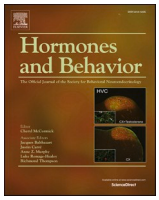
Hormones and Behavior 160 (2024) 105487

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh



Leveraging the unique social organization of California mice to study circuit-specific effects of oxytocin on behavior

Alyssa A. Lake, Brian C. Trainor *

Department of Psychology, University of California, Davis, CA 95616, United States of America

ARTICLE INFO

Keywords:
Oxytocin
Vasopressin
Anxiety
Integrative biology
Extended amygdala

ABSTRACT

Oxytocin is a versatile neuropeptide that modulates many different forms of social behavior. Recent hypotheses pose that oxytocin enhances the salience of rewarding and aversive social experiences, and the field has been working to identify mechanisms that allow oxytocin to have diverse effects on behavior. Here we review studies conducted on the California mouse (*Peromyscus californicus*) that shed light on how oxytocin modulates social behavior following stressful experiences. In this species, both males and females exhibit high levels of aggression, which has facilitated the study of how social stress impacts both sexes. We review findings of short- and long-term effects of social stress on the reactivity of oxytocin neurons. We also consider the results of pharmacological studies which show that oxytocin receptors in the bed nucleus of the stria terminalis and nucleus accumbens have distinct but overlapping effects on social approach behaviors. These findings help explain how social stress can have different behavioral effects in males and females, and how oxytocin can have such divergent effects on behavior. Finally, we consider how new technological developments and innovative research programs take advantage of the unique social organization of California mice to address questions that can be difficult to study in conventional rodent model species. These new methods and questions have opened new avenues for studying the neurobiology of social behavior.

1. Introduction

Oxytocin is an important neuromodulator that is known for its role in modulating social behaviors such as pair bonding (Young and Wang, 2004), nursing (Zik and Roberts, 2015) and reproduction (Carter et al., 2020) across many mammalian species. Initial hypotheses on the function of oxytocin focused on its ability to facilitate social interactions. Intriguingly, there is growing evidence that the behavioral effects of oxytocin are versatile. In humans, intranasal administration of oxytocin led to improved social speech and reduced anxiety in certain social situations (Domes et al., 2007; Heinrichs et al., 2003). These results generated enthusiasm that oxytocin could be a useful therapeutic for anxiety or depression. However, clinical trials have yielded mixed results (De Cagna et al., 2019; Leppanen et al., 2018). This could be that intranasal oxytocin can also increase anxiety (Eckstein et al., 2014). Indeed, stressful situations induced exaggerated oxytocin release in women with high trait anxiety (Tabak et al., 2022). Thus, while oxytocin can promote social approach behaviors in some contexts, studies across multiple species find that oxytocin can increase anxiety-related behaviors or antisocial responses (Beery, 2015). To account for these diverse behavioral effects, the social salience hypothesis poses that oxytocin strengthens the salience of both positive and negative social encounters (Bartz et al., 2011; Shamay-Tsoory and Abu-Akel, 2016). This hypothesis can account for diverse behavioral effects of oxytocin, but an important question is how this is achieved mechanistically. Initially it was hypothesized that oxytocin acting in the mesolimbic dopamine system signaled the salience of both positive and negative social experiences (Shamay-Tsoory and Abu-Akel, 2016). Recent experimental data suggest that oxytocin may act in distinct but overlapping circuits to exert different effects on social behavior (Steinman et al., 2019). Much of these data were collected in a unique species, the California mouse (*Peromyscus californicus*), that has proved to be a useful model for studying the intersection between stress, oxytocin, and social behavior.

The California mouse is a monogamous species (Jašarević et al., 2013; Ribble, 1991) in which males and females aggressively defend territories (Ribble and Salvioni, 1990). This territorial behavior translates to laboratory settings, where female California mice exhibit

* Corresponding author.
E-mail address: bctrainor@ucdavis.edu (B.C. Trainor).

https://doi.org/10.1016/j.yhbeh.2024.105487
Received 23 October 2023; Received in revised form 21 December 2023; Accepted 18 January 2024
Available online 27 January 2024

aggressive behavior in a resident-intruder test (Davis and Marler, 2003; Silva et al., 2010). High levels of female aggression facilitated the application of social defeat methods in female California mice (Kuske and Trainor, 2021). Intriguingly engaging in aggression triggers a stronger increase in corticosterone (Trainor et al., 2010) and more anxiety-related behaviors (Kuske et al., 2023) in females compared to males. Social defeat stress occurs when an individual loses an aggressive interaction, and is a widely used experimental approach that induces behavioral changes related to anxiety and depression across a diverse range of species (Cooper and Huhman, 2005; Tidey and Miczek, 1996; Van Kampen et al., 2002). During social defeat, a focal subject is placed within the home cage of another animal that will initiate aggression and defeat the focal animal, inducing a stress response. Across many rodent species, males exposed to social defeat exhibit a decrease in social approach in novel contexts (Krishnan et al., 2007; Kudryavtseva et al., 1991; Tickerhoof et al., 2020). Studying females has been more challenging because under standard laboratory conditions female aggression levels in conventional mouse and rat lines tend to be relatively low (see Kuske and Trainor, 2021 for review).

An evolutionarily conserved behavioral response to social stress is avoidance of new social situations (Blanchard et al., 1993; Huhman, 2006; Kudryavtseva et al., 1991; Martinez et al., 1998; Tornatzky and Miczek, 1993). A common behavioral assay used to assess the impact of social stress in rodents is a social interaction test. Focal subjects are placed in an open field to acclimate. Next, a small cage is placed into the open field for the focal mouse to acclimate to. Finally, an unfamiliar target mouse is placed within the cage. There is some variability in the type of cage that is used. Some studies use a Plexiglas structure with small holes cut out while others are made of a wire mesh. In California mice, higher levels of social interaction are observed with wire mesh cages (Greenberg et al., 2014; Trainor et al., 2011) compared to Plexiglas structures (Williams et al., 2022), likely because the focal animal has greater access to the target mouse. Social approach is usually quantified by time spent within one body length of the cage containing the target animal. In California mice, defeat stress reduces social approach in females to a greater extent than in males (Trainor et al., 2011) and this effect of stress in females can be reversed by chronic (but not acute) treatment with a selective serotonin reuptake inhibitor (Greenberg et al., 2014). Social defeat also increases vigilance behavior, which is defined as time the focal mouse spends orienting towards the target while avoiding it (Duque-Wilckens et al., 2018). Social vigilance is an ethologically valid behavior that may help individuals monitor threatening social situations (Wright et al., 2020), and has been observed in other species (Newman et al., 2019; Willmore et al., 2022). Social vigilance can also be induced in California mice that were raised without a father (Walker et al., 2023). Here we review studies conducted in California mice that shed light onto the diverse behavioral effects of oxytocin on social behavior. An important theme is that diverse behavioral effects of oxytocin are mediated by distinct but overlapping neural circuits. Pharmacological studies indicate that these circuits appear to function similarly in males and females. In contrast, social stress has divergent effects on the activation of oxytocin neurons in males and females. The ability to study both males and females in similar behavioral contexts such as social stress was a key feature contributing to these discoveries.

2. Social defeat and oxytocin neuron activation

Effects of stress on oxytocin release have been quantified in a variety of contexts (Kalin et al., 1985; McQuaid et al., 2016), usually by measuring oxytocin levels in plasma. Oxytocin is released into the blood from the paraventricular nucleus (PVN) or the supraoptic nucleus (SON) of the hypothalamus. In addition, oxytocin can be released within the brain without altering peripheral levels (Neumann and Landgraf, 2012). An alternative approach is to estimate the activity of oxytocin neurons within the brain by co-staining for an immediate early gene such as c-fos (Hoffman and Lyo, 2002). This double labeling approach provides an anatomically precise estimate of how different experiences alter the activity of different populations of oxytocin neurons. In Steinman et al., 2016, the impact of defeat stress on the activity of oxytocin neurons was systematically estimated using an oxytocin/c-fos immunolabeling approach in both male and female California mice.

2.1. Paraventricular nucleus

First, the acute effects of social defeat were assessed by examining brains collected one hour after one or three episodes of social defeat (Steinman et al., 2016). In PVN and SON, oxytocin/c-fos colocalizations were elevated in both male and female California mice after a third episode of stress (Table 1). Interestingly, males but not females had increased oxytocin/c-fos colocalizations after only one episode of defeat stress. After two episodes of defeat stress, male and female California mice exhibit increased autogrooming behavior immediately before a third episode of defeat (Greenberg et al., 2015). This appears to be an anxiogenic response because it can be blocked by treatment with a kappa opioid receptor antagonist (Williams et al., 2018). In one study, effects of defeat on autogrooming were more robust in males than females (Williams et al., 2018), suggesting that oxytocin release in close proximity to defeat stress may enhance the salience of this aversive event.

In contrast, the long-term effects of social defeat on oxytocin/c-fos colocalizations are more robust in females. When mice were tested in a social interaction test two weeks after defeat stress or control handling, oxytocin/c-fos colocalizations in the anterior PVN were increased in females but not males (Steinman et al., 2016). These results corresponded with behavioral effects of social defeat, which reduce social approach in females but not males 2–4 weeks after the last stress exposure (Greenberg et al., 2014; Trainor et al., 2011). No differences were observed in the posterior PVN. These results contrasted with the outcome of acute social defeat, which had equivalent effects on anterior and posterior PVN oxytocin/c-fos colocalizations. Previous studies have also observed distinct effects of hypoxia (Ruyle et al., 2018) and social interactions (Ho et al., 2010) on neuronal activity in anterior versus posterior PVN neurons. In C57Bl6/J mice, neuroanatomical tracing was used to determine that magnocellular oxytocin neurons are predominantly distributed in the anterior PVN while parvocellular oxytocin neurons are predominantly distributed in the posterior PVN (Lewis et al., 2020). Magnocellular oxytocin neurons release oxytocin into the periphery and within the brain while parvocellular oxytocin cells release oxytocin primarily within the brain (Grinevich and Ludwig, 2021). Optogenetic manipulations of parvocellular oxytocin neurons within the posterior PVN showed that these cells facilitate social learning whereas magnocellular oxytocin neurons did not (Lewis et al., 2020). There may be important species differences, as parvocellular oxytocin neurons in female Wistar rats were found to promote social approach (Tang et al., 2020). Further work is needed to determine whether there are consistent differences across species in populations of PVN oxytocin neurons. Although some behavioral effects of oxytocin neurons may be species-

Table 1
Effects of stress on paraventricular nucleus oxytocin neurons.

Male	Female
• One episode of social defeat increased oxytocin/c-fos colocalizations in anterior and posterior PVN • Three episodes of social defeat increase oxytocin/c-fos colocalizations in anterior and posterior PVN • No effect of stress on oxytocin/c-fos colocalizations in PVN during a social interaction test with novel male	• No effect of one episode of social defeat on oxytocin/c-fos colocalizations in PVN • Three episodes of social defeat increase oxytocin/c-fos in anterior and posterior PVN • Stressed females have increased oxytocin/c-fos colocalizations in anterior PVN during a social interaction test with novel female.

specific, paraventricular oxytocin neurons should not be treated as a unitary entity. In addition, a population of oxytocin neurons outside of the hypothalamus, within the bed nucleus of the stria terminalis (BNST), was found to be robustly affected by social defeat stress.

2.2. Bed nucleus of the stria terminalis

An understudied population of oxytocin neurons is present in the medioventral bed nucleus of the stria terminalis (BNSTmv, Table 2). This group of oxytocin neurons is present in C57Bl/6J mice (Nasanbuyan et al., 2018), Wistar rats (DiBenedictis et al., 2017), prairie voles (Kelly et al., 2018), and California mice (Steinman et al., 2016). Defeat stress increased oxytocin/c-fos colocalizations in the BNSTmv after a social interaction test in females but not males, and this effect could be observed 10 weeks after the last episode of defeat stress. Defeat stress also increased the number of oxytocin positive cells in females but not males. A similar effect on BNSTmv oxytocin cell numbers was observed in a C57BL6/J witness defeat model (Duque-Wilckens et al., 2020), which induced stronger social vigilance responses in females. Changes in oxytocin cell numbers could be driven by increased oxytocin synthesis or by a decrease in oxytocin release (making neurons more readily detectable via immunohistochemistry). Real-time qPCR analyses on ventral BNST punch samples demonstrated that defeat stress increased oxytocin (*Oxt*) mRNA in females but not males (Steinman et al., 2016), suggesting that defeat stress increases oxytocin synthesis and reactivity within the BNST. A subsequent study on male C57BL6/J mice observed that a single 10 min episode of social defeat increased oxytocin/c-fos colocalizations within the BNSTmv (Nasanbuyan et al., 2018). These correlational data strongly implicated BNST oxytocin neurons in mediating stress coping responses. This hypothesis was tested using antisense morpholinos, which target oxytocin mRNA and prevent translation of the mature protein, similar to previous studies in birds (Kelly and Goodson, 2014).

In female California mice, the effects of stress on social behavior were blunted by oxytocin antisense treatment in the BNSTmv (Duque-Wilckens et al., 2020). Stressed females treated with a single injection of antisense targeting *Oxt* mRNA had lower levels of social vigilance and higher levels of social approach compared to females treated with missense. Importantly, there were no effects of antisense treatment in females that were not exposed to defeat stress. These data demonstrate that oxytocin produced within the BNST plays a key role in promoting stress-induced social avoidance and vigilance. To assess where these BNST oxytocin neurons could be releasing oxytocin, an adeno-associated virus (AAV) containing an oxytocin promoter was used to drive expression of the fluorescent Venus in BNST oxytocin neurons. Venus produced within neurons was transported into axons, allowing for the visualization of oxytocinergic projections (Knobloch et al., 2012). Fluorescent fibers originating from BNSTmv oxytocin neurons were detected in the anteromedial BNST (BNSTam) as well as other brain regions mediating defensive behaviors such as the anterior and lateral hypothalamus (Duque-Wilckens et al., 2020).

Table 2
Effects of Stress on Bed Nucleus of the Stria Terminalis Oxytocin neurons.

Male	Female
• No effect of one episode of social defeat on oxytocin/c-fos colocalizations within the BNSTmv. • Three episodes of social defeat increase oxytocin/c-fos colocalizations in BNSTmv after social interaction test. • No effect of stress on oxytocin/c-fos colocalizations in BNSTmv during a social interaction test with novel male	• No effect of one or three episodes of social defeat on oxytocin/c-fos colocalizations in BNSTmv • Three episodes of defeat Stress increased the number of oxytocin positive cells and *Oxtr* mRNA in females • Stressed females have increased oxytocin/c-fos colocalizations in BNSTmv during a social interaction test with novel female. • In the female C57BL6/J witness defeat model, stress increased oxytocin cell numbers

2.3. Summary

Overall, immunostaining data in California mice show that oxytocin neurons are highly sensitive to social defeat in the short and long term. In the short term, social defeat broadly activates oxytocin neurons in both males and females. However, the long-term effects of stress on oxytocin neuron reactivity are observed in females but not males. Puberty appears to be the key developmental timepoint preventing similar changes in males (Wright et al., 2023). Prepubertal males and females show stress induced social avoidance and vigilance, and this effect is oxytocin receptor dependent. Social defeat had no effect on oxytocin/c-fos colocalizations in the anterior PVN of males that received a sham surgery before puberty. In contrast, social defeat increased oxytocin/c-fos colocalizations in males that were castrated before puberty. Gonadectomy post-puberty has no effect on stress-induced avoidance in females or males (Trainor et al., 2013), which suggests that gonadal hormones act during puberty to reduce the reactivity of oxytocin neurons following stress exposure. Increased action potentials lead to oxytocin release (Rossoni et al., 2008), which has historically been interpreted as a stress-coping response to reduce the impact of stress (Neumann, 2008; Smith and Wang, 2014). The morpholino studies suggest an alternative hypothesis, that oxytocin release during stress facilitates social avoidance and anxiety-related responses. This raises the question, how can the same neuropeptide drive such diverse behavioral effects? Pharmacological studies in California mice suggest that effects of oxytocin on social approach and avoidance are mediated by distinct neural circuits.

3. Vasopressin V1a receptor (V1aR) modulation of social behavior

Oxytocin is usually assumed to modulate behavior through the activation of oxytocin receptors, but this neuropeptide is also capable of activating vasopressin V1aR (Busnelli et al., 2013). As a first step to assess which receptors mediated the effects of oxytocin on social approach and vigilance, the effects of social defeat on receptor binding were assessed using autoradiography. Surprising, there were few effects of social defeat on oxytocin receptor binding (Duque-Wilckens et al., 2018), with only the nucleus accumbens showing a decrease in both males and females after stress exposure. Similarly, few effects of stress were observed on V1aR binding although in the nucleus accumbens (NAc) shell, stress increased in V1aR binding in females but not males (Duque-Wilckens et al., 2016). Since defeat had stronger effects on social approach in females versus males, it was hypothesized that oxytocin could drive social avoidance through activation of V1aR.

This hypothesis was tested using infusions of a V1aR antagonist into the NAc of stressed females (Duque-Wilckens et al., 2016). No differences in social approach were seen between V1aR antagonist and control infusions, while V1aR antagonist decreased time spent in the center of an open field. These data did not support the hypothesis that V1aR action in the NAc drives stress-induced social avoidance. When V1aR were pharmacologically inhibited in the BNSTmv, social approach was reduced in both unstressed males and females. Thus, these data did not support the hypothesis that oxytocin acting through V1aR promotes stress-induced social avoidance. Indeed, activation of V1aR in the BNST instead played a key role in driving social approach. While it appeared likely that oxytocin receptors drive the effects of oxytocin release, it was unclear which parts of the brain would drive these effects.

4. Oxytocin receptor modulation of social behavior

As an initial test of the role of oxytocin receptors, a systemic injection of a brain accessible oxytocin receptor antagonist or saline was

administered 15 min before a social interaction test (Duque-Wilckens et al., 2018). A single injection of oxytocin receptor antagonist to stressed female California mice increased social approach while reducing social vigilance (Table 3). This result is remarkable because to achieve similar results with a selective serotonin reuptake inhibitor (sertraline), four weeks of daily treatment was required (Greenberg et al., 2014). The effects of oxytocin receptor antagonist differed in males, as the antagonist decreased time in the interaction zone in unstressed males. Although the exact mechanism for sex differences in systemic oxytocin receptor antagonist are unclear, one possibility is oxytocin's proposed role as a neuromodulator (Stoop, 2012). A neuromodulator will not simply excite or inhibit a neuron but will alter the effects of other events within the cell (Kupfermann, 1979). If different neural circuits are activated in stressed females versus unstressed males, oxytocin could be amplifying the behavioral effects of these circuits. This is consistent with hypothesis that oxytocin amplifies the salience of rewarding and aversive social contexts (Duque-Wilckens and Trainor, 2022). A next step was to identify neural substrates modulated by oxytocin receptors so control social approach and vigilance.

To identify candidate nuclei, immunohistochemistry for the immediate early gene early growth response factor 1 (EGR1) in unstressed males and females that had been treated with intranasal oxytocin. In males, intranasal oxytocin had no effect on social approach but in females the same dose had a stress-like effect by reducing social approach (Steinman et al., 2016). Intriguingly, oxytocin treatment in females increased the number of EGR1 positive cells in the BNSTam and NAc core (Duque-Wilckens et al., 2018), regions with strong oxytocin receptor binding. Based on these results, stressed females received microinjection of oxytocin receptor antagonist or vehicle in either the BNSTam or NAc core. Oxytocin receptor inhibition in the BNSTam but not the NAc core increased social approach and reduced social vigilance. These data demonstrated that activation of oxytocin receptors in the BNSTam are necessary for stress-induced changes in approach and vigilance in females. Oxytocin acting in the BNST has also been reported to facilitate the acquisition of cued fear in a fear-potentiated startle paradigm (Martinon et al., 2019; Moaddab and Dabrowska, 2017). Subsequent studies demonstrated that microinjections of oxytocin (Duque-Wilckens et al., 2020) or the selective oxytocin receptor agonist carbetocin (Luo et al., 2022) into the BNSTam reduced social approach and increased vigilance in unstressed males and females. These findings are important because they demonstrate that the neural circuitry for social avoidance and vigilance are present in both sexes. They suggest that a primary mechanism for sex differences in the effects of defeat stress on social behavior is based on differences in the release of oxytocin within the BNSTam (supported by the tracing studies described above) and not alterations of receptor expression or downstream mechanisms. An important question is whether oxytocin receptors can facilitate social approach responses in California mice as has been found in other species.

A series of pharmacological studies demonstrated that oxytocin receptors in the nucleus accumbens core facilitate social approach in California mice (Williams et al., 2020). In unstressed male and female California mice, oxytocin receptor antagonist infusion reduced social approach without affecting other measures of behavior. A key observation was that the reduction in social approach was not accompanied by increases in social vigilance. This highlights that the neural circuitry modulating social approach and vigilance are distinct. Intriguingly, when an oxytocin receptor agonist was infused into the nucleus accumbens of stressed females, social approach was increased while social vigilance decreased. This finding suggests that circuitry modulating approach and vigilance are also overlapping. Previous studies have also found that activation of oxytocin receptors in the nucleus accumbens can promote social approach in animals exposed to social defeat (Lukas et al., 2013; Wang et al., 2018). Observations that oxytocin receptors in the nucleus accumbens promote social approach also aligns with work showing that this pathway can facilitate social learning (Dölen et al., 2013) and motivation (Smith et al., 2017).

Overall, work in female California mice suggests that social defeat stress causes a shift in oxytocin release from the nucleus accumbens to BNSTam (Fig. 1). Although oxytocin release can be measured via microdialysis, highly sensitive radioimmunoassays are required to measure the very small amount of oxytocin released in the brain (Neumann et al., 2013). New technological developments could help facilitate the measure of oxytocin release. An optogenetic gene expression system was designed by genetically modifying the oxytocin receptor to include a light-gated gene expression system (iTango2) (Mignocchi et al., 2020). Applying blue light while the oxytocin receptor is activated causes the release of a transcription factor that can serve as an indicator of oxytocin release during a defined behavioral task. Although this approach should be sensitive to small amounts of oxytocin release, it lacks the temporal resolution of other methods. An oxytocin sensor was designed by replacing the signal transduction component of the oxytocin receptor with a fluorescent reporter (Ino et al., 2022). Fluorescent sensors have the capacity to yield millisecond temporal resolution (Dong et al., 2022). This sensor could detect socially induced oxytocin release within the olfactory bulb, where large amounts concentrations of oxytocin are released. A major strength of both the iTango system and oxytocin sensor is that they have the potential to be used in multiple different rodent species and do not require the use of specific transgenic mouse or rat lines.

Table 3
Effects of oxytocin receptors on social approach and vigilance.

Male	Female
• Oxytocin or oxytocin receptor agonist injected into anteromedial BNST of unstressed males decreased social approach and increased social vigilance. • Oxytocin receptor inhibition in the NAc core decreased social approach and both had no effect on social vigilance in unstressed males.	• Oxytocin receptor antagonist injected into the anteromedial BNST of stressed females increased social approach and reduced social vigilance. • Oxytocin receptor agonist injected into anteromedial BNST of unstressed female males decreased social approach and increased social vigilance. • Oxytocin receptor inhibition in the NAc core decreased social approach and both had no effect on social vigilance in unstressed females. • Oxytocin receptor agonist infusion into the nucleus accumbens of stressed females increased social approach and decreased social vigilance.

5. Future directions

Unique behavioral attributes of California mice provided opportunities to study sex differences in how stress impacts the reactivity of oxytocin neurons in ways that would be difficult to achieve by studying more conventional rodent models. However, working with non-traditional model species can present special challenges because much of the innovation in neuroscience methods has been tailored for use in domesticated mice. Much of the work reviewed in California mice relied on immunohistochemistry (which targets evolutionarily conserved proteins and neuropeptides) and pharmacology (which manipulate evolutionarily conserved receptors). These methods are powerful but have limitations. Assessing the activity of oxytocin neurons using c-fos immunohistochemistry provides a snapshot of neural activity that varies on a millisecond scale. Combining receptor agonists and antagonists can provide strong assessment of receptor function in specific brain regions. However, receptors can be expressed on pre-synaptic axon terminals or post-synaptic cell bodies (Dölen et al., 2013), which can't be distinguished via pharmacological approaches. Fortunately, new resources and technologies are opening the door to apply modern neuroscience techniques to diverse species.

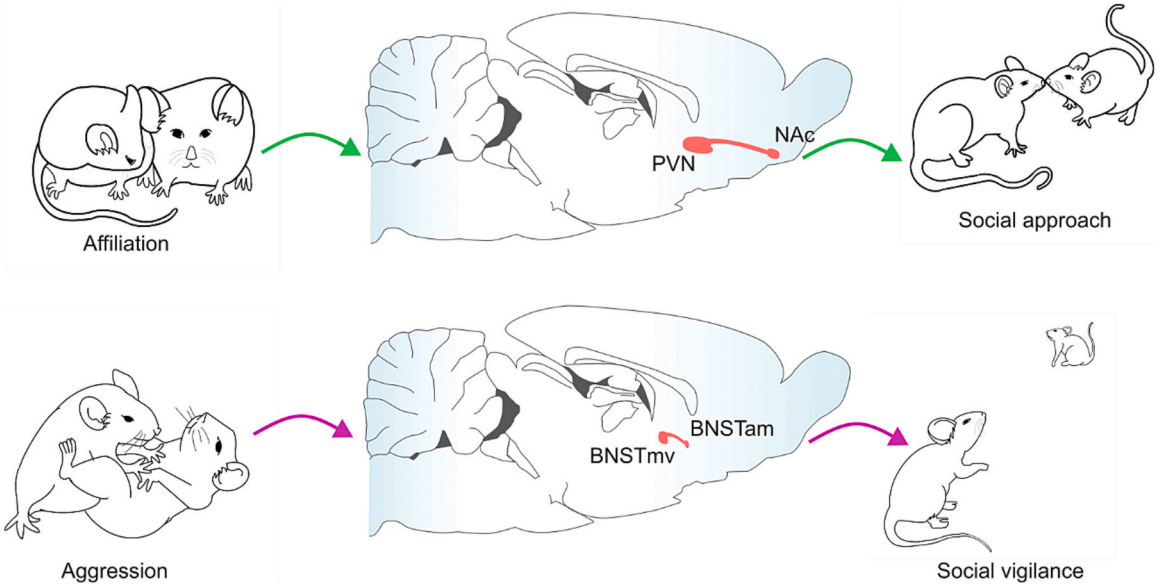


Fig. 1. Social experience affects the activation of oxytocin circuits within the forebrain. Affiliative social interactions are associated with release of oxytocin within the nucleus accumbens (Nac) from the paraventricular nucleus (PVN). The activation of oxytocin receptors in the Nac facilitates social approach in novel social contexts. Stressful social interactions activates oxytocin neurons within the medioventral bed nucleus of the stria terminalis (BNSTmv) that project to the anteromedial BNST (BNSTam). Activation of oxytocin receptors in the BNSTam induces social avoidance and social vigilance.

Rapid decreases in the costs of next generation sequencing methods have greatly reduced barriers to obtaining whole genome sequences. For example, investigators from the University of Maryland and UC Davis used short read Illumina sequencing with long read PacBio sequencing to complete the California mouse genome. One exciting application of the genome is the application of clustered regularly interspaced short palindromic repeats (CRISPR) gene editing. Gene editing is best known for its utility for producing transgenic animals, and CRISPR methodology can be applied to diverse species such as prairie voles (Berendzen et al., 2023; Horie et al., 2019) and Syrian hamsters (Miao et al., 2018; Taylor et al., 2019). The production of knockout lines using CRISPR has been extremely informative, but it can be hard to separate out developmental effects of gene knockout from how a gene functions in an adult animal. A complementary strategy is somatic gene editing, where a virus is used to deliver the Cas9 enzyme (which edits DNA), and guide RNAs (which direct the Cas9 to a specific DNA sequence) to the brain to edit a gene of interest at a specific time. Guide RNAs were designed to target a region of the oxytocin receptor gene (*Oxtr*) that is conserved across six different rodent species (Boender et al., 2023). In vivo testing showed that combining the guide RNA with Cas9 successfully reduced oxytocin receptor binding in spiny mice, Syrian hamsters, prairie voles, house mice, Norway rats, and California mice. Not only is this tool an exciting method for studying oxytocin receptor function, it demonstrates that tools can be developed for gene editing that can be applied across a range of species with unique behavioral attributes.

Innovations in calcium imaging methods are also proving to be highly portable across diverse species. Unlike immediate early gene estimates of neural activity, calcium imaging methods provide millisecond temporal resolution. Fiber photometry was used to perform calcium imaging in the BNSTmv of California mice (Wright et al., 2023), which yielded important insights in how behavioral interactions impact neural activity. Pharmacological and immediate early gene analyses suggested that oxytocin increases neural activity in the BNST to drive avoidance and social vigilance. However, it was unclear whether social threats drove increases in neural activity or whether increased neural activity occurred as animals were showing social avoidance. Calcium imaging showed that close proximity to aggressive animals increased activity in the BNST while no changes in activity were observed during avoidance or other defensive behavior. These results suggest that the BNSTmv plays a key role in encoding threats, which can be tested more directly in future studies. Fiber photometry-based calcium imaging provides a population average of activity within a discrete brain region. Microendoscopes allow for the imaging of individual neurons while the animal is engaging in different behaviors. Like fiber photometry, this approach is applicable across diverse species. For example, a distinct population of neurons in the nucleus accumbens became activated when male and female prairie voles approached a pair-bonded partner (Scribner et al., 2020).

A significant barrier that remains for comparative research is the need to identify and selectively manipulate specific neuronal cell types. For example, in C57Bl6/J BNST there are >40 different types of neurons (Welch et al., 2019). More 6 of types of neurons express oxytocin receptor (Luo et al., 2022). In house mice, the primary mechanism for targeting specific cell types is the use of transgenic lines in which a marker gene is used to express a recombinase such as Cre. However, most investigators do not have the expertise to create multiple transgenic lines, especially since CRISPR-based knockin approaches are significantly more challenging than knockout approaches. In most cases known gene promoters are too long to fit into the genome of the most commonly used adeno-associated AAV viruses (Wu et al., 2010). An alternative approach is to focus on shorter gene regulatory units referred to as enhancers. For example, inhibitory interneurons can be targeted by using enhancer sequences for *Dlx5* and *Dlx6* genes (Dimidschstein et al., 2016). An exciting aspect of this discovery was that selective targeting was possible across a range of rodent and primate species. The identification of evolutionarily conserved enhancer sequences is an active area of research (Mich et al., 2021), and should benefit investigators working with diverse species.

The unique behavioral attributes of California mice can allow these new methods to be applied to address questions that are difficult or impossible to test in conventional laboratory rodents. Unlike most mammalian species, California mouse fathers care for their young, which provides unique opportunities to study bidirectional interactions between fathers and their offspring. Fathers are critical for the survival of pups under both field (Gubernick and Teferi, 2000) and laboratory (Glasper et al., 2018) conditions. Beyond survival, California mouse fathers have an important impacts on hippocampal development (Madison et al., 2022) and stress sensitivity to stress in their offspring

(Agarwal et al., 2020). The experience of providing parental care also impacts the brain of the father (Andrew et al., 2020; Hyer et al., 2017; Perea-Rodriguez et al., 2015; Wilson et al., 2022), which could facilitate parental care and reduce anxiety-related behavior (Hyer et al., 2016). Finally, California mice vocalizations have been characterized under both field (Kalcounis-Rueppell et al., 2018) and laboratory (Pultorak et al., 2015; Rieger et al., 2021) settings such that the function of different calls such as barks (used in agonistic interactions) and sustained vocalizations (which are more affiliative) have been detailed. While vocalizations have been characterized in other rodent species, the function of specific vocalizations is often unclear. Thus, analyses of vocalizations in behavioral neuroscience studies can add a new dimension for understanding the mechanisms that modulate social interactions. The growth in technologies that are portable across species and the unique behavioral approaches available in California mice and other non-traditional model species makes it an exciting time to be engaged in comparative neuroendocrinology research.

CRediT authorship contribution statement

Alyssa A. Lake: Writing – original draft. **Brian C. Trainor:** Conceptualization, Writing – original draft, Writing – review & editing.

Acknowledgements

This work supported by NIH R01MH121829 and NSF IOS1937335 to BCT.

References

Agarwal, P., Palin, N., Walker, S.L., Glasper, E.R., 2020. Sex-dependent effects of paternal deprivation and chronic variable stress on novel object recognition in adult California mice (Peromyscus californicus). Horm. Behav. 117, 104610 https://doi.org/10.1016/j.yhbeh.2019.104610.

Andrew, J.R., Garland, T., Chappell, M.A., Zhao, M., Horrell, N.D., Saltzman, W., 2020. Long-term effects of fatherhood on morphology, energetics, and exercise performance in California mice (*Peromyscus californicus*). Physiol. Biochem. Zool. 93, 75–86. https://doi.org/10.1086/706863.

Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. Trends Cogn. Sci. (Regul. Ed.) 15, 301–309. https://doi.org/10.1016/j.tics.2011.05.002.

Beery, A.K., 2015. Antisocial oxytocin: complex effects on social behavior. Curr. Opin. Behav. Sci. 6, 174–182.

Berendzen, K.M., Sharma, R., Mandujano, M.A., Wei, Y., Rogers, F.D., Simmons, T.C., Seelke, A.M.H., Bond, J.M., Larios, R., Goodwin, N.L., Sherman, M., Parthasarthy, S., Espineda, I., Knoedler, J.R., Beery, A., Bales, K.L., Shah, N.M., Manoli, D.S., 2023. Oxytocin receptor is not required for social attachment in prairie voles. Neuron 111, 787–796.e4. https://doi.org/10.1016/j.neuron.2022.12.011.

Blanchard, D.C., Sakai, R.R., McEwen, B., Weiss, S.M., Blanchard, R.J., 1993. Subordination stress: behavioral, brain, and neuroendocrine correlates. Behavioral Brain Research 58, 113–121.

Boender, A.J., Boon, M., Albers, H.E., Eck, S.R., Fricker, B.A., Kelly, A.M., LeDoux, J.E., Motta, S.C., Shrestha, P., Taylor, J.H., Trainor, B.C., Triana-Del Rio, R., Young, L.J., 2023. An AAV-CRISPR/Cas9-Strategy for Gene Editing across Divergent Rodent Species: Targeting Neural Oxytocin Receptors as a Proof of Concept. Science Advances in press.

Busnelli, M., Bulgheroni, E., Manning, M., Kleinau, G., Chini, B., 2013. Selective and potent agonists and antagonists for investigating the role of mouse oxytocin receptors. J. Pharmacol. Exp. Ther. 346, 318–327. https://doi.org/10.1124/jpet.113.202994.

Carter, C.S., Kenkel, W.M., MacLean, E.L., Wilson, S.R., Perkeybile, A.M., Yee, J.R., Ferris, C.F., Nazarloo, H.P., Porges, S.W., Davis, J.M., Connelly, J.J., Kingsbury, M. A., 2020. Is oxytocin "Nature's medicine"? Pharmacol. Rev. 72, 829–861. https://doi.org/10.1124/pr.120.019398.

Cooper, M.A., Huhman, K.L., 2005. Corticotropin-releasing factor type II (CRF-sub-2) receptors in the bed nucleus of the stria terminalis modulate conditioned defeat in Syrian hamsters (Mesocricetus auratus). Behav. Neurosci. 119, 1042–1051.

Davis, E.S., Marler, C.A., 2003. The progesterone challenge: steroid hormone changes following a simulated territorial intrusion in female Peromyscus californicus. Horm. Behav. 44, 189–198.

De Cagna, F., Fusar-Poli, L., Damiani, S., Rocchetti, M., Giovanna, G., Mori, A., Politi, P., Brondino, N., 2019. The role of intranasal oxytocin in anxiety and depressive disorders: a systematic review of randomized controlled trials. Clin Psychopharmacol Neurosci 17, 1–11. https://doi.org/10.9758/cpn.2019.17.1.1.

DiBenedictis, B.T., Nussbaum, E.R., Cheung, H.K., Veenema, A.H., 2017. Quantitative mapping reveals age and sex differences in vasopressin, but not oxytocin, immunoreactivity in the rat social behavior neural network. J. Comp. Neurol. 525, 2549–2570.

Dimidschstein, J., Chen, Q., Tremblay, R., Rogers, S.L., Saldi, G.-A., Guo, L., Xu, Q., Liu, R., Lu, C., Chu, J., Grimley, J.S., Krostag, A.-R., Kaykas, A., Avery, M.C., Rashid, M.S., Baek, M., Jacob, A.L., Smith, G.B., Wilson, D.E., Kosche, G., Kruglikov, I., Rusielewicz, T., Kotak, V.C., Mowery, T.M., Anderson, S.A., Callaway, E.M., Dasen, J.S., Fitzpatrick, D., Fossati, V., Long, M.A., Noggle, S., Reynolds, J.H., Sanes, D.H., Rudy, B., Feng, G., Fishell, G., 2016. A viral strategy for targeting and manipulating interneurons across vertebrate species. Nat. Neurosci. 19, 1743–1749. https://doi.org/10.1038/nn.4430.

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

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

Dong, C., Zheng, Y., Long-Iyer, K., Wright, E.C., Li, Y., Tian, L., 2022. Fluorescence imaging of neural activity, neurochemical dynamics, and drug-specific receptor conformation with genetically encoded sensors. Annu. Rev. Neurosci. 45, 273–294. https://doi.org/10.1146/annurev-neuro-110520-031137.

Duque-Wilckens, N., Trainor, B.C., 2022. Oxytocin release in stressful times. Psychoneuroendocrinology 140, 105709. https://doi.org/10.1016/j.psyneuen.2022.105709.

Duque-Wilckens, N., Steinman, M.Q., Laredo, S.A., Hao, R., Perkeybile, A.M., Bales, K.L., Trainor, B.C., 2016. Inhibition of vasopressin V1a receptors in the medioventral bed nucleus of the stria terminalis has sex- and context-specific anxiogenic effects. Neuropharmacology 110, 59–68. https://doi.org/10.1016/j.neuropharm.2016.07.018.

Duque-Wilckens, N., Steinman, M.Q., Busnelli, M., Chini, B., Yokoyama, S., Pham, M., Laredo, S.A., Hao, R., Perkeybile, A.M., Minie, V.A., Tan, P.B., Bales, K.L., Trainor, B. C., 2018. Oxytocin receptors in the anteromedial bed nucleus of the Stria terminalis promote stress-induced social avoidance in female California mice. Biol. Psychiatry 83, 203–213. https://doi.org/10.1016/j.biopsych.2017.08.024.

Duque-Wilckens, N., Torres, L.Y., Yokoyama, S., Minie, V.A., Tran, A.M., Petkova, S.P., Hao, R., Ramos-Maciel, S., Rios, R.A., Jackson, K., Flores-Ramires, F.J., Garcia-Carachure, I., Pesavento, P.A., Iñiguez, S.D., Grinevich, V., Trainor, B.C., 2020. Extra-hypothalamic oxytocin neurons drive stress-induced social vigilance and avoidance. Proc. Natl. Acad. Sci. U. S. A. 117, 26406–26413. https://doi.org/10.1101/2020.06.02.129981.

Eckstein, M., Scheele, D., Weber, K.S., Stoffel-Wagner, B., Maier, W., Hurlemann, R., 2014. Oxytocin facilitates the sensation of social stress. Hum. Brain Mapp. 35, 4741–4750.

Glasper, E.R., Hyer, M.M., Hunter, T.J., 2018. Enduring effects of paternal deprivation in California mice (Peromyscus californicus): behavioral dysfunction and sex-dependent alterations in hippocampal new cell survival. Front. Behav. Neurosci. 12, 20. https://doi.org/10.3389/fnbeh.2018.00020.

Greenberg, G.D., Laman-Maharg, A., Campi, K.L., Voigt, H., Orr, V.N., Schaal, L., Trainor, B.C., 2014. Sex differences in stress-induced social withdrawal: role of brain derived neurotrophic factor in the bed nucleus of the stria terminalis. Front. Behav. Neurosci. 7 https://doi.org/10.3389/fnbeh.2013.00223.

Greenberg, G.D., Steinman, M.Q., Doig, I.E., Hao, R., Trainor, B.C., 2015. Effects of social defeat on dopamine neurons in the ventral tegmental area in male and female California mice. Eur. J. Neurosci. 42 https://doi.org/10.1111/ejn.13099.

Grinevich, V., Ludwig, M., 2021. The multiple faces of the oxytocin and vasopressin systems in the brain. J. Neuroendocrinol. 33, e13004 https://doi.org/10.1111/jne.13004.

Gubernick, D.J., Teferi, T., 2000. Adaptive significance of male parental care in a monogamous mammal. Proceedings of the Royal Society of London Series B-Biological Sciences 267, 147–150.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., Ehlert, U., 2003. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol. Psychiatry 54, 1389–1398.

Ho, J.M., Murray, J.H., Demas, G.E., Goodson, J.L., 2010. Vasopressin cell groups exhibit strongly divergent responses to copulation and male-male interactions in mice. Horm. Behav. 58, 368–377.

Hoffman, G.E., Lyo, D., 2002. Anatomical markers of activity in neuroendocrine systems: are we all "fos-ed out"? J. Neuroendocrinol. 14, 259–268.

Horie, K., Inoue, K., Suzuki, S., Adachi, S., Yada, S., Hirayama, T., Hidema, S., Young, L. J., Nishimori, K., 2019. Oxytocin receptor knockout prairie voles generated by CRISPR/Cas9 editing show reduced preference for social novelty and exaggerated repetitive behaviors. Horm. Behav. 111, 60–69. https://doi.org/10.1016/j.yhbeh.2018.10.011.

Huhman, K.L., 2006. Social conflict models: can they inform us about human psychopathology? Horm. Behav. 50, 640–646. https://doi.org/10.1016/j.yhbeh.2006.06.022.

Hyer, M.M., Hunter, T.J., Katakam, J., Wolz, T., Glasper, E.R., 2016. Neurogenesis and anxiety-like behavior in male California mice during the mate's postpartum period. Eur. J. Neurosci. 43, 703–709. https://doi.org/10.1111/ejn.13168.

Hyer, M.M., Khantsis, S., Venezia, A.C., Madison, F.N., Hallgarth, L., Adekola, E., Glasper, E.R., 2017. Estrogen-dependent modifications to hippocampal plasticity in paternal California mice (Peromyscus californicus). Horm. Behav. 96, 147–155. https://doi.org/10.1016/j.yhbeh.2017.09.015.

Ino, D., Tanaka, Y., Hibino, H., Nishiyama, M., 2022. A fluorescent sensor for real-time measurement of extracellular oxytocin dynamics in the brain. Nat. Methods 19, 1286–1294.

Jašarević, E., Bailey, D.H., Crossland, J.P., Dawson, W.D., Szalai, G., Ellersieck, M.R., Rosenfeld, C.S., Geary, D.C., 2013. Evolution of monogamy, paternal investment, and female life history in Peromyscus. J. Comp. Psychol. 127, 91–102. https://doi.org/10.1037/a0027936.

Kalcounis-Rueppell, (first), Pultorak, J.D., Marler, C.A., 2018. Chapter 22 - ultrasonic vocalizations of mice in the genus Peromyscus. In: Brudzynski, S.M. (Ed.), Handbook of Behavioral Neuroscience. Elsevier, Handbook of Ultrasonic Vocalization, pp. 227–235. https://doi.org/10.1016/B978-0-12-809600-0.00022-6.

Kalin, N.H., Gibbs, D.M., Barksdale, C.M., Shelton, S.E., Carnes, M., 1985. Behavioral stress decreases plasma oxytocin concentrations in primates. Life Sci. 36, 1275–1280. https://doi.org/10.1016/0024-3205(85)90272-3.

Kelly, A.M., Goodson, J.L., 2014. Hypothalamic oxytocin and vasopressin neurons exert sex-specific effects on pair bonding, gregariousness, and aggression in finches. Proc. Natl. Acad. Sci. U. S. A. 111, 6069–6074.

Kelly, A.M., Hiura, L.C., Ophir, A.G., 2018. Rapid nonapeptide synthesis during a critical period of development in the prairie vole: plasticity of the paraventricular nucleus of the hypothalamus. Brain Struct. Funct. 223, 2547–2560. https://doi.org/10.1007/s00429-018-1640-2.

Knobloch, H.S., A., C., Hoffmann, L.C., Eliava, M., Khrulev, S., Cetin, A.H., Osten, P., Schwarz, M.K., H., S.P., Stoop, R., Grinevich, V., 2012. Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73, 553–566.

Krishnan, V., Han, M.-H., Graham, D.L., Berton, O., Renthal, W., Russo, S.J., LaPlant, Q., Graham, A., Lutter, M., Lagace, D.C., Ghose, S., Reister, R., Tannous, P., Green, T.A., Neve, R.L., Chakravarty, S., Kumar, A., Eisch, A.J., Self, D.W., Lee, F.S., Tamminga, C.A., Cooper, D.C., Gershenfeld, H.K., Nestler, E.J., 2007. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell 131, 391–404.

Kudryavtseva, N.N., Bakshtanovskaya, I.V., Koryakina, L.A., 1991. Social model of depression in mice of C57BL/6J strain. Pharmacol. Biochem. Behav. 38, 315–320. https://doi.org/10.1016/0091-3057(91)90284-9.

Kupfermann, I., 1979. Modulatory actions of neurotransmitters. Annu. Rev. Neurosci. 2, 447–465. https://doi.org/10.1146/annurev.ne.02.030179.002311.

Kuske, J.X., Trainor, B.C., 2021. Mean girls: Social stress models for female rodents. In: Current Topics in Behavioral Neurosciences. Springer, Berlin, Heidelberg, pp. 1–30. https://doi.org/10.1007/7854_2021_247.

Kuske, J.X., Godoy, A.S., Ramirez, A.V., Trainor, B.C., 2023. Sex differences in responses to aggressive encounters among California mice. https://doi.org/10.1101/2023.12.12.571325.

Leppanen, J., Ng, K.W., Kim, Y.-R., Tchanturia, K., Treasure, J., 2018. Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans. J. Affect. Disord. 225, 167–179. https://doi.org/10.1016/j.jad.2017.08.041.

Lewis, E.M., Stein-O'Brien, G.L., Patino, A.V., Nardou, R., Grossman, C.D., Brown, M., Bangamwabo, B., Ndiaye, N., Giovinazzo, D., Dardani, I., Jiang, C., Goff, L.A., Dölen, G., 2020. Parallel social information processing circuits are differentially impacted in autism. Neuron 108, 659–675.e6. https://doi.org/10.1016/j.neuron.2020.10.002.

Lukas, M., Toth, I., Veenema, A.H., Neumann, I.D., 2013. Oxytocin mediates rodent social memory within the lateral septum and the medial amyfdala depending on the relevance of the social stimulus: male juvenile versus female adult conspecifics. Psychoneuroendocrinology 38, 916–926.

Luo, P.X., Zakharenkov, H.C., Torres, L.Y., Rios, R.A., Gegenhuber, B., Black, A.M., Xu, C. K., Minie, V.A., Tran, A.M., Tollkuhn, J., Trainor, B.C., 2022. Oxytocin receptor behavioral effects and cell types in the bed nucleus of the stria terminalis. Horm. Behav. 143, 105203 https://doi.org/10.1016/j.yhbeh.2022.105203.

Madison, F.N., Palin, N., Whitaker, A., Glasper, E.R., 2022. Sex-specific effects of neonatal paternal deprivation on microglial cell density in adult California mouse (Peromyscus californicus) dentate gyrus. Brain Behav. Immun. 106, 1–10. https://doi.org/10.1016/j.bbi.2022.07.161.

Martinez, M., Calvo-Torrent, A., Pico-Alfonso, M.A., 1998. Social defeat and subordination as models of social stress in laboratory rodents: a review. Aggress. Behav. 24, 241–256. https://doi.org/10.1002/(SICI)1098-2337(1998)24:4<241::AID-AB1>3.0.CO;2-M.

Martinon, D., Lis, P., Roman, A.N., Tornesi, P., Applebey, S.V., Buechner, G., Olivera, V., Dabrowska, J., 2019. Oxytocin receptors in the dorsolateral bed nucleus of the stria terminalis (BNST) bias fear learning toward temporally predictable cued fear. Transl. Psychiatry 9, 140. https://doi.org/10.1038/s41398-019-0474-x.

McQuaid, R.J., McInnis, O.A., Paric, A., Al-Yawer, F., Matheson, K., Anisman, H., 2016. Relations between plasma oxytocin and cortisol: the stress buffering role of social support. Neurobiol. Stress 3, 52–60. https://doi.org/10.1016/j.ynstr.2016.01.001.

Miao, J., Ying, B., Li, R., Tollefson, A.E., Spencer, J.F., Wold, W.S.M., Song, S.-H., Kong, I.-K., Toth, K., Wang, Y., Wang, Z., 2018. Characterization of an N-terminal non-Core domain of RAG1 gene disrupted Syrian Hamster model generated by CRISPR Cas9. Viruses 10, 243. https://doi.org/10.3390/v10050243.

Mich, J.K., Graybuck, L.T., Hess, E.E., Mahoney, J.T., Kojima, Y., Ding, Y., Somasundaram, S., Miller, J.A., Kalmbach, B.E., Radaelli, C., Gore, B.B., Weed, N., Omstead, V., Bishaw, Y., Shapovalova, N.V., Martinez, R.A., Fong, O., Yao, S., Mortrud, M., Chong, P., Loftus, L., Bertagnolli, D., Goldy, J., Casper, T., Dee, N., Opitz-Araya, X., Cetin, A., Smith, K.A., Gwinn, R.P., Cobbs, C., Ko, A.L., Ojemann, J. G., Keene, C.D., Silbergeld, D.L., Sunkin, S.M., Gradinaru, V., Horwitz, G.D., Zeng, H., Tasic, B., Lein, E.S., Ting, J.T., Levi, B.P., 2021. Functional enhancer elements drive subclass-selective expression from mouse to primate neocortex. Cell Rep. 34, 108754 https://doi.org/10.1016/j.celrep.2021.108754.

Mignocchi, N., Krüssel, S., Jung, K., Lee, D., Kwon, H.-B., 2020. Development of a genetically-encoded oxytocin sensor (preprint). Neuroscience. https://doi.org/10.1101/2020.07.14.202598.

Moaddab, M., Dabrowska, J., 2017. Oxytocin receptor neurotransmission in the dorsolateral bed nucleus of the stria terminalis facilitates the acquisition of cued fear in the fear-potentiated startle paradigm in rats. Neuropharmacology 121, 130–139. https://doi.org/10.1016/j.neuropharm.2017.04.039.

Nasanbuyan, N., Yoshida, M., Takayanagi, Y., Inutsuka, A., Nishimori, K., Yamanaka, A., Onaka, T., 2018. Oxytocin-oxytocin receptor systems facilitate social defeat posture in male mice. Endocrinology 159, 763–775. https://doi.org/10.1210/en.2017-00606.

Neumann, I.D., 2008. Brain oxytocin: a key regulator of emotional and social behaviours in both females and males. J. Neuroendocrinol. 20, 858–865. https://doi.org/10.1111/j.1365-2826.2008.01726.x.

Neumann, I.D., Landgraf, R., 2012. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behavior. Trends Neurosci. 35, 649–659.

Neumann, I.D., Maloumby, R., Beiderbeck, D.I., Lukas, M., Landgraf, R., 2013. Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice. Psychoneuroendocrinology 38, 1985–1993.

Newman, E.L., Covington, H.E., Suh, J., Bicakci, M.B., Ressler, K.J., DeBold, J.F., Miczek, K.A., 2019. Fighting females: neural and behavioral consequences of social defeat stress in female mice. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2019.05.005.

Perea-Rodriguez, J.P., Takahashi, E.Y., Amador, T.M., Hao, R., Saltzman, W., Trainor, B. C., 2015. Effects of reproductive status on central expression of progesterone, oxytocin, and vasopressin V1a receptors in male California mice (Peromyscus californicus), 27, pp. 245–252.

Pultorak, J.D., Fuxjager, M.J., Kalcounis-Rueppell, M.C., Marler, C.A., 2015. Male fidelity expressed through rapid testosterone suppression of ultrasonic vocalizations to novel females in the monogamous California mouse. Horm. Behav. 70, 47–56. https://doi.org/10.1016/j.yhbeh.2015.02.003.

Ribble, D.O., 1991. The monogamous mating system of Peromyscus californicus as revealed by DNA fingerprinting. Behav. Ecol. Sociobiol. 29, 161–166.

Ribble, D.O., Salvioni, M., 1990. Social organization and nest coocupancy in Peromyscus californicus, a monogamous rodent. Behav. Ecol. Sociobiol. 26, 9–15.

Rieger, N.S., Monari, P.K., Hartfield, K., Schefelker, J., Marler, C.A., 2021. Pair-bonding leads to convergence in approach behavior to conspecific vocalizations in California mice (Peromyscus californicus). PloS One 16, e0255295. https://doi.org/10.1371/journal.pone.0255295.

Rossoni, E., Feng, J., Tirozzi, B., Brown, D., Leng, G., Moos, F., 2008. Emergent synchronous bursting of oxytocin neuronal network. PLoS Comput. Biol. 4, e1000123 https://doi.org/10.1371/journal.pcbi.1000123.

Ruyle, B.C., Klutho, P.J., Baines, C.P., Heesch, C.M., Hasser, E.M., 2018. Hypoxia activates a neuropeptidergic pathway from the paraventricular nucleus of the hypothalamus to the nucleus tractus solitarii. Am. J. Phys. Regul. Integr. Comp. Phys. 315, R1167–R1182. https://doi.org/10.1152/ajpregu.00244.2018.

Scribner, J.L., Vance, E.A., Protter, D.S.W., Sheeran, W.M., Saslow, E., Cameron, R.T., Klein, E.M., Jimenez, J.C., Kheirbek, M.A., Donaldson, Z.R., 2020. A neuronal signature for monogamous reunion. Proc. Natl. Acad. Sci. U. S. A. 117, 11076–11084. https://doi.org/10.1073/pnas.1917287117.

Shamay-Tsoory, S.G., Abu-Akel, A., 2016. The social salience hypothesis of oxytocin. Biological Psychiatry, Oxytocin and Psychiatry: From DNA to Social Behavior 79, 194–202. https://doi.org/10.1016/j.biopsych.2015.07.020.

Silva, A.L., Fry, W.H.D., Sweeney, C., Trainor, B.C., 2010. Effects of photoperiod and experience on aggressive behavior in female California mice. Behav. Brain Res. 208 https://doi.org/10.1016/j.bbr.2009.12.038.

Smith, A.S., Wang, Z., 2014. Hypothalamic oxytocin mediates social buffering of the stress response. Biological Psychiatry, Neurobiological Moderators of Stress Response 76, 281–288. https://doi.org/10.1016/j.biopsych.2013.09.017.

Smith, C.J.W., Mogavero, J.N., Tulimieri, M.T., Veenema, A.H., 2017. Involvement of the oxytocin system in the nucleus accumbens in the regulation of juvenile social novelty-seeking behavior. Horm. Behav. 93, 94–98.

Steinman, M.Q., Duque-Wilckens, N., Greenberg, G.D., Hao, R., Campi, K.L., Laredo, S.A., Laman-Maharg, A., Manning, C.E., Doig, I.E., Lopez, E.M., Walch, K., Bales, K.L., Trainor, B.C., 2016. Sex-Specific Effects of Stress on Oxytocin Neurons Correspond with Responses to Intranasal Oxytocin. Biological Psychiatry, Corticotropin-Releasing Factor, FKBP5, and Posttraumatic Stress Disorder, vol. 80, pp. 406–414. https://doi.org/10.1016/j.biopsych.2015.10.007.

Steinman, M.Q., Duque-Wilckens, N., Trainor, B.C., 2019. Complementary neural circuits for divergent effects of oxytocin: social approach versus social anxiety. Biol. Psychiatry 85, 792–801. https://doi.org/10.1016/j.biopsych.2018.10.008.

Stoop, R., 2012. Neuromodulation by oxytocin and vasopressin. Neuron 76, 142–159. https://doi.org/10.1016/j.neuron.2012.09.025.

Tabak, B.A., Rosenfield, D., Sunahara, C.S., Alvi, T., Szeto, A., Mendez, A.J., 2022. Social anxiety is associated with greater peripheral oxytocin reactivity to psychosocial stress. Psychoneuroendocrinology 140, 105712. https://doi.org/10.1016/j.psyneuen.2022.105712.

Tang, Y., Benusiglio, D., Lefevre, A., Hilfiger, L., Bludau, A., Hagiwara, D., Baudon, A., Darbon, P., Shimmer, J., Kirchner, M.K., Roy, R.K., Wang, S., Eliava, M., Wagner, S., Oberhuber, M., Conzelmann, K.K., Schwarz, M., Stern, J.E., Leng, G., Neumann, I.D., Charlet, A., Grinevich, V., 2020. Social touch promotes inter-female communication via activation of oxytocin parvocellular neurons. Nat. Neurosci. 23, 1125–1137.

Taylor, J.J., Walton, J.C., McCann, K.E., Norvelle, A., Liu, Q., Vander Velden, J.M., Borland, J.M., Hart, M., Jin, C., Huhman, K.L., Cox, D.N., Albers, H.E., 2019. CRISPR Cas9 generation and behavioral characterization of a Syrian hamster V1a receptor knockout. Neuroscience Meeting Planner. 499, 24.

Tickerhoof, M.C., Hale, L.H., Butler, M.J., Smith, A.S., 2020. Regulation of defeat-induced social avoidance by medial amygdala DRD1 in male and female prairie

voles. Psychoneuroendocrinology 113, 104542. https://doi.org/10.1016/j.psyneuen.2019.104542.
Tidey, J.W., Miczek, K.A., 1996. Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. Brain Res. 721, 140–149. https://doi.org/10.1016/0006-8993(96)00159-x.
Tornatzky, W., Miczek, K.A., 1993. Long-term impairment of autonomic circadian rhythms after brief intermittent social stress. Physiol. Behav. 53, 983–993. https://doi.org/10.1016/0031-9384(93)90278-N.
Trainor, B.C., Takahashi, E.Y., Silva, A.L., Crean, K.K., Hostetler, C., 2010. Sex differences in hormonal responses to social conflict in the monogamous California mouse. Horm. Behav. 58, 506–512. https://doi.org/10.1016/j.yhbeh.2010.04.008.
Trainor, B.C., Pride, M.C., Landeros, R.V., Knoblauch, N.W., Takahashi, E.Y., Silva, A.L., Crean, K.K., 2011. Sex differences in social interaction behavior following social defeat stress in the monogamous California mouse (peromyscus californicus). PloS One 6. https://doi.org/10.1371/journal.pone.0017405.
Trainor, B.C., Takahashi, E.Y., Campi, K.L., Florez, S.A., Greenberg, G.D., Laman-Maharg, A., Laredo, S.A., Orr, V.N., Silva, A.L., Steinman, M.Q., 2013. Sex differences in stress-induced social withdrawal: Independence from adult gonadal hormones and inhibition of female phenotype by corncob bedding. Horm. Behav. 63, 543–550. https://doi.org/10.1016/j.yhbeh.2013.01.011.
Van Kampen, M., Kramer, M., Hiemke, C., Flugge, G., Fuchs, E., 2002. The chronic psychosocial stress paradigm in male tree shrews: evaluation of a novel animal model for depressive disorders. Stress 5, 37–46.
Walker, S.L., Sud, N., Beyene, R., Palin, N., Glasper, E.R., 2023. Paternal deprivation induces vigilance-avoidant behavior and accompanies sex-specific alterations in stress reactivity and central proinflammatory cytokine response in California mice (Peromyscus californicus). Psychopharmacology. https://doi.org/10.1007/s00213-023-06354-2.
Wang, L., Hou, W., He, Z., Yuan, W., Yang, J., Yang, Y., Jia, R., Zhu, Z., Zhou, Y., Tai, F., 2018. Effects of chronic social defeat on social behaviors in adult female mandarin voles (Microtus mandarinus): involvement of the oxytocin system in the nucleus accumbens. Prog. Neuropsychopharmacol. Biol. Psychiatry 82, 278–288. https://doi.org/10.1016/j.pnpbp.2017.11.002.
Welch, J.D., Kozareva, V., Ferreira, A., Vanderburg, C., Martin, C., Macosko, E.Z., 2019. Single-cell multi-omic integration compares and contrasts features of brain cell identity. Cell 177, 1873–1887.e17. https://doi.org/10.1016/j.cell.2019.05.006.
Williams, A.V., Laman-Maharg, A., Armstrong, C.V., Ramos-Maciel, S., Minie, V.A., Trainor, B.C., 2018. Acute inhibition of kappa opioid receptors before stress blocks depression-like behaviors in California mice. Prog. Neuropsychopharmacol. Biol. Psychiatry 86, 166–174. https://doi.org/10.1016/j.pnpbp.2018.06.001.
Williams, A.V., Duque-Wilckens, N., Ramos-Maciel, S., Campi, K.L., Bhela, S.K., Xu, C.K., Jackson, K., Chini, B., Pesavento, P.A., Trainor, B.C., 2020. Social approach and social vigilance are differentially regulated by oxytocin receptors in the nucleus accumbens. Neuropsychopharmacology 45, 1423–1430. https://doi.org/10.1038/s41386-020-0657-4.
Williams, A.V., Pena, C.J., Ramos-Maciel, S., Laman-Maharg, A., Ordoñes Sanchez, E., Britton, M., Durbin-Johnson, B., Settles, M., Hao, R., Yokoyama, S., Xu, C.K., Luo, P. X., Dwyer, T., Bhela, S.K., Black, A.M., Labonte, B., Serafini, R.A., Ruiz, A., Neve, R. L., Zachariou, V., Nestler, E.J., Trainor, B.C., 2022. Comparative transcriptional analyses in the nucleus accumbens identifies RGS2 as a key mediator of depression-related behavior. Biol. Psychiatry 92, 942–951.
Willmore, L., Cameron, C., Yang, J., Witten, I., Falkner, A., 2022. Behavioral and dopaminergic signatures of resilience. Nature. https://doi.org/10.1101/2022.03.18.484885.
Wilson, K.M., Arquilla, A.M., Rosales-Torres, K.M., Hussein, M., Chan, M.G., Razak, K.A., Saltzman, W., 2022. Neural responses to pup calls and pup odors in California mouse fathers and virgin males. Behav. Brain Res. 434, 114024 https://doi.org/10.1016/j.bbr.2022.114024.
Wright, E.C., Hostinar, C.E., Trainor, B.C., 2020. Anxious to see you: neuroendocrine mechanisms of social vigilance and anxiety during adolescence. Eur. J. Neurosci. 52, 2516–2529. https://doi.org/10.1111/ejn.14628.
Wright, E.C., Luo, P.X., Zakharenkov, H.C., Serna Godoy, A., Lake, A.A., Prince, Z.D., Sekar, S., Culkin, H.I., Ramirez, A.V., Dwyer, T., Kapoor, A., Corbett, C., Tian, L., Fox, A.S., Trainor, B.C., 2023. Sexual differentiation of neural mechanisms of stress sensitivity during puberty. Proc. Natl. Acad. Sci. U. S. A. 120, e2306475120.
Wu, Z., Yang, H., Colosi, P., 2010. Effect of genome size on AAV vector packaging. Mol. Ther. 18, 80–86. https://doi.org/10.1038/mt.2009.255.
Young, L.J., Wang, Z., 2004. The neurobiology of pair bonding. Nat. Neurosci. 7, 1048–1054. https://doi.org/10.1038/nn1327.
Zik, J.B., Roberts, D.L., 2015. The many faces of oxytocin: implications for psychiatry. Psychiatry Res. 226, 31–37. https://doi.org/10.1016/j.psychres.2014.11.048.