



Review article

Stress in groups: Lessons from non-traditional rodent species and housing models

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ABSTRACT

A major feature of life in groups is that individuals experience social stressors of varying intensity and type. Social stress can have profound effects on health, social behavior, and ongoing relationships. Relationships can also buffer the experience of exogenous stressors. Social stress has most commonly been investigated in dyadic contexts in mice and rats that produce intense stress. Here we review findings from studies of diverse rodents and non-traditional group housing paradigms, focusing on laboratory studies of mice and rats housed in visible burrow systems, prairie and meadow voles, and mole-rats. We argue that the use of methods informed by the natural ecology of rodent species provides novel insights into the relationship between social stress, behavior and physiology. In particular, we describe how this ethologically inspired approach reveals how individuals vary in their experience of and response to social stress, and how ecological and social contexts impact the effects of stress. Social stress induces adaptive changes, as well as long-term disruptive effects on behavior and physiology.

1. Introduction

Interactions between organisms and their environments have the capacity to shape health, physiology, and behavior. For species that live in groups, the social environment is a prominent feature of daily life. Social interactions may be beneficial, accelerating recovery from exogenous stressors, act as stressors in their own right, and everything in between. The relationship between stress and social behavior in rodents has been explored in depth elsewhere (Beery and Kaufer, 2015; Sandi and Haller, 2015). The majority of studies focus on dyadic encounters, most commonly in mice and rats. In this review, we examine the role of stress and hypothalamic-pituitary-adrenal (HPA) axis regulation in social relationships in select group-living rodents and contexts. We use examples from our own expertise to illustrate the importance of housing paradigms and consideration of variation in natural social behaviors. Specifically we explore: studies of mice and rats housed in group settings in which social hierarchies form; research on vole species that form selective social relationships; and comparative studies of African mole-rats and naked mole-rats in particular.

We begin by discussing lessons from studying mice and rats in group-housed contexts (See Fig. 1). Mice (*Mus musculus*) and rats (*Rattus norvegicus*) are the dominant subjects in animal research—representing over 90 % of mammalian subject use (Beery and Zucker, 2011). Unsurprisingly, the majority of research on social stress has occurred in these two species, providing the greatest depth of information upon which to build. This work has predominantly utilized social defeat and resident-intruder paradigms where one animal is physically attacked by a more dominant conspecific, and has revealed profound effects of social stress on behavioral and physiological functioning (Ambrée et al., 2018; Finnell et al., 2017; Krishnan et al., 2007; Russo and Nestler, 2013). The ready availability of genetic tools validated in these species serves as an additional advantage to working with mice, and to a lesser extent rats. Studies of mice and rats in group housing—essentially variants of a visible burrow system (VBS; described in detail in Section 2.2)—provide an opportunity to study the effects of complex social interactions on stress in a dynamic and ethologically relevant context.

We next discuss research exploring links between stress, anxiety,

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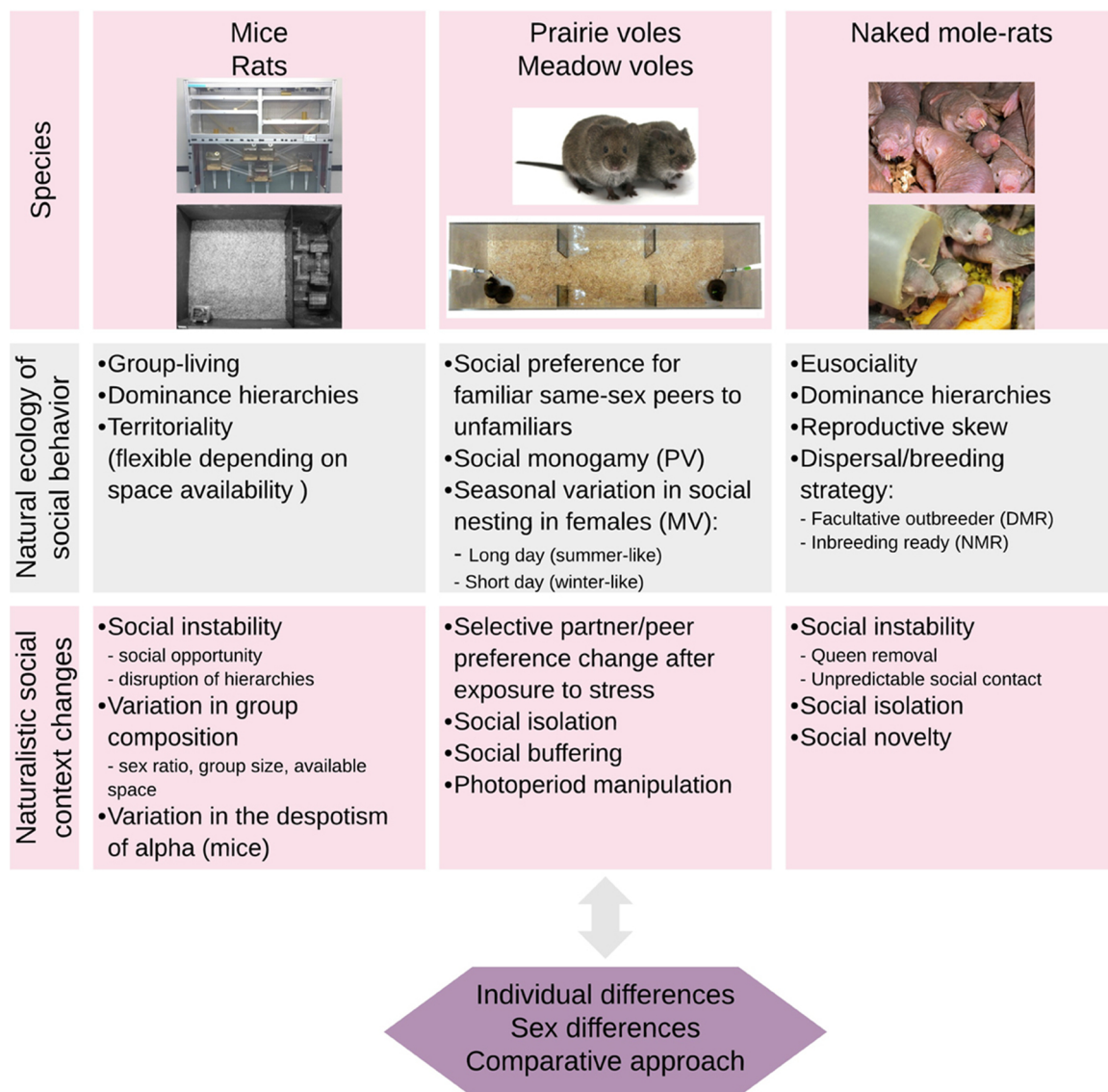


Fig. 1. Studying social stress in rodent species. Row 1: Representative photos of each species (or housing system) discussed in sections 2,3 & 4. Row 2: A summary of each species' social behavior in their natural ecology. Row 3: Example social context changes related to the natural ecology that induce social stress in the lab. Photo of the rat VBS courtesy of Caroline Blanchard.

and social relationships in voles. The social behavior of both prairie voles (*Microtus ochrogaster*) and meadow voles (*Microtus pennsylvanicus*) has been the focus of intense study in the field as well as the laboratory, adding important ecological context to laboratory findings (Taborsky et al., 2015). Decades of effort in multiple labs have gone into dissecting the molecular and neurobiological pathways underlying the formation of social bonds between mates in prairie voles (reviewed in Aragona and Wang, 2009; Carter and Keverne, 2009; Smith and Wang, 2018; Walum and Young, 2018). The effects of stress on social behavior have been documented in multiple domains, as well as the effects of manipulations of the social environment on measures of stress. Because prairie voles are unusual in forming selective attachments to mates, they provide an excellent model for exploring the role of these and other relationships in responding to stressors (Lieberwirth and Wang, 2016; Smith and Wang, 2018).

Around the same time monogamy was documented in prairie voles, seasonal changes in group living were identified in meadow voles (Madison, 1980; Madison et al., 1984). Meadow voles maintain exclusive territories in summer, but nest in social groups in the winter. Seasonal changes in social behavior are recapitulated with

manipulations of photoperiod that mimic summer and winter day-lengths in the lab. This species can thus be used to explore the factors underlying the transition from solitary to social, and how anxiety and stress relate to social relationship formation and maintenance (Beery, 2019).

In 1981, Jennifer Jarvis published the first description of mammalian eusociality, describing the unique colony structure and reproductive skew seen in naked mole-rats (*Heterocephalus glaber*). Since that time, naked mole-rats have been the source of increasing curiosity - both scientifically and societally. Yet arguably the most interesting thing about naked mole-rats is that they belong to a large family of mole-rat species (family Bathyergidae). These species of African mole-rats range across the entire spectrum of sociality from completely solitary to eusocial, providing a powerful opportunity to capitalize on an evolutionary experiment and study the relationship(s) between and mechanism(s) underlying psychosocial stress and sociality in rodents.

By focusing on these diverse examples within Rodentia, we hope to highlight the complexity of social behavior and its relationship with stress and HPA axis regulation. Stress is often described in simplified and dogmatic ways (e.g. stress is bad; social subordination is always

stressful), while here we show that context and species-specific ecological factors shape those relationships. Conversely, just as each of the examples presented highlights the importance of context in understanding behavior, there are common themes that appear to be shared across taxa. We highlight these findings and their implications throughout the text and in the concluding section. Finally, we emphasize the value of studying social organisms in housing paradigms that mimic natural environments, and of interpreting behavior in light of a species' ecology.

2. Stress and social behavior in mice and rats

Mice and rats have been used in laboratory behavioral research since the first decade of the 1900s (Beck et al., 2000; Suckow et al., 2019). Rats initially gained popularity due to their docility, ability to breed well in the laboratory, and robust cognitive, emotional, social and reproductive behaviors. Rats are also relatively large, meaning that physiological measurements and manipulations (e.g. blood collection, drug infusion) as well as neuroanatomical investigations were historically more straightforward than in mice. The use of mice for behavioral and stress studies increased tremendously in the late 1990s as this species is similarly easy to breed and keep in the laboratory but is also particularly amenable to molecular and genetic manipulations such as transgenic and gene knockout studies (Rosenthal and Brown, 2007). In the last decade, with the development of the newest generation of molecular and genetic methods that allow for ever more precise physiological and neurobiological manipulations (Ellenbroek and Yoon, 2016; Gerlai, 2016) there is an ever increasing interest in using both these species in behavioral and stress research.

Over most of this 120 years of laboratory research, the housing of laboratory mice and rats has become increasingly standardized with an emphasis on experimentally controlled conditions and minimal consideration for naturalistic behavior. For instance, most individuals are housed from weaning in small single-sex groups of 1–4 in small standard sized cages, in stark contrast to how wild animals live (Berdoy and Drickamer, 2007). However, although laboratory mice and rats have been undergoing a domestication process for approximately 1000 generations, there is strong evidence that key features of the social behavior of laboratory mice and rats are conserved (Adams and Boice, 1981; Berdoy and Drickamer, 2007; Boice, 1981). In the following sections we describe how housing mice and rats in enriched housing systems that mimic central elements of their natural habitat can provide unique insights into how social stress impacts behavior and physiology.

2.1. Natural ecology of mice and rats

The wild ancestors of laboratory mice and rats are highly social animals that live in a diverse array of habitats across the entire world (Berdoy and Drickamer, 2007). A key feature of the social systems of both species is their flexibility. When resources are sparsely distributed, rats live at low population densities with single males each occupying their own territory. As resources become more abundant, rats live in higher densities, males have reduced home ranges and there is greater male-male competition (Calhoun, 1962). Within social groups, rats sleep together in burrows in mixed-sex groups of usually up to 15 animals (Berdoy and Drickamer, 2007; Calhoun, 1963; Lore and Flannelly, 1977), but may live in large groups of up to 100 comprised of several conjoined burrow systems (Lore and Flannelly, 1977). Although aggression within rat social groups tends to be low, when more than one adult male is present, dominance hierarchies are formed and access to females is determined based on the outcome of aggressive encounters between males (Boice and Adams, 1983). These fights are most intense when groups are forming (Calhoun, 1962). Over time, levels of aggression decrease and hierarchies appear to be relatively stable across time even if individuals change in physical capabilities such as body weight or size (Berdoy et al., 1995; Boice, 1981; Calhoun, 1962; Smith

et al., 1994). Aggression between females is less well understood, but there is evidence that dominance ranks also emerge in group-housed females (Calhoun, 1963).

Similarly, wild house mice show remarkable variation in social and mating systems depending upon the distribution of resources. Most commonly, mice show male territoriality and a polygynous mating system; however, when resources are more distributed, promiscuity is reduced (Berdoy and Drickamer, 2007). Studies in the wild and in semi-natural environments reliably demonstrate that mice are extremely territorial and most male mice attempt to monopolize their own territories (Anderson, 1961; Butler, 1980; Crowcroft, 1966). Aggression can be suppressed when animals occur in high densities and individuals are forced to live in the territory of a more dominant individual (Crowcroft, 1966). However, even these animals will rapidly begin to exert territorial behavior when given more space or when space becomes compartmentalized (Crowcroft, 1966; Gray et al., 2000; Lloyd, 1975; Mackintosh, 1970). As with rats, male-male dominance dictates priority of access to resources (e.g. food, mates) as well as influencing male dispersal (Anderson and Hill, 1965; Crowcroft, 1955). However, mice are much more territorial than rats, showing much higher ongoing levels of inter-male aggression (Berdoy and Drickamer, 2007).

Aggression between female mice can also occur depending on the social context. Most commonly, females are aggressive towards unfamiliar individuals during pregnancy and lactation (Crowcroft and Rowe, 1963), but such aggression can also occur outside of this period. Female mice have also been shown to establish their own territories in wild populations (Butler, 1980; Chambers et al., 2000) and at higher population densities, aggression between females tends to increase (Chovnick et al., 1987; Yasukawa et al., 1985). Female-female aggression is reduced if individuals have prior social experience with each other (Palanza et al., 2005; Rusu and Krackow, 2004) and at low population densities (Weidt et al., 2018).

2.2. Group-housing paradigms to study social stress in mice and rats

Various paradigms have been developed to study social stress in mice and rats. The most intensively used are those that induce social defeat or subordination in subjects after being exposed either acutely or repeatedly to a more aggressive conspecific, usually in the conspecific animal's home-cage territory but sometimes in a neutral territory (Golden et al., 2011; Malatynska and Knapp, 2005). In these paradigms, the defeated animal experiences a loss of control over their social environment, ultimately leading to dramatic changes in behavioral (e.g. social withdrawal, anhedonia), physiological (e.g. impaired cardiovascular and immune functioning) and neurobiological (e.g. down-regulation of monoaminergic and neurotrophin activity) outcomes (Ambrée et al., 2018; Finnell et al., 2017; Krishnan et al., 2007; Russo and Nestler, 2013). The type and severity of these changes is dependent upon the frequency and intensity of the aggression received. Variations to these paradigms include those where animals are exposed to more aggressive individuals but not directly attacked (thus experiencing the psychosocial threat of attack), as well as situations where animals witness other animals undergoing social defeat. These methods also lead to several of the same phenotypic changes observed when animals directly experience physical attacks (Finnell et al., 2017; Sial et al., 2016). Although this work has primarily used male subjects, these paradigms have been adapted in mice and rats to enable female subjects to also undergo social defeat (Haller et al., 1999; Haney and Miczek, 1993; Iñiguez et al., 2018; Scholtens et al., 1990; Takahashi et al., 2017).

Though social defeat and resident-intruder paradigms are effective strategies for inducing physiological, neurobiological and behavioral changes in subjects, these paradigms are constrained by their limited ethological relevance. Though animals do experience social subordination in the wild, the aggressors experienced during lab-based social defeat are typically far more aggressive than would be expected

under natural conditions. Further, socially defeated animals have no possibility of escape and are unable to interact with other conspecifics – another dissimilarity to the natural context. It has been suggested that these dyadic defeat paradigms therefore are not representative of the more variable stress that is experienced by rats and mice in the wild (Tamashiro et al., 2005). These paradigms also do not consider the stress experienced by animals in other social situations such as when dominant individuals are trying to maintain their status and territory, as well as social stress related to forming and maintaining new social relationships.

In contrast to these dyadic social stress paradigms, the short and long-term behavioral and physiological consequences of living in groups has been studied in both mice and rats. In each of these paradigms, researchers have sought to create parallel features of group-living while enabling experimental manipulation. Typically, animals are housed in single or mixed-sex groups of 4 to up to 12 animals in complex enriched housing (Blanchard et al., 1995; Ely and Henry, 1978; Williamson et al., 2016b). Animals have far more space per unit area than animals housed in standard cages and are able to avoid continuous direct contact with cage mates. As a result of this increased space and number of social relationships, another common feature of these types of housing is that these relationships become more stratified, with not just dominant and subordinate animals emerging, but also sub-dominant. Animals can often also be further rank ordered into precise social ranks. We briefly describe some examples of these paradigms below.

The behavior of group-housed rats has been studied since the pioneering work of Hebb (1947) comparing the behavior of rats housed in groups of 10–12 in so-called “free environments” which consisted of a large cage (75 × 75 × 40 cm) filled with enrichment objects (e.g. wooden blocks, metal ladders and chains) to rats housed in standard or impoverished housing. Perhaps the most well-known group-housing paradigm is the visible burrow system (VBS), developed to study sociosexual behavior by Martha McClintock and Adler (1978) and further utilized to study social stress by Robert and Caroline Blanchard and Randall Sakai (Blanchard and Blanchard, 1989; McEwen et al., 2015). The standard VBS, comprised of a large open area connected to side chambers by tunnels, mimics the burrow system of wild rats. Typically, four male and two female rats are housed in this system. Within days, one male rat rapidly emerges as the dominant and remains so for as long as animals are housed (usually two weeks) (Blanchard and Blanchard, 1990). The dominant animal spends most of its time in the large open area of the VBS and by the tunnel openings, and will show aggressive behavior (biting, chasing, pinning) towards the other subordinate males who spend most of their time in the smaller chambers. Critically, it appears that the emergence of male social hierarchies within the VBS is dependent upon competition for access to females, as male only groups do not readily form social hierarchies (Blanchard et al., 1995).

Group housing environments like the VBS also allow for observation of mouse social dominance hierarchies in wild, outbred, and inbred mice, similar to those formed in the wild. When housed in pens with sufficient space, individual male mice establish territories that they patrol and defend from intruders (Crowcroft, 1966; Mackintosh, 1970). As in nature, when space becomes more limited, those mice that are unable to establish their own territory become subordinate, yielding to the more dominant mouse (Brown, 1953). Over time, the intensity of fighting reduces but dominant animals continue to patrol and scent-mark their territory and enforce their dominance through non-aggressive as well as aggressive social interactions (Drickamer, 2001; Mackintosh, 1970). In established groups, subordinates tend to avoid these alpha males by fleeing from or avoiding interacting with the dominant animal. Although one male is clearly the most territorial alpha individual in each VBS, mice other than the alpha male will also engage in aggressive behavior towards more subordinate individuals (Curley, 2016). This was first described by Ulrich who recognized that

laboratory mice do form social hierarchies when given sufficient space, and in many cases mice could be rank-ordered based on their relative aggression given and received (Ulrich, 1938). More recent studies of mice living in single-sex groups in larger VBS systems have shown that male mice will indeed form highly linear social hierarchies with each animal occupying its own social rank (Shemesh et al., 2013; Weissbrod et al., 2013; Williamson et al., 2016b, 2016a). In each group, the most alpha male directs aggression (biting, chasing, mounting) to all other animals and is never attacked. The second ranked animal directs aggression to all animals except the alpha to whom they are submissive, and so on. Linear hierarchies have also been found in female mice living in VBS (Williamson et al., 2019b), though much less work has been conducted thus far on group-housed female mice. It is notable however that in contrast to rats, both male and female mice are able to form dominance hierarchies in single sex housing suggesting that mice are competing over other resources than access to mates.

2.3. Stress responsivity in VBS housed mice and rats

Changes to the HPA axis regulation of stress responses have been extensively investigated in VBS male rats. Much less is currently known about the effects of group living on female physiology. Perhaps the strongest evidence for higher stress experienced by subordinate males is the increased mortality among subordinate rats even in the absence of wounding (Blanchard et al., 1985). Further, relative to dominants, subordinate males generally show elevated baseline corticosterone and adrenal hypertrophy coupled with reduced levels of corticotropin binding globulin (CBG) indicating higher levels of free corticosterone (Spencer et al., 1996), thymic atrophy and reduced body weights (McEwen et al., 2015; Tamashiro et al., 2005). These physiological outcomes are consistent with other chronic stress exposures such as chronic variable stress (CVS) (Herman and Tamashiro, 2017; McEwen et al., 2015). However, it should be noted that these differences are not found in all VBS studies, suggesting that social contexts between VBS colonies may vary and influence physiological outcomes (Buwalda et al., 2017; Dijkstra et al., 1992; Kozorovitskiy and Gould, 2004; McEwen et al., 2015). Further, differences in the central regulation of stress responses between dominants and subordinates are relatively small. Subordinates, but not dominants, show reduced levels of both glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) in the CA1 of the hippocampus compared to control non-VBS housed rats, but no differences in GR or MR binding are observed (Chao et al., 1993). Subordinates also have reduced glutamic acid decarboxylase 67 (GAD67) mRNA in the paraventricular nucleus (PVN) and the bed nucleus of the stria terminalis (BNST) but increased expression in the medial prefrontal cortex (mPFC) and hippocampus, suggesting that these animals are less able to inhibit the stress response (Erlander et al., 1991; Makinson et al., 2015). Dominant and subordinate animals do not differ in CRH and AVP mRNA expression in the PVN (Albeck et al., 1997). These findings suggest that the subordinate animals housed in VBS do experience chronic stress, but it is specific to the social context and is less severe than other forms of stress such as CVS. This phenomenon may reflect the differential impact of social stress compared to non-social forms of stress.

Fewer studies have explored the stress response and HPA regulation of VBS housed mice. Subordinate male mice living in mixed-sex VBS generally do have higher baseline corticosterone than dominant males and show a greater corticosterone increase in response to ACTH administration and immobilization stress (Ely and Henry, 1978). Subordinates also have reduced glucocorticoid receptor mRNA expression in the hippocampus (So et al., 2015) and higher adrenal weights than dominants in the VBS (Ely et al., 1975), but this is not consistently observed (Ely and Henry, 1978). Notably, in male mice housed in single sex triads in standard housing, subordinates do have adrenal hypertrophy and thymic atrophy compared to dominants, congruent with findings from VBS housing (Bartoš and Brain, 1993; Turney and

Harmsen, 1984). Subordinate males living in large single-sex groups have also been shown to have higher baseline corticosterone than dominant males but only in groups where alpha males are highly despotic (Williamson et al., 2017a). Further, there is little consistency in differences in plasma corticosterone between dominant and subordinate males when housed in smaller groups (Williamson et al., 2017a), indicating that social context is likely to be an important mediator between social stress and HPA axis regulation. The social stress of subordination may be higher in larger mouse groups where subordinate individuals receive more aggression from many more individuals of higher rank, and where there may be more instability in social structure. It is important to note that nearly all mouse VBS work has been carried out only in male subjects, and information regarding female social stress is limited. One study did find however that subordinate females living in large single-sex VBS groups do have significantly higher baseline corticosterone than dominant females, an effect that was even greater than observed in males (Williamson et al., 2019b). This suggests that the VBS may be an effective social stressor for female mice.

Another important source of variation in the outcomes of social stress in VBS is the background strain of rats or mice. Both rats and mice have been selectively bred in the laboratory since the early 1900s. This has led to hundreds of strains of rats and thousands of strains of mice. These inbred and outbred strains consequently differ significantly in underlying neural expression and distribution of genes, neurotransmitters and receptors that are relevant for social behavior and responses to social stress (Parmigiani et al., 1999). For instance, some mouse strains such as CD-1, Swiss and CBA/J show levels of male aggressive and territorial behavior that are similar to wild mice, whereas other strains such as C57bl/6 mice show reduced inter-male aggression and increased social tolerance (Ely and Henry, 1978; Lidster et al., 2019; Poole and Morgan, 1976; Williamson et al., 2016b). Consequently, C57bl/6 mice housed in either single-sex or mixed-sex VBS show relatively little aggression and have unclear dominant-subordinate relationships in direct contrast to group-housed CBA/J or CD1 mice (Arakawa et al., 2007; Bove et al., 2018; Ely and Henry, 1978; Pobbé et al., 2010; Williamson et al., 2016b). These differences in social organization between strains in group-housing may also explain why there are large reported differences in stress reactivity following group-housing in mice (Williamson et al., 2017a). Indeed, large strain differences in the metabolic, cardiovascular, immunological and behavioral response of male mice to social stressors such as social defeat are commonly reported (Kinsey et al., 2007; Lockwood and Turney, 1981; Razzoli et al., 2011). Much more work is needed to fully delineate the long-term effects of social stressors in the VBS on physiological and behavioral outcomes across a wider range of strains. Similarly, almost nothing is currently known about how social stress in the VBS differentially affects different strains of female mice, although this is to be expected given that strains of female mice do differ in both their aggression levels and responsiveness to standard stressors (Marchette et al., 2018; Miczek et al., 2001). Likewise, rat strains also differ in their baseline aggression levels as well as their responsiveness to social stressors (Berton et al., 1997; Pardon et al., 2002). To date, studies of rat VBS have largely focused on using the Long-Evans strain (McEwen et al., 2015) but notably strain differences in the effects of VBS housing on social stress have been observed. Rats of the Wildtype Groningen (WTG) strain also form hierarchies in the VBS, and subordinates show the characteristic loss of body weight and increased bite wounds during group housing (Buwalda et al., 2017). Despite this, dominant and subordinate WTG rats do not show any differences in HPA reactivity indicating the importance of considering strain differences. There is also evidence that the effects of social stress may be greater in wild rats than in laboratory rats. For instance, just one social defeat can lead to rapid death in rats even without signs of physical injury (Barnett, 1958a; Koolhaas et al., 1997). In sum, strain is an important consideration when interpreting the short and long-term effects of social

stress in the VBS.

The timing of measures of HPA function during group housing is an important consideration when evaluating effects on stress responsiveness. Both dominant and subordinate male mice living in VBS have higher plasma corticosterone levels than pair-housed animals, with levels rising up to two weeks after group housing (Ely and Henry, 1978; Williamson et al., 2017a), as well as heavier adrenals than individually housed mice (Benton et al., 1978). Similarly, dominant and subordinate VBS housed rats also show higher plasma corticosterone, adrenal hypertrophy, reduced CBG and thymic atrophy compared to standard housed males (Albeck et al., 1997; Blanchard et al., 1995; McKittrick et al., 1995; Spencer et al., 1996; Tamashiro et al., 2005). In both species, plasma corticosterone levels begin to decline after a few weeks corresponding with hierarchy stabilization and a reduction in the frequency of patrolling behavior by dominants, suggesting that differences in HPA axis activity are likely to be maximal when there are high periods of inter-male competition (Ely and Henry, 1978; McEwen et al., 2015; Williamson et al., 2017a). These data also suggest that ongoing long-term social interaction with multiple social partners may be stressful for all individuals not just subordinates, with the intensity of this stress decreasing over time.

Differential social stress experienced by dominant and subordinate animals in VBS also impacts other physiological systems. One of the most profound effects of living in the VBS for rats is that they lose 10–15 % of their body weight (Blanchard et al., 1995; Melhorn et al., 2010; Nguyen et al., 2007a; Tamashiro et al., 2007a, 2004). Both dominants and subordinates lose adipose tissue in the VBS and subordinates also lose lean body mass (Melhorn et al., 2010; Nguyen et al., 2007b; Tamashiro et al., 2007a, 2007b, 2004). Both dominants and subordinates show reduced food intake during initial VBS housing, with dominants returning to basal levels of intake rapidly while subordinates continue to have fewer and smaller bouts of food intake (Melhorn et al., 2010). Moreover, subordinates have lower levels of leptin and insulin than dominants in the VBS, becoming hyperinsulinemic and hyperleptinemic when taken out of the VBS and given regular food (Tamashiro et al., 2007b). This is suggestive of the social stress experienced by subordinates leading to them expressing a phenotype akin to metabolic syndrome.

There is strong evidence from social defeat, resident-intruder and other dyadic interactions paradigms that social stress can negatively impact immune function (Takahashi et al., 2018). In these paradigms, subordinates tend to have hyperactive and dysregulated immune responses and show slower wound healing than dominants. Less is known about the immune functioning of animals housed in VBS, although subordinate VBS rats do have higher spleen weights (Blanchard et al., 1995; Tamashiro et al., 2004) and fewer available splenic glucocorticoid receptors (Spencer et al., 1996) than dominants VBS rats suggesting that subordinates may have compromised immune systems. Colony-housed subordinate male rats also have reduced CD4 and CD8 T cell as well as B cell numbers in their plasma than pair-housed rats (Stefanski et al., 2001). Mice housed in groups of three to eight in large group housing also show higher spleen weights compared to standard housed animals, with the effect being most prominent in subordinates (Turney and Harmsen, 1984; Van Loo et al., 2001). These findings are suggestive that differential social stress experienced by dominant and subordinate animals living in VBS may lead to individual differences in immune functioning, but more work is needed to determine this possibility.

2.4. Individual differences in stress responsivity in groups

Unlike several stress paradigms that emphasize controlled exposures to known stressors (e.g. restraint stress, chronic variable stress, social defeat stress) (Herman and Tamashiro, 2017), clearly the social stress exposure from living in VBS is not equivalent for all individuals. Depending upon the social context (e.g. single sex versus mixed-sex

housing, number of individuals, hierarchy formation, stable versus unstable, despotic versus egalitarian individuals), different individuals are subjected to different social pressures. VBS provides an opportunity to understand how these contextual factors affect individual differences in response to stress. We have already described how the most dominant and most subordinate individuals show long-term changes in various aspects of their stress physiology; however, it is also possible to delineate further categories of animals by their social status in the VBS and examine their phenotypic plasticity.

In the rat VBS, subordinate males can be further subdivided into different subgroups. In each VBS, there is usually one subordinate that receives a disproportionately high number of attacks and wounds without being aggressive and is often referred to as the omega (Melhorn et al., 2017). These animals may even show complete social avoidance and become social outcasts (Koolhaas and Bohus, 1989). Omega males are also those who have the most dramatic body weight and lean mass reduction in the group (Melhorn et al., 2017). Dramatic changes to stress responsivity are also observed in the most subordinate males. Although they show no differences to other animals in stress response prior to hierarchy formation, following two weeks of VBS housing they display completely blunted stress responses including not showing any increase in corticosterone secretion in response to acute restraint stress (Albeck et al., 1997; Blanchard et al., 1993; McKittrick et al., 1995). Compared to other subordinates, these non-responding subordinates also have lower plasma CBG and insulin (McEwen et al., 2015; Spencer et al., 1996; Tamashiro et al., 2005) and greatly reduced CRF expression in the PVN (Albeck et al., 1997). This phenotype suggests that these subordinate rats experience chronically high levels of social stress, akin to mice who are repeatedly socially defeated and also exhibit hypocorticism (Reber et al., 2007).

Whereas the most subordinate animals undergo a complete loss of control, sub-dominant animals are tasked with having to maintain their social position above subordinates but are unable to exert control over dominant alpha individuals. Although all alpha males dominate colony life, the degree to which alphas do this varies with some being heavily despotic and others relatively more tolerant (Fokkema et al., 1995; Williamson et al., 2016b). These differences may underlie social rank effects on blood pressure. In VBS mice, the highest basal blood pressure levels is found in sub-dominants, followed by dominants and then by subordinates (Ely, 1981; Henry et al., 1986). Concomitantly, sub-dominants have activated sympathetic nervous systems compared to subordinates (Ely, 1981; Henry et al., 1986). In VBS rats, those individuals with the most elevated blood pressure are those subordinates engaged in the most aggressive behavior attempting to rise up the social hierarchy (Fokkema et al., 1995; Koolhaas and Bohus, 1989). Taken together, these data suggest that individuals of different social ranks do experience different forms of social stress at different times during colony housing, with differential consequences for their behavior and stress physiology. Further, although these findings from rats and mice indicate important differences in social stress exposures between ranks, these effects are likely to be species-specific and related to the types of hierarchy that form in each species (e.g. see Section 4.2 for mole-rats). For instance, in primates low social rank appears to be associated with increased stress responsivity only in species where subordinates experience high rates of aggression and low social support (Abbott et al., 2003).

2.5. Adaptive responses to social living in VBS

As hierarchies form, dominant, sub-dominant and subordinate animals all experience increases in social stress and undergo dramatic phenotypic changes. It is important to consider whether the behavioral and physiological changes observed in the VBS are adaptive or maladaptive. Not all changes observed are likely to be the result of chronic social stress, but rather are plastic changes induced by mild stress that shape an individual's phenotype to more appropriately adapt to its

current social context. For example, in the mouse VBS, dominant alpha males not only increase their aggressive and patrolling behavior (Williamson et al., 2016b), but also increase their eating and drinking frequency (Lee et al., 2018) to keep up with the energetic demands of producing and urinating major urinary proteins that are used to scent mark their territory (Lee et al., 2017). Conversely, subordinate mice inhibit their urination as has been previously shown for subordinate mice undergoing social defeat or other dyadic social stressors (Hou et al., 2016; Wood et al., 2009). VBS alpha male mice also show dysregulated circadian rhythmicity, with increased feeding and reduced quiescence during the light phase of the light cycle (Lee et al., 2018). Dominants exhibit increased sleep fragmentation and reduced REM sleep during the light phase but increased REM sleep during the dark phase (Karamihalev et al., 2019). Similarly, rats in the VBS also alter their feeding rhythmicity in stable hierarchies, with subordinates eating fewer meals compared to dominants as well as shifting the timing and location of their meals (Melhorn et al., 2010).

Changes in neural plasticity in VBS rats may also represent stress-induced adaptive responses to group living. Both dominant and subordinate rats show changes in neuronal morphology in hippocampal CA3 pyramidal neurons when housed in the VBS compared to controls (McKittrick et al., 2000). VBS animals show decreases in dendritic branching and dendritic length with these changes being most pronounced in dominants. Further, dominant male rats living in single-sex VBS have increased levels of new neurons in the dentate gyrus compared to subordinate males, although the levels of social stress experienced in single-sex rat VBS are likely much lower than those experienced in mixed-sex VBS (Kozorovitskiy and Gould, 2004). Dominant male mice living in VBS have reduced hippocampal expression of DNA (cytosine-5)-methyltransferases (Williamson et al., 2016a). These enzymes promote DNA methylation, suggesting that more dominant animals have generally increased hippocampal gene expression while more subordinate animals have a social suppression of gene expression. There are also several other differences in central gene expression of hormones and neurotransmitters and their receptors between dominant and subordinate rats and mice of both sexes which may be related to plastic changes in other social, emotional or cognitive behaviors (Albeck et al., 1997; McEwen et al., 2015; So et al., 2015; Williamson et al., 2017b).

The fundamental feature of social hierarchies is that more dominant animals have priority access to resources such as territory, food and mates. Although there is not a complete reproductive suppression of subordinates in either mice or rats as is seen in the social hierarchies of other species (Creel, 2001; but also see naked mole-rats described in Section 4.1), dominant male mice and rats do have higher mating success (Berdoy and Drickamer, 2007). There is some evidence that these differences may be due in part to differential regulation of the HPG axis. Subordinate VBS males typically have lower plasma testosterone, smaller testes weights and reduced preputial glands (an androgen-dependent pheromone secreting organ required for scent-marking) than dominant males (Dijkstra et al., 1992; Hardy et al., 2002; Nguyen et al., 2007b; Tamashiro et al., 2004). Subordinate rats also have reduced 11 β HSD protein levels and activity meaning that their Leydig cells are less protected from glucocorticoids and potentially less responsive to luteinizing hormone (Hardy et al., 2002; Monder et al., 1994). Testosterone levels are also reduced in more subordinate VBS males, with these differences being maximal when there is hierarchy disruption as these rank differences are not consistently observed in established stable hierarchies (Ely, 1981; Machida et al., 1981; Van Loo et al., 2001; Williamson et al., 2017b, 2017a). In mice housed in small groups there is also evidence that dominant animals have increased testes weights (Bronson and Eleftheriou, 1964; McKinney and Desjardins, 1973), sperm motility (Koyama and Kamimura, 2003, 1998), and preputial glands sizes (Brain et al., 1983; Bronson, 1973; Bronson and Marsden, 1973) indicating up-regulated HPG activity in dominant animals. Taken together, it is clear that dominant and

subordinate animals do shift their reproductive physiology in response to their differential social experiences, but the extent to which these changes are dependent or independent upon ongoing stress exposure in the VBS remains to be more fully determined.

2.6. Social context and social stress in the VBS

Mice and rats living in the wild likely experience fluctuation in social stress depending upon various social and ecological factors. For example, although hierarchies tend to be stable in the wild, they can become destabilized through aging, loss of individuals due to death or predation, or by group composition changes (Barnett, 1958b; Crowcroft, 1966). An advantage of employing the VBS approach in the laboratory is that ethologically relevant social stressors that mirror these situations can be experimentally induced and controlled.

It is already clear that social stress is not consistent across time in VBS with it being highest during initial group formation and declining as hierarchies stabilize, but even formed hierarchies vary in the degree of social stress. Some hierarchies contain exceptionally despotic alpha individuals, as described above, that control the behavior of all other individuals in the group (Blanchard and Blanchard, 1990; Curley, 2016), whereas other hierarchies have ongoing fluctuations in social ranks (Williamson et al., 2016b). It remains to be determined how this natural variation is related to stress physiology and other phenotypic outcomes. However, it is possible to experimentally induce social instability in an ethologically relevant manner into social hierarchies in the VBS.

One way this can be achieved is by varying the initial group composition of animals. Individuals and strains vary in their baseline levels of aggression and social behaviors, which can have long-term consequences for group level behavior (Buwalda et al., 2017; Davis et al., 2009; Ely and Henry, 1978; McEwen et al., 2015). In rat VBS, manipulating the number or ratio of males to females leads to different phenotypic outcomes. Subordinate males in 2 males:4 females groups receive higher levels of aggression even from females and show significantly exaggerated stress phenotypes than subordinate males in 4 males:2 females groups (Tamashiro et al., 2004).

In mice, removing the most dominant alpha male from a group leads to increased aggression in all group members within minutes, with the beta male displaying the highest levels and eventually taking over as the alpha male (Williamson et al., 2017b). This mirrors observations in nature that sub-dominant males are primed to form their own territory and capitalize on such social opportunities (Berdoy and Drickamer, 2007; Crowcroft, 1966). This form of social instability is associated with increases in central gene expression and neuronal activity (Williamson et al., 2019a, 2017b), suggesting it could be a useful ethologically valid paradigm for studying the effects of acute social stress.

Switching animals between VBS hierarchies mimics the behavioral disruption that occurs in nature as animals move between social groups and is potentially a more dramatic social stressor. Rat VBS colonies that had males transferred between them only once a month showed increased aggression and an increase in hypertension compared to stable colonies (Henry et al., 1993). Further, males of all ranks living in single-sex rat VBS that have dominant males switched between groups show reduced numbers of new neurons in the hippocampus and social inhibition compared to males from stable hierarchies (Opendak et al., 2016). There is also evidence that social instability may be an even more profound stressor than status in females compared to male (Haller et al., 1999). Little is known regarding the effects of social instability induced by disrupting the hierarchy in mice VBS. However, disrupting groups of four male or four female mice in standard cages twice a week for seven weeks is chronically stressful, as evidenced by increased corticosterone levels and adrenal weights and reduced thymus weight and hippocampal corticosteroid receptors in these animals compared to non-disrupted controls (Schmidt et al., 2010, 2007; Sterlemann et al.,

2008). These findings suggest that social instability induction in rat and mice VBS are robust and valid paradigms for studying social stress.

2.7. Conclusions and future directions

Housing mice and rats in VBS provides an ethologically relevant housing system for studying the short and long-term effects of social stress on behavior and physiology. Although the social stress experienced by animals in the VBS is not as easily controlled nor as intense as stress in other paradigms, there are clear advantages to the VBS paradigm. The VBS is an excellent paradigm for investigating individual differences in stress response related to naturalistic stressors that are in the species typical range given each species' natural ecology. All individuals experience high social stress as groups form, but as distinct social ranks emerge, dominant, sub-dominant, and subordinate animals all have different behavioral priorities. Dominants aim to monopolize resources and defend their territories from intruders, sub-dominants aim to maintain their social status whilst being ready to take over as alpha male should the opportunity arise, and subordinates aim to avoid being continuously attacked by more dominant individuals. If hierarchies remain stable, so do the social statuses and behavior of individuals, but if the composition of hierarchies changes, then individuals of different statuses must respond rapidly and appropriately. Changes in stress responsivity, metabolism, cardiovascular and immunological function are commonly related to individual differences in rank and behavior in both mice and rats.

It still remains to be precisely determined which of these changes are maladaptive dysfunctions induced by chronic stress exposure, or plastic changes that are perhaps induced by acute stress exposure and benefit individuals to adapt to their current social status in the short-term (Kozorovitskiy and Gould, 2004; McEwen et al., 2015). Further, the vast majority of research in the VBS has focused on stress responsivity and metabolic phenotypes, and much more research is needed to more fully understand the nature of those immunological, cardiovascular, and neural outcomes that are impacted by VBS social stress. However, with the advent of video capture methods capable of tracking multiple animals in large arenas, as well as minimally invasive wireless methods for the long-term capture of physiological data, it is likely that there will be increased interest in these questions (Peleh et al., 2019; Plank et al., 2016; Redfern et al., 2017). Another area of research that is relatively little understood is how social stress impacts the formation of social hierarchies in the VBS, although studies in dyads suggest that stress may actually facilitate dominance-subordinate status in rat dyads (Cordero and Sandi, 2007; Timmer et al., 2011; see also Section 3.3 in voles). Finally, both males and females living in large social groups form social hierarchies (Calhoun, 1963; Williamson et al., 2019b), yet nearly all research in VBS mice and rats has focused on male subjects. There needs to be a greatly increased focus on the social stressors experienced by females during group living and how this impacts their behavioral and physiological development, as well as how both male and female mice are affected by social stressors in mixed-sex versus single-sex VBS housing.

3. Stress and social behavior in voles

In North America, voles of the genus *Microtus* have been studied for fluctuations in population density for nearly a century. As researchers examined the factors that might influence population size, they discovered interesting and varied social behaviors between and among species, from seasonal variation in social nesting in meadow voles and taiga voles to the occurrence of social monogamy in prairie voles (Getz et al., 1981; Madison, 1980; Wolff and Lidicker, 1980). Field studies of social behavior are ongoing (e.g., Edwards et al., 2019; Ophir et al., 2008b; Sabol et al., 2018; Solomon et al., 2009). Prairie voles have primarily become popular subjects of social neuroscience research in the laboratory, because they are one of only a small fraction of rodent

species to exhibit reproductive pair-bonds. Studies of additional monogamous vole species (e.g. pine voles and Taiwan voles), as well as contrasts to promiscuous species, have contributed to our understanding of how monogamy is supported within a taxon (Fink et al., 2006; Gersten, 2008; Young, 1999).

Meadow voles have become important for understanding the mechanisms underlying group living (a.k.a. sociality), and how these compare to mechanisms involved in mate partnerships. While meadow and prairie voles have been contrasted with each other on the basis of mating system, they both share an unusual trait in exhibiting social preferences for familiar vs. unfamiliar “peers” (shorthand for same-sex age-matched conspecifics) (DeVries et al., 1997; Lee et al., 2019; Parker et al., 2001; Parker and Lee, 2003)—a behavior not typically shared by mice, rats, degus, or other social rodents tested to date (Beery et al., 2018; Schweinfurth et al., 2017). The presence of selective preferences for known peers and mates in voles provides an opportunity to better understand the role of familiarity and relationship type in the context of stress. For example, how does isolation from a bonded mate differ from isolation from a familiar peer? Following stress, does consolation behavior by a cage-mate differ by familiarity and sex? How does the experience of a stressor alter the formation of new social preferences for mates or peers? To contextualize such questions, it is helpful to first consider the ecology and behavior of these vole species in the wild in greater detail.

3.1. *Prairie vole behavior: from field to lab*

Prairie voles are native to grassland prairies across the Midwestern United States and into Canada (Stalling, 1990). This species has been of interest to behavioral neuroscientists since the discovery that in the wild, prairie voles often form long-term associations with mates (Getz et al., 1981)(Getz et al., 1981). In these “socially monogamous” relationships, females and males form long-term stable pair-bonds, and both sires and dams exhibit parental care, although extra-pair copulations do occur (hence not genetic monogamy) (Getz et al., 1981; Ophir et al., 2008a). Across and within populations, males exhibit a range of mating tactics, with a majority of socially monogamous “residents” as well as a smaller but significant proportion of non-pair-bonded “wanderers” (Getz et al., 1993; McGuire and Getz, 2010; Ophir et al., 2008b). Prairie voles exhibit greater polygyny in some habitats, such as more xeric regions of Kansas (Fitch, 1957), and these voles exhibit reduced paternal care when brought into the laboratory (Roberts et al., 1998). Variation of behavior with local ecology has also been demonstrated in other studies (Mabry et al., 2011).

The propensity to display social monogamy is recapitulated in the laboratory, as prairie voles form selective, enduring preferences for their opposite sex cage-mates over strangers in extended tests of social choice known as partner preference tests (Williams et al., 1992; Fig. 1). In this test, a focal vole is paired with a potential mate for a period of time that is either sufficient (e.g. 24 h) or insufficient (e.g. 6 h) for bond formation under normal conditions. Following cohabitation, voles are tested for social preferences in a three-chambered apparatus in which both their partner and a sex-matched stranger vole are tethered at opposite ends; the test is recorded for three hours to allow for stable differences in resting social behavior (huddling) to appear (Williams et al., 1992; Winslow et al., 1993). This test has been used to explore the effects of myriad brain-region-specific manipulations of neuropeptides and neurotransmitters on the formation of social bonds.

3.2. *Meadow vole behavior: from field to lab*

Meadow voles are a closely related species that is sometimes sympatric with prairie voles, but their range extends into more Eastern grasslands, throughout Canada and into Alaska (Reich, 1981). Meadow voles have often been used as a contrast to prairie voles in comparative studies because they exhibit a promiscuous mating system (Boonstra

et al., 1993; Getz, 1972). However, meadow voles are not asocial as sometimes described; they exhibit pronounced and well-described seasonal variation in sociality (reviewed in Beery, 2019). In summer months, female meadow voles are highly territorial and maintain home-ranges that do not overlap with other females, while male territories encompass those of multiple females (Edwards et al., 2019; Madison and McShea, 1987). In winter months, these territories collapse and voles begin to live and sleep in mixed-sex groups of 3–10 individuals (Madison and McShea, 1987). Field tests of social interactions reveal that meadow voles of both sexes are tolerant of both nest-mates and strangers in winter months, but by spring, gonadal development coincides with an increase in aggression towards strangers (McShea, 1990). Spring social groups may remain together through the first matings of the season, but they are closed to the immigration of new members (Madison and McShea, 1987; McShea, 1990). Because life in social groups is typically based on relationships between peers, winter sociality in meadow voles provides a useful opportunity to examine the role of stress and anxiety in seasonal transitions in group structure.

The transition from social to solitary is principally mediated by photoperiod, and manipulations of photoperiod mimic the effects of season in the field, from olfactory preferences to huddling behavior and tolerance of unfamiliar individuals (Beery et al., 2008; Ferkin and Kile, 1996; Ferkin and Zucker, 1991; Lee et al., 2019; Ondrasek et al., 2015). Voles housed in short, winter-like day lengths (short days) show strong preferences for huddling with conspecifics (Beery et al., 2009; Beery and Zucker, 2011; Parker and Lee, 2003), and can be used to probe the neurobiological pathways underlying social tolerance and life in groups (Anacker and Beery, 2013; Beery, 2019). These changes in social and aggressive behavior are most pronounced in females, both in the field and in the laboratory (Beery et al., 2009; Boonstra et al., 1993).

3.3. *Effects of stress on relationship formation*

The existence of familiarity preferences in voles allows for studies of how stress impacts the formation of specific relationships. In prairie voles, stress and HPA axis manipulations alter the propensity of forming a social preference for a potential mate. In females, stressful experience (a brief swim) prevented the formation of partner preference for the familiar male under conditions normally sufficient to produce a preference, but not in adrenalectomized voles (DeVries et al., 1996). Exogenous corticosterone was also capable of impairing pair-bond formation (DeVries et al., 1995), suggesting that corticosterone may mediate the effect of stress on social bonds. Interestingly, circulating corticosterone levels are naturally low immediately following co-housing with a new male, and partner preference formation occurs before they return to baseline (DeVries et al., 1995).

Similar effects of stress have been found in same-sex peer relationship formation in female meadow voles (housed in the short day lengths that promote group-living). A stressful experience (brief swim) significantly elevated corticosterone concentrations for 3 h, and this stressor impaired the formation of a partner preference for a peer introduced immediately following the stressor. This effect was specific to the formation of relationships, as stress exposure did not impair expression of partner preferences by females in long-term cohoused pairs (Anacker et al., 2016). Thus, same-sex preferences in female meadow voles were altered in a similar manner to opposite-sex preferences in female prairie voles. Prairie voles also form same-sex preferences for peers (Beery et al., 2018; DeVries et al., 1997; Lee et al., 2019), but the role of stress in familiar peer preferences in this species has not yet been determined.

While it is tempting to conclude that stress impairs affiliation across vole species and relationship types, opposite effects of stress on social bonding were found in male prairie voles. Males typically take longer than 6 h to form a partner preference for a female, but males who underwent a brief swim prior to pairing formed significant preferences after only 6 h (DeVries et al., 1996). The formation of partner

preferences in males was facilitated by corticosterone administration, and was impaired by adrenalectomy (Blondel and Phelps, 2016; DeVries et al., 1996). Some doses of central CRF administration also facilitated partner preference formation in males (DeVries et al., 2002).

Prairie voles thus provide a model for both stress facilitation of social bond formation, and impairment of affiliation, depending on sex. These differences in stress effects on social behavior provide an example of latent sex differences – when behavior (e.g. partner preferences) are outwardly similar, but are mediated by different mechanisms or are differently regulated by experience (Becker and Chartoff, 2019). Such differences underscore the importance of studying males and females (Beery, 2018; Beltz et al., 2019; Zucker and Beery, 2010).

3.4. Social isolation as a stressor

Social isolation is a well-described stressor in numerous rodent species (reviewed in Fone and Porkess, 2008; Mumtaz et al., 2018). Prairie voles show many isolation-related dysfunctions that highlight the importance of social relationships for this species as well. Extended social isolation from weaning in prairie voles has been associated with higher circulating corticosterone, and greater CRF immunoreactivity in the paraventricular nucleus (PVN) of the hypothalamus (Ruscio et al., 2007). In instances where separation occurs in previously paired animals, prairie voles can be used to study the effects of peer loss, mate loss, and their differences (although to date most studies have studied these separately).

In prairie voles reared with a same-sex sibling, extended (2 week to 2 month) separation from their cage-mate in adulthood has been associated with changes in neuroendocrine signaling, including increased plasma levels of corticosterone, ACTH, and oxytocin, altered expression of the immediate early gene c-Fos, and heightened activity of hypothalamic oxytocin neurons after a resident-intruder test (Grippe et al., 2007; Stowe et al., 2005). These changes co-occur with behavioral changes including altered exploratory behavior in the elevated plus maze, decreased sucrose preference (a measure of anhedonia), and increased immobility in the forced swim test (used as a measure of depressive behavior) (Grippe et al., 2008, 2007; Stowe et al., 2005). Separation from a sibling cage-mate has also been associated with higher heart rate, as in mice (Grippe et al., 2007; Späni et al., 2003), as well as changes in cardiac function associated with cardiovascular disease (Grippe et al., 2011; Peuler et al., 2012). This is also similar to findings in humans, for whom social support reduces heart rate and alters blood pressure following stressful tasks (Lepore et al., 1993; Thorsteinsson et al., 1998). Some of the physiological and behavioral sequelae of separation in prairie voles were prevented or reduced by oxytocin administration and environmental enrichment (Grippe et al., 2014, 2009), similar to findings in rats (Hellemans et al., 2004).

In prairie voles that have been paired with an opposite-sex mate, mate loss also leads to a host of endocrine, autonomic, and behavioral consequences. In both sexes, < 1 week separation from a mate led to increased corticosterone and ACTH secretion, as well as increased depressive behavior (Bosch et al., 2009; McNeal et al., 2014). Examination of the effects of separation on heart rate in males revealed that isolation from a mate led to increases in heart rate, including during the forced swim test (McNeal et al., 2014).

The effects of mate- and peer-separation in prairie voles thus seem overtly similar, although changes in heart rate occurred more rapidly in males experiencing mate loss than peer loss (after 5 days vs. 2–4 weeks of separation), suggesting there may also be some differences (Grippe et al., 2007; McNeal et al., 2014). In the one study that directly compared peer and mate loss, brief separation from a mate but not a same-sex sibling resulted in increased circulating corticosterone, increased adrenal weight, and depressive-like behavior (Bosch et al., 2009). Differences in either the time-line or degree of dysfunction following separation from mates versus peers are therefore likely.

The effects of social isolation are less well understood in meadow voles. One study in long-day-housed male meadow voles found no effect of 24 h or 2 week social isolation on corticosterone or behavior in the elevated plus maze, but meadow voles separated for 24 h from a sibling cage-mate had increased Fos protein in several brain regions relative to controls (Stowe et al., 2005). More information is needed on the effects of social isolation in meadow voles, particularly comparing short- and long-day housing paradigms.

3.5. Social buffering of the stress response

Whenever isolation acts as a stressor, the converse is that social cohabitation can lead to improved outcomes in the face of stress, or social buffering of the stress response. Studies across a wide variety of mammals show profound effects of cohabitation on the recovery from stressors (Beery and Kaufer, 2015). As might be expected, these effects are pronounced in species that naturally cohabit with adult conspecifics in the wild. For example, social facilitation of wound healing by pair-housing occurs in socially monogamous but not in solitary *Peromyscus* species (Glasper and DeVries, 2005). Prairie voles have provided insight into multiple aspects of social buffering, again allowing for distinctions between familiar and unfamiliar conspecifics, as well as reproductive partners vs. familiar social peers.

The presence of a mated partner may provide social buffering from a stressor. In the first study to demonstrate this, female prairie voles were subjected to immobilization stress for 1 h, and recovered alone or with their bonded male partner. Females recovering alone exhibited high levels of corticosterone and increased anxiety behavior, while females recovering with their male partner showed no such elevations (Smith and Wang, 2014). Microdialysis of oxytocin in the PVN of the hypothalamus revealed that oxytocin was elevated during stress, and remained elevated longer while recovering with a partner. Furthermore, administration of an oxytocin antagonist was sufficient to prevent the social buffering effect of cohousing on anxiety behavior in stressed, paired voles, and oxytocin reduced the anxiety behaviors of animals recovering from stress alone (Smith and Wang, 2014). These findings suggest that oxytocin is both necessary for social buffering, and sufficient to mimic its effects.

In another major study of social buffering in prairie voles, researchers assessed the effect of a stressor (foot-shocks paired with tones) on the behavior of stressed voles, as well as their pair-bonded mates who were not present for the stressor (Burkett et al., 2016). “Observer” voles of both sexes altered their behavior when reunited with their stressed partner “demonstrator” (but not a briefly separated unstressed partner) in the form of more rapid-onset and more extended allogrooming relative to baseline. No such increase in grooming occurred upon pairing with an unfamiliar opposite-sex conspecific. Observer voles also matched the state of stressed demonstrator voles, illustrated by correlations in circulating corticosterone levels between observers and demonstrators, and coordinated freezing to a tone in both animals (including the observer who did not receive conditioning). Observers also had elevated Fos production in the anterior cingulate cortex: a region linked to empathy in humans (Lamm et al., 2011). Injections of oxytocin receptor antagonist to this region prior to the task prevented increases in allogrooming (Burkett et al., 2016). Together, these two studies highlight that aspects of empathy-like behavior such as consolation and social contagion, as well as the role of specific brain regions and neurochemicals in these processes, can be found in wide-ranging social species.

Social buffering has not been explored in meadow voles housed in the short day lengths that coincide with group-living. However, male meadow voles housed in long day lengths do not alter their allogrooming with the stress state of a female mate/demonstrator—unlike prairie voles, but consistent with their solitary habits in summer (Burkett et al., 2016).

3.6. Seasonal changes in anxiety, corticosterone, and group living in meadow voles

As described in Section 3.2, day length is the primary cue driving seasonal changes in behavior in meadow voles. Photoperiod can therefore be used to manipulate social behavior and examine the neural pathways underlying the seasonal change in sociality. Females housed in winter-like short days (versus in summer-like long days) exhibit higher huddling times, prefer huddling in larger groups, and are more socially interactive with and less aggressive toward strangers (Beery et al., 2008; Lee et al., 2019; Ondrasek et al., 2015). These changes in behavior coincide with variations in neural and endocrine signaling, some of which can mediate changes in social behavior (reviewed in Beery, 2019). Unlike prairie vole mate relationships, meadow vole familiarity preferences appear to be less about social reward (Goodwin et al., 2019), and more about social tolerance, which increases in short day lengths (Beery et al., 2008; Lee et al., 2019). Mounting evidence suggests that this tolerance is shaped by seasonal changes in anxiety and HPA axis regulation.

Anxiety-like behaviors are lower in meadow voles housed in short day lengths versus long day lengths. Short day-housed meadow voles spent more time in the light portion of a light-dark box, and this effect was especially notable in females (who undergo more dramatic seasonal change in social behaviors) (Ossenkopp et al., 2005). Short day meadow vole females were also more active and spent more time in the center of an open field (Reitz, 2014); open field exploration also differed by season in field-caught males (Turner et al., 1983). Investigation of novel conspecifics in the social interaction test was first described as a measure of anxiety (File and Seth, 2003), and female meadow voles housed in short day lengths are more interactive in this test (Lee et al., 2019). Collectively, these results reveal a pattern of increased exploratory behavior and reduced avoidance behavior in short day lengths.

Meadow voles also exhibit several seasonal and photoperiodic changes in HPA axis regulation. Corticosterone varies seasonally and with reproductive status in the field (Boonstra and Boag, 1992; Galea and McEwen, 1999), and with day length in the laboratory (Anacker et al., 2016; Pyter et al., 2005). In addition, day length-dependent variation in corticosterone binding globulin may mediate photoperiodic changes in circulating free versus total corticosterone (Beery lab; unpublished data), contributing to increased free corticosterone in short day-housed females (Anacker et al., 2016). Further up the HPA axis, CRF/urocortin pathways vary with photoperiod and may form links between anxiety and social behavior. CRF receptors were measured in female meadow voles across day lengths; in multiple brain regions, CRF₂ receptors were upregulated in short day lengths, while CRF₁ receptors were downregulated (Beery et al., 2014). These opposing changes, sometimes even within the same brain region, are consistent with opposing roles of these receptors, and also with decreases in behavioral anxiety (Bale and Vale, 2004). Individual differences in receptor densities in the lateral septum (increased CRF₁ and decreased CRF₂ receptor binding) were correlated with the amount of time spent huddling during partner preference tests, further underscoring the connection between HPA axis regulation and social behavior (Beery et al., 2014). CRF production is linked to estradiol exposure (Beery et al., 2014; Haas and George, 1989; Vamvakopoulos and Chrousos, 1993), and estradiol varies seasonally in meadow voles (Galea and McEwen, 1999), potentially mediating the connection between photoperiod and CRF distribution in the brain.

In summary, female meadow voles undergo photoperiod-induced variations in anxiety, HPA-axis regulation, and social behaviors underlying group living. Multiple aspects of HPA-axis regulation predict individual variation in social behavior, and presentation of an exogenous stressor impairs the formation of peer partner preferences (Anacker et al., 2016). The presence of strong preferences for huddling with familiar conspecifics (e.g., Beery et al., 2009; Lee et al., 2019)

coupled with evidence that meadow voles experience low social reward (Beery et al., 2019; Goodwin et al., 2019) suggest that seasonal changes in anxiety and the ability to tolerate other individuals without becoming territorial or stressed may be a necessary permissive factor to promote winter sociality.

3.7. Concluding remarks and future directions

Voles have become increasingly popular subjects in studies linking stress and social behavior. Studies of prairie voles have yielded insights about broadly conserved effects of isolation in social species, as well as specific effects of social buffering and consolation behavior from known partners. Meadow voles provide an opportunity to understand how stress and anxiety relate to intraspecific changes in group living. Research in voles has benefitted from comparative approaches both within and between species, similar to those discussed for mole-rats in Section 4.0. The unusual tendency for both prairie voles and short-day housed meadow voles to form selective preferences for familiar individuals sets them apart from other social rodents investigated to date. The formation of these relationships is affected by stress and HPA axis signaling. Loss of these relationships has significant physiological and behavioral consequences in prairie voles, and mate loss may be a particularly potent stressor. Future studies may determine whether loss of peer-partners in meadow voles has similar effects.

Looking ahead, more direct comparisons between different relationship types will better inform our understanding of the nature of these relationships. For example: how does long-term loss of a mate compare to loss of a peer? Would re-pairing with a new partner compensate for loss? Are peer relationships in meadow voles similarly important to measures of health and wellbeing?

Additional benefits will come from studies of stress and social behavior in voles in more naturalistic, group-housed contexts. Unlike in Sections 2 and 4 of this review, the studies described in this section were almost exclusively conducted in pair-housed (or separated) voles. We know from studies of meadow voles that short-day housed meadow voles form equivalently strong preferences for multiple familiar partners, and prefer to huddle in larger groups (Beery et al., 2009; Ondrasek et al., 2015). Field and semi-natural enclosure studies of both meadow and prairie voles are ongoing, and may shed light on these topics. Advances in automated tracking and monitoring technologies (as described in Section 2.7) should also enable studies of voles housed in larger groups in the laboratory.

4. Stress and sociality in mole-rats

African mole-rats (family Bathyergidae) provide a powerful comparative opportunity to study the relationship between psychosocial stress and sociality in rodents. The family is comprised of at least 30 species in 6 genera that range across the entire spectrum of sociality (Bennett and Faulkes, 2000; Faulkes and Bennett, 2013). For example, both Cape mole-rats (*Georychus capensis*) and Highveld mole-rats (*Cryptomys hottentotus pretoriae*) are seasonal breeders, but Cape mole-rats live in solitary burrows whereas Highveld mole-rats live in small, transient familial groups (Bennett and Faulkes, 2000; Bennett and Jarvis, 1988a; Jarvis and Bennett, 1991; Moolman et al., 1998). Two species within the family are extremely social and meet the criteria for eusociality: naked mole-rats (*Heterocephalus glaber*) and Damaraland mole-rats (*Fukomys damarensis*, formerly *Cryptomys damarensis*) (Bennett and Jarvis, 1988b; Jarvis, 1981). Despite this rich comparative potential, surprisingly little is known about how activation of the HPA axis relates to sociality in this rodent family.

4.1. Natural ecology and sociality in African mole-rats

A unifying feature of the speciose Bathyergidae family is that all species spend their lives underground, inhabiting subterranean burrow

systems. They range across most of the southern half of the African continent and can be found in diverse microclimates. They excavate their own burrows in a variety of soil types (e.g., sand vs. clay), all of which contain geophytes, which are the underground storage organs of plants. These serve as the major food source for all *Bathyergid* species, and all foraging takes place underground. Perhaps not surprisingly, there is a relationship between soil type and species sociality where the solitary species (genera *Bathyergus*, *Georchus*, and *Heliophobius*) are found in mesic (moderate moisture) regions where soil excavation is easier, and social species (genera *Cryptomys*, *Fukomys*, and *Heterocephalus*) are found in both mesic and xeric (minimal moisture) regions (reviewed in Bennett and Faulkes, 2000; Jarvis and Bennett, 1991). Across species, burrows are organized in a similar way with networks of tunnels at varying depths: foraging paths are more superficial and permanent transit tunnels are found deeper. Species also establish set nesting and toilet chambers, which are shared among colony members in the social species. The size and complexity of the burrow systems is variable and relates to the social organization of the species and the number of animals within the colony unit (reviewed in Bennett and Faulkes, 2000).

Eusociality has evolved independently at least twice in the social mole-rats (Allard and Honeycutt, 1992; Faulkes and Bennett, 2013; Jarvis and Bennett, 1993) with naked mole-rats and Damaraland mole-rats both exhibiting cooperative brood care, overlapping generations of adults, and division of reproductive labor. In both species, reproduction is restricted to a single reproductive female – often called the queen – and a very small number of reproductive male consorts (reviewed in Holmes et al., 2009). All other adults typically remain reproductively suppressed within the colony setting. While reproductive skew is a defining feature of eusociality, the degree of skew differs between eusocial mole-rat species. In the field, naked mole-rat colonies average 60–80 individuals with a maximum of approximately 300 whereas Damaraland mole-rat colonies average 16 individuals with a maximum of approximately 40. Perhaps related to species differences in degree, the reproductive skew in naked mole-rats and Damaraland mole-rats is thought to result from distinct mechanisms. The dominant control model posits that reproductive suppression is under the control of a dominant breeding individual via direct suppression of non-breeding animals (e.g., aggression). On the other hand, the self-restraint model does not involve aggression between breeding and non-breeding animals and reproductive suppression is a consequence of inbreeding avoidance. This has important implications for understanding stress processing in social mole-rats as the dominant control model is assumed to work via stress-induced suppression of reproductive physiology while the self-restraint model is not. Comparisons between naked mole-rats and Damaraland mole-rats will be particularly useful for understanding co-evolution between stress and sociality given that naked mole-rats are proposed to fit the dominant control model (Faulkes and Abbott, 1997) whereas Damaraland mole-rats fit the self-restraint model (Clarke et al., 2001).

4.2. Stress and reproductive suppression

In contrast to the classic hypothesis that stress inhibits reproduction, chronic psychosocial stress does not appear to underlie reproductive suppression in eusocial naked mole-rats, at least as indicated by cortisol. Substantial evidence across laboratories indicates that naked mole-rats reproductively activate during periods with simultaneous increases in circulating glucocorticoids. For example, female naked mole-rats competing for dominant breeding status following removal of their queen show increases in both cortisol and progesterone (Clarke and Faulkes, 1997). In a recent case study of queen succession in naked mole-rats (Medger et al., 2019), the new queen showed mating behavior indicating reproductive activation, yet had cortisol levels that were very high (~90 ng/mL) when still in olfactory contact with the original queen. Cortisol levels then dropped to ~40 ng/mL after the original

queen was completely removed. Finally, increases in circulating gonadal steroids and gene expression of their receptors in brain are coincident with increased cortisol in animals removed from colony and paired with an opposite sex animal (Edwards et al., 2020; Swift-Gallant et al., 2015).

The absence of a relationship between cortisol and reproductive suppression is also true for Damaraland mole-rats. No differences in circulating cortisol are seen between breeding and non-breeding female Damaraland mole-rats (Molteno, 1999, as cited by Bennett, 2011; Clarke et al., 2001; Medger et al., 2018). When removed from colony, females show reduced cortisol when housed alone, increased cortisol when maintained in social contact with their previous colony mates, but no change in cortisol when kept in olfactory contact with the natal colony via soiled bedding (Clarke et al., 2001). Importantly, none of these groups showed elevated progesterone until they were introduced to an unfamiliar male (Clarke et al., 2001). Consistent with this, Young et al. (2010) found that urinary cortisol is higher in female Damaraland mole-rats during the wet season compared to the dry season, meaning that increased cortisol is seen concurrent with greatest sensitivity to a GnRH challenge. Collectively, these data indicate that removal from colony does not in and of itself trigger reproductive activation in female Damaraland mole-rats and confirm there is not a causal relationship between cortisol and reproductive suppression in this species. Ansell's mole-rats (*Fukomys anselli*) may also be eusocial (Patzenhauerová et al., 2013; Sichilima et al., 2011) and appear to align with patterns of cortisol seen in Damaraland mole-rats. Specifically, no effect of breeding status on urinary cortisol was detected (Novikov et al., 2015) though, as in Damaraland mole-rats (Medger et al., 2018), cortisol levels were positively correlated with age.

While the evidence suggests cortisol is *not* the proximate mechanism directly controlling reproductive suppression in eusocial mole-rats, it is likely that some component of HPA axis signaling is involved, at least for naked mole-rats. For this species, sex and status differences are seen in various components of the HPA axis. For example, CRF₁ receptor binding density is higher in subordinates across brain regions, and particularly in the piriform cortex and cortical amygdala (Beery et al., 2016). Sex differences were found for CRF₂ receptors, where expression is higher in females both globally and in the cortical amygdala and lateral amygdalar nucleus (Beery et al., 2016). Furthermore, quantification of expression of HPA relevant genes in distinct brain regions reveals that the HPA axis is changing throughout the reproductive transition in a sex-specific way (Faykoo-Martinez et al., 2018). Specifically, *Crhr2* mRNA in the nucleus accumbens was highest in male subordinates removed from colony and paired with an opposite sex animal for one month, but was higher in the arcuate nucleus (favoring males) and medial amygdala (favoring females) of in-colony subordinates. Glucocorticoid receptor (*Nr3c1*) mRNA expression was higher in hippocampus of subordinates vs paired animals and higher in male breeders vs male subordinates in the paraventricular nucleus. Here, it is important to acknowledge that group comparisons for asking questions about stress and reproductive suppression are potentially conflated by both social and non-social factors. For example, breeders and subordinates differ in terms of reproductive activation but also reproductive experience and social status. Similarly, the opposite sex paired animals are indeed reproductively activating, and thus serve as a transitional group between subordinates and breeders, but they are in a novel environment and also comparatively socially impoverished. Thus, experimental groups differ on more than one variable, discussed more below, which needs to be considered when interpreting how HPA signaling is or is not related to reproductive suppression.

4.3. Social status and colony stability

The extent to which HPA function is associated with social status or reproductive status (or both) can be difficult to determine because these are intertwined in eusocial species. Naked and Damaraland mole-rats

offer an opportunity to at least partially tease these apart because of their extreme reproductive skew and stable linear dominance hierarchies (Clarke and Faulkes, 1997; Jacobs et al., 1991). Their reproductive skew means that very few members of the social group actually achieve reproductive status; removing these animals from analyses and focusing on the hierarchy within non-reproductive members of the colony allows examination of social status independent of reproduction.

In naked mole-rats, most evidence to date suggests that no significant relationship exists between psychosocial stress and social status. Measuring urinary cortisol in established captive colonies, Clarke and Faulkes found no relationship between cortisol and dominance rank in three colonies (Clarke and Faulkes, 1998, 1997). Similarly, no relationship between cortisol and rank was detected using fecal cortisol metabolites in six established captive colonies in the Holmes laboratory (Edwards et al., 2020). Although the queens are the most aggressive animals in a naked mole-rat colony, subordinate cortisol levels are not clearly associated with rate of queen aggressive behavior (Clarke and Faulkes, 2001; Edwards et al., 2020). Clarke and Faulkes, however, detected a modest but significant negative correlation between cortisol and dominance rank (i.e., higher cortisol in more dominant animals) of both sexes in one captive colony (Clarke and Faulkes, 1997). Subordinates in this particular colony had increased cortisol following queen removal and this was also the only colony in which more than one female tried to take over breeding status. Medger et al. (2019) reported that plasma cortisol was approximately 70 ng/mL in subordinates after queen removal and during a period of fighting, with levels decreasing to approximately 40–45 ng/mL after the new queen was established. This pattern of results might reflect colony variation in social stability where no relationship between cortisol and status is seen in stable colonies but cortisol increases in animals anticipating or participating in competition for dominant breeding status.

There is no direct examination of cortisol and social status independent of reproductive status in Damaraland mole-rats. In three captive colonies of Damaraland mole-rats, no significant relationship between urinary cortisol and reproductive status was seen in females, although the queen had either the lowest or next to lowest level (Clarke et al., 2001). As with naked mole-rats, there is some evidence for social stability as a mediator of the relationship between status and stress. When subordinate females were removed from colony but kept in social contact with other non-breeding members of their natal colony, they had increased cortisol and increased aggression, which was not seen in animals exposed to soiled bedding from the colony, suggesting that the unpredictable social contact with familiar animals was serving as a psychosocial stressor. Similarly, (Medger et al., 2018) measured cortisol metabolites in feces of wild caught Damaraland mole-rats and did not see a significant effect of reproductive status in females, which they propose was due to stable colonies that were measured in the dry season.

Increased cortisol in mole-rats living in unstable colonies, particularly in individuals competing for dominance, might reflect a requirement of cortisol and associated behavioral arousal for ascending to breeding status. However, because cortisol is increased in animals experimentally removed from colony (i.e., reproductively activating in the absence of competition), it may also be the case that cortisol serves a physiological role associated with reproductive maturation and/or living outside of the colony. For example, naked mole-rats are poikilothermic and regulate their body temperature by huddling with colony mates (Buffenstein and Yahav, 1991). Animals living in isolation or with a single partner may face challenges with thermoregulation and energy balance that result in increased cortisol. Additional complexity for understanding the relationship between social status and stress in eusocial mole-rats comes from the fact that both naked mole-rats and Damaraland mole-rats show neuroanatomical differences associated with social and/or reproductive status. Notably, male and female breeders in both species have significantly larger regional volume of the

paraventricular nucleus (Anyan et al., 2011; Holmes et al., 2007) and, at least in naked mole-rats, the increase in volume is triggered by removal from colony and not breeding per se (Holmes et al., 2011). Also, both species show status differences in adult hippocampal neurogenesis with breeders having lower levels of neurogenesis compared to subordinates (Oosthuizen and Amrein, 2016; Peragine et al., 2014). In contrast, subordinate male rats housed in VBS show reduced hippocampal neurogenesis relative to dominants (Kozorovitskiy and Gould, 2004), which has been attributed to the stress associated with social subordination. The relative importance of psychosocial vs physiological stress to the development and maintenance of mole-rat social groups, and how this relates to structure and function of the brain, remains to be determined.

4.4. Social isolation and social novelty

Increasing evidence indicates that, as in other species (e.g., mice, rats, and voles, discussed in Section 3.4), social isolation and/or social novelty are potent stressors, depending on the mole-rat species. For social novelty, the most comprehensive direct species comparison to date examined females in solitary Cape mole-rat, transiently social Highveld mole-rats, social Mashona mole-rats (*Cryptomys darlingi*; Bennett et al., 1994), and eusocial Damaraland mole-rats. Testing the hypothesis that degree of sociality is related to social tolerance of unfamiliar conspecifics, Ganem and Bennett (2004) quantified occurrence of non-aggressive physical contact and aggressive/avoidance behavior during female dyadic encounters and measured variation in plasma cortisol prior to and at the end of each encounter. Mashona and Damaraland mole-rats had more variability in cortisol at baseline compared to Cape and Highveld mole-rats, but when lactating females were removed from the sample, species differences in cortisol disappeared. Only Cape mole-rat females showed increased cortisol when introduced to a novel female, suggesting social novelty is stressful or at least arousing for this solitary species; however, no significant correlations between cortisol and aggressive or affiliative behavior were detected in any species (Ganem and Bennett, 2004). More recently, Clive Coen and colleagues built on this work by directly comparing the distribution of CRF receptors in the brains of Cape mole-rats and naked mole-rats (Coen et al., 2015). As discussed in Section 3.6, distribution and density of CRF₁ and CRF₂ receptors can relate to species specific social behavior. The most notable species differences identified in mole-rats were that CRF₁ receptor binding in nucleus accumbens is lower in naked mole-rats versus Cape mole-rats, which may contribute to low tolerance of conspecifics in Cape mole-rats and high social tolerance in naked mole-rats, and that CRF₂ receptor density in the lateral septum is also lower in naked mole-rats, which might reduce the anxiogenic potential of social interactions in this eusocial species. Neither mole-rat species has CRF₁ receptors at measurable levels in the lateral septum or CRF₂ receptors in the nucleus accumbens.

Social isolation appears to be stressful in eusocial naked mole-rats. Naked mole-rats have increased cortisol in urine and feces for up to 4 weeks after removal from colony (Edwards et al., 2020; Peragine et al., 2016). While these studies were not designed to examine the effects of social buffering and no direct statistical comparisons were made, it is interesting that in both cases, single-housed animals had higher levels of cortisol compared to pair-housed animals, suggesting some degree of social buffering. Faulkes and Abbott (1997) did not see an increase in cortisol in isolated or paired animals, though this was based on only 2 animals so results could easily be skewed by individual variability in stress responsiveness. Among naked mole-rat subordinates, animals show increased cortisol in blood two hours after exposure to an unfamiliar conspecific in a modified resident-intruder paradigm, regardless of whether they themselves are aggressive. In this case, experimental animals remained in their home caging unit and the intruder was a pre-screened non-aggressive individual. Thus, the cortisol response was independent of agonistic behaviors on the part of either the

stimulus or experimental animals (Hathaway et al., 2016).

In contrast to naked mole-rats, female Damaraland mole-rats show decreased cortisol when removed from colony (Clarke et al., 2001) as long as they are *not* kept in social contact with former colony mates, and do not have altered cortisol when introduced to novel females (Ganem and Bennett, 2004). It is interesting to speculate that these species differences in cortisol response to removal from colony and novel conspecifics might relate to mechanism of reproductive suppression (see Section 4.1) and/or dispersal strategy. Damaraland mole-rats are facultative outbreeders; both males and females will disperse after the death of a breeder, are more likely to disperse after rainfall and also permit immigration into established colonies (Jarvis and Bennett, 1993; Torrents-Ticó et al., 2018). On the other hand, while at least some naked mole-rats show motivation to disperse both in lab and field (Braude, 2000; O'Riain et al., 1996; Toor et al., 2020; Edwards et al., 2020), they will readily inbreed if an established breeder dies and are generally more xenophobic (Lacey and Sherman, 1991).

4.5. Conclusions and future directions

Despite offering tremendous comparative potential for understanding the relationship(s) between stress and sociality, the African mole-rats are relatively understudied. This is, of course, due in part to accessibility of study organisms but also likely influenced by long-standing biases towards studying psychosocial stress in traditional laboratory models. Broadly speaking, the relationship between stress and sociality can be classified into either 1) how an animal responds to social stimuli (e.g., is an interaction stressful or not) or 2) how social context influences how an animal responds to stress (e.g., social buffering). As discussed throughout this review, these are, in turn, critically influenced by species, sex, age, status, and experience of an individual. The evidence to date, albeit limited, indicates that mole-rats have unique neural and physiological adaptations that are associated with both species differences in social organization and individual differences in social/reproductive status.

To fully capitalize on the unique opportunity provided by this rodent family, we first and foremost need to complete basic characterization of the stress response in different species of mole-rats. How do animals of different social rank mount a physiological stress response? Does it matter if it is a social vs non-social stressor? Does it matter if it is a social vs non-social study species? A programmatic and directly comparative approach (e.g., Ganem and Bennett, 2004) will efficiently test hypotheses concerning psychosocial stress and sociality. An additional key area to pursue will be determining if and how individual differences in stress responsiveness relate to social role within the colony. Naked mole-rats show some evidence of task specialization independent of age and/or size (Mooney et al., 2015). Furthermore, when queens are removed from colony, only some animals compete for dominance (e.g., Clarke and Faulkes, 1997), and newly established opposite sex pairs show significant variability in time to first litter (Holmes, unpublished data). Essentially nothing is known about the proximate mechanisms underlying these individual differences and whether or not there is a role for HPA signaling. Collectively, this proposed work will help address the remaining unanswered questions about the relationship between stress and reproductive suppression, shedding light on the evolution of eusociality in mammals.

5. General conclusions

In this paper we have summarized research from three distinct areas that highlight the importance and benefits of embracing ethologically relevant housing paradigms and diverse taxa in investigating the role and effects of social stress on behavior and physiology (see Fig. 1). Although these literatures are diverse in their emphasis and outlook, we believe that there are several commonalities across all three that illustrate the significance of ethologically inspired behavioral

neuroscience research.

Even closely related species differ in their responses to social stressors, and variation in natural ecology may underlie this variation. For example, the most potent stressor for the non-dispersing naked mole-rats appears to be socially isolating them from their colony, which can only be partially ameliorated by pair housing. Conversely, dispersing Damaraland mole-rats do not show changes in HPA activity following social isolation or when paired with conspecifics outside of the colony. Prairie and meadow voles both form selective preferences for familiar peers, but differ in mating system. Male prairie voles increased allogrooming towards their stressed female partners, while male meadow voles did not show similar consolation behavior towards their mates. Even variability in the natural ecology of rats and mice leads to differences between these species in their response to social stressors. Mice naturally engage in intra-sex conflict far more commonly than rats, so it is notable that, when forming social hierarchies, rats in the VBS show a much more profound body weight loss than mice in response to this novel social stressor. Within a species, some of the variation between individuals in the effects of social stress can also be accounted for when considering the ecological context of each species. For instance, meadow voles that are territorial in the summer but live in groups during the winter undergo changes in their stress reactivity and social behavior during short-day length photoperiods that permit social tolerance of conspecifics. To fully understand how social stress impacts behavior and physiology, there is clearly a need to study a wide range of species across ecological contexts.

Social context, which is influenced by changes in natural ecology, is also a critical factor in modulating the effects of stress across all species. For example, stress affected recently established but not long-term partner preferences in meadow voles. Social stress is not uniform across all individuals in a social group across all time periods. In both rats and mice, social rank significantly influences the timing and intensity of social stress experienced by individuals. Subordinate animals typically show elevated stress responsivity and long-term negative effects of stress on their behavior and immune, cardiovascular, metabolic and reproductive functioning. The magnitude and severity of social stress can vary dependent upon the degree of social competition within the group which is influenced by factors such as the size of groups, the group composition, space available and the despotism of the dominant individual. All of these factors can be experimentally manipulated but are also representative of natural ecological variations. Further, periods of social instability are associated with an increase in social stress experienced by all individuals compared to period of social stability. In naked mole-rats, cortisol is highest when animals are attempting to socially ascend to overtake an old queen. Likewise, in mice and in rats, social group composition changes are associated with elevated stress responses.

This review also highlights many unanswered questions. We still have much to learn about individual and species differences in the effects of social stress on many physiological systems in voles and mole-rats. Even in mouse and rat species used routinely in lab-based research, the number of studies investigating the effects of social stress in groups are relatively small compared to those that use more standard dyadic paradigms. There are even fewer studies of group housed prairie or meadow voles in the laboratory. In rats and mice, there is also a tremendous imbalance in the number of studies that have investigated male compared to female subjects. Females of both species also form social hierarchies in the VBS and appear to experience differential levels of social stress, yet almost nothing is known about the short or long-term consequences of this stress. The importance of studying both sexes is highlighted by the contrasting effects of stress on partner preference formation between male and female prairie voles. Lastly, one important domain that has been relatively under-studied is how social stress can induce adaptive physiological changes in individuals that promote short-term fitness benefits. Thus far, the majority of research has focused on disruptive long-term consequences of glucocorticoid

exposure, but work across varied taxa could provide novel insights as to how social stress induces phenotypic plasticity that enables individuals to function competently in social groups.

With the advancement of tracking methods that facilitate easier study of large groups of animals and the development of wireless technologies for the logging of physiological data, we anticipate a growing interest in research on how social stress impacts social behavior and physiology. Our objective in this paper is to encourage research in this field to further promote the study of diverse taxa, and use of research designs that integrate housing and outcome measures that better mirror the natural ecology of the species under investigation.

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Declaration of Competing Interest

The authors report no conflicts of interest

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Appendix A. Supplementary data

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