PHILOSOPHICAL TRANSACTIONS B

royalsocietypublishing.org/journal/rstb

Review

Cite this article: Paletta P, Bass N, Kavaliers M, Choleris E. 2022 The role of oxytocin in shaping complex social behaviours: possible interactions with other neuromodulators. *Phil. Trans. R. Soc. B* **377**: 20210058.
https://doi.org/10.1098/rstb.2021.0058

Received: 1 October 2021
Accepted: 8 November 2021

One contribution of 15 to a theme issue 'Interplays between oxytocin and other neuromodulators in shaping complex social behaviours'.

Subject Areas:
behaviour, neuroscience

Keywords:
social recognition, social learning, maternal care, oestrogens, dopamine

Author for correspondence:
Elena Choleris
e-mail: echoleri@uoguelph.ca

THE ROYAL SOCIETY PUBLISHING

The role of oxytocin in shaping complex social behaviours: possible interactions with other neuromodulators

Pietro Paletta[1], Noah Bass[1], Martin Kavaliers[1,2] and Elena Choleris[1]

[1]Department of Psychology and Neuroscience Program, University of Guelph, MacKinnon Building Room 4020, 50 Stone Road E., Guelph, ON, Canada N1G 2W1
[2]Department of Psychology, Western University, London, Ontario, Canada

MK, 0000-0003-2292-5963; EC, 0000-0001-5852-2176

This review explores the role of oxytocin in the mediation of select social behaviours, with particular emphasis on female rodents. These behaviours include social recognition, social learning, pathogen detection and avoidance, and maternal care. Specific brain regions where oxytocin has been shown to directly mediate various aspects of these social behaviours, as well as other proposed regions, are discussed. Possible interactions between oxytocin and other regulatory systems, in particular that of oestrogens and dopamine, in the modulation of social behaviour are considered. Similarities and differences between males and females are highlighted.

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

1. Introduction

Oxytocin (OT) is a mammalian neuropeptide that has been extensively shown to affect various functions and behaviours. These include physiological functions such as immune responses, analgesic effects, lactation, uterine contractions during birth, sexual activity and stress responses, as well as socially based behavioural functions, such as social recognition, pair bonding and parental behaviour [1–3]. OT is mainly produced in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus and can be either released peripherally into the bloodstream through projections to the pituitary gland or released to various brain regions to exert its behavioural effects [4]. OT has a single G-protein coupled receptor (OTR), which is widespread throughout the brain, including many of the regions where projections form the PVN and SON reach, and where social behaviours are mediated [5–7]. This review will explore some of the research that has been conducted investigating the effects of OT on social behaviour, focusing on females but also briefly discussing sex differences. OT's role in mediating social recognition, social learning, pathogen detection and avoidance and maternal care, including the specific brain regions where OT is proposed to act and other neurochemicals OT may interact with to mediate these behaviours, will be discussed.

2. Social recognition

Social recognition is defined here as the ability to distinguish between conspecifics based on various cues and factors of a conspecific, such as sex, condition, health, relatedness, reproductive state, hierarchal status, familiarity, through to true individual recognition [8]. This ability to recognize and/or distinguish between individuals is important for the development of social bonds. For example, the way a mother would behave towards its offspring would be very different to how it would behave towards an intruder. The ability to recognize that one individual is related to them and that another is not allows this change of behaviour towards kin and offspring. Social recognition also allows

an individual to modulate its behaviour based on the recognition of the quality, condition, and status of another individual. Familiarity recognition is especially important in that it allows you to not treat individuals like strangers each time they are encountered [9].

In laboratory settings social recognition is generally investigated with rodents, with familiarity being most commonly examined. Typically, one of two paradigms are used, either habituation/dishabituation or social discrimination, both of which capitalize on the natural preference for novelty shown by laboratory rodents. In a habituation/dishabituation paradigm the experimental rodent is exposed to a stimulus rodent several times, habituating the experimental rodent to the stimulus. Then a new stimulus animal is presented, and if an increase in the amount of investigation is observed, it is concluded that the experimental rodent 'knows' the social stimulus is different, thus indicating that it remembered the previous familiar stimulus [10]. In the social discrimination paradigm, one or two stimulus conspecifics are presented to the experimental animal either once or a number of times. Then in the test phase, two stimuli are presented: however, one has been replaced with a new individual. If the experimental subject investigates the novel social stimulus more than the previously encountered (familiar) stimulus, it suggests it recognizes the familiar individual [11]. While there is evidence that several neurotransmitters, peptides, and steroidal hormones can affect social recognition, OT has received the predominant attention.

Early studies into OT's effect on social recognition looked at the effect of 'knocking out' the gene for OT (OTKO). It was found that when OT was knocked out in female mice social recognition was impaired [12,13]. This was shown in the habituation/dishabituation paradigm, where the OTKO mice neither habituated to the repeatedly presented stimulus mouse nor increased their investigation of a novel mouse, as well as in the social discrimination paradigm, where the OTKO mice showed equal investigation of concomitantly presented familiar and novel stimulus mice [12,13]. In another study, it was found that knocking out OT in pregnant females resulted in an extension of the Bruce effect. That is the interruption of pregnancy normally seen in response to a novel male, which now occurred with both a novel male and its mate, suggesting the females did not recognize the male they had previously mated with [14]. Many of the OTKO studies show impaired social recognition, but it is possible that OT's effect on social recognition is specific to recognition within the same strain, as in an experiment where OTKO male mice were tested in a social recognition paradigm using female stimulus mice from different strains, social recognition remained intact [15]. More research is needed to see if this intrastrain specificity extends to females as well.

Brain regions associated with OT's mediation of social recognition have been investigated. Early investigations revealed that the intracerebroventricular (ICV) administration of an OTR antagonist to female rats resulted in impaired social recognition in a choice test between familiar and novel juvenile rats [16]. The medial amygdala (MeA) has also been examined (figure 1). Initial studies showed that OTKO male mice were impaired in social recognition, which could be recovered with OT administered to the MeA [17]. Subsequently, it was shown that the MeA is also important for the OT mediation of social recognition in female mice. Blocking the gene for the OTR in the MeA with antisense oligonucleotides in wild-type female mice resulted in impaired social recognition similar to what is seen in OTKO females [18]. Similarly, the administration of an OTR antagonist to the MeA of female mice impaired their ability to distinguish between familiar and novel female stimulus mice, suggesting impaired social recognition [19]. These results show the importance of the MeA for social recognition. The MeA receives direct projections from the main and accessory olfactory bulbs (OBs), making it a site where incoming olfactory cues can be processed to recognize a conspecific [20]. Social recognition may also include emotional recognition. Male and female mice can discriminate positive and negative emotional states of other mice, and chemogenetic inhibition of PVN OT projections to the central amygdala abolishes this [21]. There is also evidence suggesting that OT acts in the OB to facilitate social recognition (figure 1). Vaginocervical stimulation in female rats in the proestrus phase caused an increase in OT release in the OB, and resulted in prolonged social recognition memory of a juvenile stimulus [22]. This study also showed that this prolonging effect on social recognition could be blocked by the administration of an OTR antagonist into the OB, suggesting OT also acts directly in the OB to mediate social recognition [22]. Similarly, there is evidence that OT in the olfactory system mediates social recognition by improving the signal-to-noise ratio in odour processing, as administration of an OT agonist in the accessory olfactory nucleus (AON) activated excitatory projections from this region onto inhibitory interneurons in the main OB in female rats [23]. Additionally, the selective deletion of OTRs in the AON of male mice impaired social recognition, showing the importance of OT in odour processing for social recognition [23]. The posterior bed nucleus of the stria terminus (pBNST) is another brain region where OT can mediate social recognition (figure 1). Infusions of an OTR antagonist into pBNST of female rats was shown to impair social recognition of juvenile conspecifics [24]. However, it was also found that in female rats, pBNST infusions of OT did not result in prolonged social recognition of the juvenile stimulus rats [24]. This suggests that although OT in the pBNST is needed for social recognition, increased release of OT does not enhance recognition [24]. OT has also been shown to modulate female social behaviour and recognition through effects in prefrontal cortex (PFC) interneurons that express OTRs (figure 1). Silencing or antagonization of the interneuron OTRs in the medial PFC (mPFC) of females abolished female sociosexual responses to males [25]. These studies suggest that OT and its receptor are both necessary for the proper functioning of social recognition.

To date, other brain regions where OT mediates social recognition in females are not known with research having been primarily focused on males. In males, social recognition can be mediated by OT in the MeA, OB and pBNST [17,24,26,27]. For example, discrimination of male and female odours is impaired when OTRs are selectively deleted from aromatase-positive neurons of the MeA [28]. In males, OT has also been found to mediate social recognition in additional regions such as the lateral septum, medial preoptic area (MPOA), and hippocampus [29–33] (figure 1). Whether or not OT can affect social recognition in females in these regions as well remains to be investigated.

The effect of OT on social recognition in females has been suggested to be regulated by oestrogens, which have been

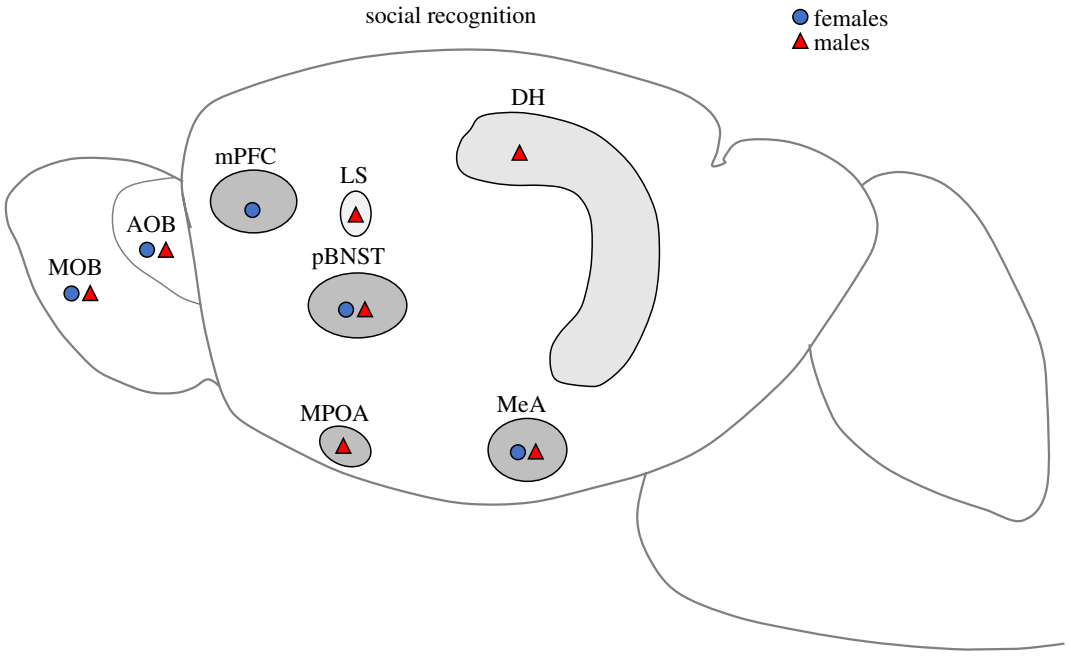

Figure 1. Brain regions where oxytocin acts to mediate social recognition. The brain regions shown are where oxytocin or the OTR acts to mediate social recognition. Blue circles represent regions in females where oxytocin mediates social recognition, and red triangles represent regions in males where oxytocin mediates social recognition. MOB, main olfactory bulb; AOB, accessory olfactory bulb; mPFC, medial prefrontal cortex; LS, lateral septum; pBNST, posterior bed nucleus of the stria terminus; MPOA; medial preoptic area; DH, dorsal hippocampus; MeA, medial amygdala. (Online version in colour.)

shown to play an important role in the regulation of the oxytocinergic system. OT and OTR levels fluctuate across the oestrous cycle, oestrogens can regulate the production and release of OT and the OTR, and oestrogens promote OT and OTR mRNA synthesis [34]. There are three main oestrogen receptors, through which oestrogens can exert their effects, oestrogen receptors alpha (ERα) and beta (ERβ) and the G-protein coupled oestrogen receptor (GPER) [35]. Similar to the findings with OTKO mice, it has been shown that ERαKO or ERβKO in female mice also results in impaired social recognition [12,13]. Similarly, the administration of 17β-oestradiol (E2) or ER agonists systemically, and into various brain regions such as the MeA and dorsal hippocampus, facilitates social recognition in female mice [36–41]. These findings raised the possibility of an interaction between the oestrogen and OT systems in the regulation of social recognition. There is some experimental evidence for this proposed interaction. Infusion of E2 into the PVN of female mice resulted in a facilitation of social recognition, which could be blocked by infusing into the MeA a subeffective dose of an OTR antagonist, that is a dose that by itself does not block social recognition [19]. This supports the proposal that oestrogens mediate the facilitatory effects of OT on social recognition in female mice.

3. Social learning

There is also evidence that OT can mediate social learning. Social learning is a highly adaptive form of learning that may be defined as 'learning that is influenced by observation of, or interaction with, another animal (typically a conspecific) or its products' [42–44]. This type of learning occurs in many species and may intercept the consequences of individual trial-and-error learning which has proven to be time-consuming and possibly maladaptive [45,46].

Social learning can be tested using several paradigms, including mate choice copying and social transmission of food preferences (STFP) [8,47]. Mate choice copying refers to an individual's choice in mate being influenced by either the actual or apparent mate choice of another individual, suggesting animals can socially learn and gain information about potential mates from the behaviour of conspecifics [47]. A mate choice copying paradigm involves two stages. In stage one an individual observes the mating or a proxy of mating (e.g. odours associated with a potential mate) between a male and female, followed by stage two, in which the observer is presented with a choice between the individual they observed being chosen and a novel potential mate [47]. Typically, they will show a preference for the individual they previously observed being chosen, indicating that social learning of mate choice occurred. It should be noted that mate copying incorporates both social recognition and social learning.

In an odour-based mate choice copying task, wild-type female mice showed a preference for a male odour paired with an oestrus female odour over an unpaired male odour, in agreement with the social transmission of mate choice [48]. Conversely, females that had the OT gene knocked out did not show this preference for the male odours paired with the oestrus female odour, suggesting OTKO females do not show mate copying [48]. Similarly, females will avoid and discriminate against the odour of a male associated with an infected female, and this effect is also blocked by the systemic administration of an OTR antagonist [49]. OT has also been implicated in the observational learning of fear [50,51]. Mice visually observing other mice receiving auditory-conditioned foot shocks develop an aversion to the conditioned stimulus, with inhibition of OT inputs to the central amygdala abolishing this effect [21]. Another example of OT mediating social learning was recently discovered in the social transmission of maternal care behaviours. When

virgin female mice observe mothers that they are co-housed with perform maternal care for their pups, PVN OT neurons in the virgin females become active and they learn to perform those maternal care behaviours as well [52]. OT's role in maternal care will be further explored later in this review.

During STFP, the preference for a novel flavoured food diet may be transmitted by odour cues from a 'demonstrator' animal to a same-sex, familiar 'observer' during social interaction [42,53]. This paradigm can be manipulated to increase difficulty, for example, by adding a delay between the 'demonstrator'–'observer' social interaction and the 'observer' food choice test [54]. In the difficult version of the STFP paradigm, the duration of the socially acquired food preference was prolonged in male rats that received systemic OT either immediately after the social interaction or 2 h before testing [55]. These findings suggest a facilitating role of OT during the memory consolidation and retrieval process of a socially learned food preference in male rats. Interestingly, although oestrogens are known to be in involved in the regulation of social learning, the few studies investigating the role of OT during STFP use only male subjects [8]. In the male brain, 'male' sex hormones such as testosterone may be converted to oestrogens via the enzyme aromatase [56]. Notably, OT may be activated by the activation of oestrogen receptors following gene transcription [57–59]. Thus, perhaps oestrogens interact with the OT system in mediating the STFP, as shown for social recognition; however, this possible interaction has not to date been investigated.

OT's role in social learning may be through its effect on social salience and reward value through interactions with dopamine. This proposal is supported by various findings: (1) several brain regions (e.g. hypothalamus) co-express OT and dopamine receptors; (2) OT and dopamine can produce similar prosocial behaviours; (3) OT can directly affect dopamine release [60–62]. Similar to OT in males, dopamine has also been shown to directly affect social learning in female mice. Dopamine receptor antagonists given systemically or directly into the dorsal hippocampus disrupted social learning of food preferences of female mice [63,64]. As well as this proposed interaction with dopamine, it may also be hypothesized that there is a similar modulatory role for sex hormones and OT in regulating social learning. Oestrogens have been shown to regulate social learning and interact with OT in the mediation of social recognition [8]. More research is needed to determine if OT interacts with dopamine and/or oestrogens to facilitate social learning. Also, more research is needed to determine which brain regions OT acts on to mediate social learning.

4. Pathogen detection and avoidance

As indicated previously, social recognition can occur for various aspects of an individual, including their health. For example, animals recognize individuals carrying parasites or pathogens and alter their behaviour to avoid interacting and/or mating with them [65]. Being able to recognize infected individuals is important as an increased risk of exposure to parasites and pathogens is a consequence of being social [66]. Many pathogens exploit their host's social behaviours and interactions between individuals, resulting in an increased likelihood of pathogen transmission [66]. In response to pathogen threat individuals exhibit a variety of aversive and avoidant responses, including faecal avoidance, escape behaviours, changes in location of habitat, and changes in social behaviours [65]. In rodents, pathogen detection is primarily based on olfactory cues. Odours of infected/parasitized individuals can cause avoidance responses, whereas odours associated with healthy individuals tend to promote approach behaviours [65,67,68]. OT mediates both approach and avoidance responses to positive and negative salient social information, respectively [61]. OT acting in the nucleus accumbens and the ventral tegmental area facilitates social approach, whereas aversive contexts that elicit social vigilance and avoidance involve OT in the BNST [62]. In addition, OT enhances social avoidance and aversive responses to threatening stimuli to a greater extent in females than in males [69].

OT has been shown to be involved in the recognition and avoidance of infected individuals as wild-type females avoided the odours of infected males and showed a preference for the clean male odours, with the OTKO mice not being able to show this preference or consistent avoidance of the infected male odour [70]. Similarly, an OTR antagonist attenuated the avoidance response of female and male rats to odours of males treated with bacterial components [49,67,71]. This suggests that OT is involved in recognition of pathogens from odours, an important function for choosing healthy mates. Related to this, there is also evidence that OT's effect on social learning can also affect pathogen avoidance [48]. It was found that wild-type females will avoid the odour of an infected male, but if that infected odour was also presented with the odour of an oestrus female the wild-type females no longer avoided the infected male odour and instead showed a preference for it [48]. However, female OTKO mice did not show avoidance of the infected male odour and did not show a preference for an infected male odour paired with an oestrus female odour [48]. A similar effect can be seen in an experiment examining the effect of an OTR antagonist on female mice on their behaviour towards male odours paired with infected female odour [49]. The females treated with the vehicle showed avoidant behaviour towards the odours of male mice pre-exposed to infected females, but the females that received the systemic injection of an OTR antagonist did not show this avoidance behaviour [49]. These results suggest that OT plays an important role in pathogen recognition and avoidance, as well as social learning to overcome this avoidance. Although several possible brain regions are potentially involved in pathogen detection and avoidance, such as the BNST and OT-mediated social vigilance, more research is required. In this regard a region that has been implicated in the mediation of pathogen avoidance and the expression of disgust-like avoidance responses is the insular cortex [65,72,73]. OT affects the activity of the insular cortex and its mediation of approach–avoidance responses, thus further supporting a likely mediation of pathogen avoidance [74].

5. Maternal care

Lastly, maternal care is another social behaviour OT has been found to mediate. Maternal care is a group of behaviours, such as licking and grooming, nursing, crouching over pups, and retrieving pups from outside the nest, that are exhibited toward the offspring to help their survival and

development [75]. In view of the involvement of OT in pregnancy and lactation, the increased binding of OT, and increased OTR mRNA expression during parturition in various regions involved in social behaviour, the role of OT in maternal care has received extensive attention [76].

OT has been found to be important for the onset of maternal behaviours in various studies, where ICV administrations of OTR antagonists to parturient or lactating rats either blocked the onset of or impaired the expression of maternal care [75]. Similarly, if the PVN of pregnant rats is lesioned before they give birth the onset of maternal care is blocked [77]. However, once maternal care behaviours are established OT seems to play a smaller role, as neither the ICV administration of the OTR antagonist to rats on postpartum day 5, nor lesioning the PVN on postpartum day 4 inhibited maternal care [77,78]. OT's role in maternal care has also been shown in mice. OTRKO in mothers resulted in them often scattering pups around the cage [79]. Additionally, when pups were placed by researchers in the corners of the cage, mothers exhibited an increased latency to retrieve them, and decreased amount of time spent crouching over those pups [79]. Interestingly, in mice the OTR may have a more significant role than OT itself, since in OTKO studies, mothers showed normal maternal care towards their offspring, even though in a different study, knocking out OT caused a reduction in licking of foster pups [79–81]. These findings support a role for OT in maternal care.

Various brain regions (e.g. PVN, SON) have been found to be important for the mediation of maternal behaviour in rats by OT (figure 2). As previously noted, lesioning the PVN before parturition blocked the onset of maternal care [77]. OTR expression in the PVN is increased after birth, and suckling by pups increases OT release in the PVN and SON [82,83]. PVN OT neurons are also found to be activated in virgin females that socially learn maternal care from mothers, suggesting that OT is needed for the onset of maternal care [52]. There is an additional circuit for maternal care within the hypothalamus, where tyrosine hydroxylase neurons in the anteroventral periventricular nucleus (AVPV) directly connect to OT-producing cells in the PVN. When these AVPV neurons are stimulated there is an increase in OT levels as well as maternal care [84]. However, ablation of these AVPV neurons reduces OT levels and impairs maternal care [84]. This AVPV circuit appears to be specific to PVN OT neurons as no connection has been found between these neurons and OT-producing neurons in the SON [84]. The presence of tyrosine hydroxylase in these AVPV neurons suggests that they are dopaminergic, although this has not been shown to date [84]. If they are found to be dopaminergic, this would suggest another social behaviour that is mediated by the interplay between OT and dopamine.

Another brain region that is important for OT-mediated maternal care is the MPOA (figure 2). In rats it has been shown that, similar to the PVN and SON, during lactation OTR expression is increased in the MPOA [85]. Additionally, infusions of an OTR antagonist into the MPOA can block the onset of maternal care as well as impair established maternal care after 5 days of infusions [75,86]. Similarly, in a comparison between rats that spontaneously showed high or low maternal care, the high maternal care females also expressed higher OTR levels in the MPOA [87]. OT in the MPOA, as well as the lateral preoptic area (LPOA), also seems to be important for the development of alloparental behaviour. When virgin female mice were exposed repeatedly to pups, they tended to develop pup retrieval behaviours, which were found to be associated with increased OT concentrations in the MPOA and LPOA [88]. Additionally, this effect could be blocked by infusing an OTR antagonist into the preoptic area, targeting the MPOA and LPOA [88].

Some other regions that have been implicated in OT-mediated maternal care are the OB, the left auditory cortex (lAC) and the mPFC (figure 2). OT levels in the OB were found to increase around the time of parturition, and infusions of OT into the OB of virgin rats induced maternal care when exposed to pups, whereas infusions of an OTR antagonist immediately after birth delayed the onset of maternal care [89,90]. Results of studies giving intranasal OT also support a role for OT acting in the OB to mediate maternal care. In rats that had undergone caesarean deliveries, which impairs maternal behaviours as well as OT release due to over-excited OT neurons, intranasal administrations of OT restored maternal care and normalized OT neuronal activity [91]. Similarly, in mice that received intranasal administrations of OT, pup retrieval became more efficient and total maternal care increased when reunited with pups after separation [92]. It is important to note that intranasal OT has been found to reach the cerebrospinal fluid and deeper brain regions, such as the amygdala, so the effects of intranasal OT on maternal care may be occurring in these regions [93,94]. The lAC is involved in maternal care through the processing of ultrasonic distress calls pups make when separated from the nest, leading to retrieval behaviours by mothers [95]. Interestingly, it was found that only the lAC was needed for processing these pup calls since inactivating the right AC (rAC) with a GABA agonist had no effect on pup retrieval but inactivating the lAC impaired it [95]. This was associated with OTR expression, which was found to be significantly higher in the lAC compared with the rAC of mothers [95]. Also, it was found that in virgin mice, when OT administration was paired with pup calls, the lAC balanced inhibitory and excitatory postsynaptic synapses to increase the call representation and social saliency of the pup calls, which would trigger pup retrieval behaviour [95]. Lastly, within the mPFC OT also acts to facilitate maternal care. The mPFC expresses OTR- and OT-sensitive neurons and the region is activated by suckling and systemic OT administrations in postpartum rats [96–98]. It was also found that infusing an OTR antagonist into the prelimbic region of the mPFC impaired pup retrieval and pup-directed behaviours in postpartum rats [99]. Together this research shows the importance of OT in a wide range of brain regions implicated in the mediation of maternal behaviours. Whether or not these regions interact in the expression of maternal behaviour, if this involves the effects of OT, and what roles oestrogens and ERs play remain to be investigated.

6. Conclusion

In this review, we have summarized the current knowledge about the significant role OT plays in mediating many social behaviours in females. We showed the importance of OT for social recognition, some of the brain regions where

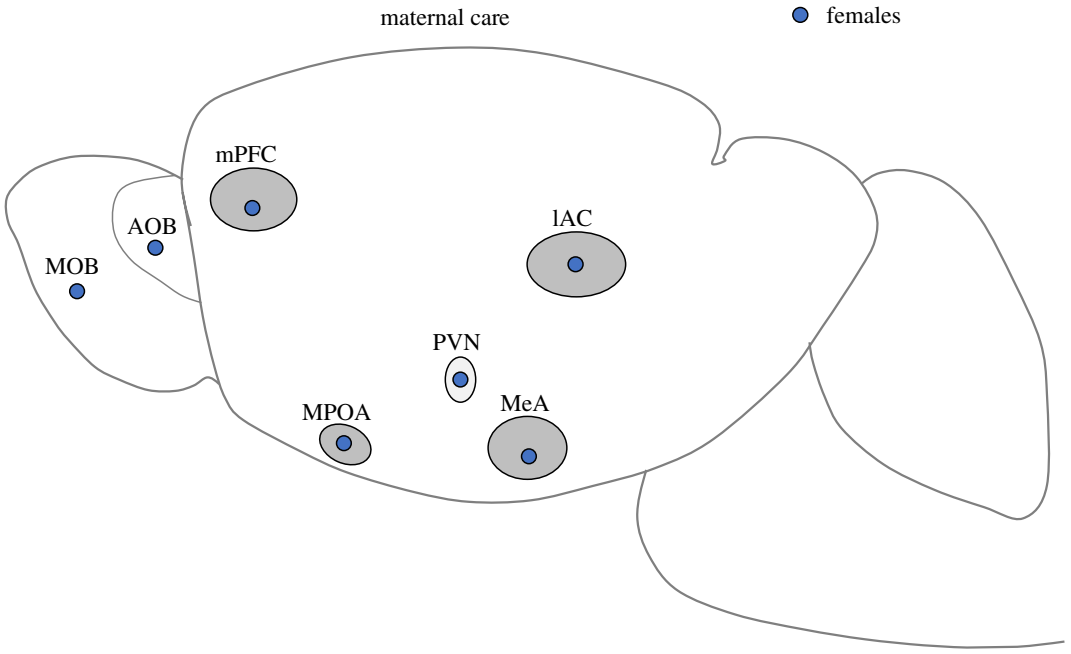

Figure 2. Brain regions where oxytocin acts to mediate maternal care. The brain regions shown are where oxytocin or the OTR acts to mediate maternal care. Blue circles represent regions in females where oxytocin mediates maternal care. MOB, main olfactory bulb; AOB, accessory olfactory bulb; mPFC, medial prefrontal cortex: MPOA, medial preoptic area; PVN, paraventricular nucleus of the hypothalamus; MeA, mdial amygdala; lAC, left auditory cortex. (Online version in colour.)

OT acts to mediate social recognition, and how OT interacts with oestrogens to have this effect. Next, we explored some of the existing research into the role OT plays in social learning and discussed dopamine and oestrogens as possible mechanisms underlining OT's modulation of social learning. OT's effect on pathogen detection and avoidance and the connections between this behaviour and social recognition and learning were reviewed next. Lastly, we discussed the role OT plays in mediating maternal care behaviours and explored the many brain regions where OT exerts these effects.

The literature discussed also highlights gaps that require more research in this field. Many of the reported studies on how OT mediates social behaviour were conducted with females and need to be expanded to males. It is important to determine if the underlying mechanism of these behaviours functions the same way in both sexes, especially if the development of treatments for disorders with disrupted social behaviours are based on the research reported here. Similarly, research that has only been developed in male rodents needs to be expanded to females. For example, some of the brain regions underlying OT-mediated social recognition in males, such as the lateral septum and MPOA, have yet to be investigated in females.

Similarly, research into the brain regions where OT acts to mediate social learning and pathogen avoidance in females is needed. Also, current research into how OT mediates social learning in females is limited and needs to be explored more, including whether the proposed interactions with dopamine and/or oestrogens are accurate. Lastly, while OT's role in maternal behaviours and the brain regions where this occurs have been extensively studied, more research is needed to explore whether these regions form an interacting network underlying the functioning of OT-dependent maternal behaviours.

As reported above, we have shown evidence of an interaction between oestrogens and OT in the mediation of social recognition [19]. However, it is very likely that this interaction is not specific to social recognition and extends to other social behaviour domains, such as the ones described in this review. This OT/oestrogen interaction may underlie social learning and maternal behaviours, both of which are also known to be regulated by hormones, as well as OT [8,76]. Similarly, the interaction between dopamine and OT suggested to underlie social learning may also extend to other social behaviours. For example, it has been shown that the formation of pair bonds in female prairie voles requires both OT and dopamine, as blocking either the OTR or the dopamine D2-type receptors in the nucleus accumbens impairs the formation of partner preferences [100]. Additionally, it has been suggested that OT and dopamine may work together to increase social saliency and rewarding properties in social learning. A similar OT/dopamine interplay may make pup calls socially salient, leading to increased maternal behaviour. It is very likely OT is interacting with both oestrogens and dopamine to regulate many of these social behaviours. A target of future research should be the exploration of the interactions between these systems to determine to what extent and in which brain regions these interactions occur.

Data accessibility. This article has no additional data.

Authors' contributions. P.P.: conceptualization, writing—original draft, writing—review and editing; N.B.: conceptualization, writing—original draft; M.K.: conceptualization, writing—original draft, writing—review and editing; E.C.: conceptualization, funding acquisition, writing—original draft, writing—review and editing.

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

Conflict of interest declaration. We declare we have no competing interests.

Funding. Grant support: NSERC RGPIN-2018-04699.

References

1. Yang H, Wang L, Han L, Wang S. 2013 Nonsocial functions of hypothalamic oxytocin. *Int. Schol. Res. Not. Neurosci.* **2013**, 179272. (doi:10.1155/2013/179272)
2. Neumann I. 2008 Brain oxytocin: a key regulator of emotional and social behaviours in both females and males. *J. Neuroendocrinol.* **20**, 858–865. (doi:10.1111/j.1365-2826.2008.01726.x)
3. Jurek B, Neumann I. 2018 The oxytocin receptor: From intracellular signalling to behavior. *Physiol. Rev.* **98**, 1805–1908. (doi:10.1152/physrev.00031.2017)
4. Katoh A, Fujihara H, Ohbuchi T, Onaka T, Hashimoto T, Kawata M, Suzuki H, Ueta Y. 2011 Highly visible expression of an oxytocin-monomeric red fluorescent protein 1 fusion gene in the hypothalamus and posterior pituitary of transgenic rats. *Endocrinology* **152**, 2768–2774. (doi:10.1210/en.2011-0006)
5. Song Z, Albers H. 2018 Cross-talk among oxytocin and arginine-vasopressin receptors: relevance for basic and clinical studies of the brain and periphery. *Front. Neuroendocrinol.* **51**, 14–24. (doi:10.1016/j.yfrne.2017.10.004)
6. Arakawa H. 2021 Dynamic regulation of oxytocin neuronal circuits in the sequential processes of prosocial behavior in rodent models. *Curr. Neurobiol.* **2**, 100011. (doi:10.1016/j.crneur.2021.100011)
7. Froemke R, Young L. 2021 Oxytocin, neural plasticity, and social behavior. *Annu. Rev. Neurosci.* **44**, 359–361. (doi:10.1146/annurev-neuro-102320-102847)
8. Choleris E, Clipperton-Allen A, Phan A, Valsecchi P, Kavaliers M. 2012 Estrogenic involvement in social learning, social recognition and pathogen avoidance. *Front. Neuroendocrinol.* **33**, 140–159. (doi:10.1016/j.yfrne.2012.02.001)
9. Ferguson J, Young L, Insel T. 2002 The neuroendocrine basis of social recognition. *Front. Neuroendocrinol.* **23**, 200–224. (doi:10.1006/frne.2002.0229)
10. Gheusi G, Bluthé R, Goodall G, Dantzer R. 1994 Social and individual recognition in rodents: methodological aspects and neurobiological bases. *Behav. Processes* **33**, 59–87. (doi:10.1016/0376-6357(94)90060-4)
11. Engelmann M, Wotjak C, Landgraf R. 1995 Social discrimination paradigm: an alternative method to juvenile recognition abilities in rats. *Physiol. Behav.* **58**, 315–321. (doi:10.1016/0031-9384(95)00053-L)
12. Choleris E, Gustafsson J, Korach K, Muglia L, Pfaff D, Ogawa S. 2003 An estrogen-dependent four-gene micronet regulating social recognition: a study with oxytocin and estrogen receptor-α and -β knockout mice. *Proc. Natl Acad. Sci. USA* **100**, 6192–6197. (doi:10.1073/pnas.0631699100)
13. Choleris E, Ogawa S, Kavaliers M, Gustafsson J, Korach K, Muglia L, Pfaff D. 2006 Involvement of estrogen receptor alpha, beta and oxytocin in social discrimination: a detailed behavioral analysis with knockout female mice. *Genes Brain Behav.* **5**, 528–539. (doi:10.1111/j.1601-183X.2006.00203.x)
14. Wersinger S, Temple J, Caldwell H, Young W. 2008 Inactivation of the oxytocin and the vasopressin (Avp) 1b receptor genes, but not the Avp 1a receptor gene, differentially impairs the Bruce effect in laboratory mice (*Mus musculus*). *Endocrinology* **149**, 116–121. (doi:10.1210/en.2007-1056)
15. Macbeth A, Lee H, Edds J, Young W. 2009 Oxytocin and the oxytocin receptor underlie intrastrain, but not interstrain, social recognition. *Genes Brain Behav.* **8**, 558–567. (doi:10.1111/j.1601-183X.2009.00506.x)
16. Engelmann M, Ebner K, Wotjak C, Landgraf R. 1998 Endogenous oxytocin is involved in short-term olfactory memory in female rats. *Behav. Brain Res.* **90**, 89–94. (doi:10.1016/S0166-4328(97)00084-3)
17. Ferguson J, Aldag J, Insel T, Young L. 2001 Oxytocin in the medial amygdala is essential for social recognition in the mouse. *J. Neurosci.* **21**, 8278–8285. (doi:10.1523/JNEUROSCI.21-20-08278.2001)
18. Choleris E, Little S, Mong J, Puram S, Langer R, Pfaff D. 2007 Microparticle-based delivery of oxytocin receptor antisense DNA in the medial amygdala blocks social recognition in female mice. *Proc. Natl Acad. Sci. USA* **104**, 4670–4675. (doi:10.1073/pnas.0700670104)
19. Paletta P. 2018 *Rapid estrogenic mediation of oxytocin in the regulation of social recognition in female mice*. MSc thesis, University of Guelph, Canada.
20. Waker D, Ludwig M. 2012 Vasopressin, oxytocin, and social odor recognition. *Horm. Behav.* **61**, 259–265. (doi:10.1016/j.yhbeh.2011.08.014)
21. Ferretti V *et al.* 2019 Oxytocin signaling in the central amygdala modulates emotion discrimination in mice. *Curr. Biol.* **29**, 1938–1953. (doi:10.1016/j.cub.2019.04.070)
22. Larrazolo-Lopez A, Kendrick K, Aburto-Arciniega M, Arriaga-Avilaa V, Morimotoc S, Friasa M, Guevara-Guzmána R. 2008 Vaginocervical stimulation enhances social recognition memory in rats via oxytocin release in the olfactory bulb. *Neuroscience* **152**, 585–593. (doi:10.1016/j.neuroscience.2008.01.024)
23. Oettl L *et al.* 2016 Oxytocin enhances social recognition by modulating cortical control of early olfactory processing. *Neuron* **90**, 609–621. (doi:10.1016/j.neuron.2016.03.033)
24. Dumais K, Alonso A, Immormino M, Bredewold R, Veenema A. 2016 Involvement of the oxytocin system in the bed nucleus of the stria terminalis in the sex-specific regulation of social recognition. *Psychoneuroendocrinology* **64**, 79–88. (doi:10.1016/j.psyneuen.2015.11.007)
25. Nakajima M, Gorlich A, Heintz N. 2014 Oxytocin modulates female sociosexual behavior through a specific class of prefrontal cortical interneurons. *Cell* **159**, 295–305. (doi:10.1016/j.cell.2014.09.020)
26. Ferguson J, Young L, Hearn E, Matzuk M, Insel T, Winslow J. 2000 Social amnesia in mice lacking the oxytocin gene. *Nat. Genet.* **25**, 284–288. (doi:10.1038/77040)
27. Dluzen D, Muraoka S, Engelmann M, Ebner K, Landgraf R. 2000 Oxytocin induces preservation of social recognition in male rats by activating alpha-adrenoceptors of the olfactory bulb. *Eur. J. Neurosci.* **12**, 760–766. (doi:10.1046/j.1460-9568.2000.00952.x)
28. Yao S, Bergan J, Lanjuin A, Dulac C. 2017 Oxytocin signaling in the medial amygdala is required for sex discrimination of social cues. *Neuroscience* **6**, e31373. (doi:10.1101/178210)
29. Lukas M, Toth I, Veenema A, Neumann I. 2013 Oxytocin mediates rodent social memory within the lateral septum and the medial amygdala depending on the relevance of the social stimulus: male juvenile versus female adult conspecifics. *Psychoneuroendocrinology* **36**, 916–926. (doi:10.1016/j.psyneuen.2012.09.018)
30. Popik P, van Ree J. 1991 Oxytocin but not vasopressin facilitates social recognition following injection into the medial preoptic area of the rat brain. *Eur. Neuropsychopharmacol.* **1**, 555–560. (doi:10.1016/0924-977X(91)90010-R)
31. Raam T, McAvoy K, Besnard A, Veenema A, Sahay A. 2017 Hippocampal oxytocin receptors are necessary for discrimination of social stimuli. *Nat. Commun.* **8**, 2001–2014. (doi:10.1038/s41467-017-02173-0)
32. Lin Y, Hsieh T, Tsai T, Chen C, Huang C, Hsu K. 2018 Conditional deletion of hippocampal CA2/CA3a oxytocin receptors impairs the persistence of long-term social recognition memory in mice. *J. Neurosci* **38**, 1218–1231. (doi:10.1523/JNEUROSCI.1896-17.2017)
33. Cilz N, Cymerblit-Sabba A, Young W. 2019 Oxytocin and vasopressin in the rodent hippocampus. *Genes Brain Behav.* **18**, e12535. (doi:10.1111/gbb.12535)
34. Gabor C, Phan A, Clipperton-Allen A, Kavaliers M, Choleris E. 2012 Interplay of oxytocin, vasopressin, and sex hormones in the regulation of social recognition. *Behav. Neurosci.* **126**, 97–109. (doi:10.1037/a0026464)
35. Nilsson S *et al.* 2001 Mechanisms of estrogen action. *Physiol. Rev.* **81**, 1535–1565. (doi:10.1152/physrev.2001.81.4.1535)
36. Phan A, Lancaster K, Armstrong J, MacLusky N, Choleris E. 2011 Rapid effects of estrogen receptor α and β selective agonists on learning and dendritic spines in female mice. *Neuroendocrinology* **152**, 1492–1502. (doi:10.1210/en.2010-1273)
37. Phan A, Gabor S, Favaro K, Kaschack S, Armstrong J, MacLusky N, Choleris E. 2012 Low doses of 17β-estradiol rapidly improve learning and increase hippocampal dendritic spines. *Neuropsychopharmacology* **37**, 2299–2309. (doi:10.1038/npp.2012.82)
38. Phan A *et al.* 2015 Rapid increases in immature synapses parallel estrogen-induced hippocampal

learning enhancements. *Proc. Natl Acad. Sci. USA* **112**, 16 018–16 023. (doi:10.1073/pnas.1522150112)

39. Gabor C, Lymer J, Phan A, Choleris E. 2015 Rapid effects of the G-protein coupled oestrogen receptor (GPER) on learning and dorsal hippocampus dendritic spines in female mice. *Physiol. Behav.* **149**, 53–60. (doi:10.1016/j.physbeh.2015.05.017)
40. Lymer J, Robinson A, Winters B, Choleris E. 2017 Rapid effects of dorsal hippocampal G-protein coupled estrogen receptor on learning in female mice. *Psychoneuroendocrinology* **77**, 131–140. (doi:10.1016/j.psyneuen.2016.11.019)
41. Lymer J, Sheppard P, Kuun T, Blackman A, Jani N, Mahbub S, Choleris E. 2018 Estrogens and their receptors in the medial amygdala rapidly facilitate social recognition in female mice. *Psychoneuroendocrinology* **89**, 30–38. (doi:10.1016/j.psyneuen.2017.12.021)
42. Heyes C. 1994 Social learning in animals: Categories and mechanism. *Biol. Rev.* **69**, 207–231. (doi:10.1111/j.1469-185X.1994.tb01506.x)
43. Galef B. 1988 Imitation in animals: history, definition and interpretation of data from the psychological laboratory. In *Social learning: psychological and biological perspectives* (eds T Zentall, B Galef), pp. 3–28. Hillsdale, NJ: Erlbaum.
44. Box H. 1984 *Primate behavior and social ecology*. London: Chapman & Hall.
45. Hoppitt W, Laland K. 2013 *Social learning: an introduction to mechanisms, methods, and models*. Princeton, NJ: Princeton University Press.
46. Dore R, Phan A, Clipperton-Allen A, Kavaliers M, Choleris E. 2013 The involvement of oxytocin and vasopressin in social recognition and social learning. In *Oxytocin, vasopressin, and related peptides in the regulation of behaviour* (eds E Choleris, D Pfaff, M Kavaliers), pp. 232–255. New York, NY: Cambridge University Press.
47. Kavaliers M, Matta R, Choleris E. 2017 Mate-choice copying, social information processing, and the roles of oxytocin. *Neurosci. Biobehav. Rev.* **72**, 232–242. (doi:10.1016/j.neubiorev.2016.12.003)
48. Kavaliers M, Choleris E, Ågmo A, Braun W, Colwell D, Muglia L, Ogawa S, Pfaff D. 2006 Inadvertent social information and the avoidance of parasitized male mice: a role for oxytocin. *Proc. Natl Acad. Sci. USA* **103**, 4293–4298. (doi:10.1073/pnas.0600410103)
49. Kavaliers M, Colwell D, Waha D, Bishnoia I, Ossenkopp K, Choleris E. 2019 Conspecific infection threat rapidly biases the social responses of female mice: involvement of oxytocin. *Horm. Behav.* **113**, 67–75. (doi:10.1016/j.yhbeh.2019.04.016)
50. Allsop S *et al.* 2018 Corticoamygdala transfer of socially derived information gates observational learning. *Cell* **173**, 1329–1342. (doi:10.1016/j.cell.2018.04.004)
51. Pisansky M, Hanson L, Gottesman I, Gewirtz J. 2017 Oxytocin enhances observational fear in mice. *Nat. Commun.* **8**, 2102. (doi:10.1038/s41467-017-02279-5)
52. Carcea I *et al.* 2021 Oxytocin neurons enable social transmission of maternal behaviour. *Nature* **596**, 553–557. (doi:10.1038/s41586-021-03814-7)
53. Galef B, Wigmore S. 1983 Transfer of information concerning distant foods: a laboratory investigation of the 'information-centre' hypothesis. *Anim. Behav.* **31**, 748–758. (doi:10.1016/S0003-3472(83)80232-2)
54. Choleris E, Clipperton-Allen A, Phan A, Kavaliers M. 2009 Neuroendocrinology of social information processing in rats and mice. *Front. Neuroendocrinol.* **30**, 442–459. (doi:10.1016/j.yfrne.2009.05.003)
55. Popik P, van Ree J. 1993 Social transmission of flavoured tea preferences: facilitation by a vasopressin analog and oxytocin. *Behav. Neur. Biol.* **59**, 63–68. (doi:10.1016/0163-1047(93)91173-K)
56. Naftolin F. 1994 Brain aromatization of androgens. *J. Reprod. Med.* **39**, 257–261.
57. Dellovade T, Zhu Y, Pfaff D. 1999 Thyroid hormones and estrogen affect oxytocin gene expression in hypothalamic neurons. *J. Neuroendocrinol* **11**, 1–10. (doi:10.1046/j.1365-2826.1999.00250.x)
58. de Kloet E, Voorhuis D, Boschma Y, Elands J. 1986 Estradiol modulates density of putative 'oxytocin receptors' in discrete rat brain regions. *Neuroendocrinology* **44**, 415–421. (doi:10.1159/000124680)
59. Quinones-Jenab V, Jenab S, Ogawa S, Adan R, Burbach J, Pfaff D. 1997 Effects of estrogen on oxytocin receptor messenger ribonucleic acid expression in the uterus, pituitary, and forebrain of the female rat. *Neuroendocrinology* **65**, 9–17. (doi:10.1159/000127160)
60. Baskerville T, Douglas A. 2010 Dopamine and oxytocin interactions underlying behaviors: potential contributions to behavioral disorders. *CNS Neurosci. Ther.* **16**, 92–123. (doi:10.1111/j.1755-5949.2010.00154.x)
61. Shamay-Tsoory S, Abu-Akelb A. 2016 The social salience hypothesis of oxytocin. *Biol. Psychiatry* **79**, 194–202. (doi:10.1016/j.biopsych.2015.07.020)
62. Steinman M, Duque-Wilckens N, Trainor B. 2018 Complementary neural circuits for divergent effects of oxytocin: social approach versus social anxiety. *Biol. Psychiatry* **85**, 792–801. (doi:10.1016/j.biopsych.2018.10.008)
63. Choleris E, Clipperton-Allen A, Gray D, Diaz-Gonzalez S, Welsman R. 2011 Differential effects of dopamine receptor D1-type and D2-type antagonists and phase of the estrous cycle on social learning of food preferences, feeding, and social interactions in mice. *Neuropsychopharmacol.* **36**, 1689–1702. (doi:10.1038/npp.2011.50)
64. Matta R, Tiessen A, Choleris E. 2017 The role of dorsal hippocampal dopamine D1-type receptors in social learning, social interactions and food intake in male and female mice. *Neuropsychopharmacology* **42**, 2344–2353. (doi:10.1038/npp.2017.43)
65. Kavaliers M, Choleris E. 2018 The role of social cognition in parasite and pathogen avoidance. *Phil. Trans. R. Soc. B* **373**, 20170206. (doi:10.1098/rstb.2017.0206)
66. Kavaliers M, Choleris E, Ågmo A, Pfaff D. 2004 Olfactory-mediated parasite recognition and avoidance: linking genes to behavior. *Horm. Behav.* **46**, 272–283. (doi:10.1016/j.yhbeh.2004.03.005)
67. Arakawa H, Arakawa K, Deak T. 2009 Acute illness induces the release of aversive odor cues from adult, but not prepubertal, male rats and suppresses social investigation by conspecifics. *Behav. Neurosci.* **123**, 964–978. (doi:10.1037/a0017114)
68. Arakawa H, Arakawa K, Deak T. 2010 Sickness-related odor communication signals as determinants of social behavior in rat: a role for inflammatory processes. *Horm. Behav.* **57**, 330–341. (doi:10.1016/j.yhbeh.2010.01.002)
69. Johnson Z, Walum J, Xiao Y, Riefkohl P, Young L. 2017 Oxytocin receptors modulate a social salience network in male prairie voles. *Horm. Behav.* **87**, 16–24. (doi:10.1016/j.yhbeh.2016.10.009)
70. Kavaliers M, Colwell D, Choleris E, Ågmo A, Muglia L, Ogawa S, Pfaff D. 2003 Impaired discrimination of and aversion to parasitized male odors by female oxytocin knockout mice. *Genes Brain Behav.* **2**, 220–230. (doi:10.1034/j.1601-183X.2003.00021.x)
71. Arakawa H, Arakawa K, Deak T. 2010 Oxytocin and vasopressin in the medial amygdala differentially modulate approach and avoidance behavior toward illness related odors. *Neuroscience* **171**, 1141–1151. (doi:10.1016/j.neuroscience.2010.10.013)
72. Dolenesk N, Gehrlach D, Klein A, Gogolla N. 2020 Facial expression of emotion states and their neuronal correlates in mice. *Science* **368**, 89–94. (doi:10.1126/science.aaz9468)
73. Rieger N, Worley N, Ng A, Christianson J. 2021 Insular cortex modulates social avoidance of sick rats. *Behav. Brain Res.* **416**, 113541. (doi:10.1016/j.bbr.2021.113541)
74. Rogers-Carter M, Christianson J. 2019 An insular view of social decision-making network. *Neurosci. Biobehav. Rev.* **103**, 119–132. (doi:10.1016/j.neubiorev.2019.06.005)
75. Bosch O, Neumann I. 2012 Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: from central release to sites of action. *Horm. Behav.* **61**, 293–303. (doi:10.1016/j.yhbeh.2011.11.002)
76. Pedersen C. 2013 Oxytocin regulation of maternal behavior. In *Oxytocin, vasopressin, and related peptides in the regulation of behaviour* (eds E Choleris, D Pfaff, M Kavaliers), pp. 148–182. New York, NY: Cambridge University Press.
77. Insel T, Harbaugh C. 1989 Lesions of the hypothalamic paraventricular nucleus disrupt the initiation of maternal behavior. *Physiol. Behav.* **45**, 1033–1041. (doi:10.1016/0031-9384(89)90234-5)
78. Fahrbach S, Morrell J, Pfaff D. 1985 Possible role for endogenous oxytocin in estrogen-facilitated maternal behavior in rats. *Neuroendocrinology* **40**, 526–532. (doi:10.1159/000124125)
79. Takayanagi Y *et al.* 2005 Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. *Proc. Natl Acad. Sci. USA* **102**, 16 096–16 101. (doi:10.1073/pnas.0505312102)
80. Nishimori K, Young L, Guo X, Wang Z, Insel T, Matzuk M. 1996 Oxytocin is required for nursing but is not essential for parturition or reproductive

behavior. *Proc. Natl Acad. Sci. USA* **93**, 11 699–11 704. (doi:10.1073/pnas.93.21.11699)

81. Pedersen C, Vadlamudi V, Boccia M, Amico J. 2006 Maternal behavior deficits in nulliparous oxytocin knockout mice. *Genes Brain Behav.* **5**, 274–281. (doi:10.1111/j.1601-183X.2005.00162.x)
82. Bealer S, Lipschitz D, Ramoz G, Crowley W. 2006 Oxytocin receptor binding in the hypothalamus during gestation in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **291**, 53–58. (doi:10.1152/ajpregu.00766.2005)
83. Neumann I, Russell J, Landgraf R. 1993 Oxytocin and vasopressin release within the supraoptic and paraventricular nuclei of pregnant, parturient and lactating rats: a microdialysis study. *Neuroscience* **53**, 65–75. (doi:10.1016/0306-4522(93)90285-N)
84. Scott N, Prigge M, Yizhar O, Kimchi T. 2015 A sexually dimorphic hypothalamic circuit controls maternal care and oxytocin secretion. *Nature* **525**, 519–522. (doi:10.1038/nature15378)
85. Bosch O, Pfortsch J, Beiderbeck D, Landgraf R, Neumann I. 2010 Maternal behaviour is associated with vasopressin release in the medial preoptic area and bed nucleus of the stria terminalis in the rat. *J. Neuroendocrinol.* **22**, 420–429. (doi:10.1111/j.1365-2826.2010.01984.x)
86. Pedersen C, Caldwell J, Walker C, Ayers G, Mason G. 1994 Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. *Behav. Neurosci.* **108**, 1163–1171. (doi:10.1037/0735-7044.108.6.1163)
87. Champagne F, Diorio J, Sharma S, Meaney M. 2001 Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. *Proc. Natl Acad. Sci. USA* **98**, 12 736–12 741. (doi:10.1073/pnas.221224598)
88. Okabe S *et al.* 2017 Pup exposure facilitates retrieving behavior via the oxytocin neural system in female mice. *Psychoneuroendocrinology* **79**, 20–30. (doi:10.1016/j.psyneuen.2017.01.036)
89. Meddle S, Bishop V, Gkoumassi E, van Leeuwen F, Douglas A. 2007 Dynamic changes in oxytocin receptor expression and activation at parturition in the rat brain. *Endocrinology* **148**, 5095–5104. (doi:10.1210/en.2007-0615)
90. Yu G, Kaba H, Okutani F, Takahashi S, Higuchi T. 1996 The olfactory bulb: a critical site of action for oxytocin in the induction of maternal behaviour in the rat. *Neuroscience* **72**, 1083–1088. (doi:10.1016/0306-4522(95)00600-1)
91. Li T *et al.* 2021 Intranasal oxytocin restores maternal behavior and oxytocin neuronal activity in the supraoptic nucleus in rat dams with cesarean delivery. *Neuroscience.* **468**, 235–246. (doi:10.1016/j.neuroscience.2021.06.020)
92. Guoynes C, Marler C. 2021 An acute dose of intranasal oxytocin rapidly increases maternal communication and maintains maternal care in primiparous postpartum California mice. *PLoS ONE* **16**, e0244033. (doi:10.1371/journal.pone.0244033)
93. Lee M, Scheidweiler K, Diao X, Akhlaghi F, Cummins A, Huestis M, Leggio L, Averbeck B. 2017 Oxytocin by intranasal and intravenous routes reaches the cerebrospinal fluid in rhesus macaques: determination using a novel oxytocin assay. *Mol. Psychiatry* **23**, 115–122. (doi:10.1038/mp.2017.27)
94. Smith A, Krogan A, Young W. 2019 Oxytocin delivered nasally or intraperitoneally reaches the brain and plasma of normal and oxytocin knockout mice. *Pharmacol. Res.* **146**, 104324. (doi:10.1016/j.phrs.2019.104324)
95. Marlin B, Mitre M, D'amour J, Chao M, Froemke R. 2015 Oxytocin enables maternal behaviour by balancing cortical inhibition. *Nature* **520**, 499–504. (doi:10.1038/nature14402)
96. Gould B, Zingg H. 2003 Mapping oxytocin receptor gene expression in the mouse brain and mammary gland using an oxytocin receptor-LacZ reporter mouse. *Neuroscience.* **122**, 155–167. (doi:10.1016/S0306-4522(03)00283-5)
97. Ninan I. 2011 Oxytocin suppresses basal glutamatergic transmission but facilitates activity-dependent synaptic potentiation in the medial prefrontal cortex. *J. Neurochem.* **119**, 324–331. (doi:10.1111/j.1471-4159.2011.07430.x)
98. Febo M, Numan M, Ferris C. 2005 Functional magnetic resonance imaging shows oxytocin activates brain regions associated with mother–pup bonding during suckling. *J. Neurosci.* **25**, 11 637–11 644. (doi:10.1523/JNEUROSCI.3604-05.2005)
99. Sabihi S, Dong S, Durosko N, Leuner B. 2014 Oxytocin in the medial prefrontal cortex regulates maternal care, maternal aggression and anxiety during the postpartum period. *Front. Behav. Neurosci.* **8**, 258. (doi:10.3389/fnbeh.2014.00258)
100. Liu Y, Wang Z. 2003 Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. *Neuroscience* **121**, 537–544. (doi:10.1016/S0306-4522(03)00555-4)