

Review



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Interplay between the oxytocin and opioid systems in regulating social behaviour

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The influence of neuromodulators on brain activity and behaviour is undeniably profound, yet our knowledge of the underlying mechanisms, or ability to reliably reproduce effects across varying conditions, is still lacking. Oxytocin, a hormone that acts as a neuromodulator in the brain, is an example of this quandary; it powerfully shapes behaviours across nearly all mammalian species, yet when manipulated exogenously can produce unreliable or sometimes unexpected behavioural results across varying contexts. While current research is rapidly expanding our understanding of oxytocin, interactions between oxytocin and other neuromodulatory systems remain underappreciated in the current literature. This review highlights interactions between oxytocin and the opioid system that serve to influence social behaviour and proposes a parallel-mechanism hypothesis to explain the supralinear effects of combinatorial neuropharmacological approaches.

This article is part of the theme issue 'Interplays between oxytocin and other neuromodulators in shaping complex social behaviours'.

1. Introduction

Understood to have evolved from a lineage of vertebral nonapeptides [1–3], oxytocin was identified early as a hormone crucially involved in birth and lactation [4,5], and was in fact the first polypeptide hormone to be synthesized [6]. Subsequent investigations discovered that behaviours such as learning [7,8], maternal bonding [9,10] or social interactions [11–13] are also modulated by oxytocin. Continuation on these lines of research revealed that oxytocin, which can act as a neuromodulator in the brain [14–18], robustly affects social behaviours in both humans and animal models [19–24]. In humans, oxytocin has been shown to increase gaze to faces [25], improve the ability to infer the mental state of others [26,27], enhance socially reinforced learning [28], and possibly increase trust in social interactions [29–34]. In non-human primates, oxytocin increases time spent looking at faces [35,36], improves socially reinforced learning [37], increases the frequency of gaze following behaviours [38] and promotes the donation of rewards to social partners [39,40]. Likewise, in rodents, the oxytocin system mediates the formation of pair-bonding in monogamous prairie voles [11,12,41–45], is crucial for the ability recognize conspecifics [13], and promotes maternal and social behaviours through balancing inhibition in sensory cortex [16,17,46,47]. These results strongly point toward the oxytocin system being a core component in the neural substrates of social cognition [20,21,24,48], and have prompted interest in the enormous potential of oxytocin as a therapeutic to augment socio-behavioural deficits observed in psychiatric disorders [49–55]. This prospective application has prompted a great deal of oxytocin research, both basic and clinical, which in turn has revealed many gaps in our knowledge [18,19,29,56–58].

Three important realizations are helping to reshape our understanding of how oxytocin modulates social behaviours in the brain. Firstly, a myriad of studies have demonstrated that oxytocin is not uniformly a 'pro-social' influence in the brain as sometimes popularly characterized [19,59]. The effects of oxytocin on social behaviour instead can be highly contextualized. For example, in some contexts oxytocin serves to promote ingroup behaviours [59,60] at the expense of others. Secondly, just as oxytocin does not exert a uniformly 'pro-social' influence in the brain, it also does not uniformly modulate behaviours across all individuals [19]. Instead, the behavioural effects from oxytocin are often sexually dimorphic [61–64] and can vary with developmental experience [65,66] or between genetic variations in the oxytocin receptor [67–69]. This individual variability is compounded by methodological or statistical shortcomings in existing research, leading to many results being either underpowered [70] or biased [71,72]. These concerns suggest that the current methodical approach to studying the effects of oxytocin on behaviour should be reevaluated, with future studies being designed around an increased level of statistical robustness, and that previous findings should always be examined critically. Lastly, it is evident that endogenous oxytocin does not work alone in the brain; instead, interaction effects between neuromodulatory systems may critically account for many of the behavioural and neural effects of oxytocin. Interactions between oxytocin and serotonin [73–76], endocannabinoids [77,78] or opioids [36,79–81] have been demonstrated to underlie or enhance many behavioural effects once attributed to just a single neuromodulator. Despite these impressive results, the importance of a combinatorial perspective in understanding neuromodulation remains underrepresented in the literature.

This review will specifically highlight interactions between oxytocin and opioidergic circuits [82]. Existing reviews have done an excellent job summarizing known behavioural effects of oxytocin [43,48,50,52,58,71,82,83], the neural mechanisms underlying these effects [15–17,84,85] and potential hypotheses about the role of oxytocin in the brain and social behaviour [20,22,24]. We will not attempt to duplicate those here. Instead, we will examine how the opioid system influences social behaviours, detail the known interactions between the oxytocin and opioid systems, and finally present a general hypothesis to explain the supralinear enhancements of social behaviour [36] observed after combinational oxytocin and opioid-antagonist naloxone.

2. Opioidergic modulation of social behaviour

Although the extraction of opiates from poppy seeds dates back before the common era [86], opioid receptors in the brain were not identified until 1973 [87–89]. Opioid receptors are classified into three general categories, μ -, δ - and κ -types, which are distributed widely across the brain in rodents [90] and humans [91,92], with particularly high concentrations in reward-related areas [93–95]. The opioid system is most identified for a role in analgesia [96,97] but is well established in mediating behaviours. Classically rats will self-administer morphine intracranially into the mesolimbic reward system and this effect is blocked by naloxone, an opioid antagonist [98]. The endogenous μ -opioid receptor system or naturally occurring peptides that act on μ -opioid receptors (principally β -endorphin, but also enkephalins and dynorphin) has been

shown to mediate reward processing [90,99–101] through mesocorticolimbic reward circuitry.

Given the ubiquity of reward-related processing across a variety of behaviours [102], it is unsurprising that effects of opioid manipulation have been observed in the domain of social behaviours as well. One of the earliest results, documented by Herman & Panksepp [103], was the modulation of distress in guinea pigs after infant-separation from their mothers. Subcutaneous morphine injections attenuated separation distress vocalizations for both adults and infants in a dose-dependent manner, while naloxone injections potentiated these responses [103]. Subsequent experiments localized this effect to brain opiate receptor interactions through central injections of naloxone [104], extended the behavioural finding to dogs [105], chickens [104] and non-human primates [106], and attempted to rule out anxiolytic or analgesic mechanisms [107]. These findings suggested that opioid agonism in the brain was, at least partially, able to alleviate the social isolation-induced distress, although subsequent work attempting to specifically localize receptor binding had mixed results [108,109]. Similar studies, examining how social isolation modulated social play in juvenile rats, found isolation increased social play time as well as the time spent in active social interactions, and that low-dose injections of morphine further compounded this effect [110,111], while naloxone reduced play fighting in a dose-dependent fashion [112,113]. By contrast, intraperitoneal morphine injections in rats reduced group proximity, a metric for social cohesion, and was theorized to be displacing the rewarding aspects of social interactions with an opiate proxy [114]. These powerful opioidergic behavioural effects led to the discussion of excessive opioid activity in the brain as a factor in the development of early childhood autism [115] and of a strong role of opioid receptors in social behaviours [116].

Another key series of findings by the research group of Eric Barrington Keverne was that opiate antagonism in non-human primates was able to stimulate social behaviours. Intramuscular injections of naloxone increased the frequency of social grooming amongst a group of talapoin monkeys, while not affecting aggressive behaviours, rates of self-grooming, or general locomotor movements [117]. The opiate receptor blockade increased plasma levels of luteinizing hormone, testosterone and cortisol in samples taken 60 min post-injection; however, there were no preemptive or anticipatory changes in samples taken prior to injection. Corroborating these findings was the observation that β -endorphin, an endogenous opioid neuropeptide, increases in the cerebrospinal fluid after social grooming between talapoin monkeys [118], which suggests a feedback interaction between endogenous opioid function and social grooming behaviours. Somewhat incongruently, intramuscular injections of naloxone to postpartum female rhesus monkeys decreased social grooming and maternal behaviours [119], although this result may likely be due to the disruption of endogenous opioidergic function of mothers during the critical postpartum period of bond formation between the mother and infant.

Indeed, a subsequent study of rhesus monkeys ranging in age from nine weeks to adulthood living in large family groups found that intramuscular injections of naloxone increased the frequency of affiliative social behaviours, where younger monkeys were more likely to spend time in contact with their mothers and older females spent more time socially grooming [120]. This result was replicated in a cohort of rhesus

macaque mothers that had a history of abusive parenting, finding that naltrexone (another opioid antagonist) increased the frequency of grooming received by mothers from others in the group [121].

More recent studies from the laboratory of Dario Maestri-pieri using modern genetic approaches have identified that variations in the mu-opioid receptor gene influence both infant and maternal behaviour in non-human primates. In a robustly large study of infant rhesus monkeys it was found that infants carrying a gain-of-function polymorphism in the mu-opioid receptor gene, the *OPRM1* C77G allele, exhibited an increased level of distress during separation from their mothers, and upon return would also spend more time with them when compared with infants homozygous for the C allele [122]. Likewise, mothers with the G allele also exhibit a different maternal attachment style compared with females homozygous for the C allele, restraining their infants more frequently [123]. These polymorphisms provide evidence of endogenous opioid function in regulating infant and maternal behaviours and further corroborates studies with exogenous manipulations.

The effects of the opioid system on human social behaviour are also well documented. Positron emission tomography scans paired with a μ -opioid-receptor-specific ligand ($[^{11}\text{C}]$ carfentanil) have enabled the examination of μ -opioid receptors in the human brain [124]. Using this technique researchers performed scans of human subjects both while alone in the scanner as a baseline and then with their partners non-sexually caressing them as an experimental model of social touch. The comparison of these two conditions revealed that social touch increased μ -opioid availability in the thalamus, striatum and frontal, cingulate, and insular cortices. These findings support previous hypotheses that opioidergic mechanisms mediate the rewarding aspects of social touch [125,126] and the role of endogenous μ -opioid signalling in social behaviours. In a similar experiment, experimenters scanned human participants before, and then after, viewing laughter-evoking comedy videos with close friends. The comparison of the pre- and post-social-laughter scans showed an increase in endogenous μ -opioid release in the thalamus, caudate nucleus and anterior insula [127], suggesting a mechanism for the rewarding effects of laughter in the brain.

Importantly, it should be noted that although many of these results have focused on the μ -opioid system, other opioid receptor types also have important contributions to social behaviour. The κ -opioid system has been strongly implicated in mediating stress responses [128] that are strongly interlinked with social behaviour [129,130]. Activation of the κ -opioid system in rats suppresses social behaviour, while κ -opioid antagonism negates the normal inhibition of social play in an unfamiliar environment [131]. Pretreatment of mice with the κ -opioid receptor antagonist nor-binaltorphimine can reduce or block behavioural responses to social defeat-induced stress [132]. Consistent with this, the genetic knockout of the prodynorphin gene, which codes a precursor protein for endogenous opioid ligand dynorphin, also blocks these responses, suggesting that the behavioural responses of social defeat stress are mediated through the κ -opioid system [132].

It is worthwhile to note that distinguishing the contributions of each opioid receptor type experimentally is challenging as many agonists or antagonists are non-specific or have differential binding based on dose. For example, naloxone, often used as a μ -opioid receptor antagonist,

binds preferentially to μ -opioid receptors at clinically relevant doses [133,134], but also competitively binds to κ -opioid (and to a lesser extent and δ -opioid) receptors at larger doses [135,136]. Thus, in the absence of highly selective ligands at calibrated doses, we must consider the effects of agonism or antagonism across all opioid receptors as additional layers in the complexity of opioid receptor function [92].

Cumulatively studies examining how the impact of opioid-ergic manipulation on social behaviour demonstrate a clear role for the opioid system in social cognition; however, they present an unclear picture of how precisely both opioid agonism and antagonism drive social behaviours. For example, opioid agonism through low-dose morphine injections amplifies social behaviours in socially deprived animals [110–113] but also decreases social contact in more commonplace settings [114]. Similarly, injections of naloxone in monkeys can increase social grooming in normal group settings [117] but alternately can also decrease social grooming in postpartum individuals [119]. An attempt has been made to unify these seemingly contrasting studies under the *State-dependent μ -Opioid Modulation of SOcial Motivation* (SOMSOM) model proposed by Loseth *et al.* [137]. This hypothesis postulates a state-dependent model for μ -opioid influences on social behaviour, where a μ -opioid agonism under a distressed state acts to displace potential social rewards, leading to less seeking of social comfort. Meanwhile, μ -opioid antagonism under a continued distressed state further increases distress and incentivizes more social comfort seeking. With a comfortable initial state, the results of μ -opioid manipulation are inverted, such that agonism results in increased social exploration and antagonism reduces social comfort seeking. While future studies purposely manipulating these initial states are required to fully test this theory, the current data strongly suggest that initial state and social context influence how opioid receptor activation (or blockage) modulates subsequent social behaviour and may potentially supersede any species-specific differences. Importantly these state- and context-dependent effects may also be explanatory in examining how the opioid system interacts with oxytocinergic mechanisms in modulating social behaviours, as we will expand upon next.

3. Combinatorial effects of oxytocin and naloxone on social behaviour

While both oxytocin and opioids are separately implicated in regulating social behaviours, a strong relationship between these systems is also well established. A landmark study in 1982 by Bicknell & Leng tested *in vitro* how opioid antagonists modified the electrically stimulated release of oxytocin and vasopressin from the rat posterior pituitary (figure 1a). They found that naloxone drastically enhanced electrically stimulated oxytocin release (nearly three times increase), without altering the amount of vasopressin secreted (figure 1b) [81]. The same experiment with the dopamine D2 receptor antagonist spiperone did not markedly change the release of either oxytocin or vasopressin [81]. This experiment was repeated after almost total removal of intermediate lobe tissue, with the same results, demonstrating the endogenous opioid function blocked by the naloxone application comes from the posterior lobe of the pituitary itself [138]. Furthermore, strong evidence of opioid–oxytocin interactions at the level of oxytocin cell bodies was demonstrated

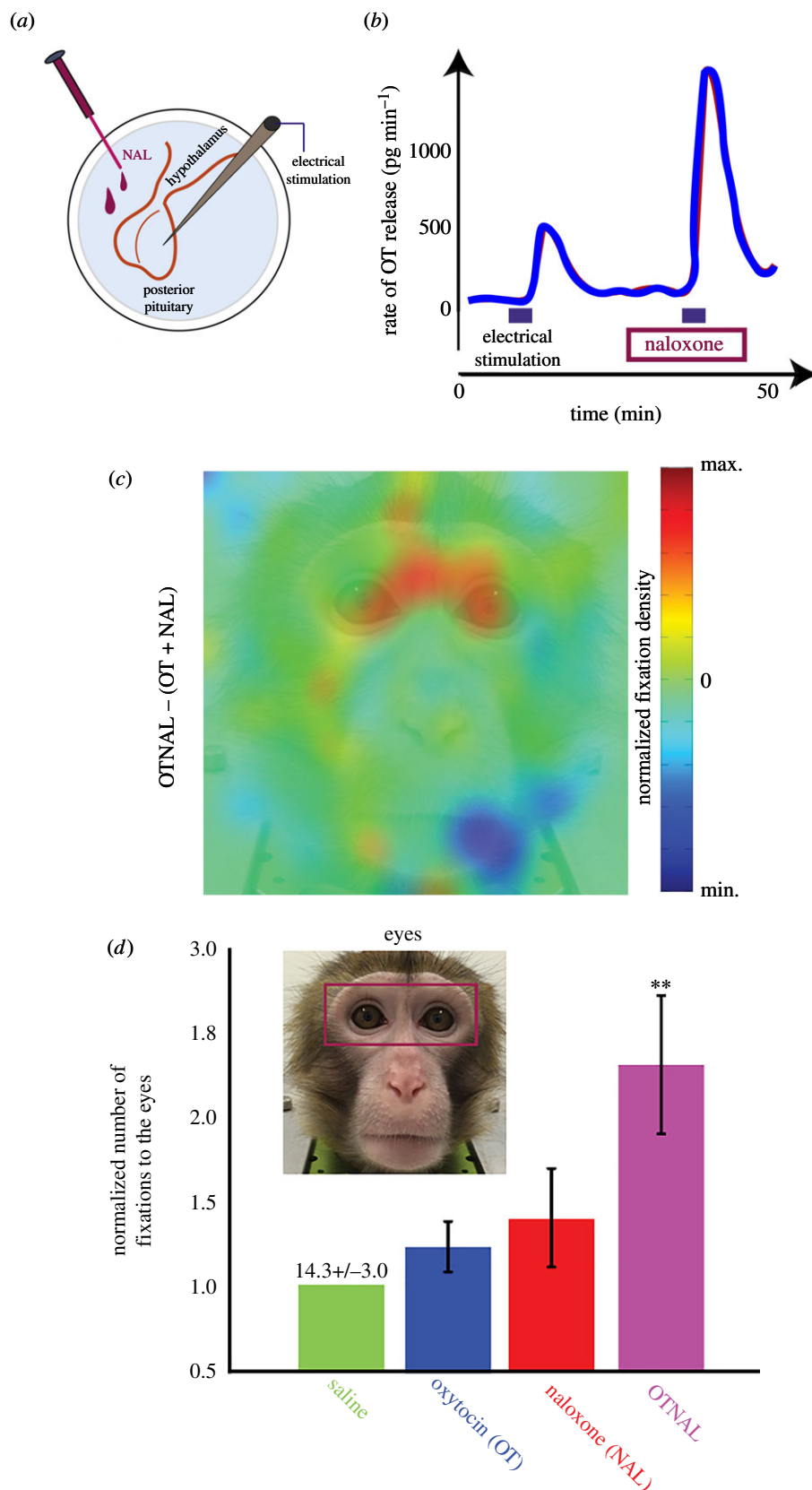


Figure 1. Combinatorial effects of oxytocin and naloxone (*a,b*) Foundational study by Bicknell & Leng [81], which demonstrated enhanced rate of oxytocin release from the posterior pituitary following naloxone opioid receptor blockade. (*a*) Experimental diagram showing *in vitro* preparation of the posterior pituitary with electrical stimulation and addition of naloxone (NAL). (*b*) Rate of oxytocin release (OT) shown first during normal stimulation, and then after naloxone opioid receptor blockade by naloxone. Diagrams adapted from Fan *et al.* [82]. (*c,d*) Supralinear increase in social attention following combinatorial oxytocin and naloxone (OTNAL) inhalation. (*c*) Heatmap of normalized fixation density on the partner's face showing difference between combinatorial oxytocin and naloxone and the summation of oxytocin and naloxone separately. Note the increase in fixation density (yellow and red coloration) around the eyes of the partner. (*d*) Normalized fixation frequency to the eyes of the partner monkey for saline, oxytocin, naloxone and combinatorial oxytocin and naloxone. Error bars: \pm standard error of the mean; **: $p < 0.01$ over 'saline' condition, one-way ANOVA with Tukey–Kramer *post hoc* tests for multiple comparisons. Diagrams adapted from Dal Monte *et al.* [36].

through examination of oxytocin-releasing neurons in the rat supraoptic nucleus, both *in vitro* and *in vivo* [139]. Injections of naloxone into the supraoptic nucleus of lactating rats following chronic morphine administration increased the firing rates of putative oxytocin neurons [79]. By contrast, firing rates of oxytocin and vasopressin cells in the rat supraoptic nucleus were reduced by endogenous opioid peptides, and naloxone was shown to block this effect [140,141]. In morphine-dependent rats, injections of naloxone increased the post-spike excitability of oxytocin neurons, likely reflecting altered intrinsic cellular membrane dynamics, as both the after-hyperpolarization and transient outward rectification of these neurons were reduced [142]. Opioid withdrawal even was shown to modulate oxytocin gene expression, increasing measurements of oxytocin heterogeneous nuclear RNA in the magnocellular neurosecretory system of rats experiencing naloxone-precipitated morphine withdrawal [143]. Collectively, these numerous regulatory connections between oxytocin-releasing neurons and the opioid system [79–81,138–148] demonstrate that the endogenous functioning of these neuromodulator systems is strongly linked at the cellular level. However, relatively few studies have tested this connection in the realm of social behaviours.

Studies examining pair-bonding in monogamous prairie voles have revealed much about the neuroendocrinology that underlies these behaviours, including the role of oxytocin and dopamine [12,41–43,149–151]. Both the opioid and oxytocin systems have been demonstrated to interact with dopaminergic circuits in pair-bonding behaviours [100,152,153], leading to a theorized tripartite link between these systems [154]. Likewise, oxytocinergic and opioidergic interactions in combination with social attachment have been postulated to modulate corticostriatal circuits in a protective response against stress [155]. Clear social-behavioural evidence for opioid–oxytocin interactions comes from a study by Dal Monte and colleagues [36], where pairs of rhesus monkeys, seated across from each other, participated in a series of naturalistic social gaze interactions while the gaze position of both monkeys was monitored at high spatial and temporal resolution. One of the two monkeys was intranasally administered either saline, oxytocin, naloxone or combinatorial oxytocin and naloxone. When the frequency of fixations to the face and eyes by each monkey to its partner was quantified as a measure of social attention (figure 1c), it was found that while oxytocin or naloxone each individually increased fixations to the face or eyes when administered alone, the combinatorial oxytocin and naloxone supralinearly increased social attention (i.e. greater than the sum of the oxytocin and naloxone together, figure 1d). This effect extended to the dynamics of social gaze exchanges, such as mutual eye contact.

Taken together, these striking results highlight that oxytocinergic and opioidergic interactions strongly influence social behaviours beyond the contributions of the individual neuromodulators alone. However, the precise mechanism of this interaction is still unknown. Several possibilities exist, the most straightforward of which is that the supralinear effects of combinatorial oxytocin and naloxone are a result of increased endogenous oxytocin release via opioid receptor blockade as has been observed *in vitro* [81]. The behavioural result of increased endogenous oxytocin release may not be identical to increased doses of exogenously administered oxytocin, as endogenously released oxytocin may act in a

spatially or temporally specific fashion [156], which cannot be duplicated by systemically administered oxytocin [157–161]. Indeed, much of our knowledge regarding how oxytocin functions in the brain has been gained through relatively blunt manipulations of oxytocin or oxytocin receptors, which cannot mimic the natural functioning of this system during social behaviours. In order to better understand the mechanisms of oxytocin action in the brain, sophisticated new approaches are necessary to precisely dissect these circuits, such as optogenetically controlled release of oxytocin from hypothalamic axonal projections [156], the use of such optogenetic oxytocin-activation in semi-naturalistic experiments [162], and fast scan cyclic voltammetry or genetically encoded fluorescent sensors to sample endogenous function [163–165].

Although increased endogenous oxytocin release likely *partially* explains the supralinear increases of social attention following combinatorial oxytocin and naloxone, it does not exclude other concurrent mechanisms. Another likely hypothesis is that oxytocin and opioid receptors act to modulate social behaviour through different underlying mechanisms at the neural level, and that this parallel manipulation of both neuromodulators can fully impact measured behaviours at two intersections instead of one. As described earlier, although opioid agonism or antagonism alone can drive social behaviours, these effects are likely state- or context-dependent. Using the example of social grooming between monkeys, where opioid antagonism results in an increase in social behaviours [117,120], this effect could be hypothetically explained by an increased seeking of social reward after opioid blockade, perhaps due to dampening of the natural reward circuitry (figure 2a). By contrast, opioid activation could artificially activate these same neural circuits, displacing the seeking of social reward in lieu of a drug-induced reward [118]. Likewise, in monkeys, inhalation of oxytocin also modulates social behaviours, which are usually manifested by an increase in attention to social stimuli or pro-social behaviours [35–38,40]. One proposed mechanism for these results is an increase in the saliency of social stimuli [166,167] (figure 2b). We postulate that, in addition to stimulating the release of endogenous oxytocin, opioid blockade through naloxone increases social reward seeking. When this effect is combined with oxytocin, which likely acts to enhance the processing or saliency of social stimuli, combinatorial oxytocin–naloxone can increase social attention beyond the summation of either drug alone, as has been observed experimentally.

While both of these neuromodulators can affect social behaviour through separate mechanisms, their combined action can modulate both the drive for social reward (opioid system) and the saliency of stimuli (oxytocin system). Like the SOMSOM model, which proposes a state-dependent modulation of opioidergic influences on social behaviours [137], naloxone could be driving a social-reward-seeking state in which the underlying neural effects of oxytocin are uniquely potent. In a social-reward-seeking state, where the rewarding effects of social interactions are specifically powerful (possibly because other reward circuitry is suppressed), increasing the saliency of social stimuli could explain the supralinear effects of combinatorial oxytocin and naloxone. Endogenous opioidergic signalling under normal functioning may provide a ‘ceiling’, limiting how much social reward an individual seeks, but opioid receptor blockade via naloxone may even shift this limit higher, enabling further social behaviours.

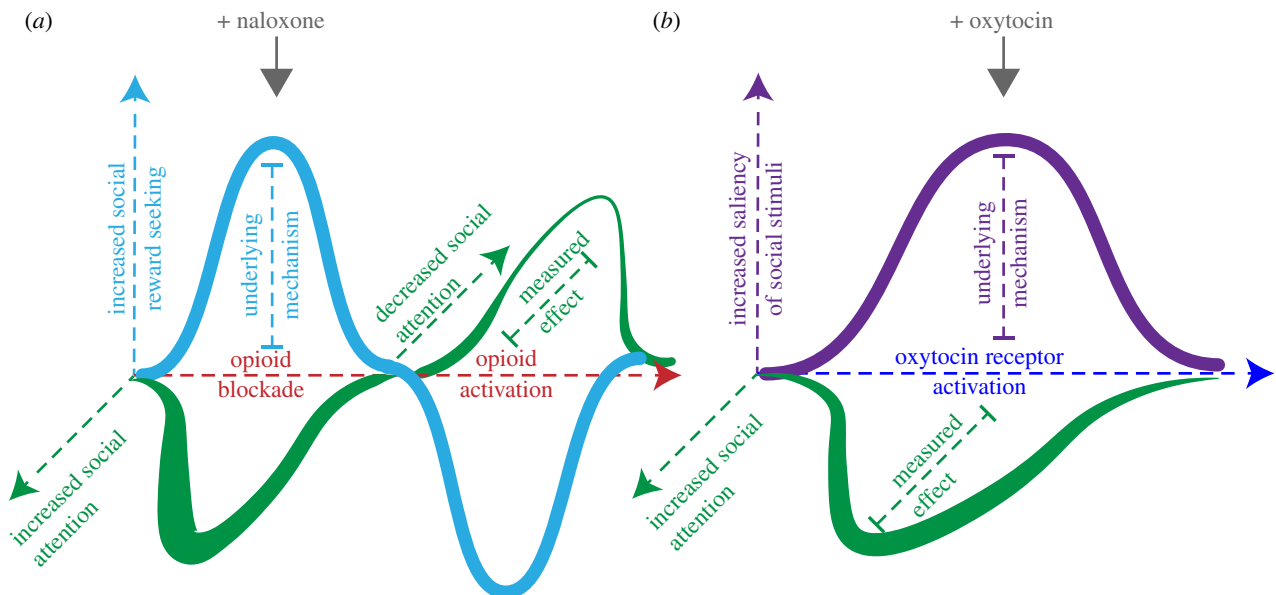


Figure 2. Hypothetical parallel mechanisms of opioid and oxytocin receptor modulation on social attention. Both idealized diagrams show the experimentally measured behaviour, social attention, on the x (green)-axis. Receptor activation for opioid (left, red) and oxytocin (right, blue) systems is shown on the y -axis. The z -axis represents potentially underlying mechanisms that both intersect with the measured behaviour. (a) Both opioid antagonism and agonism can drive social behaviours, although the effects are state- or context-dependent. Here opioid antagonism leads to an increased seeking of social reward, which in turn manifests itself as increased social attention. Conversely, in this context opioid agonism would displace reward from social interactions, leading to a decrease in social attention. (b) Administration of exogenous oxytocin is documented to increase social attention, possibly owing to oxytocin enhancing the saliency of social stimuli. Note that for both the neuromodulator systems the measured effects can appear similar even though the underlying mechanisms differ.

Our proposed hypothesis has several testable predictions. Firstly, this hypothesis would predict that morphine administration in parallel with oxytocin could significantly reduce, or even block, the effects of oxytocin on social behaviour beyond any impacts of morphine alone on social behaviour. If the rewarding properties of morphine displaced a social-reward-seeking state, then the enhancement of social stimuli by oxytocin would be effectively discounted owing to social disengagement. Similarly, owing to the state- or context-dependent effects of opioidergic manipulations, varying experimental conditions should be able to increase or diminish the supralinear effects of combinatorial oxytocin and naloxone. For example, according to the SOMSOM model, an entirely relaxed initial state should yield less social exploration following opioid antagonism. Undoubtedly, continued investigations are necessary to understand the neural mechanisms responsible for the combinatorial behavioural effects of concurrently manipulating the oxytocin and opioid systems in the brain.

Several brain regions stand out as particular targets for investigation owing to their shared connection to oxytocinergic, opioidergic and social brain circuits. The amygdala, hypothesized to be a candidate for the site of oxytocinergic action on social behaviour [28,156,168–172], also contains κ - and μ -opioid [173–176] receptor-linked pathways, and is one potential target for investigation. The anterior cingulate cortex, another node of the limbic system, is a similar intersection for the effects of oxytocin [177–179] and opioids [180] in the brain and is another potential candidate. Likewise, the nucleus accumbens is strongly linked to both the oxytocin [75,152,181] and opioidergic [182–185] systems and is a third potential target. Most likely the interactions between the opioid and oxytocin systems are not limited to a single brain region, but instead are distributed across these areas, and the coordination between brain regions

may be as important as the intraregional processing in coordinating social behaviour [186,187].

4. Conclusion

Oxytocin and opioids have well-established roles in modulating social behaviours. However, increasing evidence suggests that the interactions between these neuromodulators are critical and have the therapeutic potential to be more powerful than manipulating either system alone. Manipulation of opioid receptors, particularly μ -opioid receptors, can potentiate or attenuate rewarding social interactions [101,127,137,154]. Oxytocin modulates social behaviours and enhances the processing of social stimuli in the brain [17,48,84]. Opioid receptor blockades in combination with oxytocin can supralinearly increase social attention [36,82]. This effect could simply be driven by increased endogenous oxytocin release following opioid antagonism [81]. However, here we proposed parallel mechanisms of opioid and oxytocin receptor modulation on social attention. According to this hypothesis, concurrently administering oxytocin and an opioid receptor blockade, like naloxone, could result in an enhancement of a social-reward-seeking state by opioid antagonism, which in turn is exploited by an enhancement of social saliency by oxytocin. Better understanding combinatorial effects of oxytocin and naloxone on social behaviours may provide novel angles to study social functions in the brain. Moreover, strategically exploiting such combinatorial effects may provide novel and effective ways to clinically improve social functions [49,50,82]. We hope future studies will be able to elucidate how varying behavioural contexts impact these neuromodulator interactions as well as the cellular mechanisms underlying their combinatorial effects.

Data accessibility. This article has no additional data.

Authors' contributions. P.T.P.: conceptualization, writing—original draft, writing—review and editing; S.W.C.C.: conceptualization, writing—original draft, writing—review and editing.

Both authors gave final approval for publication and agreed to be held accountable for the work performed herein.

Conflict of interest declaration. S.W.C.C. is one of the inventors who hold a US patent 'Oxytocin and opioid antagonists for the treatment of social dysfunction disorder', patent no. 11160843, application no. 16/398,744, issue date of 11/02/2021.

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