



# The social network: Neural control of sex differences in reproductive behaviors, motivation, and response to social isolation

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## Abstract

Social animal species present a vast repertoire of social interactions when encountering conspecifics. Reproduction-related behaviors, such as mating, parental care, and aggression, are some of the most rewarding types of social interactions and are also the most sexually dimorphic ones. This review focuses on rodent species and summarizes recent advances in neuroscience research that link sexually dimorphic reproductive behaviors to sexual dimorphism in their underlying neuronal circuits. Specifically, we present a few possible mechanisms governing sexually-dimorphic behaviors, by hypothalamic and reward-related brain regions. Sex differences in the neural response to social isolation in adulthood are also discussed, as well as future directions for comparative studies with naturally solitary species.

## Addresses

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## Introduction

Rodent species form various social organizations, ranging from solitary to dyads and families, to groups of tens or even hundreds of individuals. Living in a group bears many advantages that increase evolutionary fitness, such as mutual protection, assistance in resource acquisition, and more mating opportunities [1,2]. However, it also carries some costs, such as having to share valuable resources and the need to fight for one's social ranking [3]. Above all costs, social species endure life-threatening stress in the case of forced social isolation [4,5]. Despite the heavy costs, all social individuals show strong

motivation to seek for, approach, and physically interact with social stimuli [6], yet substantial sex-based differences in these behaviors have been reported [2,7–11].

Despite major efforts and recent advances in pinpointing the key neural mechanisms underlying social behaviors in rodent models, many open fundamental questions still remain. Particularly, we have limited understanding regarding the extent of sex differences in the mechanisms governing social behaviors: Are sexually dimorphic social behaviors controlled by dimorphic brain structures, circuits, or molecularly defined neuronal populations? Do specific social signals have a different incentive value for males and females, governing sex-specific behavioral responses?

In this review, we discuss the recent literature regarding behavioral sex differences in social displays and social reward in reproductive behaviors, specifically parental care mating, and aggression, focusing on rodents. We then present an emerging neural and molecular circuit logic underlying these sexually dimorphic social behaviors, which includes several hypothalamic and reward-related brain regions that are anatomically and functionally interconnected. This is followed by a discussion of the sexually dimorphic effects of social isolation in adulthood on social behaviors and their governing circuitries. Finally, we survey the fascinating diversity of social organizations in wild rodent species, which are barely used in neuroscience research but can provide unique and novel insights.

## Sex differences in social motivation and social displays

In social species, individuals prefer a social stimulus over a nonsocial one, indicating that an interaction with a conspecific is more rewarding; thus, it is termed *social reward* [12,13]. The most rewarding social behaviors are sexually dimorphic reproductive behaviors, such as mating, parental care, and aggression, which are presented in a sex-typical manner and are essential for species survival [14].

Sexual reward is considered highly salient, motivating all vertebrate species, including solitary ones, to seek sexual partners and pursue mating [8,15,16]. However,

evolutionary forces drive clear distinctions between males and females in their sexual motivation [8]. In most mammals, males are driven to inseminate as many females as possible, which is why their sexual motivation remains constantly high, while females must choose the best mate available, due to their enormous investment in breeding [8]. Indeed, studies that employed operant or classical conditioning paradigms have repeatedly shown that male rodents are highly rewarded by various sexual stimuli [17–21], while females usually require specific contexts and timing for sexual interactions to be rewarding [8,22–24].

As to parental care, in most mammalian species, it is considered a female-typical behavior, although it can also be executed by males [25,26]. Substantial sex differences, in terms of both quantity and quality, are found in all components of parental behavior (e.g. nest building, pup retrieval, licking, and grooming) [25,27,28]. In laboratory mice, for example, sexually naïve males often attack and kill unfamiliar pups [25,29], but cease attacking and become paternal for a short period after mating with a female [30–32]. In contrast, sexually naïve laboratory female mice show spontaneous parental care toward unfamiliar pups [33,34].

Mother–pup interactions are highly rewarding. For example, postpartum mice will exert efforts to cross a barrier in order to reach their pups [35]. Mother rats will compulsively lever press for pups [36], and such pup rewards were even more salient for postpartum females than an artificial drug reward [37,38] or natural rewards, such as food [39,40].

Aggression is usually considered a male-typical behavior in common laboratory mice, as males present robust aggression when competing over territory or potential breeding partners [8]. Laboratory females are usually aggressive toward unfamiliar individuals only during lactation, defending their offspring (i.e. maternal aggression) [41]. However, sexually naïve females of either wild or some outbred lab mouse strains can also present robust aggression while establishing their own territory and their social ranking in the group [42–44]. Nevertheless, females are less likely to engage in physical assault, and their attack patterns are less robust compared to males [45]. Also, the aggression of wild female rodents is claimed to be more influenced by environmental conditions, such as the sex composition of the group [46,47], and by their estrus phase [48,49].

For males, aggressive behavior can be as rewarding as sexual behavior [50–52] and may even show similarities to addictive behaviors [53]. Male mice will lever press for a subordinate intruder introduced into their cage to be attacked [53] and will prefer an aggression-associated chamber in a conditioned place preference paradigm

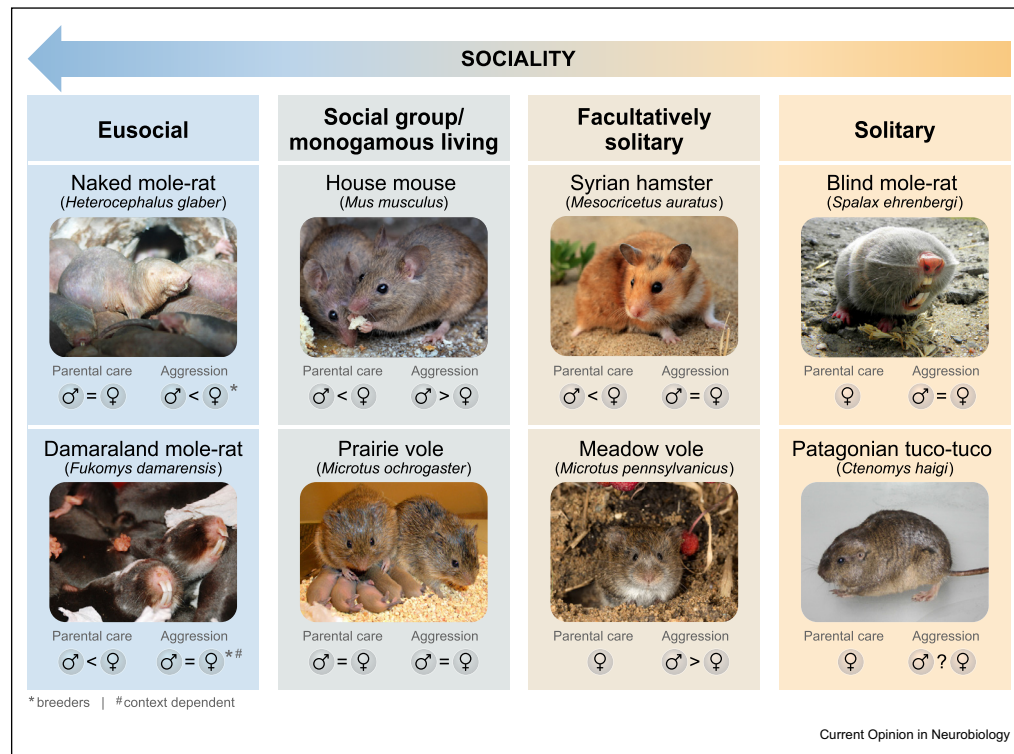
[54,55]. Male mice will also cross an electrified grid [56] and exert efforts [57,58] to reach and attack a subordinate. Whether aggression is also rewarding for females remains unresolved, since most domesticated female rodents typically do not present aggression outside the postpartum period [27,33,59–61]. Some insights might come from the Syrian hamster, where females showed a conditioned place preference for a chamber associated with aggressive encounters with males [62]. Interestingly, same-sex aggressive interactions were found to be rewarding in both sexes of the Syrian hamster [9,63,64] and prairie vole [65], though the rewarding value seems more robust in females than in males (see Figure 1).

These remarkable sex differences in reward and motivated social behaviors suggest an underlying sexual dimorphism in the neural circuits or neuromodulatory systems regulating them. Notably, it is known that both sexes might retain the capacity to express the behavioral repertoire typical of the opposite sex. For example, it was shown that female mice can present male-typical mounting and courtship [66,67] and that sexually naïve males can perform female-typical pup retrieval [32]. Thus, some of the neural circuits governing sexual dimorphism are shared between the sexes [67]. In the following sections, we will present the growing amount of data regarding cell-specific neuronal populations and their connecting neuronal network that govern sexually dimorphic reproductive behavior, and their crosstalk with the brain's reward system, focusing on mice and rats. Of important note, despite the abundant literature demonstrating quantitative and qualitative sex differences in behavior, our understandings of the neurobiology of many fundamental neuronal processes are interpreted from male-exclusive studies [59,68]. Moreover, as shown in Figure 1, nature provides a wide diversity of social and reproductive strategies even within the Rodentia order. Yet, modern neuroscientists have only recently accepted the importance of using ecologically relevant species in order to better understand the mechanisms underlying social behavior, in males and females.

### **Are dimorphic behaviors driven by dimorphic circuits? Neuronal circuits underlying sex differences in social reward and behaviors**

A few brain regions, most of them located within the hypothalamus, have been identified as critical nodes in the rodent social network and have also been shown to be sexually dimorphic. Within each dimorphic brain region, only specific, molecularly distinct subsets of neurons have been found to be sexually dimorphic and required for one or a few specific displays of social behavior [27]. These brain regions, including the anteroventral periventricular nucleus (AVPV), medial preoptic nucleus (MPOA), ventromedial hypothalamus

Figure 1



#### Diversity of social strategies within the Rodentia order: the uncharted territories of social neuroscience.

Within the Rodentia order, the social scale ranges from eusocial and social to solitary, even within the same subfamilies and between closely related species [42,219]. Interestingly, within these diverse social lifestyles, an additional layer of diversity exists with respect to sexual dimorphism in parental care and aggression [220]. Presented from top to bottom—eusocial rodents: naked mole-rat [219,221,222], Damaraland mole-rat (picture courtesy of Dr. Markus Zöttl) [223–225]; social group/monogamous living: house mouse [33,59,219], prairie vole (picture courtesy of Prof. Larry Young) [219,226,227]; facultatively solitary: Syrian hamster [228,229], meadow vole [219,226]; and solitary: blind mole-rat [197,199,203,230], Patagonian tuco-tuco (picture courtesy of Prof. Annaliese Beery) [231,232]. The symbols ♀ (female) and ♂ (male) denote sexual dimorphism or sex similarities for each behavior within a given species. (\*) In the eusocial naked mole-rat and Damaraland mole-rat, only the breeding indare aggressive.(#) In the Damaraland mole-rat, the level of aggression depends on the sex of the attacked individual. Toward other females, the breeding female is more aggressive compared to breeding males. In contrast, toward other males from outside the colony, the breeding males are more aggressive compared to the breeding females [225].

(VMH), bed nucleus of the stria terminalis (BNST), and medial amygdala (MeA), send and receive multiple projections from one another to form robust ‘social networks.’ These social networks communicate with brain reward regions and play an essential role in the regulation of most, if not all, sexually dimorphic reproductive behaviors [69,70].

To what extent are these anatomically interconnected dimorphic brain regions involved in the regulation of distinct sex-specific social behaviors? And, in case the functions of the social brains of adult males and females are partially bivalent, to what extent can we experimentally disrupt the circuit to drive behavior that is typically presented by the opposite sex? Recent technological advances in neuroscience now allow anatomical and functional mapping of these circuits, providing new insights into these fundamental questions, described below for each of the key regions involved in sexually dimorphic behavior.

#### The anteroventral periventricular nucleus

Sexually dimorphic brain regions are usually larger in males than in females [71,72]. For example, the sexually dimorphic nucleus of the preoptic area [73], the posterodorsal MeA [74], and the lateral septum [75], are all larger in males. A notable exception is the AVPV of the hypothalamus, which is larger in volume, contains more cells, and sends more projections to multiple reproduction-related brain regions in females compared to males [25,34,71,72,76–79]. Importantly, it also expresses several sexually dimorphic molecularly defined neuronal populations, including the tyrosine hydroxylase (TH)-expressing population, which contains 3–4 times more neurons in females than in males [34,72]. Examining the role of sexually dimorphic TH<sup>+</sup> AVPV neurons in mice reveals a sex-specific function: in females, these neurons regulate maternal behavior, and in males, they repress inter-male aggression [34]. Specifically, ablation of TH<sup>+</sup> AVPV neurons in females reduces maternal behavior and activation increases maternal

behavior, while in males, their ablation increases aggression, whereas optogenetic activation reduces aggression [34]. The activation of  $TH^+$  AVPV neurons also leads to increased oxytocin (OT) release from the paraventricular hypothalamic nucleus (PVN) in females but not in males, suggesting that this circuit governs maternal behavior through the regulation of neuropeptides [25,34]. Notably, although manipulation of  $TH^+$  AVPV neurons markedly altered sex-specific behaviors in both males and females, the behaviors displayed by manipulated animals of both sexes remained within the boundaries of their sex-typical behaviors (i.e. manipulations of  $TH^+$  AVPV could not induce parental care in sexually naïve males or aggression in sexually naïve females) (see Figure 2a).

### The medial preoptic nucleus

A large hypothalamic structure, the MPOA sends projections to multiple downstream brain regions and is both larger and contains more neurons in males than in females [35]. Notably, the MPOA is home to various heterogeneous, molecularly defined, neuronal clusters, including many sexually dimorphic populations, such as androgen receptor (AR)-expressing population and estrogen receptor alpha (ESR1)-expressing population [80]. The MPOA has been shown to be strongly activated by sex-typical social behaviors, functioning as one of the main brain regions that control parental care [35,81,82] and sexual behavior [81], in both sexes. Studies have found that MPOA lesions disrupt the onset of maternal behavior in both sexually naïve and postpartum females and alter sexual behavior in both sexes [83]. Most recently, *in-vivo* calcium imaging of the MPOA has revealed sharp increases in neuronal activity during sexual

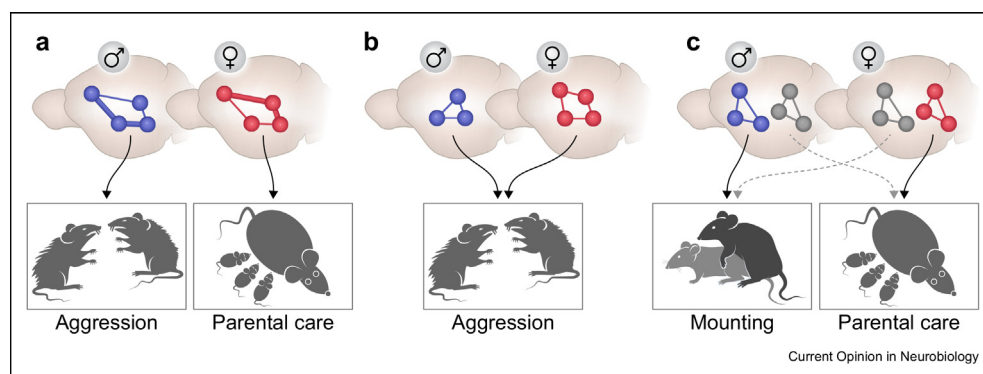
interactions as well as during social investigation of pups, in both sexes [84].

At least two different subpopulations within the MPOA were shown to be required for the regulation of pup-directed behavior. The first is the  $ESR1^+$  population, which is highly sexually dimorphic in its distribution and projection patterns [85]. Suppression of  $ESR1$  expression in the MPOA significantly reduced maternal behavior, but not maternal aggression, in female mice [86], whereas optogenetic activation of this population increased pup retrieval in females and in castrated males [84]. The second subpopulation is the galanin-expressing ( $Gal^+$ ) neurons, which showed increased activity during parental behavior in both female and male mice. Ablation of these cells reduced parental behavior in parenting females and males, whereas optogenetic activation suppressed pup-directed aggression in sexually naïve males and increased pup grooming in sexually naïve males and in fathers [32]. Notably, it was reported that both of these neuronal subpopulations are also involved in the regulation of sexual behavior in both sexes [83]. Taken together, it appears that multiple molecularly defined subpopulations within the MPOA, and their segregated neuronal circuits, control the same sex-typical social behaviors.

### The ventromedial hypothalamus

Over the past decade, the central role of the VMH, and specifically its ventrolateral part (VMHvl), in the initiation and execution of aggression has been well established in laboratory male mice [76,87–92]. In addition, it was shown that the activation of this region is necessary for promoting aggression seeking (i.e. reward) in male mice [89]. The role of VMHvl in female

Figure 2



### Alternative models for neural mechanisms underlying sexually dimorphic behaviors.

Sexually dimorphic reproductive behaviors might be governed by at least three principal sexually dimorphic mechanisms: (a) a sexually dimorphic neuronal circuit that controls different sex-typical social behaviors in males and females [34]. (b) The same social behavior in both sexes is controlled by different neural circuits in males and females [27,95]. (c) The neural circuit that drives a behavior typically displayed by the opposite sex is present in both sexes, but is tonically repressed by external and/or internal stimuli [66,67].



aggression has been scarcely studied, albeit it was recently shown that similar to males, female's VMHvl neurons are activated during aggressive behavior and that activation of ESR1<sup>+</sup> VMHvl neurons is sufficient to induce fighting behavior in sexually naïve females [93].

Another molecularly defined sexually dimorphic VMHvl subpopulation that controls sex-typical behaviors in both sexes is the progesterone receptor (PR)-expressing neurons. This subpopulation is required for the normal display of mating in both sexes and for fighting in males [76]. Ablation of PR<sup>+</sup> VMHvl neurons led to a profound decrease in female sexual receptivity and in male sexual behavior and aggression. Moreover, it was recently shown that projections of PR<sup>+</sup> VMHvl neurons into the AVPV nucleus change across the female mouse estrous cycle, with connectivity and function profoundly increasing during the estrus phase. This fluctuation in connectivity was found in adult females, but not in adult males, and was regulated by estrogen signaling in PR<sup>+</sup> VMHvl neurons [94]. These findings highlight, once more, the critical role of intrinsic sex differences in the brain in setting the distinct behavioral repertoire displayed by each sex, as detailed above for the AVPV. Furthermore, transcriptome analysis of VMHvl subpopulations provides evidence that different molecularly defined dimorphic populations in males and females may drive similar social behavior displays (i.e. fighting behaviors) [95] (Figure 2b).

### The bed nucleus of the stria terminalis

The BNST is a critical component in the social behavioral network, interfacing with brain regions that are essential for social decision-making and reproductive behaviors [96–98]. The BNST is anatomically and functionally connected to many brain regions shown to regulate sexually dimorphic behaviors [69,96,99].

Recently, it was shown that ablation of the sexually dimorphic male-biased AVP<sup>+</sup> BNST neuronal population reduces male–male social investigation and increases scent marking, but does not affect aggression or other sexual behaviors of male mice. In females, the same ablation altered sexual behavior alone [100] (Figure 2a).

Several experiments on California mice (*Peromyscus californicus*) have demonstrated the key role of the BNST in the control of sex-specific behavioral responses to social defeat stress (for a review, see Ref. [99]). For example, it was shown that social defeat decreases the number of social approaches and increases OT<sup>+</sup> BNST neuronal activity following social interaction, but only in females [101], while knockdown of OT in the BNST of females prevented the social-defeat-induced reduction in social approaches [102]. The role of OT<sup>+</sup> BNST neurons in males remains to be elucidated.

### The medial amygdala

The MeA is a nucleus within the amygdalar complex, which receives essential social information from the vomeronasal system and relays these pheromonal signals to the rest of the brain [70,103,104], thus playing a critical role in social behavior [105]. Electrophysiological recordings in anesthetized [106] and in awake behaving [107] mice have shown that MeA subpopulations respond differently to conspecific cues in males and females. Specifically, it was shown that the sex-specific response to social cues in the MeA of both males and females undergoes experience-dependent changes. Moreover, in sexually naïve mice, the number of neurons activated by female stimuli was higher in females compared to males [107].

Recently, a single-cell RNA sequencing analysis in mice identified a number of distinct neuronal subpopulations of GABAergic and glutamatergic MeA neurons, some of which displayed high levels of sexually dimorphic expression patterns [108]. Moreover, optogenetic activation of GABA<sup>+</sup> MeA neurons induced parental care in both males and females; however, high-intensity stimulation in males promoted pup-attack behavior [108] (Figure 2a). A separate important neuronal population identified in the MeA was found to express the androgen-catalyzing enzyme aromatase and to regulate aggression, but not other reproductive behaviors, in both sexes [60].

### The ventral tegmental area and the nucleus accumbens

Social reward is known to play a critical role in social interactions [13], by triggering the activation of the well-described dopaminergic reward pathway leading from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), in both males and females [109–111]. This classic reward pathway sends and receives multiple innervations from the brain's 'social network' [70,96,97,112–115].

In female mice, a prominent increase in the activity of the dopamine (DA) projections from the VTA to the NAc occurs during the initiation of approach/investigation of a novel female [110]. Moreover, optogenetic activation of this DA circuit promotes social interaction with a novel female but not with a novel object [110]. In males, these neuronal projections were shown to play a key role in precopulatory behaviors and in sexual motivation [116–118].

Recently, *in-vivo* microdialysis detected a robust transient increase in DA levels in the NAc of male mice as they conducted an olfactory investigation of a female and initiated sexual behavior, but not when they socially interacted with an unfamiliar male [109]. This DA surge was dependent on proper pheromone signaling via the

vomeroneasal system and was essential for olfactory sexual preference toward female stimuli and for sexual motivation [19,109]. Specifically, the administration of a D1R antagonist into the NAc blocked the development of place preference to a chamber previously associated with female pheromones and altered the olfactory preference to female chemosignals [109]. Similarly, optogenetic activation of NAc D1R cells in females sufficed to drive same-sex social interactions [110]. On the other hand, a sexual encounter with a male has been shown to increase DA in the NAc of female rats only in cases of paced mating [119].

Finally, a Gal<sup>+</sup> MPOA neuronal population was shown to send multiple inputs to several regions of the brain's reward system in mice [35]. These projections were shown in parental mice of both sexes, with specific activation of Gal<sup>+</sup> MPOA neuronal projections to the VTA increasing parental care in both mothers and fathers [35]. Similarly, activation of the adjacent ESR1<sup>+</sup> MPOA projections to the VTA increased maternal behavior in females [120].

### Sex differences in the response to social isolation

Social isolation induces severe stress in social species and might even be life-threatening [4,5,121–124]. In rodents, social isolation, during either adolescence or adulthood, was shown to dramatically disrupt behavior and brain function, in a sex-specific manner [125]. The effects of postweaning social isolation (i.e. adolescence), which are distinct from those of social isolation at adulthood [126,127], have been extensively reviewed [121,123,128] and will not be discussed here.

In adult mice and rats of both sexes, even a brief period of social isolation can cause an aversive, 'loneliness-like' brain state [129], prompting animals to seek social interactions [129–133] and elevating the salience of social reward [121,131]. Social isolation in rodents also leads to many negative behavioral effects in both sexes, including increased territoriality and aggression [123,133–140], elevated anxiety-related behaviors [141], and depression-like symptoms [141–144]. In socially monogamous adult prairie voles, for example, both sexes display depressive-like and anxiety-related behaviors when separated from their bonded partner of the opposite sex [142,145–149] (Figure 1).

Nevertheless, these effects seem to inflict females more than males [123,143,150–152]. For example, in female mice, individual housing appears to increase plasma corticosterone and anxiety levels in the elevated plus maze assay [153] and in a modified open-field test [150], compared to females living in group housing. In contrast, individually housed males were not affected, and their levels of anxiety and plasma corticosterone did

not differ from group-housed controls [150,154–156]. Socially isolated adult female mice also displayed increased immobility in the forced-swim and tail-suspension tests, indicating depression-like symptoms [157], while similar effects in males were induced only when isolation occurred throughout adolescence [158] or after prolonged isolation [127,144,159,160]. In prairie voles, a 4-week isolation period reduces sucrose preference and increases corticosterone secretion in females, but not in males [143,145].

Social isolation also produces sexually dimorphic responses when it comes to sexually dimorphic reproductive behaviors. The social isolation of lactating female mice and rats reduced the duration of maternal care [161,162], while the isolation of male mice actually induced paternal behaviors toward unfamiliar pups and, in line, reduced their typical infanticide response [163,164].

Despite these profound sex differences in the behavioral output of social isolation in adulthood, we know very little about the neural mechanism underlying this dimorphism. In adult rats, prolonged isolation reduced spine density and the expression of synaptic proteins in the prefrontal cortex (PFC) of both males and females; in females, however, these parameters were also robustly influenced by the estrus state, with elevations during proestrus [144]. Similarly, social isolation reduced the expression of myelin transcripts in the PFC of both male and female mice [165]. Conversely, prolonged isolation increased the total expression of brain-derived neurotrophic factor (BDNF) and cAMP response element-binding protein (CREB) in the cerebral cortex of female mice [166]. In the hippocampus, the social isolation of adult mice and rats led to reduced BDNF expression in both males [141,167–169] and females [167,170], and to increased neurogenesis in males [171] as well as females [172].

Notably, sex differences in the neural responses to social isolation were identified in the neuromodulator systems of OT and arginine vasopressin (AVP). In socially isolated male mice, OT plasma levels were elevated [155], with IP administration of OT abolishing isolation-induced aggression [134], while in isolated female rats, the baseline OT levels measured in the CSF were similar to those of group-housed controls [135]. In socially monogamous prairie voles, prolonged isolation reduced oxytocin receptor (OTR) expression in the hypothalamus of both sexes [173], but elevated plasma OT levels [143,173] and the number of activated OT<sup>+</sup> PVN cells [143], only in females. Moreover, chronic systemic administration of OT to isolated female prairie voles blocked some of the behavioral [174,175] and physiological [174–176] effects of isolation. An IP administration of AVP abolished isolation-induced aggression of male mice [134] and isolation-induced

cognitive impairments of male rats [130]. In female rats, isolation-induced aggression was associated with reduced levels of AVP receptor V1Ra in the lateral septum [135]. Notably, in the facultatively solitary Syrian hamster (see Figure 1), isolation reduced OTR levels in the dorsal raphe nucleus (DRN) and increased OTR levels in the anterior hypothalamus, but both effects were seen only in females [133]. The isolation also reduced the levels of the vasopressin V1a receptor in the BNST of both sexes, but in the DRN, V1Ra levels were reduced only in males [133].

Finally, a recent study on mice revealed a brain-wide signaling mechanism that mediates the effects of adult isolation on aggressive and anxiety-related behaviors [136]. The researchers noted a massive increase in the expression levels of the neuropeptide Tachykinin 2 (*Tac2*) throughout the brain of socially isolated mice of both sexes [136]. Further viral and pharmacological manipulations in males revealed that blocking *Tac2*'s increase in the dorsomedial hypothalamus abolished social isolation-induced aggression, while blocking *Tac2*'s increase in the central amygdala (CeA) abolished both acute and persistent stress responses [136]. Interestingly, manipulating *Tac2* in the CeA produced sex-opposite effects on fear learning in mice. While the administration of a *Tac2* antagonist, or chemogenetic inhibition, impaired fear memory in males, it enhanced fear memory consolidation in females, and both effects were mediated by sex hormones [177].

All in all, most of the studies involving the social isolation of adult rodents showed similarities in the effects on neural plasticity in both sexes. Thus, the robust sex differences in the behavioral responses to isolation might be attributed to sex differences in various neuropeptide systems, such as OT [125,178,179] and AVP [125,180], or perhaps to fluctuations in the stress response throughout the estrus cycle [181]. Further studies are needed to unveil the underlying molecularly defined populations within the above-described brain regions that contribute to sex-differences in the behavioral effects of social isolation in adulthood.

A special insight can be gained from observing the effects of social isolation on animal species maintaining a eusocial lifestyle. These species live in large communities, where typically only a few individuals bear offspring, while all the others share the burden of foraging food and caring for the young [42] (see Figure 1). In the eusocial naked mole-rat (*Heterocephalus glaber*) individuals removed from the colony displayed robust and stable increases of corticosterone levels for days and weeks [182,183] and increases in same-sex aggression among females [183]. Only two mammalian species are known to maintain a eusocial lifestyle, the naked mole-rat and its evolutionary relative, the Damaraland mole-rat (*Fukomys damarensis*) [42,184], and

in male and female breeders of both species the PVN is significantly larger [185,186]. Notably, in naked mole-rats, this effect is triggered by social isolation (i.e. removal from the colony) and not by breeding itself [187]. Also, in both species breeders of both sexes display lower levels of hippocampal neurogenesis compared to subordinates [188,189]. Although further research is needed in males and females of eusocial species, the available literature suggests an intriguing hypothesis: that their level of sexual dimorphism is substantially reduced compared to other social species, both for processing of social stimuli, as well as in the response to social isolation (see Figure 1).

## Conclusions and future research suggestions

The evidence that males and females are able to present most of the social behavioral repertoires typically presented by the opposite sex indicates that components in the underlying circuits driving sex-typical behaviors are shared between the sexes. The accumulating recent studies in the field indicate that within these shared neuronal components (social network), there are distinct molecularly defined neuronal populations that are anatomically and functionally dimorphic. These neuronal populations are those orchestrating the degree of and the manner by which specific sex-typical behaviors are displayed in each sex and each social condition.

Sexually dimorphic behaviors can be governed by at least three possible neural mechanisms (see Figure 2) [13,27,67]:

- (1) A sexually dimorphic neuronal circuit, which promotes a distinct sex-specific behavior in each sex (Figure 2a) [34].
- (2) The same social behavior expressed in both sexes could be controlled by different neural circuits in males and females (Figure 2b) [27,95].
- (3) A network that is present in both sexes, but either sex differences in the circuit or external stimuli allow the conveyance of synaptic inputs in a sex-specific manner (Figure 2c) [66,67].

Despite the accumulating recent studies laying out the mechanisms underlying sex-typical social behavior, it seems that most of them were performed exclusively in males. Thus, in many cases, it is impossible to draw a clear conclusion whether the same network underlies same or sex-specific social behavior, or whether a sexually dimorphic brain region contributes to sex differences in social behavior.

Moreover, classical neuroscience tools were built for and applied almost exclusively on laboratory (i.e. inbred and domesticated) mice, which present an altered, artificially selected social behavior repertoire, compared to

### Box 1. Social isolation by nature: a-social behavior in wild rodent species.

There are plenty of loners across the animal kingdom, including many mammalian species, ranging from primates to carnivores, to small rodents. The definition for *solitary living species* is that “the general activity, and particularly, the movements of different individuals about their habitat are not synchronized” [190], i.e. they usually live, sleep, and forage alone [191,192], with possible exceptions for mating and raising their young.

The solitary lifestyle is highly common in subterranean taxa [193,194]. Interestingly, even within some families of subterranean rodents, social strategies range from solitary to eusocial [42,193,195], providing a unique opportunity to perform comparative studies and investigate the neural and evolutionary substrates driving the transitions across the ‘social scale’ (see Figure 1).

Among these subterranean rodents, the blind mole-rat (BMR, *Spalax ehrenbergi*) exhibits one of the most solitary and aggressive life strategies, with relatively low levels of behavioral sex differences [196–201] (see Figure 1). Each individual excavates its own tunnel system to fit its body width and never leaves it unless forced to do so [196,201]. In the lab, introducing two adults of any sex (same sex or opposite sex) into the same cage will immediately lead to severe aggression, which will likely end in critical injuries and death [202]. Even prolonged exposure to non-direct social stimuli (pheromones or seismic signals) will induce severe chronic stress, leading to illness and, eventually, death [203].

During the rainy breeding season, it appears that the males socially communicate with potential females from a long distance and orient themselves to the female territory [204,205]. The males resume their solitary lifestyle immediately after successful copulation, while the females care for the pups alone [197,199,201,204]. Therefore, in order to ensure survival and reproductive success, BMRs must constantly be aware of the location and social status (e.g. sex, reproductive stage, and dominance) of their neighboring BMRs. Consequently, BMRs have developed a set of unique light-independent sensory modalities, perfectly adapted for social communication in their underground niche [206,207]. For example, for long-distance communication between conspecifics, BMRs use vibratory (seismic) signals produced by tapping their head against the roof of the tunnel [208,209].

Unfortunately, virtually nothing is known about the brain regions, neuronal circuits, and neuromodulators driving social reward and behaviors in solitary species. Many basic questions remain open, such as what are the neuronal and molecular processes that ‘guard’ solitary species from the harmful physiological damages of social isolation? What changes occur in their brain during the breeding period, when solitary individuals need to physically interact with conspecifics?

We believe that the BMR, as well as other a-social, solitary rodents, can provide a natural powerful model with which to study the adaptive neural principles governing social brain plasticity and social isolation stress. Moreover, solitary models can assist in studying sex differences in behavior and in the brain functions underlying social withdrawal and antisocial symptoms in psychiatric disorders (see Figure 1).

wild mice [59]. This is particularly evident in females, and specifically regarding reproductive behaviors such as aggression and prenatal care [25,33]. It remains to be determined whether the governing neuronal principles underlying sex-typical social behavior, discovered in inbred domesticated rodents, can also be applied to wild-derived rodents. It is repeatedly stated that scientists must expand the diversity of animal models beyond laboratory mice and rats, which are the subjects of more than 80% of current scientific research in animals [59,192,210–214]. The minority of neuroscience studies employing this approach have found unique phenotypes, alongside unique neural mechanisms underlying social behavior. For example, research on social ranking in the naked mole-rat showed higher oxytocin levels in subordinate individuals [215,216], while cross-species comparative analysis revealed a role for oxytocin in the monogamous behavior of prairie voles [217], and for vasopressin in parental behavior of deer-mice (*Peromyscus*) [218]. In summary, further research with various animal models, including highly social or solitary mammalian species (see Box 1 and Figure 1), as well as research on the neural effects of social isolation in both sexes, in a comparable manner, is needed [5]. This should provide a more comprehensive understanding of the mechanisms through which behavior alterations and neuropathologies like depression are induced by social isolation, as experienced worldwide during the COVID-19 pandemic, or by perceived social isolation (i.e. loneliness).

### Conflict of interest statement

Nothing declared.

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