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Authors

Kenkel, William M
Gustison, Morgan L
Beery, Annaliese K

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Neuroscientist's Guide to the Vole

William M. Kenkel¹, Morgan L. Gustison², Annaliese K. Beery^{3,*}

¹Department of Psychological & Brain Sciences, University of Delaware, Newark, DE 19716

²Department of Integrative Biology, University of Texas at Austin, Austin, TX 78712 USA

³Department of Integrative Biology, University of California, Berkeley, Berkeley, CA 94720 USA

Abstract

Prairie voles have emerged as an important rodent model for understanding the neuroscience of social behavior. Prairie voles are well known for their capacity for pair bonding and alloparental care. These behavioral phenomena overlap with human social behavior but are not commonly observed in traditional rodent models. In this review, we highlight the many benefits of using prairie voles in neuroscience research. We begin by describing the advantages of using diverse and non-traditional study models. We then focus on social behaviors including pair bonding, alloparental care, and peer interactions that have brought voles to the forefront of social neuroscience. We then describe many additional features of prairie vole biology and behavior that provide researchers with opportunities to address an array of research questions. We survey neuroethological methods that have been used with prairie voles, spanning from classic to modern techniques. Finally, we conclude with a discussion of other vole species, particularly meadow voles, and their own unique advantages for neuroscience studies. Together, this review provides a foundation for researchers who are new to working with voles, as well as for experienced neuroscientists who want to expand their research scope.

Keywords

Prairie vole; vole; meadow vole; research model; neuroscience; social behavior

INTRODUCTION

Prairie voles are small herbivorous rodents native to alfalfa, bluegrass, and tallgrass prairie found in eastern and central North America (~40 to 70°N) (Figure 1) (Getz et al., 1979) (Cole and Batzli, 1979). Prairie voles have become increasingly prominent in neuroscience research since the discovery in the early 1980s by Lowell Getz and colleagues that wild prairie voles exhibit social monogamy—i.e. stable behavioral associations between mates (Getz et al., 1981). Early investigations into pair bonding established that prairie voles preferred to interact with familiar mates in dyadic or group social interactions (Thomas and Birney, 1979; Getz et al., 1981). These social choices were subsequently assessed using the Partner Preference Test (PPT; Williams et al., 1992b, 1992a), a choice test that assesses the

*Correspondence to: abeery@berkeley.edu.

extent of preference for a familiar mate over an unfamiliar stranger, and that remains the predominant assay of social behavior in voles today (see *Techniques* below and protocol: Beery, 2021 *this issue*). Although not genetically exclusive, prairie vole partnerships nonetheless represent long-term social relationships, or ‘pair bonds’, with males and females both taking part in direct parental care of young.

While monogamy is prevalent in some taxonomic groups, it is rare in rodents, and the discovery of pair bonding in prairie voles has launched four decades of exploration into the causes and consequences of social bond formation between mates. Prairie voles (Figure 1B) are now the mostly widely studied monogamous rodent, and have provided numerous insights into the mechanisms that underlie pair bond formation. Prairie vole research has also shed light on several social phenomena from alloparental care to social buffering. Moreover, their social behavior and physiology has translational value for mental and physical health, from the effects of endocrine disruptor exposure to long-term developmental impacts of pharmaceuticals such as antidepressants (Sullivan et al., 2014; Lawrence et al., 2020).

In this review, we highlight the advantages of using prairie voles and other vole species (Figure 1A) in neuroscience research. An exhaustive survey of prairie vole neuroscience is beyond the scope of the present review. Instead, we describe the benefits of using diverse and non-traditional rodent models, then discuss the uncommon social behavioral traits of prairie voles that exhibit substantial overlap with human behavior. We provide a foundation for researchers new to working with voles by detailing a host of other physiological characteristics, from autonomic nervous system regulation to reproductive biology, and survey the variety of neuroethological methods employed in vole research. Finally, we discuss research in sister vole taxa, particularly meadow voles, with behaviors of interest to comparative neuroscience.

Benefits of non-traditional model organisms

Contemporary biological research has focused primarily on rats and mice, in part because of their ease of use in laboratory settings, availability of genetic engineering tools, and the accumulated bodies of knowledge in these species. There is no particular homology between rats or mice and humans relative to other rodent species, however (Figure 1C), and despite advantages of “drilling deep” within a few model systems, there are pitfalls of relying on one or two species to model human biology. Use of diverse species provides opportunities to a) examine species with specific traits of interests, which may not be present or easily studied in rats and mice, and to b) shed light on the extent to which physiological and behavioral processes are conserved or vary across species. There is a growing movement to study the neural basis of diverse, species-specific natural behaviors within the context of natural ecology, uniting mechanistic and evolutionary explanations for behavior (Phelps et al., 2010; Hofmann et al., 2014; Taborsky et al., 2015; Hale, 2019).

Neuroscience is rife with examples of species studied for particular features of interest, from the giant axon of the longfin inshore squid to impressive sound-triangulation in barn owls. The idea that “for many problems there is an animal on which it can be most conveniently studied” was dubbed Krogh’s principle (Krebs, 1975; Krogh, 1929). Prairie voles, other

monogamous rodents (such as California mice: *Peromyscus californicus*), and rodents with varied social systems provide this sort of opportunity to study social behavioral traits not present in mice and rats.

Krogh also believed that comparative studies across multiple species are critical for obtaining a complete understanding of mammalian physiology, and others have added the sentiment that no single species can stand as a model for others (Jørgensen, 2001; Wayne and Staves, 1996). A diversity of model organisms enables the discovery and empirical exploration of a wide range of distinct phenomena (Hodgkin, 2019). Comparative studies allow researchers to test questions about conserved and derived mechanisms that underlie physiological and behavioral traits. Such comparative work has the potential to yield insights into the evolution of mechanisms underlying behaviors, including monogamy in voles (described below in Neuroendocrinology of monogamy across voles).

BENEFITS OF PRAIRIE VOLES

The natural history of prairie voles renders them an excellent model for investigating the connections between social behavior and health. Here, we review some of these behavioral traits, particularly in regards to selective social bonding, biparenting and alloparental care (Young et al., 2011). Finally, we discuss some lesser-known behavioral traits for which prairie voles are a useful model species for neuroscience.

Field-lab crossover

Although the bulk of recent prairie vole research has taken place in the lab, a complementary line of work has explored their behavior and physiology in naturalistic field environments (Madrid et al., 2020; Sabol et al., 2018). This field-lab crossover is possible because prairie voles behave similarly across research settings. Prairie voles in the field are frequently trapped in opposite-sex pairs that remain stable across seasons (Getz et al., 1981, 1993). Voles brought into the lab environment readily engage in species-typical behaviors like intra-pair affiliation, extra-pair aggression, nest building and direct biparental care (Getz et al., 1981; Thomas and Birney, 1979). This ease of translation from field to lab and back is an important advantage when using voles over traditional rodent models in neuroscience studies. Researchers can be confident that lab paradigms to investigate social bonding, alloparental care (with some caveats, discussed below), and aggression have high ecological validity.

An additional benefit to studying prairie voles living in (or derived from) the field is that their behavior naturally varies between and within populations (Madrid et al., 2020). Inter-group variation in genetic monogamy, biparental care, and aggression has been documented in voles from Kansas, Illinois and Indiana (Mabry et al., 2011; Roberts et al., 1998b). Behavioral variation amongst these populations corresponds to neural characteristics such as resting state functional connectivity (Ortiz et al. 2021). Variation also occurs within populations, where reproductive behavior and fitness depends on habitat fluctuations and predation risk (Desy and Batzli, 1989; Getz et al., 1990) as well as population demographics and individual strategies (Getz et al., 1993; Sabol et al., 2020; Shuster et al., 2019; Madrid et al., 2020). For instance, many males express a “resident” strategy and align their home

ranges with a single female, while other “wanderer” males have home ranges that overlap with multiple females (Getz and Hofmann, 1986; McGuire and Getz, 1998). These distinct male strategies correspond to neuropeptide (i.e., vasopressin) receptor expression in the retrosplenial cortex, a brain area involved in spatial memory (Okhovat et al., 2015; Ophir et al., 2008). Collectively, these studies show that prairie vole behavior is flexible. Researchers can capitalize on this intraspecific flexibility to model interactions between ecology, behavior, and physiology in both field and laboratory settings.

Pair bonding

Romantic attachment is a cross cultural human universal (Fletcher et al., 2015) and social monogamy is the most common human reproductive tactic (Schacht and Kramer, 2019). These reproductive behaviors are critical to study because of their relevance to health and well-being in humans. In contemporary, western societies, married individuals report higher happiness and life satisfaction than those who have never married, are widowed, or are divorced (Gove et al., 1990; Lawrence et al., 2019; Myers and Diener, 1995), a pattern also seen in terms of improved mental and physical health among the married (Holt-Lunstad et al., 2008; Robles et al., 2014; Sbarra et al., 2014). Romantic attachment is particularly relevant to affective state, with associations to mood, anxiety, depression, and substance use. This suggests that while better mental health facilitates romantic attachment, the reverse is also true, with romantic attachment promoting mental health (Braithwaite and Holt-Lunstad, 2017).

Prairie voles are one of the few mammalian models where this human social phenomenon, the formation of long-term social attachments, can be studied experimentally in the lab. Traditional laboratory species do not readily form selective social attachments, even with same-sex peers (Beery and Shambaugh, 2021). For example, mice and rats often prefer social novelty (Moy et al., 2004; Smith et al. 2005; Hackenberg et al. 2021), whereas voles typically prefer familiar social partners. Selective familiarity preferences have been described in both meadow and prairie voles (Lee et al. 2019), which are unique among social rodents tested thus far, including mice (Beery et al., 2018), rats (Beery and Shambaugh, 2021), and degus (Insel et al., 2020).

Prairie voles are well known for their capacity for social monogamy, wherein adult males and females form selective social bonds. These bonds are marked by a preference for the familiar ‘partner’ over novel ‘strangers’ in the Partner Preference Test (described with additional context and variations in the accompanying protocol; Beery, 2021 *this issue*), as well as defensive territoriality and distress upon separation from the pair mate (Bosch et al., 2008). Research in this area has benefited from the presence of closely related species that do not demonstrate social monogamy (e.g. meadow voles or montane voles), which has allowed for intra- and inter-species comparisons at the behavioral, neuroendocrine and genetic levels (Carter and Getz, 1993; Hammock and Young, 2005b; Lim et al., 2004; Madrid et al., 2020).

Pair bonding in prairie voles also provides an opportunity to study social bonds as a dependent variable in response to the effects of a wide variety of socially relevant early life experiences and exposures. For example, the formation and expression of partner

preferences can be shaped by early social experience and developmental exposures (Bales and Perkeybile, 2012). Researchers have also examined how adult prairie vole social behaviors vary in response to early life conditions such as perinatal oxytocin administration during delivery (Kenkel et al., 2019; Kenkel, 2020), or gestational exposure to endocrine disruptors (Sullivan et al., 2014).

Biparental and alloparental care

In order to achieve large, expensive, slowly developing brains, humans have had to rely on biparental care and cooperative breeding (reproduction with the help of others, termed ‘alloparents’ when caring for offspring other than their own) (Fletcher et al., 2015; Isler and van Schaik, 2012; Kenkel et al., 2017; Navarrete et al., 2011). Care from unrelated adults is a universal experience among modern human societies (NICHD Early Child Care Research Network, 2001; Sear and Mace, 2008). The quality of such alloparental care can predict social competence and emotional regulation (Pluess and Belsky, 2009). Likewise, care from fathers is an important contributor to health and development outcomes in children. Human fathers’ presence improves children’s educational achievement (Jeynes, 2015), emotional health and cognitive development (Cherlin et al., 1991; DuBois et al., 1994; Florsheim et al., 1998; Furstenberg and Teitler, 1994; Sarkadi et al., 2008). Furthermore, fathers’ care appears protective against anxiety (Bögels and Phares, 2008; Möller et al., 2016), attention-deficit / hyperactivity disorder (Fabiano, 2007) and substance abuse (Stein et al., 2009). Indeed, in the case of anxiety, meta-analysis suggests fathers’ parenting contributions appear to outweigh mothers’ (Möller et al., 2016). A better understanding of non-maternal caregiving could inform the etiology of its dysfunction, which is a major source of child neglect and maltreatment (Kenkel et al., 2017).

Traditionally, the neurobiological study of caregiving was limited to maternal behavior and its strong endocrine regulation (Glasper et al., 2019). In prairie voles, fathers (Kenkel et al., 2014; Rogers and Bales, 2019; Campbell et al., 2009), virgin adults, and older siblings (Rogers and Bales, 2020) all exhibit care towards pups, allowing vole studies to disentangle the contributions of the hormones of pregnancy and parturition. Prairie vole research has also been able to document the consequences of non-maternal care and its absence (Ahern and Young, 2009; Rogers and Bales, 2020).

Same-sex “peer” social behaviors

While male-female interactions have been the focus of the majority of prairie vole research, study of interactions with same-sex “peers” has contributed to our understanding of peer relationships, the effects of isolation and cohabitation on physiology and behavior, and social interactions that console or buffer stress. Prairie voles exhibit selective preferences for familiar same-sex partners after ~18–24 hours of cohabitation (DeVries et al., 1997; Beery et al., 2018, Lee et al., 2019). These preferences may be of importance by supporting the formation of extended family groups with undispersed offspring in fall and winter months (Getz et al., 1993). While the formation of small groups is seasonal, interestingly, prairie voles exhibit peer partner preferences and extensive huddling behavior in both long (summer-like) and short (winter-like) day lengths (Lee et al., 2019), suggesting familiarity preferences are not conditional on the environment in this species.

Isolation from a same-sex cagemate for extended intervals (2 weeks to 2 months) results in changes in neuroendocrine function, anxiety and depression-like behaviors, and cardiovascular function (Stowe et al., 2005; Grippo et al., 2007a, 2008a). In particular, separation leads to higher heart rate and changes in cardiac function associated with cardiovascular disease (Grippo et al., 2011; Peuler et al., 2012), similar to findings in mice and rats (reviewed in Beery et al., 2020). Just as isolation can act as a stressor, social cohabitation can lead to improved outcomes in the face of stress. Studies across a variety of social mammals show profound effects of cohabitation on the recovery from stressors (Beery and Kaufer, 2015). In prairie voles, familiarity plays a further role in stress buffering: females exposed to a stressed same-sex cagemate but not a stressed stranger exhibit ‘consolation behavior’ in the form of increased allogrooming. They also exhibit several empathy-like behaviors, including matching their cage-mate’s corticosterone levels, showing coordinated freezing to a stressor only their cagemate experienced, and showing elevated fos activity in the anterior cingulate cortex, a brain region associated with empathy in humans (Burkett et al., 2016).

These consolation behaviors and social buffering of stress have also been demonstrated in opposite-sex prairie vole relationships (Smith and Wang, 2014; Burkett et al., 2016), as have behavioral and cardiac consequences of isolation from a mate (Bosch et al., 2009; McNeal et al., 2014). Because prairie voles form selective preferences for both mates and same-sex peers, they can be used to study the effects of relationship type on a wide variety of social behaviors. For example, brief (<1 week) separation from a mate but not a same-sex sibling resulted in increased circulating corticosterone, adrenal weight, and depressive-like behaviors (Bosch et al., 2009). Most studies to date have focused on either peer or mate relationships without such comparisons, but this represents a promising realm for future exploration. Between the variety of social behaviors that can be assessed, the variety of factors that shape them, and the added variable of relationship type (familiar/unfamiliar, same-sex/opposite sex), prairie voles provide many benefits for social neuroscience research.

ANCILLARY FEATURES OF WORKING WITH PRAIRIE VOLES

Prairie vole neuroscience research began with investigations into social behavior, but over the course of such studies, several unique features of their physiology and natural history have become especially useful or noteworthy to researchers. What follows is a list of select features accompanied by either brief explanations as to how they make the prairie vole an attractive model system for research questions *beyond* the realm of social behavior, or how they can be taken into consideration. These attributes can be thought of as secondary, ancillary features that are an important part of prairie vole biology. Although these features are “ancillary” for now, emphasis on these traits may grow in the future.

Ultradian Rhythms

In contrast to the circadian rhythms displayed by laboratory rodents that are nocturnal, or in some cases diurnal, vole species show rhythms of activity throughout the day and night with periods of 1–4 hours (Gerkema and van der Leest, 1991). These shorter than one day “ultradian” rhythms in physical activity are accompanied by ultradian rhythms in core body

temperature, heart rate, and blood pressure (Grippeo et al., 2007b; Beery et al., 2008; Nieminen et al., 2013; Lewis and Curtis, 2016). The presence of ultradian rhythmicity can be convenient for researchers, as there is no need to conduct studies during the dark phase in order to coincide with periods of activity. Ultradian rhythms are synchronized by the light cycle and follow consistent patterns over time and across individuals (e.g. Beery et al., 2008), hence testing can be performed at any time that can be held reasonably consistent within a study. As discussed in the next section, prairie voles differ from laboratory rodents not only in activity rhythms, but also in lacking spontaneous estrous cyclicity. These species differences have important implications for husbandry and experimental design.

Reproduction

Prairie vole reproduction differs from that of mice and rats in several important ways, including ovulatory cycle, litter size, and cross-fostering potential—each of which can be leveraged by researchers. Most laboratory rodents undergo spontaneous ovulatory cycles, for example mice, rats, and hamsters are spontaneous ovulators with a mating-induced pseudopregnancy (i.e. luteal phase). In contrast, prairie voles are induced ovulators, meaning that females do not ovulate until exposed to an unfamiliar male, or his urine (Carter et al., 1980). Until this happens, the female hypothalamic-pituitary-gonadal axis is relatively quiescent. This may be of use to researchers interested in the organizational effects of sex hormones separate from their activational effects, as unpaired females do not undergo estrous cycles. Furthermore, it provides more control over reproductive pairings, as mating pairs can be put together at any time. Females can be prepared for mating by advance exposure to a male or soiled bedding, or may be hormonally primed by injection of estradiol benzoate (Roberts et al., 1998b). Unprimed females typically ovulate ~10.5 hours after mating, and females continuously housed near males may remain in persistent estrus for ~1 month (Stalling, 1990).

In continuously cohoused breeding pairs, most matings occurs during post-partum estrus, leading to the birth of a new litter every ~21 days. One noteworthy consideration is that in most lab-housed prairie vole colonies, offspring are separated from parents at 20–21 days of age, prior to the birth of the next litter, whereas in the wild, most vole offspring remain with their parents until at least 6–7 weeks of age (Carter and Roberts, 1997; Getz et al., 1994). This is important because exposure to a pup in early life alters an individual's developmental trajectory, such that voles exposed to the next litter show higher rates of alloparental responsiveness (Lonstein and Vries, 2001; Roberts et al., 1998a; Stone et al., 2010). Thus, conventional husbandry practices that deviate from what is most common in the wild may have meaningful consequences.

Mate pairs can continue to produce year-round if housed in long day lengths (i.e. >12 hours of light/day). Exposure to short (winter-like) day lengths leads to gonadal regression and cessation or reduction of reproduction in multiple vole species, in conjunction with temperature and dietary cues (Craven and Clarke, 1982; Dark et al., 1983; Nelson et al., 1983; Kriegsfeld et al., 2000). Maternal photoperiodic history can also influence offspring development, and interacts with the availability of compounds found in new vegetation (Lee and Zucker, 1988).

Prairie voles have small litters (~3–5) relative to mice (~5–10) and rats (~8–12), which have each been artificially selected for increased fecundity. Litter size is an important determinant of a number of metabolic characteristics in rodents (Parra-Vargas et al., 2020). Furthermore, litter effects are routinely (>80%) not controlled for in developmental studies of prenatal stress or variation in maternal care (Williams et al., 2017). Although prairie voles' small litters will necessitate slower subject pool growth, this is offset by the diminished propensity for litter effects and variation in litter size to bias results.

Multiple aspects of development, including stress reactivity and metabolism, are affected by cross-fostering in traditional laboratory species (Bartolomucci et al., 2004; Cox et al., 2010; Curley et al., 2010; Maccari et al., 1995; Matthews et al., 2011; Santangeli et al., 2016; Maxson and Trattner, 1981). For instance, in mice, the experience of being cross-fostered in and of itself increases depressive-like behavior, decreases maternal nest-building (Lerch et al., 2014) and increases appetite, body weight, and abdominal fatness (Matthews et al., 2011), which may relate to differences in maternal behavior on the part of foster dams. While, prairie voles readily and indiscriminately adopt unrelated pups and show no differences in parental behavior toward them (Perkeybile et al., 2015), further research is needed to determine whether prairie voles avoid the developmental consequences of cross-fostering observed in mice and rats.

Domestication

Reproduction in laboratory rodents has been extensively modified by domestication in traditional laboratory species (Chalfin et al., 2014; Perrigo et al., 1993). Recently, conventional wisdom has begun to cede ground to the contention that outbred mice may be more appropriate than inbred strains for biomedical research (Tuttle et al., 2018). Moreover, domestication results in changes to brain and behavior in several domains such as: neuropeptide receptor expression, temperament, social behavior, stress reactivity and reproduction, especially in females (Chalfin et al., 2014). For instance, whereas domesticated female lab mice generally tolerate pups as virgins (70% parental), wild virgin female mice react aggressively to pups (100% infanticidal) (Chalfin et al., 2014). Similar patterns can be found in males (Perrigo et al., 1993; Jakubowski and Terkel, 1982). In contrast, prairie voles are recently descended from wild-caught stock, are often purposefully outbred to wild-caught voles, and have not undergone substantial domestication. Additionally, prairie voles have not had the diversity of their microbiomes artificially reduced via abnormally hygienic housing conditions—conditions which have been shown to reduce the translational relevance of mice (Beura et al., 2016; Rosshart et al., 2019). The prairie vole microbiome is markedly distinct from that of rats and mice, with novel dominant bacterial strains, as well as more variability between individuals (Donovan et al., 2020a, 2020b). Finally, domestication also affects the expression of oxytocin and vasopressin in brain regions of rats and mice known to regulate social behavior and emotion (Ruan and Zhang, 2016). Thus, the use of prairie voles in lab research can avoid issues associated with domestication in traditional study models.

Oxytocin and Vasopressin

The impact of domestication on oxytocin and vasopressin is important because these two neuropeptides have been central to the study of sociality (Caldwell, 2017). Indeed, much of the prairie vole research to date has focused on these pleiotropic hormones. The distributions of oxytocin and vasopressin receptors in prairie voles have been extensively studied, although most often in subcortical brain regions related to affect and social behavior (McGraw and Young, 2010). Recently, characterization of oxytocin receptor localization has been extended to the periphery of neonates (Greenwood and Hammock, 2019) and cortex of adults (Duchemin et al., 2017) (see also Cortical Organization, below). It was recently observed that the promoter region of the oxytocin receptor has greater sequence homology to humans in prairie voles than either rats or mice (Perkeybile et al., 2019). The methylation of CpGs within the promoter is relevant for epigenetic investigations of how oxytocin's actions in early life can steer brain and behavior throughout development (Perkeybile et al., 2019; Kenkel et al., 2019).

Early studies noted the high levels of plasma oxytocin concentrations in prairie voles (2–4x higher than in rats) (Kramer et al., 2004). This was originally taken as evidence that prairie voles have high, human-like levels of circulating oxytocin. However, readers should be cautioned that measurement of oxytocin levels in the blood is an unresolved topic of debate (Leng and Sabatier, 2016; Brandtzaeg et al., 2016; MacLean et al., 2019). In the central nervous system, the prairie vole paraventricular nucleus (a major source nucleus for oxytocin) does not show the same clear distinction between magnocellular and parvocellular neurons as seen in rats and mice. In other species, magnocellular neurons project to the forebrain and pituitary, while parvocellular neurons project to the hindbrain and spinal cord.

Corticosteroids

The hypothalamic-pituitary-adrenal (HPA) axis is intimately tied to oxytocin and vasopressin via the regulation of stress, metabolism, and affect. Prairie voles have much higher circulating levels of two major HPA-axis signaling molecules, the glucocorticoid corticosterone and adrenocorticotrophic hormone (ACTH) (Taymans et al., 1997) than either rats or mice, even after accounting for the effects of domestication (Chalfin et al., 2014) (Table 1). Prairie voles are also resistant to dexamethasone induced suppression of corticosterone, which, together with their higher basal set-point, has led to prairie voles being characterized as 'glucocorticoid resistant' (Taymans et al., 1997).

Thermoregulation & Metabolism

Oxytocin, vasopressin and the HPA-axis are all important regulators of not only social behavior but also more fundamental processes such as thermoregulation and metabolism, two domains where voles again show important differences from traditional laboratory species. Across the *Microtus* genus, vole species have 20%–40% greater basal metabolic rates than is expected from allometric predictions (Wunder, 1985). In traditional laboratory housing, prairie voles also appear to have relatively low fat mass (~5% body weight, (Seelke et al., 2018)) compared to rats (25–40% (Martin et al., 2010)) or mice (23–26% (Martin et al., 2010; Reed et al., 2007)). Because human environments require very little energy expenditure on thermogenesis (Brychta and Chen, 2016), such conditions are important

when modeling human health in animal studies (Bastías-Pérez et al., 2020; Maloney et al., 2014). Housing temperature is one the largest determinants of energy expenditure in mice (Corrigan et al., 2020). Indeed, basal metabolic rate and food intake of mice housed at room temperature 20°C are both ~50% higher than those housed at mouse-thermoneutral 30°C, which speaks to the magnitude of the chronic cold stress lab mice experience (Maloney et al., 2014; Hylander and Repasky, 2016; Hankenson et al., 2018). As detailed below, voles are better suited to room temperature housing and thereby avoid these effects.

Voles are adapted to boreal habitats, have thick coats of fur, and tolerate cool temperatures (Wunder, 1985; Wunder et al., 1977). Voles' short tails likely help reduce heat loss compared to rats or mice (Škop et al., 2020) and presumably, so too would the *Microtus* genus' eponymous small ears. Standard room temperature housing therefore represents a less stress-confounded approach to housing prairie voles, avoiding the chronic cold stress experienced by mice housed at room temperature (Maloney et al., 2014). Thermoneutrality in mice is 30–32°C (Cannon and Nedergaard, 2011; Hylander and Repasky, 2016), whereas prairie voles tolerate a wide range of temperature (Wunder et al., 1977). Thermoneutrality in voles is ~25–30°C (Beck and Anthony, 1971; Packard, 1968), which expands to 20–30°C when nesting is considered (Beck and Anthony, 1971). The prairie vole has the added benefit of biparental care, where fathers routinely huddle their litters, providing added warmth for vulnerable pups. Group housing and nesting only slightly ameliorates the chronic cold stress experienced by mice at 20°C (Maher et al., 2015).

Autonomic 'balance', the relative contributions of sympathetic and parasympathetic tone, is both a window into metabolic state (Green, 2011) and a fundamental aspect of stress and emotional reactivity that underlies much of social behavior (Grippe, 2017). The previously held conventional wisdom, that mice have high heart rates driven predominantly by sympathetic tone, has been overturned by work on mice housed in thermoneutral conditions. In these conditions, mice have lower heart rates and higher levels of parasympathetic cardiac tone (Swoap et al., 2008). Prairie voles show similarly low heart rates and high parasympathetic cardiac tone when housed at 22°C (Grippe et al., 2007b). Thus, it would appear that prairie voles avoid the chronic cold stress that traditional housing conditions present to mice.

Alcohol consumption

Drug use and social relationships are inter-related in humans, and prairie voles have emerged as a model system to study these interactions (Potretzke and Ryabinin, 2019). Voles consume alcohol at high rates and show robust preferences for ethanol over pure water (Anacker et al., 2011, 2012). Prairie vole alcohol use is particularly sensitive to peers. Same-sex cagemates will adjust their drinking levels to match each other (Anacker et al., 2011; Anacker and Ryabinin, 2013), and having a peer around appears to attenuate relapse drinking behavior (Hostetler and Ryabinin, 2014). Interactions between social environment and alcohol use also occur with respect to pair bonding. Partner preferences decrease when males consume alcohol during bond formation, and the opposite effect occurs for females (Anacker et al., 2014). Moreover, bonded males show decreased partner preferences when a pair shows discordant patterns of alcohol consumption, and this effect is absent in females

(Walcott and Ryabinin, 2017, 2019). Thus, prairie voles are an interesting model system to study social facilitation of drinking, and in reverse, how drinking behavior influences social bonding.

Vocal communication

Prairie vole social interaction involves multiple sensory modalities, and yet, research tends to be biased towards conspicuous modalities, including touch (e.g., huddling) and olfactory cues (e.g., anogenital investigation). Another important sensory modality is acoustic signaling. Early observations showed that prairie vole adult males produce high rates of ultrasonic vocalizations (USVs) when exposed to novel females (Lepri et al., 1988), but only a couple studies have followed up on these early observations. This recent work shows that prairie voles produce a diverse repertoire of USVs (25–80 kHz) that are spectrally similar to mouse and rat USVs (Ma et al., 2014; Stewart et al., 2015). Both sexes vocalize when exposed to conspecifics, producing different USVs depending on partner traits like familiarity, sex, and reproductive state (Ma et al., 2014). The most elaborate calls are made by males exposed to estrus females, and these elaborate calls also occur when adults are given the dopamine agonist amphetamine. Another context where vocalizations occur is when adults are physically separated from, but in audiovisual contact with, familiar cagemates (Stewart et al., 2015). In this context, USV acoustic structure (e.g., fundamental frequency) is tightly linked with heart rate. Together, these findings indicate that prairie vole USVs are involved in the formation and maintenance of adult social bonds. Underlying mechanisms likely involve, but are not limited to, the dopaminergic system and autonomic nervous system.

Vocalizations also occur in parent-offspring interactions. Prairie vole pups are incredibly vocal when isolated from their parents (Robison et al., 2016), calling at rates that are several times higher than the pups of sister taxa (Blake, 2002; Rabon Jr. et al., 2001; Shapiro and Insel, 1990). These calling rates are positively correlated with corticosterone levels during separation (Shapiro and Insel, 1990). Calling rates peak in the first 1–2 weeks after birth, and then decrease quickly thereafter (Kenkel et al., 2015). Pup vocalizations span both audible (~12 kHz) to ultrasonic (~36 kHz) frequencies, with more acoustically complex calls occurring in early infancy (Terleph, 2011). Playback experiments show that USVs are particularly attractive to postpartum and late gestation parents (Terleph, 2011). Therefore, pup vocalizations may help solicit parental attention during early infancy. This vocal response to separation could be mediated by the “stress” system (i.e., HPA axis). Our understanding of prairie vole vocalizations has only just begun. Future research is needed to determine the precise social functions of juvenile and adult vocalizations, and to identify neural substrates that govern this complex behavior.

Cortical organization

Prairie vole neuroanatomy is highly conserved with other mammals, yet it has some distinctive features that differ from sister taxa and other rodents. One of the most distinctive features is the size and structural connectivity of sensorimotor areas. Prairie voles are known to have a strikingly large auditory cortex and auditory-responsive areas (relative to neocortex) compared to mice and mammals with similarly sized neocortex (Campi et al.,

2007; Krubitzer et al., 2011). In somatosensory cortex, there is a disproportionate area devoted to perioral facial hairs and the snout as compared with non-vole species (Campi et al., 2007). Another unique feature of prairie vole somatosensory areas is that they are broadly inter-connected with each other (Campi et al., 2010). This cross-modality connectivity differs from rats, mice and squirrels, for which connections are focused within a single sensory modality. Both of these features – sensorimotor organization and connectivity – are highly sensitive to early life experience. Prairie voles that received high parental care have larger primary motor and visual areas, but smaller and more intrinsically connected somatosensory areas, than do voles that received low parental care in infancy (Seelke et al., 2016a, 2016b). Thus, strong multisensory integration appears to be an important component of prairie vole physiology and developmental plasticity.

Prairie vole limbic-associated frontal cortex and extended amygdala also have unique features related to size and structural connectivity. Prairie vole medial prefrontal cortex (mPFC) takes up a smaller proportion of cortex than does meadow vole mPFC, while other parts of cortex (e.g., retrosplenial cortex) are similarly sized (Kingsbury et al., 2012). These frontal regions also are sensitive to early life experience. Infants with high parental care exhibit thicker cortex in prelimbic and anterior cingulate regions, compared to infants with low parental contact (Bottom et al., 2020). As for structural connectivity, the prairie vole medial agranular cortex has pronounced corticocortical connections as compared to rats (Reep and Kirkpatrick, 1999). Another region where prairie voles show unique connectivity is in extended amygdala. Males have a species-specific network of TH-ir cell projections involving principal nucleus of the BNST, posterodorsal medial amygdala, and medial preoptic area. These TH-ir projections are not commonly found in rats, hamsters, or meadow voles (Ahmed et al., 2012; Northcutt et al., 2007; Northcutt and Lonstein, 2011). Taken together, this body of work shows that the organization of the prairie vole brain is distinctive from other rodents, and these differences may be partially influenced by early life experiences.

One of the most distinctive features of the prairie vole brain is the distribution pattern of neurotransmitter, neuropeptide, and hormone receptors. Among neurotransmitters, dopamine receptors have been studied best in a comparative context. Prairie voles have high densities of D2-like receptors in mPFC but low densities of D1-like receptors in mPFC and nucleus accumbens (NAcc) compared to meadow voles (Aragona et al., 2006; Smeltzer et al., 2006). Among neuropeptides, oxytocin and vasopressin receptors (OXTR and AVPR, respectively) also show distinct species-specific expression patterns (Insel and Shapiro, 1992; Duchemin et al., 2017; Insel et al., 1994; Smeltzer et al., 2006; Wang et al., 1997). For example, prairie voles have higher OXTR and AVPR densities in parts of the mPFC and BNST as compared to non-monogamous vole species. Hormone-related receptors also are well-studied in a comparative context. Corticotropin releasing factor (CRF) has two receptor subtypes (CRFR1 and CRFR2) that differ in neural expression across vole species, especially in NAcc (Lim et al., 2005). Estrogen beta receptors (ER β) also exhibit species-specific patterns. ER β expression is focused within distinct hypothalamic subregions in prairie voles but widely distributed across the brains of rats and mice (Ploskonka et al., 2016). Collectively, these studies show that there are a variety of brain regions – notably mPFC, BNST, amygdala,

NAcc, lateral septum, and thalamus – for which prairie voles show species-specific expression patterns of dopamine, neuropeptide, and hormone receptors.

Sex Differences

Male and female prairie voles exhibit remarkable similarity in pair bonding and parental care behaviors. Nonetheless this behavioral convergence is built on somewhat different underlying neurochemical pathways. Research on prairie vole pair bond formation has focused on the role of oxytocin in the nucleus accumbens of females, and on arginine vasopressin acting in the ventral pallidum of males (Liu and Wang, 2003; Keebaugh et al., 2015; Pitkow et al., 2001a), although the extent of these sex differences has not been thoroughly explored and oxytocin also plays a role in male pair bond formation (Johnson et al., 2016). Differential modulation of pair bonding in males and females in response to both stress and glucocorticoid administration indicates latent differences in the pathways underlying bond formation (DeVries et al., 1996). The idea that behavioral similarity across the sexes may arise from mechanisms that compensate for differences in gonadal hormone exposure has been espoused by Geert De Vries (De Vries and Boyle, 1998; De Vries, 2004). In essence, while female social bonding builds on female-specific oxytocin pathways involved in lactation and maternal care, male social bonding and parental care has co-opted vasopressin signaling—with strikingly different patterns of expression in males and females—to reach similar ends (Wang et al., 1994). There is a growing appreciation of the importance of including both females and males in preclinical research (Mogil and Chanda, 2005; Beery and Zucker, 2011; Clayton and Collins, 2014; Klein et al., 2015; Woitowich et al., 2020), and multiple guides to practices around inclusion and analysis (Clayton, 2016; Maney, 2016; Beltz et al., 2019). By studying both male and female prairie voles, we will gain particular insights into how parallel mechanisms can support social attachments.

TECHNIQUES

Many neuroethological techniques that were developed in traditional rodent models are broadly applicable to prairie voles (Table 2, Table 3). Despite these similarities, there are notable exceptions where techniques either work differently in voles, were designed specifically for voles, or have yet to be modified for voles. A variety of behavioral assays for socio-cognitive traits like anxiety, depression, parental investment, and social reward, have been applied to prairie voles (Table 2), and yet, voles behave differently in some of these assays than do other rodents. In the Light-Dark Box Test, prairie voles are quick to enter and spend more time in the light chamber than the dark, which is opposite to how mice and rats typically behave (Sun et al., 2014; Lee et al., 2019). Stressors do still lead to voles spending less time in the light, however, similar to other rodents. In the Morris swim test, prairie voles are slow to complete the task relative to rats, possibly due to species differences in cognitive ability, motivation, or physiology (Blankenship et al., 2019). Additionally, voles are not ideal for the Tail Suspension Test of depressive-like behavior because of their short tails, and it is widely reported that prairie voles jump or fall off of Elevated Plus Mazes more frequently than do other rodents (Grippe et al., 2008b).

The Partner Preference Test (PPT) is one behavioral assay that was designed with prairie voles in mind as the primary study species. As described in the introduction, the PPT is used

to assess the selective social relationships that so far appear unique to voles among lab rodents (Williams et al., 1992b). In this test, the focal animal is placed in the center chamber of a three-chamber arena. In the opposite-sex (original) version, the focal animal's familiar mating "partner" is tethered in one of the adjacent chambers, while a novel opposite-sex "stranger" is tethered in the other adjacent chamber. In the same-sex "peer PPT", the partner and stranger are of the same sex as the focal vole. The focal animal is given a predetermined amount of time (typically ~3h) to freely explore the entire arena and interact with both stimulus animals (see Beery, 2021 *this issue*). In prairie voles, focal animals that have undergone extended cohabitation (~6–24h) with a mating partner or a familiar peer spend more time in contact with their partner over a stranger. The formation of partner preferences can be enhanced or accelerated by specific experimental manipulations, while other manipulations impair preference formation, providing insight into neural pathways underlying bond formation.

Although many well-established neuroscience tools are used in prairie vole research (Table 3), some of the newest technologies have not yet been adopted. A surge in computational, genetic, and viral tools has greatly advanced rodent research with traditional lab species (reviewed in Navabpour et al., 2020; Nectow and Nestler, 2020; Ueda et al., 2020). Some of these state-of-the-art tools have recently been applied to prairie voles, including calcium imaging (Scribner et al., 2020), free-moving electrophysiology (Amadei et al., 2017), optogenetics (Amadei et al., 2017), and CRISPR knockin/knockouts (Horie et al., 2019, 2020)). Many of these newly designed tools, however, remain untested or are undergoing development, validation and refinement in voles. It is likely that the coming decade will be a golden age for prairie vole research as researchers adopt some of these more specific and nuanced tools.

MEADOW VOLES AND OTHER VOLE SPECIES IN NEUROSCIENCE RESEARCH

Although prairie voles are the best studied *Microtus* species, other vole species exhibit attributes of interest for neuroscience research. In particular, group-living meadow voles are used to probe the neurobiological basis of life in social groups and peer relationships, and additional monogamous and promiscuous vole species are used in comparative investigations of social monogamy. Non-neuroscience related studies also make use of diverse vole species.

Neuroendocrinology of group living in meadow voles

Meadow voles are closely related to prairie voles, but they exhibit seasonal group living in the absence of monogamy (Getz, 1972; Madison, 1980; Boonstra et al., 1993). This predictable and environmentally inducible variation in sociality provides an opportunity to study the neuroendocrine mechanisms that underlie this change in peer social behavior to support group living, and the biology of affiliation outside the realm of reproductive attachments (Beery, 2019).

Changing environmental conditions lead to variation in meadow vole social behavior in the field and lab. In summer months, females are highly territorial and maintain home-ranges that do not overlap with other females (Edwards et al., 2019; Madison and McShea, 1987). In winter months, these territories collapse, and voles live and sleep in mixed-sex groups of up to 10 individuals (Madison and McShea, 1987). Seasonal changes in sociality in the field are recapitulated in the laboratory under conditions of changing day length. In winter-like, short day lengths (10h of light/day) females form enduring and specific peer partner preferences for same-sex cagemates (e.g. Parker and Lee, 2003; Beery et al., 2008), huddle with conspecifics more, and are less aggressive than long-day (14h light) housed voles (Beery et al., 2008; Lee et al., 2019). Male meadow voles are less territorial than females in the summer (Madison, 1980; Edwards et al., 2019), and do not exhibit changes in peer social preferences with day-length in the laboratory, but also exhibit same-sex partner preferences for cage-mates (Beery et al., 2009; Beery and Shambaugh, 2021).

Peer social interactions are the foundation of life in social groups, and selective peer relationships are of particular importance in human societies. Peer relationships also can be compared and contrasted across meadow and prairie voles. Studies show that peer relationships in both species are less behaviorally rewarding and less dopamine dependent rewarding than mate relationships in prairie voles (Beery and Zucker, 2010; Goodwin et al., 2019; Lee and Beery, 2021). Social tolerance, promoted by both seasonally reduced anxiety and aggression, appears to play an important role in peer affiliation in meadow voles (Beery et al., 2014; Anacker et al., 2016b; Lee et al., 2019). Oxytocin signaling shapes the selectivity of affiliation in meadow voles; oxytocin receptor density changes with day length, and oxytocin administration can increase or eliminate peer partner selectivity, depending on the brain region in which oxytocin is acting (Parker et al., 2001; Beery and Zucker, 2010; Anacker et al., 2016a; Beery, 2019).

Stress and elevated glucocorticoid signaling impairs the formation of social preferences for peers or mates in both meadow and prairie vole females, suggesting common underlying mechanisms for social avoidance among females of these species (DeVries et al., 1996; Anacker et al., 2016b). However, oxytocin appears to alter social selectivity for peers and mates in distinct brain regions and in different ways (Ross and Young, 2009; Beery and Zucker, 2010; Anacker et al., 2016a), indicating that peer relationships must be studied separately. Investigations of the similarities and differences between these types of selective relationships within and across vole species will inform our understanding of how social behaviors and underlying pathways vary or are conserved.

Neuroendocrinology of monogamy across voles

Several studies have examined the comparative basis of monogamy in voles by making use of mating system variation within the genus. Multiple vole species exhibit monogamy or pair-bonding behavior in at least some populations or circumstances, while other species mate promiscuously, as is typical of most rodent species (Figure 1A). Comparative studies have focused primarily on neuropeptide receptor densities in the brains of monogamous (pine and prairie) vole species compared to promiscuous (montane and meadow) vole species (Insel and Shapiro, 1992; Lim et al., 2005; Smeltzer et al., 2006; described in detail

above), or on genetic differences in sequences regulating expression of the arginine vasopressin 1a receptor (*avpr1a*) gene (Young et al., 1996; Hammock and Young, 2002; Fink et al., 2006; Donaldson and Young, 2013). Genetic variation has also been examined across behavioral phenotypes within populations (reviewed in Madrid et al., 2020).

More recently, studies of the Taiwan vole (*Microtus kikuchii*) have attempted to establish whether this putatively monogamous species exhibits space use consistent with monogamy, whether they exhibit partner preferences for familiar mates, and how oxytocin receptors are distributed in their brains (Wu et al., 2012; Chappell et al., 2016; Lee et al., 2014). Other closely related species that have been described as monogamous include the European water vole (*Arvicola amphibious*), Southwestern water vole (*Arvicola sapidus*), Northern mole-vole (*Ellobius talpinus*), and the Alai vole (*Ellobius alaicus*) (Lukas and Clutton-Brock, 2013), although relatively little is known about these species. Study of additional vole species will enhance our understanding of the evolution of mechanisms underlying variation in social behaviors.

CONCLUSION

Neuroscience research benefits from comparative study, which allows researchers to validate prior research outcomes and explore traits that are not found in traditional model systems. Already we have begun to encounter the limits of biasing our translational and preclinical research toward only two species of laboratory rodents. Beyond the value of diversifying model organisms, prairie voles have proven invaluable for neuroscience research because of a distinctive suite of social behaviors including the formation of selective social bonds. Additional differences from the physiology of rats and mice provide further opportunities for study. With the adoption of new tools and technologies, we expect to see the success of the prairie vole model grow, and for the scope of prairie vole research to expand going forward.

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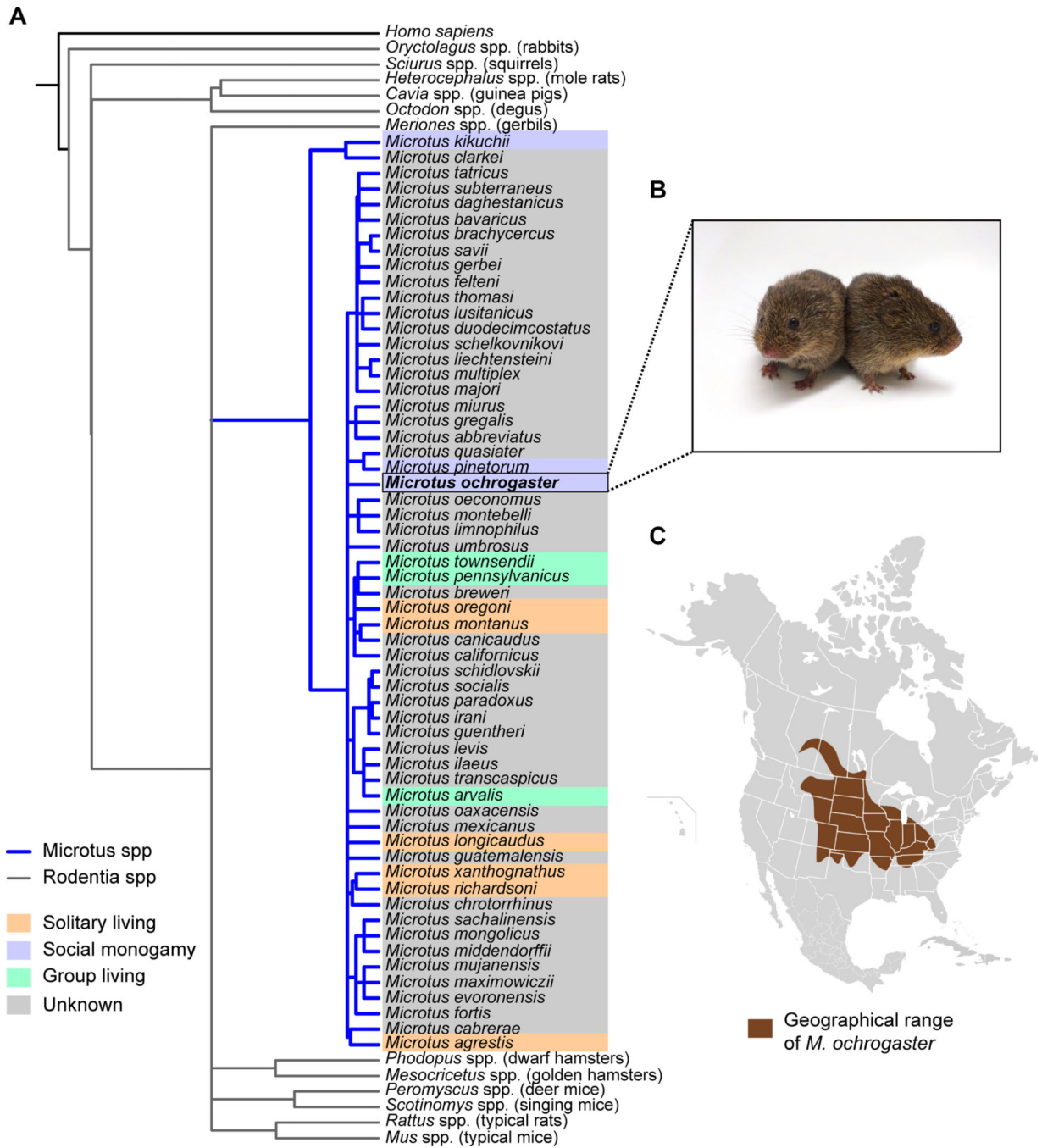


Figure 1. Prairie voles have become popular for studies of social neuroscience, and have many additional advantages and features described in this review. **A.** Phylogeny of *Microtus* (blue lines), representative species from other Rodentia groups (gray lines), and *Homo sapiens* as an outgroup. Phylogenetic data are from a published mammalian supertree (Fritz et al., 2009), and the tree was plotted with R software (R v3.5.3) using the ‘ape’ package (Paradis and Schliep, 2019). Social systems for *Microtus* spp are color coded based on previously published descriptions (Lukas and Clutton-Brock, 2013). **B.** Laboratory bred prairie voles

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(Image ©Beery Lab). C. Distribution of prairie voles in North America. (Image by Simon Pierre Barrette / CC BY-SA 4.0, adapted from (Naughton et al., 2012).

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Table 1.

Baseline plasma corticosterone concentrations across voles and traditional laboratory rodent species considering domestication status.

Species	Plasma Corticosterone (ng/ml)	Source
Rats (domesticated Sprague-Dawley)	72 ± 7	(Taymans et al., 1997)
Mice (domesticated C57BL/6J)	19 ± 3	(Chalfin et al., 2014)
Mice (wild-derived)	165 ± 35	(Chalfin et al., 2014)
Meadow voles (wild-derived)	130 ± 34	(Taymans et al., 1997)
Prairie voles (wild-derived)	666 ± 90	(Taymans et al., 1997)

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Table 2.

Overview of ethological techniques used to investigate social and cognitive behavioral traits in prairie voles.

Socio-cognitive traits and related tests	Example references
Anhedonia (e.g., sucrose preference test, forced swim test)	(Grippe et al., 2008b)
Anxiety (e.g., elevated plus maze, open field test, light-dark box test)	(Insel et al., 1995; Sun et al., 2014)
Empathy and social contagion (e.g., consolation test, social-facilitated drinking)	(Anacker et al., 2011; Burkett et al., 2016)
Mating strategies (e.g., radiotelemetry, powder tracking, RFID tagging)	(Jike et al., 1988; Sabol et al., 2018)
Pair bond formation and maintenance (e.g., partner preference test, selective aggression “resident-intruder” test)	(Williams et al., 1992b; Insel et al., 1995; PPT protocol Beery, 2021 <i>this issue</i>)
Parental care (e.g., pup retrieval)	(Wang et al., 1994)
Social reward (e.g., conditioned place preference, operant conditioning)	(Goodwin et al., 2019; Matthews et al., 2013; Lee and Beery, 2021)
Spatial memory (e.g., Morris swim task)	(Sawrey et al., 1994)

Table 3.

Overview of neuroscience tools used to investigate physiological mechanisms in prairie voles.

Neurophysiological constructs and related tools	Example references
Peripheral nervous system functioning (e.g., electrocardiograms of heart rate, hormone assays)	(Blondel et al., 2016; Grippo et al., 2007b; Klein et al., 1997)
Genotyping, genomics, and transcriptomics (e.g., PCR and sequencing, genome linkage maps)	(Duclot et al., 2020; Hammock and Young, 2005a; McGraw et al., 2011; Okhovat et al., 2015)
Transgenic manipulation (e.g., AAV gene transfer, shRNA-targeted knockdown, CRISPR knockin/knockout)	(Keebaugh et al., 2015; Pitkow et al., 2001b; Horie et al., 2019, 2020)
Neural activity (e.g., calcium imaging, electrophysiology, fMRI, immediate early gene expression)	(Amadei et al., 2017; Cushing et al., 2003; Scribner et al., 2020; Yee et al., 2016)
Neural manipulation (e.g., optogenetics, peripheral administration and microinjection of compounds)	(Amadei et al., 2017; Winslow et al., 1993; Witt et al., 1990)
Neural mapping (e.g., anterograde/retrograde tracing, autoradiography, cell proliferation, electrophysiology, immunohistochemistry)	(Ahmed et al., 2012; Campi et al., 2007; Reep and Kirkpatrick, 1999; Smith et al., 2001; Witt et al., 1991)
Neuropeptide and neurotransmitter release (e.g., fast-scan cyclic voltammetry, microdialysis)	(Resendez et al., 2016; Gingrich et al., 2000)

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