intricate role of VTA-DA neurons in social defeat outcomes (Friedman et al., 2014). Although these studies did not directly address the interconnected relationship between OXT and DA, they highlight the role of OXT and DA in modulating social behaviour, particularly in the context of social avoidance and social vigilance.

4.2. Autism models

Several studies have investigated the interaction between OXT and DA in the context of autism. Young individuals with ASD showed improved learning following intranasal OXT administration in a probabilistic reinforcement learning task (Kruppa et al., 2019). Interestingly, this learning enhancement was specific to scenarios where the learning target and feedback were social, as opposed to non-social conditions. Moreover, the influence of OXT was reflected in altered brain activity, manifested as an increased correlation in the reward prediction error signal within the NAc activation when social feedback was compared with non-social feedback.

By contrast, a study involving children and adolescents with ASD failed to show a significant impact of intranasal OXT administration on reward perception during a social and non-social incentive delay task (Greene et al., 2018). However, OXT treatment led to notable alterations in brain activity among ASD patients, reducing frontal pole activation during the outcome phase of social rewards and increasing NAc activation during non-social reward anticipation. In addition, a positive correlation between salivary OXT levels and NAc activation was found following intranasal OXT administration, indicating the NAc's responsiveness to OXT in individuals with ASD. The absence of OXT effects on social rewards is surprising. One possible explanation may be related to how social reward anticipation and outcomes are measured in ASD. For instance, dynamic stimuli have been shown to have a more substantial impact on eliciting social impairments in ASD than static stimuli (Chevallier et al., 2015). Therefore, the lack of OXT effects in social reward conditions in this study may be attributed to static social rewards impeding the detection of OXT-related neuronal changes. Future studies examining the effects of OXT on neuronal responses to dynamic social rewards will be necessary to explore this possibility.

In animals, some studies have shown the prosocial effects of OXT in rodent models of ASD. For instance, male mice lacking *Shank3B* KO, an

animal model for autism-like behaviour, exhibited reduced social interaction and sociability, alongside decreased OXT immunoreactivity in the PVN. The intranasal administration of OXT successfully ameliorated the social deficits observed in *Shank3B* KO mice while enhancing dopaminergic synaptic plasticity within the VTA (Sgritta et al., 2019). Similarly, i.c.v. OXT administration elevated social novelty preference in HPC-1 syntaxin 1 A (*Stx1a*) KO mice, another animal model exhibiting autism-like behaviour. This enhancement in the social response was subsequently followed by a reduction in DA release in the striatum (Fujiwara et al., 2021). Notably, the intranasal administration of OXT did not succeed in enhancing social interaction among mice with a conditional deletion of OXTR in dopaminergic neurons (Sgritta et al., 2019), indicating that the presence of OXTR in dopaminergic neurons plays a pivotal role in mediating the prosocial effects of OXT.

The role of OXTR expression in contributing to the social deficits observed in individuals with ASD has been a subject of significant interest. Recent research using competitive-binding receptor autoradiography has unveiled intriguing findings, particularly in the SNc. Notably, a decrease in OXTR binding has been identified in postmortem brain samples from females with ASD (Frehner et al., 2022). Interestingly, males with ASD did not display significant changes in OXTR binding, raising the possibility of a sex-related distinction in the regulation of mature OXTR levels. Furthermore, additional investigations employing in situ hybridization techniques to visualise and quantify OXTR and TH mRNA have yielded results indicating no significant alterations. These findings collectively suggest that the observed effect on OXTR binding is unlikely to be driven by underlying differences in the DA system of the SNc.

In a study involving boys diagnosed with ASD, significant differences were observed in their plasma levels of OXT and DA when compared with control boys (Alabdali et al., 2014). Specifically, children with ASD exhibited markedly reduced levels of both OXT and DA. In addition, the decrease in OXT levels, but not DA, was strongly correlated with the severity of ASD scores in these patients. The findings of this study stand in contrast to previous research that reported elevated blood DA levels in children with ASD (El-Ansary et al., 2011). It is mentioned that few studies have assessed variations in the levels of DA, its metabolites or the activity of enzymes involved in DA metabolism in the blood, as DA cannot cross the blood-brain barrier. Rather, brain imaging studies are generally more accurate in showing dysfunction of the central DA system in ASD (DiCarlo and Wallace, 2022).

4.3. Schizophrenia models

There are very few studies that have explored the interaction between OXT and DA in the context of schizophrenia. One study involving schizophrenia patients examined the effects of intranasal OXT administration on brain activity during a social learning task. In this task, participants played a trust game with investment decisions with sessions against a computer and a human player, though both were computer programs. Although the study did not find a statistically significant impact of OXT, there was a noteworthy trend towards a significant increase in social trust in a cooperative task (Mouchlianitis et al., 2022). Specifically, schizophrenia patients treated with OXT exhibited heightened trust when they believed they were interacting with a human player as opposed to a computer player, suggesting that OXT could enhance social aspects in these patients. This behavioural change was accompanied by a significant increase in activation in the right lateral parietal cortex and the right anterior insula when interacting with human players. These two cortical regions are involved in reward processing (Schultz, 2015). Additionally, OXT led to a significant decrease in AMY activity when interacting with human players. These findings imply that a single intranasal dose of OXT can modulate an extended neuronal network comprising both cortical and subcortical components associated with reward processing and cognition. This modulation may involve interactions between OXT and DA systems, as both neurotransmitters play significant roles in regulating social behaviour and neuronal activity related to reward processing and social cognition.

In another investigation, the impact of intranasal OXT administration on an eye gaze task was examined (Bradley et al., 2019). In this task, participants engage in prolonged eye contact, a behaviour often diminished in individuals with schizophrenia. This reduction may suggest lower attention to important social cues and potentially reduced sensitivity to the social significance of eye contact. In schizophrenia patients, OXT administration increased eye contact, highlighting a heightened focus on facial expressions and social cues. However, it is noteworthy that the same OXT treatment reduced eye gaze among control individuals. These findings underscore the complex and context-dependent impact of OXT on social behaviour.

Although there were no indications of alterations in the interaction between OXT and DA in schizophrenia patients in the two studies mentioned (Bradley et al., 2019; Mouchlianitis et al., 2022), the observed differences in response to OXT between schizophrenia patients and control individuals could potentially be attributed to variations in the functioning of the DA system in these groups. This suggestion is supported not only by findings from the abovementioned neuroimaging study (Mouchlianitis et al., 2022) but also by research involving animal models. The phenotypes of Neuregulin-1 (*Nrg1*) and Disrupted-in-schizophrenia 1 (*Disc1*) mutant mice -both genes associated with schizophrenia- were characterised (O'Tuathaigh et al., 2017). The *Nrg1* heterozygous/*Disc1* homozygous ($Ngr1^{HET}/Disc1^{HOM}$) mutant mice exhibited decreased sociability and increased self-grooming behaviour, accompanied by increased expression of OXT in the hypothalamus. In addition, $Ngr1^{HET}$ /$Disc1^{HOM}$ mice showed lower striatal D2R expression, an essential component of DA signalling. However, no significant changes were found in the levels of DA and its associated metabolites (i.e., 3,4-dihydroxyphenylacetic acid and homovanillic acid) in the PFC and hippocampus. Because this is a singular study, further research is essential to elucidate the role of OXT and DA in modulating social deficits within the context of schizophrenia.

5. Conclusion and outlook

In summary, the interconnected relationship between OXT and DA, governing social behaviour, represents a complex and evolving research domain. Fig. 1 depicts the hypothesised neuronal circuits implicating DA and OXT in rodent social behaviour. As outlined in this review, OXT and DA are pivotal in shaping diverse social aspects such as sociability, cooperation, pair bonding, and parental care. Insights from studies in both humans and rodents illustrate how OXT amplifies the significance of social cues, possibly through interactions with the brain's reward circuitry involving DA pathways. Furthermore, research using animal models underscores the importance of understanding disruptions in the OXT-DA balance, contributing to maladaptive social behaviour relevant to human disorders.

Ongoing studies may reveal the complex relationship between OXT and DA enhancing our understanding of the neurobiological basis of social behaviour, and then offering new therapeutic approaches for social-related disorders.

As discussed in Section 4.1, animal models of depression induced by social stress have provided valuable insights into the interaction between OXT and DA in social behaviour. Social isolation during adolescence led to altered OXT neuronal activity and impaired social behaviour in adult male mice (Musardo et al., 2022). Suppression of PVN-OXT neurons normalised social behaviour and VTA-DA neuron excitability in isolated mice, indicating the pivotal role of altered PVN-OXT neuron activity in mediating the effects of adolescent social isolation on adult social behaviour. Additionally, studies on SDS have underscored the complex roles of OXT and DA in modulating social behaviour, particularly in social avoidance and social vigilance (Anstrom et al., 2009; Cao et al., 2010; Chaudhury et al., 2013; Duque-Wilckens et al., 2020; Friedman et al., 2014; Lukas et al., 2011;

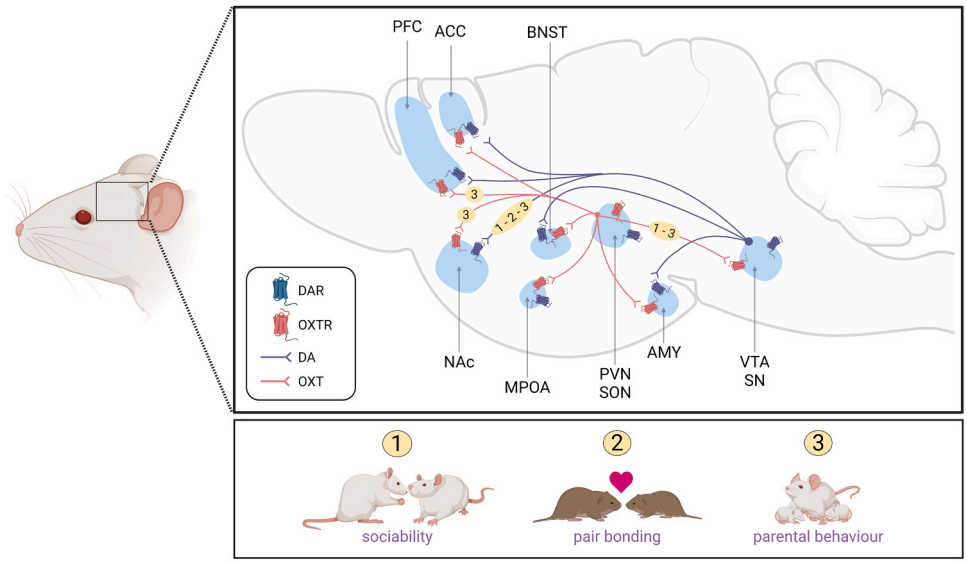

Fig. 1. Neuronal pathways of oxytocin and dopamine in rodent social behaviour. This schematic representation illustrates the proposed neuronal pathways involving oxytocin (OXT) and dopamine (DA) during social behaviour in rodents. OXT neurons originating primarily from the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei project to various brain areas involved in regulating non-reproductive and reproductive social behaviours. These areas expressing oxytocin receptors (OXTR) include the prefrontal cortex (PFC), anterior cingulate cortex (ACC), nucleus accumbens (NAc), bed nucleus of the stria terminalis (BNST), medial preoptic area (MPOA), amygdala (AMY), and ventral tegmental area (VTA). The nigrostriatal, mesocortical, and mesolimbic DA pathways originating from the substantia nigra (SN) and ventral tegmental area (VTA) innervate key brain regions expressing dopamine receptors (DAR) such as the PFC, NAc, and AMY. Although not depicted here, the incertohypothalamic DA pathway also involves projections from the zone incerta to the MPOA, SON, and PVN of the hypothalamus. Our review of the literature highlights specific circuits involving OXT and DA in modulating various social behaviours. For example, OXT via Circuit 1 influences social interaction and their rewarding properties, while Circuit 2 modulates pair bonding, and Circuit 3 affects parental behaviour. Figure created with Biorender (https://www.biorender.com/).

Tidey and Miczek, 1996). Thus, understanding the interplay between PVN-OXT neuronal activity and VTA-DA neuronal excitability offers promising avenues for developing targeted therapies aimed at modulating these pathways to alleviate depression-relevant symptoms induced by social stress.

Despite the complexity of the interactions between OXT, DA, and ASD pathology, the studies reviewed in Section 4.2 collectively suggest the development of drugs targeting the OXT and DA systems to ameliorate social cognition and communication deficits often observed in individuals with ASD. One study found improved learning in individuals with ASD following intranasal OXT administration, with increased correlation in the reward prediction error signal in the NAc during social feedback (Kruppa et al., 2019). Conversely, another study showed no significant impact of intranasal OXT administration on reward perception in ASD individuals, although notable alterations in brain activity, including the NAc, were observed (Greene et al., 2018). Other studies showed that OXTR binding was decreased in the SNc in postmortem brain samples from females with ASD (Frehner et al., 2022), while plasma levels of OXT and DA were significantly reduced in boys diagnosed with ASD compared with the controls (Alabdali et al., 2014). Animal studies demonstrated the prosocial effects of OXT in rodent models of ASD, with OXT administration ameliorating social deficits and modulating DA synaptic plasticity (Sgritta et al., 2019). Considering the insights gained from these studies, one could envision drugs that might modulate OXT and DA levels or enhance receptor sensitivity in brain regions essential for social behaviour such as the NAc. These pharmacological interventions could offer promising avenues for addressing social deficits associated with ASD but also with other psychiatric disorders such as schizophrenia (see Section 4.3).

To achieve these objectives, further basic research is imperative to identify novel drug targets and mechanisms of action. More *in vivo* imaging and behavioural studies are necessary to explore the dynamic changes in OXT and DA activity following pharmacological interventions like OXT and DA drugs. Moreover, additional studies using animal models are needed to validate potential drug targets at the convergence of the OXT and DA systems and to assess the efficacy and safety of novel therapeutic approaches in clinical trials. The use of cutting-edge technologies, such as single-cell RNA sequencing and proteome analysis, can aid in identifying cell-specific gene expression patterns and protein profiles associated with OXT and DA signalling in the brains of individuals with neurodevelopmental and neuropsychiatric disorders. By integrating these state-of-the-art technologies and adopting interdisciplinary approaches, we can advance our comprehension of OXT and DA interactions and develop innovative therapies.

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References

Alabdali, A., Al-Ayadhi, L., El-Ansary, A., 2014. Association of social and cognitive impairment and biomarkers in autism spectrum disorders. J. Neuroinflamm. 11, 4. https://doi.org/10.1186/1742-2094-11-4.

Anderson, K.L., Colón, L., Doolittle, V., Rosario Martinez, R., Uraga, J., Whitney, O., 2023. Context-dependent activation of a social behavior brain network during learned vocal production. Brain Struct. Funct. 228, 1785–1797. https://doi.org/10.1007/s00429-023-02693-0.

Anstrom, K.K., Miczek, K.A., Budygin, E.A., 2009. Increased phasic dopamine signaling in the mesolimbic pathway during social defeat in rats. Neuroscience 161, 3–12. https://doi.org/10.1016/j.neuroscience.2009.03.023.

Atzil, S., Touroutoglou, A., Rudy, T., Salcedo, S., Feldman, R., Hooker, J.M., Dickerson, B.C., Catana, C., Barrett, L.F., 2017. Dopamine in the medial amygdala network mediates human bonding. Proc. Natl. Acad. Sci. 114, 2361–2366. https://doi.org/10.1073/pnas.1612233114.

Bariselli, S., Hörnberg, H., Prévost-Solié, C., Musardo, S., Hatstatt-Burklé, L., Scheiffele, P., Bellone, C., 2018. Role of VTA dopamine neurons and neuroligin 3 in sociability traits related to nonfamiliar conspecific interaction. Nat. Commun. 9, 3173. https://doi.org/10.1038/s41467-018-05382-3.

Baskerville, T.A., Douglas, A.J., 2010. Dopamine and oxytocin interactions underlying behaviors: potential contributions to behavioral disorders. CNS Neurosci. Ther. 16, e92–e123. https://doi.org/10.1111/j.1755-5949.2010.00154.x.

Baskerville, T.A., Allard, J., Wayman, C., Douglas, A.J., 2009. Dopamine-oxytocin interactions in penile erection. Eur. J. Neurosci. 30, 2151–2164. https://doi.org/10.1111/j.1460-9568.2009.06999.x.

Beaulieu, J.-M., Gainetdinov, R.R., 2011. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol. Rev. 63, 182–217. https://doi.org/10.1124/pr.110.002642.

Blumenthal, S.A., Young, L.J., 2023. The neurobiology of love and pair bonding from human and animal perspectives. Biology 12, 844. https://doi.org/10.3390/biology12060844.

Bosch, O.J., Young, L.J., 2018. Oxytocin and social relationships: from attachment to bond disruption. Curr. Top. Behav. Neurosci. 35 97–117. https://doi.org/10.1007/7854_2017_10.

Bradley, E.R., Seitz, A., Niles, A.N., Rankin, K.P., Mathalon, D.H., O'Donovan, A., Woolley, J.D., 2019. Oxytocin increases eye gaze in schizophrenia. Schizophr. Res. 212, 177–185. https://doi.org/10.1016/j.schres.2019.07.039.

Buijs, R.M., Geffard, M., Pool, C.W., Hoorneman, E.M., 1984. The dopaminergic innervation of the supraoptic and paraventricular nucleus. A light and electron microscopical study. Brain Res. 323, 65–72. https://doi.org/10.1016/0006-8993(84)90265-8.

Cao, J.-L., Covington, H.E., Friedman, A.K., Wilkinson, M.B., Walsh, J.J., Cooper, D.C., Nestler, E.J., Han, M.-H., 2010. Mesolimbic dopamine neurons in the brain reward circuit mediate susceptibility to social defeat and antidepressant action. J. Neurosci. 30, 16453–16458. https://doi.org/10.1523/JNEUROSCI.3177-10.2010.

Chaudhury, D., Walsh, J.J., Friedman, A.K., Juarez, B., Ku, S.M., Koo, J.W., Ferguson, D., Tsai, H.-C., Pomeranz, L., Christoffel, D.J., Nectow, A.R., Ekstrand, M., Domingos, A., Mazei-Robison, M.S., Mouzon, E., Lobo, M.K., Neve, R.L., Friedman, J. M., Russo, S.J., Deisseroth, K., Nestler, E.J., Han, M.-H., 2013. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. Nature 493, 532–536. https://doi.org/10.1038/nature11713.

Chevallier, C., Parish-Morris, J., McVey, A., Rump, K., Sasson, N.J., Herrington, J., Schultz, R.T., 2015. Measuring social attention and motivation in Autism spectrum disorder using eye-tracking: stimulus type matters. Autism Res. 8, 620–628. https://doi.org/10.1002/aur.1479.

Clow, D.W., Jhamandas, K., 1989. Characterization of L-glutamate action on the release of endogenous dopamine from the rat caudate-putamen. J. Pharmacol. Exp. Ther. 248, 722–728.

Cochran, D.M., Fallon, D., Hill, M., Frazier, J.A., 2013. The role of oxytocin in psychiatric disorders: a review of biological and therapeutic research findings. Harv. Rev. Psychiatry 21, 219–247. https://doi.org/10.1097/HRP.0b013e3182a75b7d.

D'Cunha, T.M., King, S.J., Fleming, A.S., Lévy, F., 2011. Oxytocin receptors in the nucleus accumbens shell are involved in the consolidation of maternal memory in postpartum rats. Horm. Behav. 59, 14–21. https://doi.org/10.1016/j.yhbeh.2010.09.007.

Day, N.F., Saxon, D., Robbins, A., Harris, L., Nee, E., Shroff-Mehta, N., Stout, K., Sun, J., Lillie, N., Burns, M., Korn, C., Coleman, M.J., 2019. D2 dopamine receptor activation induces female preference for male song in the monogamous zebra finch. J. Exp. Biol. 222, jeb191510 https://doi.org/10.1242/jeb.191510.

Decavel, C., Geffard, M., Calas, A., 1987. Comparative study of dopamine- and noradrenaline-immunoreactive terminals in the paraventricular and supraoptic nuclei of the rat. Neurosci. Lett. 77, 149–154. https://doi.org/10.1016/0304-3940(87)90577-5.

Desce, J.M., Godeheu, G., Galli, T., Artaud, F., Chéramy, A., Glowinski, J., 1992. L-glutamate-evoked release of dopamine from synaptosomes of the rat striatum: involvement of AMPA and N-methyl-D-aspartate receptors. Neuroscience 47, 333–339. https://doi.org/10.1016/0306-4522(92)90249-2.

DiCarlo, G.E., Wallace, M.T., 2022. Modeling dopamine dysfunction in autism spectrum disorder: from invertebrates to vertebrates. Neurosci. Biobehav Rev. 133, 104494 https://doi.org/10.1016/j.neubiorev.2021.12.017.

Dobewall, H., Keltikangas-Järvinen, L., Saarinen, A., Lyytikäinen, L.-P., Zwir, I., Cloninger, R., Raitakari, O.T., Lehtimäki, T., Hintsanen, M., 2021. Genetic differential susceptibility to the parent-child relationship quality and the life span development of compassion. Dev. Psychobiol. 63, e22184 https://doi.org/10.1002/dev.22184.

Dölen, G., Darvishzadeh, A., Huang, K.W., Malenka, R.C., 2013. Social reward requires coordinated activity of accumbens oxytocin and 5HT. Nature 501, 179–184. https://doi.org/10.1038/nature12518.

Domes, G., Heinrichs, M., Gläscher, J., Büchel, C., Braus, D.F., Herpertz, S.C., 2007. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol. Psychiatry 62, 1187–1190. https://doi.org/10.1016/j.biopsych.2007.03.025.

Donovan, A., Ryan, E., Wood, R.I., 2020. Cooperative responses in rats playing a 2 × 2 game: Effects of opponent strategy, payoff, and oxytocin. Psychoneuroendocrinology 121, 104803. https://doi.org/10.1016/j.psyneuen.2020.104803.

Duque-Wilckens, N., Torres, L.Y., Yokoyama, S., Minie, V.A., Tran, A.M., Petkova, S.P., Hao, R., Ramos-Maciel, S., Rios, R.A., Jackson, K., Flores-Ramirez, F.J., Garcia-Carachure, I., Pesavento, P.A., Iñiguez, S.D., Grinevich, V., Trainor, B.C., 2020. Extrahypothalamic oxytocin neurons drive stress-induced social vigilance and avoidance. Proc. Natl. Acad. Sci. 117, 26406–26413. https://doi.org/10.1073/pnas.2011890117.

El-Ansary, A.K., Bacha, A.B., Ayahdi, L.Y.A.-, 2011. Relationship between chronic lead toxicity and plasma neurotransmitters in autistic patients from Saudi Arabia. Clin. Biochem. 44, 1116–1120. https://doi.org/10.1016/j.clinbiochem.2011.06.982.

Ferretti, V., Maltese, F., Contarini, G., Nigro, M., Bonavia, A., Huang, H., Gigliucci, V., Morelli, G., Scheggia, D., Managò, F., Castellani, G., Lefevre, A., Cancedda, L., Chini, B., Grinevich, V., Papaleo, F., 2019. Oxytocin signaling in the central amygdala modulates emotion discrimination in mice. Curr. Biol. 29, 1938–1953.e6. https://doi.org/10.1016/j.cub.2019.04.070.

Frehner, S.S., Dooley, K.T., Palumbo, M.C., Smith, A.L., Goodman, M.M., Bales, K.L., Freeman, S.M., 2022. Effect of sex and autism spectrum disorder on oxytocin receptor binding and mRNA expression in the dopaminergic pars compacta of the human substantia nigra. Philos. Trans. R. Soc. Lond. B Biol. Sci. 377, 20210118 https://doi.org/10.1098/rstb.2021.0118.

Friedman, A.K., Walsh, J.J., Juarez, B., Ku, S.M., Chaudhury, D., Wang, J., Li, X., Dietz, D.M., Pan, N., Vialou, V.F., Neve, R.L., Yue, Z., Han, M.-H., 2014. Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. Science 344, 313–319. https://doi.org/10.1126/science.1249240.

Fujiwara, T., Kofuji, T., Akagawa, K., 2021. Disturbance of the reciprocal-interaction between the OXTergic and DAergic systems in the CNS causes atypical social behavior in syntaxin 1A knockout mice. Behav. Brain Res. 413, 113447 https://doi.org/10.1016/j.bbr.2021.113447.

Galli, T., Godeheu, G., Artaud, F., Desce, J.M., Pittaluga, A., Barbeito, L., Glowsinki, J., Chéramy, A., 1991. Specific role of N-acetyl-aspartyl-glutamate in the in vivo regulation of dopamine release from dendrites and nerve terminals of nigrostriatal dopaminergic neurons in the cat. Neuroscience 42, 19–28. https://doi.org/10.1016/0306-4522(91)90146-f.

Grace, A.A., 2016. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nat. Rev. Neurosci. 17, 524–532. https://doi.org/10.1038/nrn.2016.57.

Greene, R.K., Spanos, M., Alderman, C., Walsh, E., Bizzell, J., Mosner, M.G., Kinard, J.L., Stuber, G.D., Chandrasekhar, T., Politte, L.C., Sikich, L., Dichter, G.S., 2018. The effects of intranasal oxytocin on reward circuitry responses in children with autism spectrum disorder. J. Neurodev. Disord. 10, 12. https://doi.org/10.1186/s11689-018-9228-y.

Gregory, R., Cheng, H., Rupp, H.A., Sengelaub, D.R., Heiman, J.R., 2015. Oxytocin increases VTA activation to infant and sexual stimuli in nulliparous and postpartum women. Horm. Behav. 69, 82–88. https://doi.org/10.1016/j.yhbeh.2014.12.009.

Grinevich, V., Knobloch-Bollmann, H.S., Eliava, M., Busnelli, M., Chini, B., 2016. Assembling the puzzle: pathways of oxytocin signaling in the brain. Biol. Psychiatry 79, 155–164. https://doi.org/10.1016/j.biopsych.2015.04.013.

Groppe, S.E., Gossen, A., Rademacher, L., Hahn, A., Westphal, L., Gründer, G., Spreckelmeyer, K.N., 2013. Oxytocin influences processing of socially relevant cues in the ventral tegmental area of the human brain. Biol. Psychiatry 74, 172–179. https://doi.org/10.1016/j.biopsych.2012.12.023.

Gunaydin, L.A., Grosenick, L., Finkelstein, J.C., Kauvar, I.V., Fenno, L.E., Adhikari, A., Lammel, S., Mirzabekov, J.J., Airan, R.D., Zalocusky, K.A., Tye, K.M., Anikeeva, P., Malenka, R.C., Deisseroth, K., 2014. Natural neural projection dynamics underlying social behavior. Cell 157, 1535–1551. https://doi.org/10.1016/j.cell.2014.05.017.

Hammels, C., Pishva, E., De Vry, J., van den Hove, D.L.A., Prickaerts, J., van Winkel, R., Selten, J.-P., Lesch, K.-P., Daskalakis, N.P., Steinbusch, H.W.M., van Os, J., Kenis, G., Rutten, B.P.F., 2015. Defeat stress in rodents: from behavior to molecules. Neurosci. Biobehav. Rev. 59, 111–140. https://doi.org/10.1016/j.neubiorev.2015.10.006.

He, Z., Zhang, L., Hou, W., Zhang, X., Young, L.J., Li, L., Liu, L., Ma, H., Xun, Y., Lv, Z., Li, Y., Jia, R., Li, J., Tai, F., 2021. Paraventricular nucleus oxytocin subsystems promote active paternal behaviors in Mandarin Voles. J. Neurosci. 41, 6699–6713. https://doi.org/10.1523/JNEUROSCI.2864-20.2021.

Hostetler, C.M., Phillips, T.J., Ryabinin, A.E., 2016. Methamphetamine consumption inhibits pair bonding and hypothalamic oxytocin in Prairie voles. PLoS One 11, e0158178. https://doi.org/10.1371/journal.pone.0158178.

Hung, L.W., Neuner, S., Polepalli, J.S., Beier, K.T., Wright, M., Walsh, J.J., Lewis, E.M., Luo, L., Deisseroth, K., Dölen, G., Malenka, R.C., 2017. Gating of social reward by oxytocin in the ventral tegmental area. Science 357, 1406–1411. https://doi.org/10.1126/science.aan4994.

Ikemoto, S., Yang, C., Tan, A., 2015. Basal ganglia circuit loops, dopamine and motivation: a review and enquiry. Behav. Brain Res. 290, 17–31. https://doi.org/10.1016/j.bbr.2015.04.018.

Ilango, A., Kesner, A.J., Keller, K.L., Stuber, G.D., Bonci, A., Ikemoto, S., 2014. Similar roles of substantia nigra and ventral tegmental dopamine neurons in reward and aversion. J. Neurosci. 34, 817–822. https://doi.org/10.1523/JNEUROSCI.1703-13.2014.

Johns, J.M., Joyner, P.W., McMurray, M.S., Elliott, D.L., Hofler, V.E., Middleton, C.L., Knupp, K., Greenhill, K.W., Lomas, L.M., Walker, C.H., 2005. The effects of dopaminergic/serotonergic reuptake inhibition on maternal behavior, maternal aggression, and oxytocin in the rat. Pharmacol. Biochem Behav. 81, 769–785. https://doi.org/10.1016/j.pbb.2005.06.001.

Jurek, B., Neumann, I.D., 2018. The oxytocin receptor: from intracellular signaling to behavior. Physiol. Rev. 98, 1805–1908. https://doi.org/10.1152/physrev.00031.2017.

Kappeler, P., 2022. Animal Behaviour: An Evolutionary Perspective. Springer International Publishing, Suisse.

Kawamichi, H., Sugawara, S.K., Hamano, Y.H., Makita, K., Kochiyama, T., Sadato, N., 2016. Increased frequency of social interaction is associated with enjoyment enhancement and reward system activation. Sci. Rep. 6, 24561 https://doi.org/10.1038/srep24561.

Kim, H.F., Ghazizadeh, A., Hikosaka, O., 2015. Dopamine neurons encoding long-term memory of object value for habitual behavior. Cell 163, 1165–1175. https://doi.org/10.1016/j.cell.2015.10.063.
Koyama, Y., Nawa, N., Ochi, M., Surkan, P.J., Fujiwara, T., 2022. Joint roles of oxytocin- and dopamine-related genes and childhood parenting experience in maternal supportive social network. Child Psychiatry Hum. Dev. https://doi.org/10.1007/s10578-022-01434-4.
Krebs, M.O., Kemel, M.L., Gauchy, C., Desban, M., Glowinski, J., 1989. Glycine potentiates the NMDA-induced release of dopamine through a strychnine-insensitive site in the rat striatum. Eur. J. Pharmacol. 166, 567–570. https://doi.org/10.1016/0014-2999(89)90378-6.
Kruppa, J.A., Gossen, A., Oberwelland Weiß, E., Kohls, G., Großheinrich, N., Cholemkery, H., Freitag, C.M., Karges, W., Wölfle, E., Sinzig, J., Fink, G.R., Herpertz-Dahlmann, B., Konrad, K., Schulte-Rüther, M., 2019. Neural modulation of social reinforcement learning by intranasal oxytocin in male adults with high-functioning autism spectrum disorder: a randomized trial. Neuropsychopharmacology 44, 749–756. https://doi.org/10.1038/s41386-018-0258-7.
Landgraf, R., Neumann, I.D., 2004. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. Front. Neuroendocr. 25, 150–176. https://doi.org/10.1016/j.yfrne.2004.05.001.
Lee, H.-J., Macbeth, A.H., Pagani, J.H., Young, W.S., 2009. Oxytocin: the great facilitator of life. Prog. Neurobiol. 88, 127–151. https://doi.org/10.1016/j.pneurobio.2009.04.001.
Li, T., Chen, X., Mascaro, J., Haroon, E., Rilling, J.K., 2017. Intranasal oxytocin, but not vasopressin, augments neural responses to toddlers in human fathers. Horm. Behav. 93, 193–202. https://doi.org/10.1016/j.yhbeh.2017.01.006.
Liu, Y., Wang, Z.X., 2003. Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. Neuroscience 121, 537–544. https://doi.org/10.1016/s0306-4522(03)00555-4.
Lukas, I., So, Da, Veenema, Id, 2011. The neuropeptide oxytocin facilitates pro-social behavior and prevents social avoidance in rats and mice. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 36. https://doi.org/10.1038/npp.2011.95.
Melis, M.R., Melis, T., Cocco, C., Succu, S., Sanna, F., Pillolla, G., Boi, A., Ferri, G.-L., Argiolas, A., 2007. Oxytocin injected into the ventral tegmental area induces penile erection and increases extracellular dopamine in the nucleus accumbens and paraventricular nucleus of the hypothalamus of male rats. Eur. J. Neurosci. 26, 1026–1035. https://doi.org/10.1111/j.1460-9568.2007.05721.x.
Menon, R., Neumann, I.D., 2023. Detection, processing and reinforcement of social cues: regulation by the oxytocin system. Nat. Rev. Neurosci. https://doi.org/10.1038/s41583-023-00759-w.
Merrer, J.L., Detraux, B., Gandía, J., Groote, A.D., Fonteneau, M., d'Exaerde, A., de, K., Becker, J.A.J., 2024. Balance between projecting neuronal populations of the nucleus accumbens controls social behavior in mice. Biol. Psychiatry 95, 123–135. https://doi.org/10.1016/j.biopsych.2023.05.008.
Mouchlianitis, E.D., Tracy, D.K., Wigton, R., Vanes, L.D., Fett, A.-K., Shergill, S.S., 2022. Neuroimaging oxytocin modulation of social reward learning in schizophrenia. BJPsych Open 8, e175. https://doi.org/10.1192/bjo.2022.577.
Musardo, S., Contestabile, A., Knoop, M., Baud, O., Bellone, C., 2022. Oxytocin neurons mediate the effect of social isolation via the VTA circuits. Elife 11, e73421. https://doi.org/10.7554/eLife.73421.
Neumann, I.D., 2008. Brain oxytocin: a key regulator of emotional and social behaviours in both females and males. J. Neuroendocr. 20, 858–865. https://doi.org/10.1111/j.1365-2826.2008.01726.x.
Neumann, I.D., 2009. The advantage of social living: brain neuropeptides mediate the beneficial consequences of sex and motherhood. Front. Neuroendocr. 30, 483–496. https://doi.org/10.1016/j.yfrne.2009.04.012.
Neumann, I.D., Maloumby, R., Beiderbeck, D.I., Lukas, M., Landgraf, R., 2013. Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice. Psychoneuroendocrinology 38, 1985–1993. https://doi.org/10.1016/j.psyneuen.2013.03.003.
Nowicki, J.P., Pratchett, M.S., Walker, S.P.W., Coker, D.J., O'Connell, L.A., 2020. Gene expression correlates of social evolution in coral reef butterflyfishes. Proc. Biol. Sci. 287, 20200239. https://doi.org/10.1098/rspb.2020.0239.
O'Connell, L.A., Hofmann, H.A., 2012. Evolution of a vertebrate social decision-making network. Science 336, 1154–1157. https://doi.org/10.1126/science.1218889.
O'Tuathaigh, C.M.P., Fumagalli, F., Desbonnet, L., Perez-Branguli, F., Moloney, G., Loftus, S., O'Leary, C., Petit, E., Cox, R., Tighe, O., Clarke, G., Lai, D., Harvey, R.P., Cryan, J.F., Mitchell, K.J., Dinan, T.G., Riva, M.A., Waddington, J.L., 2017. Epistatic and independent effects on schizophrenia-related phenotypes following co-disruption of the risk factors neuregulin-1 × DISC1. Schizophr. Bull. 43, 214–225. https://doi.org/10.1093/schbul/sbw120.
Patin, A., Scheele, D., Hurlemann, R., 2018. Oxytocin and interpersonal relationships. Curr. Top. Behav. Neurosci. 35, 389–420. https://doi.org/10.1007/7854_2017_22.
Pavlov, K.A., Chistiakov, D.A., Chekhonin, V.P., 2012. Genetic determinants of aggression and impulsivity in humans. J. Appl. Genet. 53, 61–82. https://doi.org/10.1007/s13353-011-0069-6.
Rilling, J.K., Chen, Xiangchuan, Chen, Xu, Haroon, E., 2018. Intranasal oxytocin modulates neural functional connectivity during human social interaction. Am. J. Prima 80, e22740. https://doi.org/10.1002/ajp.22740.
Rilling, J.K., Sanfey, A.G., Aronson, J.A., Nystrom, L.E., Cohen, J.D., 2004. Opposing BOLD responses to reciprocated and unreciprocated altruism in putative reward pathways. Neuroreport 15, 2539–2543. https://doi.org/10.1097/00001756-200411150-00022.
Rivkees, S.A., Lachowicz, J.E., 1997. Functional D1 and D5 dopamine receptors are expressed in the suprachiasmatic, supraoptic, and paraventricular nuclei of primates. Synapse 26, 1–10 https://doi.org/10.1002/(SICI)1098-2396(199705)26:1<1::AID-SYN1>3.0.CO;2-D.
Roeling, T.A., Veening, J.G., Peters, J.P., Vermelis, M.E., Nieuwenhuys, R., 1993. Efferent connections of the hypothalamic "grooming area" in the rat. Neuroscience 56, 199–225. https://doi.org/10.1016/0306-4522(93)90574-y.
Rossato, J.I., Bevilaqua, L.R.M., Izquierdo, I., Medina, J.H., Cammarota, M., 2009. Dopamine controls persistence of long-term memory storage. Science 325, 1017–1020. https://doi.org/10.1126/science.1172545.
Salamone, J.D., Correa, M., 2012. The mysterious motivational functions of mesolimbic dopamine. Neuron 76, 470–485. https://doi.org/10.1016/j.neuron.2012.10.021.
Sauer, C., Montag, C., Reuter, M., Kirsch, P., 2019. Oxytocinergic modulation of brain activation to cues related to reproduction and attachment: differences and commonalities during the perception of erotic and fearful social scenes. Int. J. Psychophysiol. 136, 87–96. https://doi.org/10.1016/j.ijpsycho.2018.06.005.
Saul'skaya, N.B., 1997. Monoamine metabolism in the striatum of the rat brain during drug infusion into the nucleus accumbens. Neurosci. Behav. Physiol. 27, 728–733. https://doi.org/10.1007/BF02461936.
Scheele, D., Wille, A., Kendrick, K.M., Stoffel-Wagner, B., Becker, B., Güntürkün, O., Maier, W., Hurlemann, R., 2013. Oxytocin enhances brain reward system responses in men viewing the face of their female partner. Proc. Natl. Acad. Sci. 110, 20308–20313. https://doi.org/10.1073/pnas.1314190110.
Schultz, W., 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. 80, 1–27. https://doi.org/10.1152/jn.1998.80.1.1.
Schultz, W., 2015. Neuronal reward and decision signals: from theories to data. Physiol. Rev. 95, 853–951. https://doi.org/10.1152/physrev.00023.2014.
Scott, N., Prigge, M., Yizhar, O., Kimchi, T., 2015. A sexually dimorphic hypothalamic circuit controls maternal care and oxytocin secretion. Nature 525, 519–522. https://doi.org/10.1038/nature15378.
Sgritta, M., Dooling, S.W., Buffington, S.A., Momin, E.N., Francis, M.B., Britton, R.A., Costa-Mattioli, M., 2019. Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder. Neuron 101, 246–259. e6. https://doi.org/10.1016/j.neuron.2018.11.018.
Shahrokh, D.K., Zhang, T.-Y., Diorio, J., Gratton, A., Meaney, M.J., 2010. Oxytocin-dopamine interactions mediate variations in maternal behavior in the rat. Endocrinology 151, 2276–2286. https://doi.org/10.1210/en.2009-1271.
Shamay-Tsoory, S.G., Abu-Akel, A., 2016. The social salience hypothesis of oxytocin. Biol. Psychiatry 79, 194–202. https://doi.org/10.1016/j.biopsych.2015.07.020.
Sibley, D.R., Monsma, F.J., Shen, Y., 1993. Molecular neurobiology of dopaminergic receptors. Int. Rev. Neurobiol. 35, 391–415. https://doi.org/10.1016/s0074-7742(08)60573-5.
Sippel, L.M., Allington, C.E., Pietrzak, R.H., Harpaz-Rotem, I., Mayes, L.C., Olff, M., 2017. Oxytocin and stress-related disorders: neurobiological mechanisms and treatment opportunities, 2470547016687996 Chronic Stress 1. https://doi.org/10.1177/2470547016687996.
Solié, C., Girard, B., Righetti, B., Tapparel, M., Bellone, C., 2022. VTA dopamine neuron activity encodes social interaction and promotes reinforcement learning through social prediction error. Nat. Neurosci. 25, 86–97. https://doi.org/10.1038/s41593-021-00972-9.
Steinman, M.Q., Duque-Wilckens, N., Trainor, B.C., 2019. Complementary neural circuits for divergent effects of oxytocin: social approach versus social anxiety. Biol. Psychiatry 85, 792–801. https://doi.org/10.1016/j.biopsych.2018.10.008.
Succu, S., Sanna, F., Cocco, C., Melis, T., Boi, A., Ferri, G.-L., Argiolas, A., Melis, M.R., 2008. Oxytocin induces penile erection when injected into the ventral tegmental area of male rats: role of nitric oxide and cyclic GMP. Eur. J. Neurosci. 28, 813–821. https://doi.org/10.1111/j.1460-9568.2008.06385.x.
Tidey, J.W., Miczek, K.A., 1996. Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. Brain Res. 721, 140–149. https://doi.org/10.1016/0006-8993(96)00159-x.
Triana-Del Rio, R., Ranade, S., Guardado, J., LeDoux, J., Klann, E., Shrestha, P., 2022. The modulation of emotional and social behaviors by oxytocin signaling in limbic network. Front. Mol. Neurosci. 15 https://doi.org/10.3389/fnmol.2022.1002846.
Valtcheva, S., Issa, H.A., Bair-Marshall, C.J., Martin, K.A., Jung, K., Zhang, Y., Kwon, H.-B., Froemke, R.C., 2023. Neural circuitry for maternal oxytocin release induced by infant cries. Nature 621, 788–795. https://doi.org/10.1038/s41586-023-06540-4.
Wang, J., Tai, F., Lai, X., 2014. Cocaine withdrawal influences paternal behavior and associated central expression of vasopressin, oxytocin and tyrosine hydroxylase in mandarin voles. Neuropeptides 48, 29–35. https://doi.org/10.1016/j.npep.2013.10.016.
Wang, P., Wang, S.C., Liu, X., Jia, S., Wang, X., Li, T., Yu, J., Parpura, V., Wang, Y.-F., 2022. Neural functions of hypothalamic oxytocin and its regulation, 17590914221100706 ASN Neuro 14. https://doi.org/10.1177/17590914221100706.
Wise, R.A., 2004. Rewards wanted: molecular mechanisms of motivation. Discov. Med. 4, 180–186.
Wood, R.I., Kim, J.Y., Li, G.R., 2016. Cooperation in rats playing the iterated Prisoner's Dilemma game. Anim. Behav. 114, 27–35. https://doi.org/10.1016/j.anbehav.2016.01.010.
Xiao, L., Priest, M.F., Nasenbeny, J., Lu, T., Kozorovitskiy, Y., 2017. Biased oxytocinergic modulation of midbrain dopamine systems. Neuron 95, 368–384.e5. https://doi.org/10.1016/j.neuron.2017.06.003.
Yang, X., Wang, W., Wang, X.T., Wang, Y.W., 2021. A meta-analysis of hormone administration effects on cooperative behaviours: oxytocin, vasopressin, and

testosterone. Neurosci. Biobehav Rev. 126, 430–443. https://doi.org/10.1016/j.neubiorev.2021.03.033.
Yoshihara, C., Numan, M., Kuroda, K.O., 2018. Oxytocin and parental behaviors. Curr. Top. Behav. Neurosci. 35 119–153. https://doi.org/10.1007/7854_2017_11.
Young, K.A., Liu, Y., Gobrogge, K.L., Wang, H., Wang, Z., 2014. Oxytocin reverses amphetamine-induced deficits in social bonding: evidence for an interaction with nucleus accumbens dopamine. J. Neurosci. 34, 8499–8506. https://doi.org/10.1523/JNEUROSCI.4275-13.2014.