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Review article

Oxytocin and dopamine in psychostimulant-induced changes in social behaviour

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A B S T R A C T

Oxytocin (OXT) plays a significant role in regulating social behaviour across various species, making it a key focus in neuroscience. Recent research has expanded beyond the established prosocial effects of OXT to explore its complex interplay with dopamine (DA), a key regulator of both reward processing and social behaviour. DA influences these behaviours both independently and in coordination with OXT. Emerging evidence highlights how psychostimulants disrupt OXT-DA interaction, exacerbating maladaptive social behaviours. This narrative review synthesises findings from pharmacological, optogenetic, and chemogenetic studies to elucidate mechanistic insights into OXT-DA crosstalk in both healthy and drug-compromised social functioning. We examined OXT-DA interaction in non-reproductive social behaviours, such as social approach and aggression, as well as reproductive behaviours, including parental care, offspring attachment, and pair bonding, both in the presence and absence of drugs of abuse. Understanding OXT-DA interaction offers important insights into the neurobiological mechanisms underlying both healthy and pathological social functioning.

1. Introduction

Social behaviour constitutes a fundamental aspect of social animals' life, with significance for reproductive success, the establishment and maintenance of social bonds, and overall survival within a community (Kappeler, 2022). Among the numerous neurobiological systems involved in regulating social behaviours, oxytocin (OXT) and dopamine (DA) are key players.

The nonapeptide OXT is mainly produced in the paraventricular (PVN) and supraoptic (SON) hypothalamic nuclei and released into the blood and brain, for example, in response to reproductive stimuli (birth, suckling, and mating) (Jurek and Neumann, 2018; Wotjak et al., 2008). OXT release within the brain has also been observed during non-reproductive social interactions, such as social investigation and aggression, as well as following exposure to various social and non-social stressors (Jurek and Neumann, 2018; Neumann, 2009). OXT acts via OXT receptor (OXTR), G-protein-coupled receptors that are expressed in various brain regions associated with social cognition, emotion, stress regulation, and reward processing such as the amygdala, nucleus accumbens (NAc), medial prefrontal cortex (mPFC), PVN, lateral septum, and ventral tegmental area (VTA). Accordingly, brain OXT regulates multiple aspects of socio-emotional and reproductive behaviours, including sociability, pair bonding, and parental behaviour (Froemke and Young, 2021; Jurek and Neumann, 2018; Menon and Neumann, 2023).

The DA system, particularly the mesolimbic pathway, originates in the VTA and projects to the NAc. The neurotransmitter DA has traditionally been linked to the processing of motivationally relevant stimuli, in particular to the reinforcing effects of drugs of abuse, thus regulating the neurobiological changes underlying substance use disorders (Lisman and Grace, 2005; Schultz, 1998; Wise, 2004). Many addictive substances elevate DA levels in the NAc, and their rewarding effects can be experimentally manipulated by targeting local DA receptor or DA transporter functions. A primary mechanism of action of substances of abuse such as cocaine, involves alterations in DA transporter function. Thus, the DA system plays a crucial role in reinforcing reward-seeking behaviour, motivation, and reinforcement learning (Lisman and Grace, 2005; Schultz, 1998; Wise, 2004). In the context of this review, it is important

Abbreviations: CPP, conditioned place preference; DA, dopamine; DAT, dopamine transporter; *Drd1*/D1R, DA D1-like receptor; *Drd2*/D2R, DA D2-like receptor; i.c.v, intracerebroventricular; METH, methamphetamine; MPOA, medial preoptic area; NAc, nucleus accumbens; OXT, oxytocin; *Oxtr*/OXTR, oxytocin receptor; mPFC, medial prefrontal cortex; MSN, medium spiny neurons; PVN, paraventricular nucleus; SDS, social defeat stress; SON, supraoptic nucleus; TH, tyrosine hydroxylase; VTA, ventral tegmental area.

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to mention that DA also regulates the rewarding properties of social interactions in humans and rodents (Bariselli et al., 2018; Gunaydin et al., 2014; Kawamichi et al., 2016). DA receptors are expressed both pre- and post-synaptically in key brain regions such as the NAc, mPFC, hypothalamus, amygdala, and VTA. In the VTA, these receptors are modulated by somato-dendritic release of DA within the region itself (Hikima et al., 2021; Rice and Patel, 2015; Tong et al., 2023). The effects of DA on reward-related behaviour involve two distinct families of DA receptors with opposing roles. D1-like receptors (D1R; e.g., D1/D5) enhance reward processing via Gq protein-coupled pathways, including PKA and PLC activation, which potentiate neuronal excitability and reward-seeking behaviour. In contrast, D2-like receptors (D2R), including D2, D3, and D4 subtypes, are Gi-protein-coupled and generally inhibit neuronal activity. However, their influence on reward-related responses varies depending on the specific neuronal circuits and projection pathways involved (Beaulieu and Gainetdinov, 2011; Gallo et al., 2018; Grima et al., 2022; Nagai et al., 2016; Xu et al., 2024). The NAc is primarily composed of D1R-expressing medium spiny neurons (D1-MSNs) and D2R-expressing MSNs (D2-MSNs). When released from the VTA, DA activates D1-MSNs promoting approach behaviour, reward-seeking, and motivation via the direct pathway, while inhibiting D2-MSNs, thereby suppressing avoidance and effort via the indirect pathway (Kravitz et al., 2012; Soares-Cunha et al., 2022).

OXT interacts with multiple neurotransmitter and neuromodulator systems, including GABA (Bowen et al., 2015), serotonin (Grieb and Lonstein, 2022), arginine vasopressin (Song and Albers, 2018), and also DA (Hung et al., 2017; Musardo et al., 2022; Xiao et al., 2017). The OXT and DA systems are anatomically and functionally coupled, exhibiting complex interactions. Anatomically, OXT and DA signalling components co-localise in key reward and social cognition regions, including the VTA, NAc, hypothalamus, and amygdala (Baskerville and Douglas, 2010; Buijs et al., 1984). OXTRs are expressed in both DA and glutamatergic neurons projecting to mesolimbic targets (Peris et al., 2017), while PVN-OXT neurons directly innervate VTA-DA cell bodies (Melis et al., 2007; Roeling et al., 1993). This proximity enables bidirectional modulation: OXT infusion into the VTA enhances DA release in the NAc and hypothalamus (Melis et al., 2007; Shahrokh et al., 2010; Xiao et al., 2017), while DA regulates OXT secretion via receptors on hypothalamic neurons (Baskerville et al., 2009).

Functionally, OXT amplifies social stimulus salience by potentiating mesolimbic DA pathways (Love, 2014). In the VTA, OXT increases DA neuron activity, thus facilitating reward learning and social approach behaviours (for review, Steinman et al., 2019). Conversely, in the amygdala, OXTR-DA receptor (D2R) heteromers enhance anxiolytic signalling through integrated MAPK and Ca^{2+}/calcineurin pathways (de la Mora et al., 2016). On a molecular level, these heteromers modulate presynaptic DA release and dynamic changes in DA receptor signalling in the NAc and striatum, underpinning context-dependent behavioural outcomes (de la Mora et al., 2016; Romero-Fernandez et al., 2013).

The interaction between OXT and DA systems also serves to mitigate maladaptive behaviours. Notably, OXT attenuates drug reward by suppressing psychostimulant-induced DA elevations in mesolimbic circuits, shifting preference toward social rewards (Leong et al., 2018). Preclinical studies demonstrate the efficacy of OXT in decreasing drug self-administration and facilitating extinction of drug-associated cues, highlighting therapeutic potential for addiction (Bowen and Neumann, 2017, 2018). These findings position OXT as a neuromodulatory bridge linking social salience to DA-driven motivation, providing a mechanistic framework for targeting OXT-DA pathways in social dysfunction and addiction therapeutics.

Previous reviews have dissected OXT-DA interaction in social bonding, reward, and emotion (Arakawa, 2021; Baskerville and Douglas, 2010; Loth and Donaldson, 2021; Love, 2014; Steinman et al., 2019). This review focuses on how OXT-DA interaction shape both reproductive and non-reproductive social behaviours in rodents. Additionally, we address the clinically relevant aspect regarding the impact of psychostimulant drugs on social behaviour and OXT-DA interaction, which has recently been highlighted (Weber and Venniro, 2025). Rodents, as primary models, provide a well-characterised neurobiological framework and allow targeted experimental manipulations. Here, we highlight studies using pharmacological, genetic, chemogenetic, and optogenetic tools to examine the bidirectional effects of OXT and DA systems on social behaviours, including the impact of psychostimulant drugs on these systems. During the literature search, we evaluated potential reporting bias in accordance with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines, ensuring the inclusion of high-quality original research in this narrative review (see Supplementary Fig. 1).

2. OXT-DA interaction shapes non-reproductive behaviours

2.1. Same-sex sociability and aggression

This section presents a summary of studies investigating OXT-DA interaction in non-reproductive social behaviours (summary in Table 1).

Several studies investigated the role of the OXT system in the NAc and VTA in social approach and the rewarding value of same-sex social interactions. Administering OXTR antagonists into the NAc decreased same-sex social approach reflected by reduced time spent near unfamiliar individuals in male and female California mice (*Peromyscus californicus*) (Williams et al., 2020). In Syrian hamsters (*Mesocricetus auratus*), administration of OXT or an OXTR agonist into the VTA increased social-conditioned place preference (CPP), i.e., the time spent in the social chamber after three social-conditioning sessions, in males, but decreased it in females, while an OXTR antagonist reduced social CPP in both sexes (Borland et al., 2019a, 2018; Song et al., 2016). The sex-dependent role of OXT signalling in the VTA in mediating the rewarding aspects of same-sex social interactions might be influenced by the number of social conditioning sessions during CPP. Indeed, intra-VTA OXT administration increased social CPP in females after a single social-conditioning session (Borland et al., 2019a). The authors propose that, for females, the relationship between social interaction and social reward regulated by OXT follows an inverted U-shape dynamic, being more sensitive to lower doses of social interaction than males (Borland et al., 2019b). Despite these effects, no sex differences were found in the activation of OXT-containing neurons in the PVN or SON, key regions projecting to the VTA (Borland et al., 2019a). These studies (Borland et al., 2019a, 2018; Song et al., 2016) did not examine DA directly. However, a recent study in Syrian hamsters showed that phasic DA release in the NAc core and medial VTA activity encode social salience, while tonic DA release in the NAc shell and lateral VTA activity encode social valence (Cross et al., 2025). However, as this study did not assess OXT, further research is needed to elucidate how OXT-DA interaction shape the rewarding properties of social behaviour in Syrian hamsters.

Another pharmacological study investigated the impact of OXT on sociability in male mandarin voles (*Microtus mandarinus)* (Du et al., 2017). Intracerebroventricular (i.c.v.) OXT applied via osmotic minipumps over 12 consecutive days reduced the preference for interacting with a novel social stimulus compared with a novel object, indicating decreased sociability. This reduction was associated with lower *Oxtr* and dopamine receptor 1 (*Drd1)* mRNA expression in the NAc, as well as lower *Oxtr* and increased dopamine receptor 2 (*Drd2)* mRNA in the medial amygdala. Optogenetic stimulation of OXT neurons has also deepened our understanding of the involvement of OXT in sociability (Hung et al., 2017). In male C57Bl/6 mice, PVN-OXT and VTA-DA neuronal activity increased during same-sex social interaction. Optogenetic stimulation of PVN-OXT terminals in the VTA enhanced sociability and social CPP, while inhibition or *Oxtr* knockout in VTA-DA neurons impaired them. OXTR agonists elevated spontaneous spiking of VTA-DA neurons, an effect blocked by OXTR antagonists, indicating that local OXT enhanced DA neuron excitability toward the NAc.

Table 1
Summary of studies examining the interaction of OXT and DA in the context of social interactions and social approach in rodents.

Species Strain	Age Sex Housing conditions	Intervention and group comparison	Social behaviour outcome	OXT system outcome	DA system outcome	Ref.
California mouse	Adult ♂/♀ GH	Intra-NAc OXTR antagonist L368,899 (5 μg/μl) Atosiban (5 ng/μl) Drug vs veh	↓ Social interaction			Williams et al., 2020
Syrian hamster	Adult ♂/♀ SH	Intra-VTA OXT (9 μM) Drug vs veh	↑ Social CPP ♂			Borland et al., 2019a
		Intra-VTA OXT selective agonist [Thr4,Gly7]OT (23 μM) Drug vs veh	↓ Social CPP ♀			
		Intra-VTA OXTR antagonist Vasotocin (90 μM) Drug vs veh	↓ Social CPP ♂/♀			
Syrian hamster	Adult ♂ SH	Intra-VTA OXT (9 or 90 μM) Drug vs veh	↓ Entries into social chamber			Borland et al., 2018
		Intra-VTA OXTR antagonist Vasotocin (0.9 or 9 μM) Drug vs veh	↑ Entries the social chamber			
Syrian hamster	Adult ♂ SH	Intra-VTA OXT (9 or 90 μM) Drug vs veh	↑ Social CPP			Song et al., 2016
		Intra-VTA OXTR selective agonist [Thr4,Gly7]OT (27 μM) Drug vs veh	↑ Social CPP			
		Intra-VTA OXTR antagonist Vasotocin (90 μM) Drug vs veh	↓ Social CPP			
Mandarin vole	Adult ♂ Housing NS	OXT Osmotic minipump (0.25 μl/h for 14 days, 1 ng, i.c.v.) Drug vs veh	↓ Sociability ↔ Aggression	NAc, MeA ↓ *Oxtr*	NAc ↓ *Drd1* ↔ *Drd2* MeA ↔ *Drd1* ↑ *Drd2*	Du et al., 2017
Mouse (B6)	Adult ♂ GH	Chemogenetic silencing of PVN OXT to VTA projections CNO vs veh	↓ Social CPP			Hung et al., 2017
		Selective OXTR KO in DA VTA neurons KO vs WT	↓ Social CPP			
		Optogenetic activation of PVN to VTA OXT projections ChETA vs eYFP	↑ Real-time CPP ↑ Sociability			
		Optogenetic inhibition of PVN to VTA OXT projections ChETA vs eYFP	↓ Real-time CPP ↓ Sociability			
Mouse (B6)	Adult ♂ GH	OXT KO KO vs WT	↔ Sexual behaviour ↑ Social interaction ↓ Aggression	HC ↑ *Oxtr* Hyp ↔ *Oxtr*	HC ↓ *Drd2* Hyp ↔ *Drd2*	Lazzari et al., 2019
Mouse (outbred albino)	Adult ♂ SH	OXT (5 U/ml; 10 μl/nostril, intranasal) Drug vs veh	↔ Aggression		CC, STR, HC ↔ DA ↔ DOPAC	Karpova et al., 2017
Mouse (B6)	Adult ♂ SH	OXT (5 U/ml; 10 μl/nostril, intranasal) Drug vs veh	↓ Aggression		CC, STR, HC ↓ DA ↔ DOPAC STR, HC ↔ DA ↔ DOPAC	Karpova et al., 2016
Mouse (B6)	Adult ♂/♀ SH	No intervention Dominant vs subordinate	↑ Dominance ♀	PVN ↑ OXT-ir	VTA ↑ OXT PVN inputs	Sofer et al., 2024
		Viral silencing of PVN-OXT neurons Caspase 3 vs control	↓ Aggression ♀ ↓ Dominance hierarchy ♀			
		Chemogenetic activation of PVN-OXT neurons Compound 21 vs veh	↑ Aggression ♀ ↑ ♀/↓♂ Dominance hierarchy	Plasma ↑ OXT level		
		Chemogenetic activation of OXT PVN-VTA Compound 21 vs veh	↑ Aggression ♂/♀			

(continued on next page)

Table 1 (*continued*)

Species Strain	Age Sex Housing conditions	Intervention and group comparison	Social behaviour outcome	OXT system outcome	DA system outcome	Ref.
Cairo spiny mouse	Adult ♂/♀ PH	No intervention Social vs object	High sociability	PVN-OXT neurons ↑ neuronal activity	VTA-TH neurons ↑ neuronal activity	Gonzalez Abreu et al., 2022
Mongolian gerbil			Low sociability	PVN-OXT neurons ↑ neuronal activity	VTA-TH neurons ↔ neuronal activity	
Rat (Sprague-Dawley)	Adult ♂ SH	OXTR KD mPFC Cocaine (0.5 mg/kg/infusion) Drug vs veh	↓ Cocaine reinstatement ↑ Social approach			Penrod et al., 2023
		OXTR KD NAc Cocaine (0.5 mg/kg/infusion) Drug vs veh	↓ Cocaine reinstatement ↔ Social approach			
Mouse (ICR)	Adult ♂ GH	DA reuptake inhibitor Cocaine (4*20 mg/kg, i.p.) Social/cocaine CPP vs social CPP	↓ Social CPP	PVN ↓ OXT-ir	NAc core ↓ neuronal activation	Liu et al., 2016
Mouse (Swiss)	Adult ♂ GH	No intervention Environmental enrichment vs standard housing	↑ Social CPP ↓ Ethanol vs social CPP ↑ Social dominance	Hyp ↑ *Oxt* STR ↓ OXTR signalling activity	NAc ↑ D1R	Rae et al., 2024
		OXTR antagonist L368,899 (5 mg/kg) Drug vs veh			NAc ↓ D1R	
Rat (Sprague-Dawley)	Adult ♀ SH	Cocaine (30 mg/kg; chronic or intermittent) Drug vs veh	↑ Aggression ↑ Drinking behaviour	MPOA ↓ OXT VTA, AMY ↔ OXT		Johns et al., 2010

Abbreviations: AMY: amygdala; ChETA: channelrhodopsin; CNO: clozapine N-oxide; CPP: conditioned place preference; DA: dopamine; DAT: dopamine reuptake inhibitor *Drd1*/D1R: DA D1-like receptor; *Drd2*/D2R: DA D2-like receptor; eYFP: enhanced yellow fluorescent protein; GH: group-housed; HYP: hypothalamus; i.c.v.: intracerebroventricular; ir: immunoreactivity; KD: knockdown; KO: knockout; MeA: medial amygdala; mPFC: medial prefrontal cortex; MPOA: medial preoptic area; NAc: nucleus accumbens; NS: not specified; OXT: oxytocin; *Oxtr*/OXTR: oxytocin receptor; PH: pair-housed; PVN: paraventricular nucleus of the hypothalamus; SH: single-housed; SON: supraoptic nucleus; STR: striatum; veh: vehicle; vs.: versus; VTA: ventral tegmental area; WT: wild type.
Symbols: ♂: male; ♀: female; ↑: significant increase; ↓: significant decrease; ↔: no significant differences.

Research on the role of OXT in aggression also led to interesting findings, though evidence regarding OXT-DA interaction is still limited. In male OXT knockout mice, decreased aggression along with increased social contact during a one-on-one encounter within the home cage of a resident male was found (Lazzari et al., 2019). The lack of OXT was associated with reduced *Drd2* and increased *Oxtr* mRNA expression in the hippocampus. Chronic social isolation increased intermale aggression in home-cage C57Bl/6 male mice. (Karpova et al., 2016), an effect not observed in albino male mice (Karpova et al., 2017). Intranasal treatment with a large dose of OXT reduced their aggression and lowered DA levels in the cerebral cortex (Karpova et al., 2016, 2017). Furthermore, a study investigated sexually dimorphic OXT circuits in regulating social conflict and aggression in adult wild house mice (Sofer et al., 2024). Following social exposure, female mice exhibited increased same-sex aggression, associated with elevated cFos expression in PVN-OXT neurons. Dominant females had more OXT-expressing neurons in the PVN and stronger PVN-OXT projections to the VTA. Chemogenetic activation of PVN-OXT terminals in the VTA intensified aggression in both sexes, with males displaying more severe behaviours. Conversely, viral caspase-3-mediated ablation of PVN-OXT neurons reduced aggression and disrupted the female dominance hierarchy. These findings underscore a sexually dimorphic role of PVN-OXT neurons in modulating aggression and social rank via DA-related circuits.

Finally, a comparative study investigated the PVN-OXT and VTA-TH (tyrosine hydroxylase) neuronal activity measured by c-Fos expression in male and female Cairo spiny mice (*Acomys cahirinus*) and Mongolian gerbils (*Meriones unguiculatus*) during same-sex social interactions (Gonzalez Abreu et al., 2022). The Cairo spiny mouse is known to live in large social groups and displays higher gregariousness and lower aggression than the Mongolian gerbil. In this study, Cairo spiny mice exposed to a novel same-sex conspecific showed increased VTA-TH neuronal response compared to their Mongolian gerbil counterparts, whereas no differences between species were observed in PVN-OXT neuronal response. This suggests a more rewarding response to social novelty in Cairo spiny mice in non-reproductive situations.

In summary, evidence from rodent studies using diverse manipulation techniques shows that OXT facilitates social approach and the rewarding aspects of social interactions by acting on DA-associated regions like the VTA and NAc (Borland et al., 2018; 2019a). Activation of OXT signalling enhances sociability, while its inhibition impairs it. Notably, deletion of OXTR in DA neurons disrupts social reward learning, underscoring their functional interplay. However, chronic OXT exposure may reduce sociability, and its role in aggression remains unclear.

2.2. Effects of psychostimulants on sociability and aggression

Substances of abuse have been shown to affect non-reproductive social interactions by altering OXT and DA systems in several studies. One such study investigated the effects of conditional OXTR knockdown through the use of short hairpin RNA in the mPFC or NAc of cocaine-self-administered rats (Penrod et al., 2023). After 14 days of cocaine self-administration, rats were tested for cued and cocaine-primed reinstatement of drug-seeking behaviour. OXTR knockdown specifically in the mPFC, but not NAc, delayed the successful acquisition of lever pressing. Both in the mPFC and NAc, OXTR knockdown decreased cued reinstatement, but did not affect drug-primed reinstatement. Additionally, OXTR knockdown in the mPFC, but not in the NAc, facilitated social interactions, highlighting the differential role of OXTR in the mPFC and NAc. These findings also suggest that OXTR knockdown in the mPFC affects the salience of drug cues rather than directly modulating drug reward.

The role of the DA and OXT systems in modulating the rewarding value of same-sex social interactions has also been studied in cocaine-treated mice. Male ICR mice were conditioned in a dual-chamber CPP paradigm where one chamber was paired with cocaine and the opposite chamber with social interaction (Liu et al., 2016). Whereas mice displayed CPP when conditioned with either unfamiliar conspecifics or cocaine alone, simultaneous conditioning with both stimuli (social/cocaine) resulted in no CPP. Thus, at the doses tested, neither cocaine nor the social stimulus was inherently more rewarding than the other. Social/cocaine CPP resulted in decreased NAc shell neuronal activity, as indicated by a reduced number of c-Fos-immunoreactive neurons, and lower OXT immunoreactivity in the PVN compared to social CPP. Both social/cocaine CPP and social CPP were correlated with heightened NAc core activation compared to control mice. Thus, cocaine may diminish social preference by competing with social rewards, affecting the DA system in different NAc subregions and influencing the reinforcement of social interaction.

In the context of the effects of substances of abuse on non-reproductive social interactions, environmental factors also play a substantial role. Environmental enrichment was found to increase preference for both social and ethanol rewards in adult male Swiss mice, although the preference for ethanol was stronger (Rae et al., 2024). Environmental enrichment also enhanced social dominance, increased *Oxt* mRNA expression in the hypothalamus, and reduced OXTR signalling in the striatum. Notably, D1R expression in the NAc was upregulated, an effect that was blocked by an OXTR antagonist. These results suggest that environmental enrichment modulates OXT-DA interaction, particularly favouring ethanol over social stimuli in terms of reward processing.

Drug effects also seem to depend on the social environment. For example, social housing attenuated the progressive self-administration of methamphetamine (METH), but did not affect reinstatement (Westenbroek et al., 2019). These findings suggest that while social housing mitigates METH use escalation, combining it with OXT may better reduce reinstatement.

Social behaviour was evaluated 10–30 days after chronic or intermittent cocaine treatment in non-lactating dams (Johns et al., 2010). Both chronic and intermittent cocaine treatment led to significantly increased aggression compared to control rats. Additionally, cocaine treatment was associated with reduced OXT levels specifically in the MPOA. These findings suggest that the decrease in OXT may play a critical role in the aggression observed following cocaine exposure.

In summary, psychostimulants disrupt OXT-DA interaction, leading to altered same-sex sociability and aggression. Cocaine reduces the rewarding value of social interaction by decreasing PVN-OXT and NAc shell activity and differentially affects drug reinstatement and social behaviours depending on prefrontal OXTR expression. Environmental factors like enrichment or social housing further modulate these effects by shifting OXT and DA signalling, often favouring drugs over social rewards.

3. OXT-DA interaction shapes reproductive social behaviour

3.1. Parental care

Due to the specific functions of OXT and DA in reproductive behaviour, OXT-DA interaction, specifically within the NAc, is essential for parental care and bidirectional mother-offspring attachment (summary in Table 2).

OXTR-mediated signalling within the NAc is important for the re-establishment of maternal behaviour after prolonged separation from offspring (D'Cunha et al., 2011). Immediately after parturition, Sprague-Dawley rats were separated from their offspring. One day after parturition they were allowed to experience maternal behaviour with donor pups for 1 h. Immediately thereafter, an OXTR antagonist was infused into the NAc and dams were further isolated for 10 days. During a maternal retention test (post-partum day 11), blockade of OXTR prolonged the latency to perform maternal behaviour towards new donor pups compared to control dams (D'Cunha et al., 2011). Increased levels of OXT in the MPOA and PVN along with more OXT projections from these regions into the VTA were found in rat dams with high compared with low levels of pup licking/grooming (Shahrokh et al., 2010). Notably, direct administration of OXT into the VTA increased DA signalling in the NAc of virgin female rats (Shahrokh et al., 2010). Moreover, high licking/grooming dams showed a more pronounced rise in DA signalling in the NAc during licking/grooming episodes. Highlighting the role of local OXT signalling, VTA infusion of an OXTR antagonist eliminated behavioural differences between high and low licking/grooming dams. The involvement of DA in maternal behaviour was further demonstrated in Sprague-Dawley dams, where gestational administration of amfonelic acid, a selective DA reuptake inhibitor, reduced crouching duration postpartum, a key nurturing posture (Johns et al., 2005) resulting in decreased crouching duration (nurturing posture). Additionally, maternal aggression, a component of the maternal behavioural repertoire (Neumann et al., 2001), was impaired following DA system disruption during late gestation.

Regarding paternal care studied in biparental mandarin voles, chemogenetic activation and inhibition of PVN-OXT neurons projecting to the VTA increased and decreased pup-licking behaviour in fathers, respectively (He et al., 2021). Similar effects were observed after optogenetic manipulation of DA terminals in the NAc (He et al., 2021). Furthermore, chemogenetic inhibition of PVN-OXT projections to the NAc resulted in reduced pup-licking behaviour in fathers, accompanied by a decrease in DA release in the NAc, underscoring the significance of OXT-DA interplay in regulating paternal behaviour in voles.

In summary, OXT-DA interaction is important for maternal and paternal behaviours, showing different effects depending on brain region and sex (see Table 2). In rats, OXT signalling in the NAc helps restore maternal care after pup separation. Maternal care is linked to OXT input to the VTA and local DA release in the NAc. Gestational changes in DA can disrupt maternal care and increase aggression. In mandarin voles, PVN-OXT projections to the VTA or NAc, and the resulting DA release, are important for paternal care.

3.2. Offspring attachment to parents

In the context of offspring attachment to the mother tested in an adapted version of the social preference test, systemic administration of an OXTR antagonist to pre-weaning mandarin voles reduced the motivation to approach the mothers and increased the latency to enter the mother's zone (He et al., 2017). This was accompanied by decreased serum OXT concentrations, TH immunoreactivity, and DA levels in the VTA, along with reduced D1R and D2R expression in the NAc of pups. In juvenile ICR male mice, conditioning to either maternal or paternal cues induced CPP (Wang et al., 2017b). Preference for the mother was associated with elevated OXT immunoreactivity in the SON and increased TH immunoreactivity in the VTA, whereas father preference was linked only to the latter. These results suggest that maternal preference engages both the OXT and DA systems, while paternal preference primarily involves VTA-DA activity.

OXT and DA system responses were also studied in the context of pre-weaning paternal deprivation and its effects on parental responses in adult mandarin voles (Yuan et al., 2020). Compared with biparental care, both male and female deprived voles showed impaired pup-directed behaviour, with increased latency to approach pups, reduced sniffing duration, and diminished pup contact. Further, pre-weaning paternal deprivation decreased serum OXT levels in adult females, and OXTR expression in the MPOA, NAc, and mPFC in both sexes. Additionally, increased D1R expression and decreased D2R expression were found in the NAc. These findings suggest that pre-weaning paternal deprivation induces long-lasting and sex-specific changes in key brain regions, and adult parental responses.

Table 2
Summary of studies examining the impact of OXT system manipulations on the DA system in the context of parental behaviour and pair bonding in rodents.

Species Strain	Age Sex Housing conditions	Intervention and group comparison	Social behaviour outcome	OXT system outcome	DA system outcome	Ref.
Parental care						
Rat (Sprague-Dawley)	Adult ♀ SH	Intra-NAc shell OXT (100 or 200 ng/μl) Drug vs veh	↔ Onset of maternal behaviour			D'Cunha et al., 2011
		Intra-NAC shell OXTR antagonist (0.25 or 0.75 μg/μl) Drug vs veh	↑ Onset of maternal behaviour			
		Intra-HC OXTR antagonist Vasotocin (0.75 μg/μl) Drug vs veh	↔ Onset of maternal behaviour			
Rat (Long-Evans)	Adult ♀ SH	Intra-VTA OXT (0.25 μg/μl) Drug vs veh	↔ Maternal behaviour		NAc ↑ DA release (virgin) ↓ DA release (lactating)	Shahrokh et al., 2010
		Intra-VTA OXTR antagonist (0.25μg/μL) Drug vs veh				
Rat (Sprague-Dawley)	Young adult ♀ PH	DA reuptake inhibitor amfonelic acid (2.5 mg/kg, i.p.) Drug vs veh	↓ Maternal behaviour	HC ↓ OXT level MPOA, AMY ↔ OXT level		Johns et al., 2005
Mandarin vole	Adult ♂ Housing NS	Chemogenetic activation of PVN OXT to VTA projections CNO vs. Veh	↑ Pup licking		NAc ↑ DA release	He et al., 2021
		Chemogenetic inhibition of PVN OXT to VTA or NAc projections CNO vs veh	↓ Pup licking		NAc ↓ DA release	
Mandarin vole	Pups ♂/♀ GH	OXTR antagonist Vasotocin (0.01; 0.05 or 0.1 mg/kg, i.p.) Drug vs veh	↓ Preference for mother	Serum ↓ OXT level	VTA ↓ TH-ir ↓ DA NAc ↓ D1R ↓ D2R	He et al., 2017
Mouse (ICR)	Adolescent ♀ PH	No intervention MC vs FC vs MFC	Preference for parental chamber (MC, FC) ↔ Preference for mother or father chamber (MFC)	SON ↑ OXT-ir (MC, MFC) PVN↔ OXT-ir	VTA ↑ TH-ir	Wang et al., 2017a
Mandarin vole	Adults ♂/♀ PH	No intervention Paternal deprivation vs biparental care	↑ Latency to approach pups↓ Contact to pups	Serum ↓ OXT ♀ NAc, mPFC, MPOA ↓ *Oxtr*/OXTR MeA ↑ *Oxtr*/OXTR	NAc ↑ *Drd1*/D1R ↓ *Drd2*/ D2RmPFC ↓ *Drd1*/D1R ↓ D2R ♂ ↑ *Drd2*/D2R ♀	Yuan et al., 2020
Mandarin vole	Adults ♂/♀ Same-sex PH	No intervention Post-weaning parent-offspring cohabitation, D45 vs D21	⊘ Partner preference	PVN ↑ OXT-ir NAc ↓ *Oxtr* ♂ MPOA ↑ OXT-ir ♂ MeA ↑ OXT-ir ♂ ↑ *Oxtr* ♀ ↑ Oxtr/OXTR	VTA ↔ TH-ir NAc ↓ *Ddr2* ↓ *Ddr1* ♀ MeA ↔ *Ddr1*, *Drd2*	Wu et al., 2018
Mandarin vole	Adults ♂/♀ PH	No intervention First litter cares for second litter from day 21. Controls: first litter stays with parents until day 45, no second litter.	↑ Partner preference	PVN ↔ OXT-ir Hyp ↓ OXT-ir ♂ NAc ↑ Oxtr ♂ AMY↔ Oxtr	NAc ↑ *Drd2* ↔ *Ddr1* AMY ↔ *Ddr1* ↔ *Drd2*	Wu et al., 2023
		No intervention Second litter cared for by first litter from day 21. Controls: second litter receives only parental care after first litter weaned at day 21.	↑ Partner preference	PVN, MeA, MPOA ↑ OXT-ir Hyp ↔ OXT-ir NAc, AMY ↔ *Oxtr*	VTA ↑ TH-ir NAc ↓ *Drd1* ↔ *Ddr2* AMY ↔ *Ddr1* ↔ *Drd2*	

(*continued on next page*)

Table 2 (*continued*)

Species Strain	Age Sex Housing conditions	Intervention and group comparison	Social behaviour outcome	OXT system outcome	DA system outcome	Ref.
Mouse (B6)	Adult ♂ GH	Cocaine (0.5 mg/ml for 40 days; oral) Offspring of cocaine-treated fathers (F1) vs veh	↑ Social investigation ↔ Aggression	NAc ↑ OXTR binding AMY, BNST, LS, LH ↓ OXTR binding		Yaw et al., 2022
Rat (Sprague-Dawley)	Adult ♀ SH	Cocaine (30 mg/kg; chronic or intermittent until PND20) Drug vs veh	↑ Maternal aggression	AMY↓ OXT		Johns et al., 1998
	Juvenile or adult ♂/♀ Housing NS	Offspring of cocaine-treated mothers (F1) vs veh	↑ Aggression Atypical social behaviour			
Rat (Sprague-Dawley)	Adult ♀ SH	Cocaine (30 mg/kg gestation; sc) Drug vs veh	↔ Maternal aggression			Lubin et al., 2003
		Intra-CeA OXTR antagonist Vasotocin (500-1000 ng) Drug vs veh or VTA	↑ Maternal aggression			
Rat (Sprague-Dawley)	Adult ♀ SH PPD8	Cocaine (30 mg/kg; sc; GD 1–20 or every five days during gestation + PPD2-21) Intermittent or chronic vs veh	↑ Maternal aggression			Mcmurray et al., 2008
	Adult ♀ SH First generation dams	Cocaine (30 mg/kg gestation; sc) Drug vs veh	↑ Maternal aggression	AMY ↓ OXT VTA, MPOA, HC ↔ OXT		
Mandarin vole	Adult ♂ PH	DA reuptake inhibitor cocaine (4*20 mg/kg, sc) Drug vs veh	↓ Paternal behaviour	PVN ↓ OXT-ir	VTA ↑ TH-ir	Wang et al., 2014
Mandarin vole	Adult ♂ PH	No intervention Pup- vs coc-conditioned voles	↑ Preference for both pups and cocaine	MeA ↑ OXTR (pup) Serum ↑ OXT level (pup)	NAc ↓ D2R	Fang & Wang, 2017
Mandarin vole	Adolescent ♀ Same-sex GH PC or PD	DA reuptake inhibitor cocaine (2*20 mg/kg, sc) Drug vs veh	↓ Social interaction	Serum ↓ OXT level PVN, SON ↓ OXT-ir PC		Wang et al., 2017b
Pair bonding						
Prairie vole	Adult ♂ Same-sex PH	No intervention Separated vs paired	↓ Aggression to ♂ ↑ Affiliation with ♀	PVN, SON ↑ OXT-ir	VTA ↔ TH-ir	Sun et al., 2014
Prairie voles Meadow voles	Adult♂/♀ GH	No intervention Monogamous vs promiscuous	↑ Bonding	mPFC ↑ OXTR binding	mPFC ↓ D1R binding ↑ D2R binding	Smeltzer et al., 2005
Prairie vole	Adult ♀ PH	D2R/D3R antagonist eticlopride (0.3 mg/kg, i.p.) Drug vs veh	↓ OXT-induced partner preference			Liu & Wang, 2003
		OXT Osmotic minipum (0.5ul/h, 1 ng/ul, i.c.v.) Drug vs veh	↑ Partner preference			
Prairie vole	Adult ♀ PH	No intervention Pregnant vs nulligravid		NAc, MPOA ↑ *Oxtr* ACC ↔ *Oxtr*	NAc, MPOA ↑ *Drd1, Drd2* NAc ↔ *Drd1, Drd2*	Forero et al., 2024
		No intervention Mothering vs nulligravid		NAc ↑ *Oxtr* ACC ↔ *Oxtr*	NAc, ACC, MPOA ↔ *Drd1, Drd2*	
		No intervention Cohabitation 4 weeks vs 2 weeks		MPOA ↑ *Oxtr* NAc, ACC ↔ *Oxtr*	NAc ↔ *Drd1, Drd2* ACC ↑ Drd1, Drd2	
Prairie vole	Adult ♀ PH opposite sex	No intervention Separated vs paired	↑ Partner-seeking behaviour	PVN ↔ OXT PVN, NAc, ACC	MPOA ↑ DRD1HC ↑ DRD1 PVN, NAc, ACC	Kirckof et al., 2025

(continued on next page)

Table 2 (*continued*)

Species Strain	Age Sex Housing conditions	Intervention and group comparison	Social behaviour outcome	OXT system outcome	DA system outcome	Ref.
				↔ OXTRHC ↑ OXTR	↔ DRD1 ↔ DRD2	
		Intra-MPOA D1R antagonist (40ng/200nl) Drug vs veh	↓ Partner-seeking behaviour			
Prairie vole	Adult ♀ PH	Intra-PLC OXT (1ng/200nl) (AMPH treatment) Drug vs veh	↑ Mating-induced partner preference formation		NAc ↑ DA release	Young et al., 2014
Prairie vole	Adult ♂/♀ SH	DA reuptake inhibitor METH (100 mg/L, 3 days, oral) Drug vs veh	↓ Partner preference ↔ Aggression ↔ Mating	PVN ↓ OXT-ir		Hostetler et al., 2016

Abbreviations: AMPH: amphetamine; AMY: amygdala; BNST: bed nucleus of stria terrminalis; CC: cerebral cortex; CeA: central amygdala; CNO: clozapine N-oxide; DA: dopamine; DOPAC: 3,4-Dihydroxyphenylacetic acid; *Drd1*/D1R: DA D1-like receptor; *Drd2*/D2R: DA D2-like receptor; GD: gestation day; GH: group-housed; HC: hippocampus; Hyp: hypothalamus; i.c.v.: intracerebroventricular; ir: immunoreactivity; KO: knockout; LH: lateral habenula; LS: lateral septum; MeA: medial amygdala; METH: methamphetamine; mPFC: medial prefrontal cortex; MPOA: medial preoptic area; NAc: nucleus accumbens; NS: not specified; OXT: oxytocin; *Oxtr*/OXTR: oxytocin receptor; PH: pair-housed; SON: supraoptic nucleus; PLC: prelimbic cortex; PVN: paraventricular nucleus of the hypothalamus; SH: single-housed; STR: striatum; veh: vehicle; vs.: versus; VTA: ventral tegmental area; WT: wild type.
Symbols: ♂: male; ♀: female; ↑: significant increase; ↓: significant decrease; ↔: no significant differences.

The impact of post-weaning cohabitation with parents (an enriched environment) on offspring behavioural development in mandarin voles was assessed (Wu et al., 2018). Cohabitation with parents post-weaning inhibited partner preference in adult male and female voles. Males housed with parents until postnatal day 45 showed elevated OXT immunoreactivity in the PVN, MPOA, and medial amygdala, while females exhibited increases only in the PVN. Parent cohabitation also altered gene expression: males showed reduced *Oxtr* and *Drd2* mRNA in the NAc, whereas females displayed lower *Drd2* in the NAc but elevated *Oxtr* in the medial amygdala. These results highlight sex-specific modulation of partner preference by post-weaning social experience via OXT and DA systems.

OXT-DA interaction also plays a role in alloparental care, i.e., care given to non-descendant young (Stead et al., 2022). In mandarin voles, both providing and receiving alloparental care during adolescence enhanced adult partner preference (Wu et al., 2023). Voles that provided care showed increased *Oxtr* and *Drd2* mRNA expression in the NAc. In contrast, voles that received care exhibited elevated OXT immunoreactivity in the PVN, MPOA, and amygdala, and increased TH immunoreactivity in the VTA. These findings indicate that distinct early social experiences shape partner preference via sex-specific modulation of OXT and DA pathways. In contrast to Wu et al. (2018), who reported reduced partner preference after post-weaning parental cohabitation, this study found the opposite. The enhanced partner preference may result from alloparenting, which provides enriching social interactions and increased care, likely strengthening OXT and DA signalling to support adult bonding.

In summary, the interplay between OXT and DA systems is pivotal in shaping offspring attachment, influencing bonding and parental preferences through their coordinated signalling. Early social experiences, such as paternal deprivation or alloparental care, lead to lasting effects on brain regions involved in attachment, including the VTA, NAc, and amygdala.

3.3. *Effects of psychostimulants on parental behaviour*

Paternal cocaine use prior to mating can have lasting effects on offspring. (Yaw et al., 2022) examined how paternal cocaine self-administration affects social behaviour and the OXT system in male F1 mice. One day after withdrawal, cocaine-exposed and control males were mated with drug-naïve females. Male offspring of cocaine-exposed fathers showed increased social investigation, indicating heightened social motivation, while aggression was unchanged. Receptor autoradiography revealed elevated OXTR binding in the NAc and reduced binding in the basolateral amygdala, bed nucleus of stria terminalis, lateral septum, and lateral habenula. These findings suggest that paternal cocaine use may alter offspring social behaviour through disrupted OXT-DA signalling. While mechanisms remain unclear, changes in sperm physiology appear more likely than altered paternal behaviour, highlighting the need for further investigation into intergenerational transmission. A related study examined the impact of chronic cocaine exposure on maternal and offspring social behaviours (Johns et al., 1998). Postpartum cocaine treatment increased maternal aggression, which was associated with reduced OXT levels in the amygdala. Prenatal cocaine exposure in offspring led to age- and sex-dependent socio-emotional alterations, including heightened neophobia, aggression, hypoactivity, and disrupted social interactions and stress responses. Offspring exposed to a DA uptake inhibitor also showed increased aggression, underscoring the role of DA in these behavioural changes.

Similarly, gestational cocaine exposure has been linked to enhanced maternal aggression (Lubin et al., 2003). Notably, direct OXTR antagonism in the central amygdala further amplified aggression, while neither cocaine nor OXTR blockade affected maternal care behaviours. These findings implicate OXT signalling in the central amygdala in cocaine-induced maternal aggression, warranting further investigation into whether enhancing OXT activity in this region can mitigate these effects.

Gestational cocaine exposure in female rats has been shown to exert intergenerational effects on maternal aggression and OXT signalling in the amygdala (McMurray et al., 2008). Cocaine-treated dams exhibited heightened maternal aggression, which was associated with reduced OXT levels in this region. These findings suggest that prenatal cocaine exposure not only disrupts maternal behaviour, but also alters neuroendocrine systems critical for social regulation, with potential consequences for offspring development and behaviour.

Cocaine withdrawal in mandarin vole fathers impaired paternal behaviour, increasing latency to crouching, pup contact, and retrieval, while reducing licking/grooming and overall pup interaction (Wang et al., 2014). These behavioural changes were accompanied by decreased OXT immunoreactivity in the PVN and increased TH immunoreactivity in the VTA. Additionally, the OXT system appears to be differentially activated by pup- versus cocaine-associated cues. In a CPP paradigm, pup-conditioned fathers showed elevated OXTR expression in the medial amygdala and higher plasma OXT levels compared to controls (Fang and Wang, 2017). Notably, both pup- and cocaine-conditioned fathers exhibited lower D2R expression in the NAc, suggesting overlapping OXT-DA mechanisms underlying social and drug-related reward.

In female mandarin voles, biparental care and paternal deprivation led to distinct effects on social behaviour and altered DA and OXT systems following cocaine exposure (Wang et al., 2017a). Cocaine-treated females consistently showed reduced social contact, indicating that the effect of cocaine on social behaviour is not solely dependent on paternal presence. However, neuroendocrine responses differed. In biparentally raised females, cocaine treatment significantly reduced OXT immunoreactivity in the PVN and SON compared to saline controls. In contrast, females raised without paternal care, regardless of treatment, exhibited fewer OXT-immunoreactive neurons in the hypothalamus compared to biparentally raised controls. These findings suggest that paternal deprivation alone alters OXT signalling, potentially modulating the behavioural impact of cocaine exposure.

In summary, psychostimulants disrupt OXT-DA signalling, leading to significant alterations in parental care, social interactions, and aggressive behaviours in both sexes. Studies in rats and mandarin voles revealed altered OXT and DA receptor expression in key brain regions such as the PVN, NAc, and amygdala, influencing both maternal and paternal caregiving. These disruptions often result in increased aggression, reduced social interactions, and changes in parental care behaviours. Substances of abuse may indirectly affect social behaviour by altering stress, motivation, or arousal, underscoring the need for targeted approaches, such as optogenetic or chemogenetic manipulation of OXT and DA systems, to clarify their roles during psychostimulant exposure.

3.4. Pair bonding

The involvement of OXT and DA and their interactions in the context of pair-bonding has been well studied in the monogamous prairie vole (*Microtus ochrogaster*) (Blumenthal and Young, 2023) summarized in Table 2.

The effects of OXT on partner preference and the DA system were investigated in female prairie voles (Liu and Wang, 2003), which form long-lasting social bonds. In the absence of mating, i.c.v. OXT infusion induced partner preference, emphasising the role of OXT in pair bond formation. Additionally, administration of D2R and D3R antagonists prevented OXT-induced partner preference, highlighting the requirement of OXT, D2R, and D3R for pair bond formation in female prairie voles.

Adult female prairie voles were tested after same-sex (female cage mate) or opposite-sex (male partner) loss for one week to assess social motivation using the odor preference test (Kirckof et al., 2025). Opposite-sex loss increased partner-seeking behaviour, with higher olfactory investigation of partner-associated cues (scented bedding) compared to food-associated cues, in contrast to females that lost a same-sex cage mate or remained with a male partner. Molecular analysis revealed increased D1R protein expression in the MPOA and hippocampus, along with elevated OXTR content in the hippocampus following opposite-sex loss. No significant changes were found in OXT content in the PVN or in the expression of OXTR, D1R, and D2R in the PVN, NAc, or anterior cingulate cortex. Pharmacological blockade of MPOA D1R with SCH23390 reduced partner cue investigation, highlighting the critical role of D1R in partner-seeking behaviour. These findings, aligned with previous studies on DR1 signalling in pair bond maintenance (Aragona and Wang, 2009), reveal a novel DA-mediated mechanism for partner-seeking behaviour during partner loss in female prairie voles.

After separation from the female partners (4 weeks), male prairie voles exhibited more affiliative behaviour and less aggression towards unfamiliar females and intruding males, alongside heightened anxiety-related behaviour and a more passive stress-coping style (Sun et al., 2014). This behavioural shift was accompanied by increased OXT-immunoreactive cell density in the PVN and SON, suggesting stress-induced activation of the OXT system, while TH immunoreactivity in the VTA remained unchanged. In a different study performed in our lab, partner loss (3 days) induced increased passive stress-coping behaviour, accompanied by reduced *Oxt* mRNA in the PVN and decreased OXTR binding in the NAc shell (Bosch et al., 2016), suggesting distinct compensatory adaptations in the OXT and DA systems following acute versus prolonged loss of social contact.

Monogamous prairie voles (*Microtus ochrogaster*) and promiscuous meadow voles (*Microtus pennsylvanicus*), which differ in social strategies such as pair bonding, selective aggression, and parental care, also show distinct neurobiological profiles in the mPFC (Smeltzer et al., 2006). Compared to promiscuous voles, monogamous voles exhibit higher OXTR and D2R binding but lower D1R binding in the mPFC. These receptor distribution patterns suggest that species-specific differences in the OXT and DA systems may contribute to divergent social behaviours and mating strategies.

The transition to motherhood involves neuromodulatory changes in the OXT and DA systems that support maternal behaviour (Forero et al., 2024). In monogamous prairie voles, *Oxtr*, *Drd1*, and *Drd2* mRNA expression increased in the NAc of lactating mothers compared to nulligravid females, resembling patterns seen in pair bonding. In the anterior cingulate cortex, *Drd1* mRNA expression was elevated in mothers compared to pregnant females, and extended cohabitation with a male also increased *Drd1* and *Drd2* mRNA expression in nulligravid females. In the MPOA, *Oxtr*, *Drd1*, and *Drd2* mRNA expression increased in pregnant and cohabitated females. These findings highlight stage-specific OXT-DA shifts across motherhood and bonding.

In summary, the interplay between OXT and DA systems is important for pair bonding. Studies in prairie voles show that OXT is essential for partner preference, and involves D2R and D3R. Changes in the expression of OXTR and DA receptors in the NAc and mPFC were linked to partner-seeking behaviour. Differences in the densities of these receptors between monogamous and promiscuous voles further suggest their role in mate preference and bonding. In monogamous species, OXT promotes pair bonding and nurturing via DA release in reward circuits, whereas in promiscuous species, OXT-DA interaction modulate social novelty-seeking.

3.5. Effects of psychostimulants on pair bonding

Few studies have explored how psychostimulants like amphetamine and METH affect pair bond formation. These drugs elevate brain DA by enhancing release and inhibiting reuptake. Repeated amphetamine exposure impaired partner preference in female prairie voles, reduced OXTR immunoreactivity in the mPFC, and increased DA levels alongside decreased D2R expression in the NAc (Young et al., 2014). Remarkably, OXT administration in the prelimbic subregion of the mPFC reversed these deficits, restoring partner preference and further increasing DA in the NAc, underscoring the modulatory role of OXT in drug-disrupted bonding. Similarly, voluntary METH consumption reduced partner preference in both male and female prairie voles and was associated with decreased OXT immunoreactivity in the PVN (Hostetler et al., 2016). Social housing (single- vs. group-housed) had no effect on METH intake or its impact on bonding, suggesting that the presence of conspecifics does not mitigate METH-induced disruptions in partner preference.

In summary, psychostimulants disrupt OXT-DA signalling and impair pair bonding, as demonstrated by altered receptor expression and reduced partner preference in prairie voles. While OXT can counteract some of these drug-induced deficits, more targeted studies are needed to clarify its modulatory role in psychostimulant-altered social behaviour.

4. Impact of combined stress and psychostimulants on OXT-DA

There is also evidence for a role of OXT-DA interaction in shaping the consequences of exposure to social stress, as summarised in Table 3.

The consequences of exposure to chronic psychosocial stress during adolescence on the development of social behaviours have been studied using a social isolation paradigm (from postnatal days 28 to 35) (Musardo et al., 2022). Adult isolated male mice displayed increased social interaction in a direct free interaction task, but showed deficits in social recognition in a three-chamber task when compared with group-housed mice. These behavioural changes were linked to an increase in the number and activity of OXT neurons in the PVN at the end of social isolation. In support, whole-cell patch clamp recordings showed hyper-excitability of PVN-OXT neurons projecting to the VTA on the final day of isolation. Additionally, increased synaptic plasticity in VTA-DA neurons projecting to the mPFC was observed. Chemogenetically suppressing PVN-OXT neurons projecting to the VTA during isolation normalised social interaction time to group-housed levels and restored the excitability of VTA-DA neurons. This suggests that altered PVN-OXT neuron activity may drive the effects of adolescent social isolation on adult social behaviours.

Several studies have shown that the OXT system can buffer against social avoidance induced by repeated exposure to social defeat stress (SDS) in adults. One study in female prairie voles linked SDS-induced avoidance to altered OXTR expression and signalling in limbic regions (Nerio-Morales et al., 2024). After three days of SDS, adult female prairie voles exhibited reduced sociability one week later. OXTR binding decreased in the NAc but remained stable in the anterior cingulate cortex and BLA. OXT levels increased in the BLA but were unchanged in the PVN and the anterior cingulate cortex. CRISPR/Cas9-mediated OXTR knockdown in these regions reduced social investigation in unstressed females and lowered OXT in the PVN, underscoring OXTR dysregulation as a key driver of social behaviour disruption. In male Syrian hamsters, infusion of OXT into the VTA reduced social avoidance (measured as time spent on the far side of the resident cage) after acute SDS, an effect absent in females (Grieb et al., 2024). In contrast, VTA infusion of an OXTR antagonist increased social avoidance in stressed females but not males, suggesting sex-dependent regulation of social stress salience by OXT signalling in the VTA. In California female mice, infusion of a biased OXTR-Gq agonist into the NAc increased social interaction subjected to chronic SDS (Williams et al., 2020). These results, in addition to the effects observed in naive mice (as mentioned in section 3.3), indicate that OXTR signalling in the NAc, primarily through an OXTR-Gq mechanism, reverses the stress-induced impairment of

Table 3
Summary of studies examining the interaction of OXT and DA in the context of chronic social stress, aggression, and genetic animal models of psychiatric disorders in rodents.

Species Strain	Age Sex Housing conditions	Intervention and group comparison	Social behaviour outcome	OXT system outcome	DA system outcome	Ref.
Mouse (B6)	Adolescent ♂ SH	Chemogenetic silencing of PVN OXT neurons CNO vs veh	↓ Social interaction		VTA ↓ DA neuron excitability	Musardo et al., 2022
Prairie vole	Adult ♀ GH	No intervention Physical stress vs control	↓ Social interaction	BLA ↑ OXT PVN, ACC ↔ OXT NAc ↓ OXTR binding ACC, BLA ↔ OXTR binding		Nerio-Morales et al 2024
		CRISPR/Cas9 silencing of OXTR Cas9 vs control vector, unstressed	↓ Social interaction	NAc, ACC, BLA ↓ OXTR binding PVN ↓ OXT		
California mouse	Adult ♂/♀ SH	Intra-NAc OXTR-Gq agonist Carbetocin (1 μg/μl) Drug vs veh, stressed	↑ Social interaction			Williams et al., 2020
Syrian hamster	Adult ♂/♀ SH	Intra-VTA OXT (9 μM) Drug vs veh, stressed	↑♂/↔♀ Social interaction			Grieb et al., 2024
		Intra-VTA OXTR selective antagonist desGly-NH2-d(CH2)5[D-Tyr2,Thr4]OVT (90 μM) Drug vs veh, stressed	↔♂/↓♀ Social interaction			
Mouse (B6)	Adult ♂ Housing NS	Intra-mPFC OXT (2 or 10 μg/μL) Drug vs veh, stressed	↑ Social interaction		mPFC ↑ DA ↑ D1R-related signalling	Li et al., 2019
		Intra-mPFC OXTR antagonist L-368, 899 (10 μg/μl) Drug vs veh, stressed			mPFC ↓ DA ↓ D1R-related signalling	
Mandarin vole	Adult ♂/♀ PH	No intervention Physical stress vs control	↓ Allogrooming ↓ Sociability	ACC ↓ *Oxtr*/OXTR	ACC ↓D2R ↔ *Drd2* ↔ *Drd1*/D1R	Li et al., 2020

Abbreviations: ACC: anterior cingulate cortex; AMY: amygdala; CC: cerebral cortex; CNO: clozapine N-oxide; DA: dopamine; DOPAC: 3,4-Dihydroxyphenylacetic acid; *Drd1*/D1R: DA D1-like receptor; *Drd2*/D2R: DA D2-like receptor; GH: group-housed; Hyp: hypothalamus; i.c.v.: intracerebroventricular; ir: immunoreactivity; KO: knockout; mPFC: medial prefrontal cortex; NS: not specified; OXT: oxytocin; *Oxtr*/OXTR: oxytocin receptor; PH: pair-housed; PVN: paraventricular nucleus of the hypothalamus; SH: single-housed; STR: striatum; STX1A: syntaxin 1A; veh: vehicle; vs.: versus; VTA: ventral tegmental area; WT: wild type.
Symbols: ♂: male; ♀: female; ↑: significant increase; ↓: significant decrease; ↔: no significant differences.

social approach.

Stress can induce a depression-related phenotype, prompting the exploration of the potential antidepressant properties of OXT (Li et al., 2019). Intra-mPFC administration of OXT reduced social avoidance in male mice subjected to SDS. In non-stressed mice, OXT infusion into the mPFC facilitated active stress-coping behaviour in the forced swim test, an effect blocked by pre-treatment with either an OXTR or D1R-antagonist (SCH23390). OXT treatment also increased DA release and altered signalling molecules like DARPP32, related to D1R in the mPFC. These findings suggest that OXT and DA signalling interact within the mPFC, potentially contributing to "antidepressant" effects by enhancing presynaptic DA release.

The role of OXT and DA in pair-housed mandarin voles has been examined in the context of neuronal mechanisms of empathy (Li et al., 2020). Male and female voles exposed to chronic SDS showed decreased grooming behaviour toward partners who had experienced a single SDS, along with reduced sociability compared to non-stressed animals. These behavioural changes were associated with increased anxiety-related behaviour and a passive stress-coping style. Chronic SDS also led to reduced neuronal activity and lower OXTR and D2R receptor density in the anterior cingulate cortex, a key area for empathy. Pre-treatment with an OXTR agonist in this region improved consolation behaviour in SDS-exposed voles, but reduced it in non-stressed voles. This highlights the complex interplay of OXT and DA in empathy-related behaviour under stress.

In summary, social stress exposure can affect social interactions by disrupting OXT-DA signalling in the VTA, NAc, and mPFC, with beneficial effects of OXT to restore social behaviour and reverse stress-induced changes in DA signalling. However, more research is needed to clarify the mechanisms underlying OXT-DA interaction, especially under combined stress and psychostimulant exposure.

5. Concluding remarks

This review underscores the complex interplay between OXT and DA systems in regulating a broad spectrum of social behaviours in rodents, including social approach, aggression, parental care, and pair bonding. It also highlights how psychostimulants can disrupt these neuromodulatory circuits, leading to altered social functioning. By integrating findings from pharmacological, genetic, chemogenetic, and optogenetic studies, we provide compelling evidence that OXT-DA interaction are pivotal in modulating both reproductive and non-reproductive social behaviours. Figs. 1 and 2 summarise the methodologies used and the key sites and behaviours associated with OXT-DA signalling.

However, several limitations constrain current interpretations. First, the predominant focus on male rodents restricts understanding of sex-specific mechanisms, especially given the known sexual dimorphism in OXT and DA systems (Becker and Chartoff, 2019; Quintana et al., 2024; Zachry et al., 2021). Second, species differences, particularly between monogamous and promiscuous species (Bendesky et al., 2017), limit the generalisability of findings, and the relevance to human social behaviour is still not fully established.

Methodologically, while tools such as chemogenetics and optogenetics allow to dissect neuronal circuits, they may not precisely isolate the roles of OXT or DA due to neurotransmitter co-release, particularly glutamate, from PVN-OXT and VTA-DA neurons (Descarries et al., 2008; Meeker et al., 1991; Trudeau and El Mestikawy, 2018). This co-transmission complicates interpretation, highlighting the need for more refined approaches, such as combinatorial pharmacology or genetic targeting, that can disentangle the contributions of each signalling molecule.

It is also important to mention that synthetic drugs and endogenous neurotransmitters/neuromodulators differ substantially in their pharmacodynamics and kinetics. Endogenous substances, which are

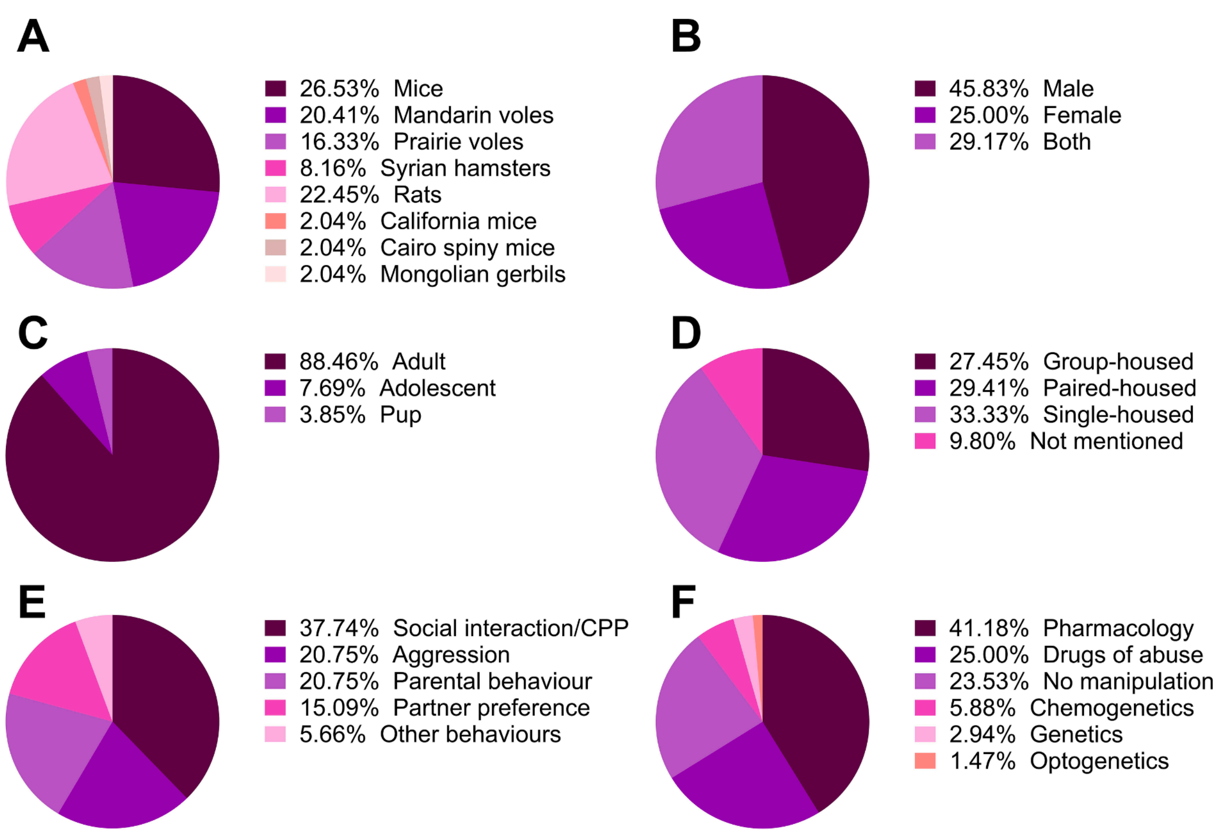

Fig. 1. Characteristics and quality assessment of the included studies. (A–F) Pie charts showing the study characteristics reported as the percentage of experiments. (A) rodent species, (B) sex, (C) age, (D) housing conditions, (E) social behavioural tests, and (F) type of manipulation. Abbreviation: CPP: Conditioned place preference.

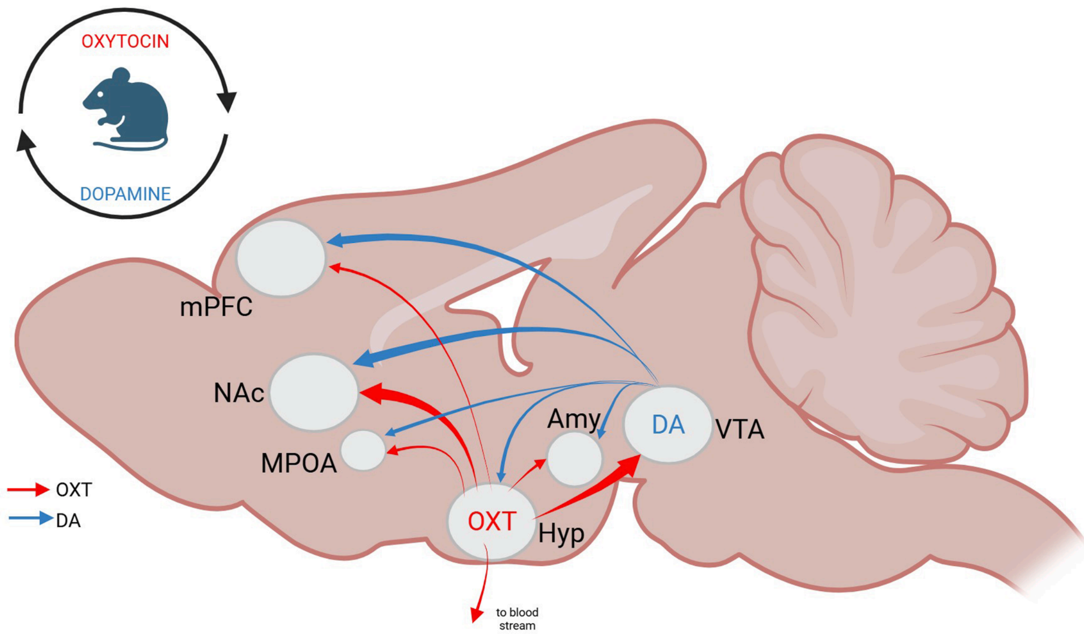

Fig. 2. Interplay between oxytocin and dopamine systems in regulating rodent social behaviours. The scheme of the rodent brain illustrates neuronal pathways involving oxytocin (OXT) and dopamine (DA) in various brain regions involved in the regulation of social behaviour in rodents. The key brain regions depicted include the hypothalamus (Hyp), ventral tegmental area (VTA), nucleus accumbens (NAc), medial prefrontal cortex (mPFC), amygdala (Amy) and medial preoptic area (MPOA). The thick arrows represent the major OXT and DA connections in non-reproductive and reproductive behaviours.

naturally produced within the body are typically regulated by controlled feedback systems and are rapidly metabolised and cleared in a way that maintains physiological balance. In contrast, exogenous drugs may not follow these regulatory mechanisms, often leading to different absorption rates, broader tissue distribution and sometimes unanticipated effects due to bypassing or the body's normal metabolic and excretory pathways (Tomlin, 2010). In this way, psychostimulants can alter DA signalling differentially compared with the natural DA signalling in the brain.

Emerging technologies, such as fiber photometry and GRAB sensors for OXT and DA (Qian et al., 2023; Sun et al., 2020), offer exciting opportunities to monitor real-time neuromodulatory dynamics during social interactions. These tools may help clarify how OXT-DA signalling is modulated by internal states such as stress, hormonal fluctuations, or drug exposure. Furthermore, these methods are well-suited for examining disrupted social behaviour in neuropsychiatric models, including addiction.

Future research should prioritise sex-balanced and cross-species designs, integrate longitudinal approaches to capture developmental effects, and develop better circuit-specific tools to delineate the unique and interactive roles of OXT and DA. This will be critical not only for advancing basic science but also for identifying novel therapeutic targets for social dysfunctions.

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Author contribution

FCD and VR performed the literature search, the assessment of available evidence, the data collection, and prepared the manuscript. IN repeatedly revised the manuscript. All authors reviewed and approved the last version of this manuscript.

CRediT authorship contribution statement

Fernando Castillo Díaz: Writing – review & editing, Writing – original draft, Visualization, Data curation. **Inga D. Neumann:** Writing – review & editing. **Virginie Rappeneau:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2025.101200.

Data availability

Data sharing does not apply to this article as no data sets were generated or analysed during the current study. Supplementary information is available at MP's website.

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