Gut Microbiome (2026), **7**, e4, 1–19
doi:10.1017/gmb.2026.10021

GUTMICROBIOME

MINI REVIEW

The prairie vole gut–brain–microbiota-axis: a narrative review

Daniel A. Nuccio[1], Angela Grippo[2] and Pallavi Singh[1]

[1]Department of Biological Sciences, Northern Illinois University, USA and [2]Department of Psychology, Northern Illinois University, USA

Corresponding author: Pallavi Singh; Email: psingh1@niu.edu

(Received 14 October 2025; revised 05 February 2026; accepted 03 March 2026)

Abstract

The microbiota–gut–brain axis (MGBA) has garnered considerable attention for its role in health, disease, and higher psychological processes. One area of particular importance is the relationship between the MGBA and stress. Although numerous animal models are suitable for research on stress, the number suitable for research on the impact of social stressors with translatability to humans is limited. The prairie vole is regarded as an ideal organism for probing the impact of social stress, as these animals not only exhibit social behaviours rare in mammals but also lack many drawbacks that come with using non-human primates. Moreover, the neurophysiological basis of their social behaviours is well characterized, and numerous studies have examined the impact of social stress, particularly social isolation, on these animals. However, only a limited number of studies have examined the prairie vole gastrointestinal system, intestinal microbiome, or MGBA. Consequently, this leaves ample opportunity for future research. In this review article, we summarize basic aspects of prairie vole ecology, behaviour, and neurophysiology, then review the limited but valuable body of research examining the gastrointestinal system and microbiome of prairie voles. Additionally, we note potential challenges and opportunities for future MGBA research utilizing prairie voles.

Keywords: gut–brain–microbiota axis; stress; metabolic diseases; prairie vole; metabolomics

Introduction

The dynamic relationship between the nervous, endocrine, gastrointestinal, and immune systems, in addition to an organism's microbiome, is increasingly gaining recognition for its role in health, disease, emotion, cognition, and behaviour. Often referred to as the microbiota–gut–brain axis (MGBA), the conceptual framework associated with this integrated system has been used to explore how gut microbial communities are involved in mental health and stress (Carabotti et al., 2015; Liu and Zhu, 2018; Ilchmann-Diounou and Menard, 2020; Misiak et al., 2020; Costa et al., 2024).

As a natural corollary, the impact of stress on gastrointestinal physiology has garnered attention, with studies showing that stress alters intestinal motility and permeability. Although the extent to which these changes are direct responses by the host to stress or downstream of changes in the host's gut microbiome is unclear, these changes are of particular interest to researchers given their role in the development and progression of numerous pathologies. Increased intestinal permeability, whether caused by stress, perturbations to microbial communities, or diet, may lead to the passage of microbial endotoxins (e.g., lipopolysaccharide [LPS]) into the circulatory system, and low-grade systemic inflammation, in turn, resulting in cardiovascular and metabolic disease (Cani et al., 2007; Delzenne and Cani, 2011; Devaraj et al., 2013; Misiak et al., 2020; Wu et al., 2021; Zhang et al., 2021; Martel et al., 2022; Page et al., 2022;

© The Author(s), 2026. Published by Cambridge University Press in association with The Nutrition Society. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (http://creativecommons.org/licenses/by/4.0), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

Salas-Venegas et al., 2022; Sadagopan et al., 2023; Costa et al., 2024). Additionally, the MGBA can influence an organism's social behaviour and be influenced by its social environment. For instance, bacterial genera found in faecal samples from non-captive macaques can predict sociality, and the transplantation of the faecal microbiota of human patients with social anxiety disorder into mice can alter sensitivity to social fear (Johnson et al., 2022; Ritz et al., 2024).

However, despite the value of studying human clinical populations and samples from non-human primates, as well as performing experimental work using mice and rats, we present prairie voles (*Microtus ochrogaster*) as an underutilized model organism for unravelling the link between social stress and the MGBA. Unlike many other animal models, prairie voles share several social behaviours with humans that are generally considered rare in mammals. These include forming largely monogamous social pair bonds with mates, engaging in biparental care, and sometimes living in extended family units in which non-reproductive adult offspring remain in the parental nest and assist with the care of younger siblings (Carter and Getz, 1993; McGraw and Young, 2010; Kenkel et al., 2017; Kenkel et al., 2021). Furthermore, a large body of work amassed over the past 45 years provides a detailed characterization of prairie vole ecology and behaviour, the neuroendocrine basis of their social behaviours, and the effects of social stress on these animals (Carter and Getz, 1993; Grippo et al., 2007a, 2007b, 2007c, 2008; McGraw and Young, 2010; Kenkel et al., 2021; Normann et al., 2021).

Conversely, although mice and rats are utilized far more frequently in biomedical research, the social characteristics of these animals do not match those of humans as closely. Rats, although gregarious, do not form social pair bonds with mates, while the care of offspring is left solely to females. Mice, when living in natural or quasi-natural environments, sometimes form social systems considerably different than those of humans, as they can be characterized by extended family groups comprising a dominant male, multiple subordinate males, multiple reproductive females, and the offspring. Mice also do not form monogamous social pair bonds with familiar partners, although paternal care may show variability in lab settings based on mouse strain (Lonstein and De Vries, 2000; Lee and Beery, 2019). Additionally, although specific mutant strains (e.g., BTBR mice) may be useful models for understanding deficits in social behaviour associated with particular conditions, such as autism spectrum disorder, such animals can have genetic and physiological abnormalities that make them less suitable models for normal human social behaviours or how mammals with such behavioural profiles respond to social stress (Careaga et al. 2015).

Looking at future MGBA research, there is ample opportunity for the greater utilization of prairie voles in examining how social stressors act through the MGBA to influence gastrointestinal physiology and metabolic disease, as well as how gastrointestinal disturbances and gut microbiome changes can alter social behaviour. In the present review, we provide a detailed account of prairie vole ecology and behaviour, the neurophysiological basis of their social behaviours, and the impacts of social stress on these animals. We also discuss the small but valuable body of work that has already examined the prairie vole gastrointestinal system and gut microbiome, as well as potential limitations and opportunities when using these animals in MGBA research.

Ecology and behaviour

Prairie voles are a species of rodent native to the central portions of North America (Roberts et al., 1998; Ophir et al., 2007). Despite being capable of reproducing year-round, wild prairie voles are less reproductively active during the winter (Cole and Batzli, 1979). Litters, which are born after ~22 days of gestation, typically contain three to six pups (Cole and Batzli, 1979; Solomon et al., 2004; Kenkel et al., 2017, 2023). Laboratory-bred prairie voles are commonly separated from their parents and housed with one or more same-sex siblings after 20–21 days to avoid exposure to subsequent litters, as this exposure can influence neurophysiology and behaviour (Lonstein and De Vries, 2000; Greenberg et al., 2012). In the wild, however, offspring often reside in the parental nest their entire lives, likely engaging in the care of younger siblings, while those that leave to start their own families may wait until they are 34–36 days old (Getz and Hofmann, 1986; Kenkel et al., 2017).

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

Reproductive behaviour, pair-bonding, and biparental care

Females, although capable of reaching reproductive maturity and becoming sexually active at the time of weaning, require exposure to an unrelated, intact male or his soiled bedding to attain reproductive maturity (e.g., increased uterine weight and displays of behavioural oestrus in the form of lordosis; Carter et al., 1980, 1987; Witt et al., 1988). Mating in prairie voles occurs in extended bouts often lasting more than 24 hours (Witt et al., 1988). Unlike most mammals, after mating, prairie voles form long-term, quasi-monogamous social pair bonds, as well as engage in biparental care.

Although not all individuals are strictly sexually monogamous (Solomon et al., 2004), evidence of pair bond formation has been recorded both in the field and laboratory (Getz et al., 1981; Getz and Hofmann, 1986; Roberts et al., 1998; Barrett et al., 2013). Evidence of such relationships in the field comes from live-trap data of specific animals regularly captured near particular nests or repeatedly trapped with the same opposite-sex partner over time (Getz et al., 1981; Getz and Hofmann, 1986). In laboratory settings, pair bonding is operationally measured as a preference for spending time with a familiar opposite-sex partner with which an individual has mated or cohabited over a novel opposite-sex stranger, as well as increased aggression towards strangers of both sexes (Getz et al., 1981; Winslow et al., 1993; Roberts et al., 1998; Barrett et al., 2013).

Paternal care has been inferred from field observations of males residing in nests with partner females and their offspring, as well as recorded in laboratory settings (Getz and Hofmann, 1986; Roberts et al., 1998; Terleph et al., 2004; McGuire and Bemis, 2007; Ophir et al., 2007). Variability in paternal care has also been observed between populations. Male prairie voles from Kansas, for example, are less paternal than males from Illinois, potentially due to differences in responses to peripheral vasopressin, neural sensitivity to oestrogen, and their sometimes more xeric environments (Roberts et al., 1998; Cushing et al., 2001, 2004).

Neurophysiology

Given the rarity of monogamous pair bonding and biparental care in mammals, the presence of such social characteristics in prairie voles has made them a preferred rodent model for research on the biological basis of these social behaviours. Consequently, for more than 30 years, researchers have used prairie voles to characterize the neurophysiological and endocrine basis of pair bonding and biparental care, as well as the impact of social isolation on social mammals. Investigations utilizing these animals have given considerable attention to oxytocin and vasopressin, although the roles of dopamine, corticotropin releasing factor (CRF), corticosterone (CORT), and opioid receptors have also been examined (Aragona et al., 2006; Barrett et al., 2013; Berendzen et al., 2023; Burkett et al., 2011; DeVries et al., 1995; Inoue et al., 2013; Keebaugh and Young, 2011; Lim et al., 2004; Lim et al., 2005; Lim et al., 2007; Liu and Wang, 2003; Resendez et al., 2012, 2013; Williams et al., 1994; Winslow et al., 1993).

Oxytocin and vasopressin

Central oxytocin and vasopressin activity, often respectively in the female nucleus accumbens (NACC) and male ventral pallidum (VP), have long been associated with social behaviours in prairie voles (Winslow et al., 1993; Williams et al., 1994; Liu and Wang, 2003; Lim et al., 2004; Keebaugh and Young, 2011; Barrett et al., 2013; Berendzen et al., 2023). Research has demonstrated that infusions of oxytocin into the lateral ventricle of ovariectomized females induce a preference for a partner male over a novel stranger, while simultaneously infusing an oxytocin antagonist blocks partner preference formation (Williams et al., 1994; Liu and Wang, 2003). Furthermore, overexpression of oxytocin receptors (OTRs) in the female NACC also induces more affiliative behaviours towards partners by females and more alloparental behaviours towards unfamiliar pups (Keebaugh and Young, 2011). Notably, however, one recent study utilizing prairie voles lacking functional OTRs has called into question the necessity of oxytocin for pair bonding in prairie voles, as both males and females lacking OTRs still exhibited pair

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

bonding (Berendzen et al., 2023). Similar studies of the role of vasopressin in social monogamy in male prairie voles demonstrate that blocking V1a receptors (V1aRs) in the brain before mating can prevent selective aggression towards unfamiliar conspecifics and partner preference formation, while down-regulating V1aRs in the VP impairs partner preference formation without impacting alloparental behaviours (Winslow et al., 1993; Barrett et al., 2013).

Dopamine, corticotropin releasing factor, corticosterone, and opioid receptors

Research into the roles of other potential neurochemical and endocrine mediators of social behaviour highlights several additional mechanisms, with many acting in the NACC and other parts of the striatum (e.g., caudate putamen [CP]). In the NACC, the binding of dopamine to D2-like receptors (D2Rs) facilitates pair bond formation while binding to D1-like receptors (D1Rs) prevents it (Liu and Wang, 2003; Aragona et al., 2006; Loth and Donaldson, 2021). CRF activity in the NACC, likely mediated through CRF1 and CRF2 receptors, helps facilitate partner preference formation in males (Lim et al., 2007). In females, μ-opioid receptors (MORs) in the rostral dorsomedial area of the NACC shell and CP help facilitate partner preference formation, while MORs in the dorsal striatum are important for mating behaviour (Burkett et al., 2011; Resendez et al., 2013). Additionally, κ-opioid receptors in the NACC shell play a role in selective aggression, although MORs in this region do not (Resendez et al., 2012). Peripherally, CORT, a stress hormone released downstream of the actions of CRF, blocks the formation of new pair bonds but does not effect established pair bonds when administered to female prairie voles (DeVries et al., 1995; Cacioppo et al., 2015a).

Social isolation as a form of chronic stress

Mammalian stress responses can be activated by real or perceived threats, trauma, minor chronic stressors, psychosocial stress, and, in humans, maladaptive coping mechanisms. Such responses are largely mediated by the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS;Carabotti et al., 2015 ; Cacioppo et al., 2015a ; Misiak et al., 2020).

When the HPA axis is activated by signals from the prefrontal cortex (PFC), as well as limbic regions such as the amygdala and bed nucleus of the stria terminalis (BNST), CRF is released from the hypothalamus. CRF then acts on both the locus coeruleus and the anterior pituitary. The locus coeruleus, which can also receive signals from the PFC and various limbic structures, proceeds to release norepinephrine throughout the brain, while the anterior pituitary releases adrenocorticotropic hormone (ACTH) into the animal's circulation, where it is transported to the adrenal glands. Upon activation by ACTH, the adrenal cortices release CORT into the animal's blood, where it is transported throughout the body (Carabotti et al., 2015; Cacioppo et al., 2015a; Misiak et al., 2020). CORT's major effects include increased gluconeogenesis, increased protein metabolism, and attenuation of immune responses (Misiak et al., 2020). Notably, CORT also serves as a negative feedback mechanism, acting on both the hypothalamus and anterior pituitary (Misiak et al., 2020). The SNS comprises numerous sympathetic nerve fibres that act on major organ systems both directly through the release of norepinephrine and indirectly through the stimulation of the adrenal medulla, which, in turn, releases epinephrine and norepinephrine, which then influence the functions of various organs, as well as metabolic and immune activity (Cacioppo et al., 2015a).

Although beneficial in the context of surviving an immediate or short-term threat, chronic activation of these systems, even when stressors are relatively mild, can lead to low levels of systemic inflammation and signs of metabolic disease (McEwen, 2007; Cacioppo et al., 2015a; Gjerstad et al., 2018; Misiak et al., 2020). Additionally, *in vitro*, norepinephrine is associated with the increased growth and possible virulence of some pathogenic bacterial species (Anderson and Armstrong, 2006; Cogan et al., 2007).

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

Effects of social stress on social mammals

For social mammals, extended social isolation is a form of chronic stress that affects such organisms through the same systems as more standard stressors and has comparable effects on health and well-being (Hawkley et al., 2012; Cacioppo et al., 2015a). In humans, perceived loneliness is associated with premature death and reduced mental, cardiovascular, cognitive, and metabolic health (Cacioppo et al., 2015b; Valtorta et al., 2016; Holt-Lunstad, 2018; Sutin et al., 2020; Henriksen et al., 2023). Additionally, isolation following a stressful life event is associated with greater symptoms of clinical illness following rhinovirus exposure (Cohen et al., 2012).

Given the highly social nature of prairie voles and extensive research on the biological basis of their social behaviours, these animals have long been considered an excellent model organism for exploring questions about the impact of social stressors on social mammals in general and social isolation more specifically. In social isolation studies utilizing prairie voles, animals are generally housed either with a same-sex sibling or in isolation for 4–8 weeks, then behaviourally assessed before euthanasia and tissue sample collection (Grippo et al., 2007a, 2007b, 2007c, 2008; Normann et al., 2021).

Behavioural assessments typically entail placing animals in one or more behavioural assays to measure proxies of anxiety and depression. The elevated plus maze (EPM), forced swim test (FST), and sucrose preference test (SPT) are among those that have been utilized (Grippo et al., 2007a, 2007b, 2007c, 2008; Normann et al., 2021). The EPM is used to assess behavioural signs of anxiety (Walf and Frye, 2007; Normann et al., 2021). The FST and SPT are behavioural tests of depressive symptomology (Grippo et al., 2002, 2003, 2008; Strekalova et al., 2004). Sometimes, additional physiological measures (e.g., heart rate and heart rate variability) are also collected (Grippo et al., 2007c, 2008).

Analyses generally show isolated prairie voles engage in more behaviours indicative of anxiety and depression than paired controls (Grippo et al., 2007a, 2007b, 2007c, 2008; Normann et al., 2021). Additionally, isolated prairie voles demonstrate more signs of cardiovascular dysfunction, including tachycardia and decreased heart rate variability, likely due to dysregulated autonomic nervous system (ANS) activity (Grippo et al., 2007c, 2008). Research on social isolation's cardiovascular and autonomic effects indicates isolated prairie voles physiologically respond to non-threatening environments in the same manner they respond to threatening ones, as well as take longer to recover from additional social stressors like being placed in the cage of an unfamiliar conspecific as part of a resident intruder test (RIT; Grippo et al., 2007c).

Studies examining the neurophysiological and hormonal effects of social isolation on prairie voles beyond the ANS, although sometimes inconsistent, generally reveal changes in parts of the brain and in central and peripheral neurohormones associated with both stress and social behaviour such as increased CRF immunoreactivity in the paraventricular nucleus of the hypothalamus (PVN) and vasopressin immunoreactivity in the supraoptic nucleus of the hypothalamus (Ruscio et al. 2007).

Some sex-specific differences in responses to social isolation have also been found in prairie voles. Females, but not males, show an increase in circulating OT, an increase in OT immunoreactive cell density in the PVN, and a decrease in AVP immunoreactivity in the PVN (Grippo et al., 2007b; Ruscio et al. 2007). Findings regarding the impact of social isolation on circulating CORT have been inconsistent (Donovan et al., 2020b; Grippo et al., 2007b; Ruscio et al., 2007).

Research assessing whether social isolation alters how prairie voles respond to additional social stressors, such as those experienced in the RIT, shows that following the RIT, isolated females exhibit elevated circulating oxytocin, vasopressin, and CORT, as well as more oxytocin and CRF immunoreactive cells in the PVN (Grippo et al., 2007a, 2007b). Circulating ACTH has sometimes been shown to be elevated in isolated females following the RIT (Grippo et al., 2007a, 2007b). The impact of social isolation on responses to other social stressors for males appears less pronounced, with isolated males showing increases in oxytocin immunoreactive cells in the PVN and circulating oxytocin following the RIT but no changes in CRF immunoreactive cells in the PVN or circulating ACTH or CORT (Grippo et al., 2007b).

Compared to other rodent models of stress (e.g., chronic unpredictable mild stress [CUMS]), the behavioural and physiological effects of social isolation on prairie voles are broadly consistent (Grippo et al., 2002, 2003; Walf and Frye, 2007; Jianguo et al., 2019).

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

Prairie vole gastrointestinal physiology and gut microbiota

Despite the extensive body of work examining the nervous and endocrine systems of prairie voles, and the impact of social isolation on these systems, there has been limited examination of the prairie vole gastrointestinal system and microbiome, or how it is impacted by social isolation, leaving ample opportunity for further inquiry (Assefa et al., 2015; Curtis et al., 2018; Supeck et al. 2018; Donovan et al., 2020a, 2020b; Hume et al., 1993; Kenkel et al., 2023; Nuccio et al., 2023; Young Owl and Batzli, 1998). Animal microbiomes comprises the microbial organisms living in or on a host, although many discussions focus specifically on bacteria. In humans, estimates suggest bacterial cells roughly equal the number of host cells and include representatives from 500 to 1000 species, although this number ultimately may be substantially higher as previously uncharacterized taxa are discovered (Sender et al., 2016; Gilbert et al., 2018; Pasolli et al. 2019). Across mammalian microbiomes, Firmicutes and Bacteroidetes are the dominant bacterial phyla present, exhibiting considerable variability in species (Krych et al., 2013; Bleich and Fox, 2015; de Jonge et al., 2022). Evolutionary history, diet, and stress are among the factors that influence microbiome composition, as is exposure to natural environments (Gilbert et al., 2018; de Jonge et al., 2022). Generally, the microbiomes of wild animals are more diverse than those of their captive counterparts (de Jonge et al., 2022). In rodents specifically, studies comparing the gut microbiota of lab-raised animals and wild conspecifics demonstrate this pattern in mice (*Mus musculus domesticus*) and deer mice (*Peromyscus maniculatus*; Rosshart et al., 2019; Schmidt et al., 2019).

Different body sites and their subdivisions are generally treated as distinct ecosystems by microbiome researchers. Of the different body sites, the gut tends to be the most intensely studied, likely because the colon microbiome contains a greater number of bacterial cells and greater community diversity than other locations (Fukuda and Ohno, 2014; Bleich and Fox, 2015). The potential influence of these communities on host behaviour, physiology, and disease is among the dominant topics explored in microbiome research (Gilbert et al., 2018; Johnson and Foster, 2018; Wu et al., 2021). In part, this is likely because perturbations to an animal's gut microbiome play a role in numerous diseases, including inflammatory bowel disease, colorectal cancer, diabetes, obesity, and Alzheimer's (Delzenne and Cani, 2011; Devaraj et al., 2013; Kostic et al., 2014; Halfvarson et al., 2017; Zhang et al., 2021; Noureldein et al., 2022; Molinero et al., 2023; Sadagopan et al., 2023).

Although further investigation is necessary for the determination of precise mechanisms, evidence suggests certain microbes induce inflammation in the gut and damage gut barriers either directly or through components of their cell wall (e.g., LPS) and byproducts of their metabolism (e.g., ethanol); moreover, research shows once this damage occurs, LPS, whole bacteria, and various chemicals and antigens can enter host circulation and cause further inflammation or damage organs such as the liver and pancreas (Fukuda and Ohno, 2014). Conversely, there is also considerable research focused on the identification of probiotic bacterial taxa that can improve host health and alleviate disease (Fukuda and Ohno, 2014; Wolfe et al., 2023).

Prairie vole gastrointestinal anatomy and physiology

Early research examining the prairie vole gastrointestinal system largely focused on basic anatomy and physiology, often approaching questions from an ecological perspective. This work elucidated how food intake by prairie voles appears to be limited by the amount of time necessary for digestion, thus requiring animals to engage in regular feeding bouts every 2–4 hours, interspersed with periods of rest (Zynel and Wunder, 2002).

Such studies also provided morphometric and functional details concerning different prairie vole gastrointestinal areas, revealing the caecum to have a greater nominal surface area compared to other hindgut regions and considerable acetate abundance in the caecum and proximal colon (Hume et al., 1993). This work also demonstrated proline uptake in the small intestine via an active transport system, greater acetate uptake in the distal colon than in the caecum or proximal colon through a passive

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

mechanism when acetate is present in high concentrations, and equal levels of acetate uptake in the proximal and distal colon via a mediated system when acetate is present in low concentrations, as might occur during periods of fasting or starvation (Hume et al., 1993).

Prairie vole gastrointestinal development

More recently, a limited number of studies have examined histological, cellular, and molecular aspects of the prairie vole gastrointestinal system. One of the most comprehensive studies, Supeck et al. (2018), provided a detailed description of the postnatal maturation of the intestinal epithelial barrier in prairie vole pups. Using animals ranging in age from 2 to 8 weeks, Supeck et al. (2018) characterized the development of the prairie vole intestinal epithelial barrier using a variety of techniques. Dextran permeability assays revealed greater intestinal permeability in 2-week-old animals compared to 3-week-old animals. Histological comparisons of colon tissue from 1- and 3-week-old animals demonstrated that 3-week-old animals had a greater number of goblet cells, increased smooth muscle width, and greater gland length and distance. Examination of the expression of genes involved in tight junction formation and paracellular permeability showed several such genes were upregulated at 3 weeks compared to 2 weeks. Subsequently, Supeck et al. (2018) concluded the prairie vole intestine is mature by 3 weeks of age, suggesting this would be the minimum appropriate age for using prairie voles in MGBA research, given that a mature intestinal epithelium would decrease permeability to macromolecules that could act as confounding factors.

Later work by Kenkel et al. (2023), examining the impact of caesarean delivery on prairie vole behaviour and MGBA physiology, found that adult male prairie voles delivered in this manner, when compared to animals delivered vaginally, exhibited a lower expression of multiple proteins relevant to gut maturation. This study also found that such animals exhibited lower abundances of the bacterial family *Prevotellaceae* and higher abundances of the taxa *Clostridiales* and *Ruminococcus*. No procedures were performed, however, to determine if these reported differences were causally linked or accompanied by abnormalities in gastrointestinal histology or functioning.

Prairie vole gut microbiome characterization

Other investigations of the prairie vole microbiome include the assembly of five metagenome-assembled genomes from members of the prairie vole gut microbiome, a report on the general composition of the prairie vole gut microbiome, two studies examining the impacts of social isolation, and two studies assessing bacteria for potential probiotic properties or effects (Assefa et al., 2015; Curtis et al., 2018; Donovan et al., 2020a; Donovan et al., 2020b; Donovan et al., 2023; Nuccio et al., 2023). In addition to the study focused solely on the characterization of the prairie vole microbiome, such data are also reported in both social isolation studies and one of the probiotic studies (Curtis et al., 2018; Donovan et al., 2020b; Donovan et al., 2023; Nuccio et al., 2023).

Reports on the general composition of the prairie vole gut microbiome indicate Bacteroidetes and Firmicutes are the most abundant phyla, while *Muribaculaceae*, *Prevotellaceae*, *Ruminococcaceae*, and *Lachnospiraceae* are the most abundant families (Curtis et al., 2018; Donovan et al., 2020b; Donovan et al., 2023; Nuccio et al., 2023). These findings are consistent with descriptions of the gut communities of humans and other rodent models at the phylum level; they also bear some family-level similarities (Krych et al., 2013; Nagpal et al. 2018).

Notably, though, there have been some differences in the exact proportional abundances of some taxa between studies, as well as within studies. For example, the first study to characterize the prairie vole gut microbiome reported Firmicutes to make up 58.4% of gut communities and Bacteroidetes to make up only 26.96% of gut communities (Curtis et al., 2018). However, other researchers have found a greater proportion of the gut microbiota comprising Bacteroidetes, with some reporting this phylum to make up at least 50% of the prairie vole gut microbiome and Firmicutes to account for 40% or less of its

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

composition (Donovan et al., 2020b, 2023). Additionally, one study that used two different sequencing techniques to process the same samples found inconsistencies in community composition (Donovan et al., 2023).

The impact of social isolation on the prairie vole gut microbiome

The two studies that examined the impacts of isolation on the prairie vole gut microbiome both followed the basic experimental design of previous work in this area, but included faecal collection and analysis for microbiome comparison (Donovan et al., 2020b; Nuccio et al., 2023).

Donovan et al. (2020b) entailed the placement of prairie voles in either paired or isolated housing conditions for 6 weeks, with faecal collections gathered both before and after this period. Microbiome comparisons revealed isolated voles to exhibit a decrease in the abundance of an uncultured *Anaeroplasma* bacterium and an increase in the abundance of an uncultured *Candidatus Saccharimonas* rumen bacterium, an uncultured *Desulfovibrio* bacterium, and *Gastranaerophilales.* Paired animals exhibited a decrease in uncultured *C. Saccharimonas* rumen bacterium and an increase in a *Clostridiales* vadinBB60 group species. Additionally, sex-specific changes were observed, including a decrease in an uncultured *Ruminococcaceae* member in isolated females. Notably, members of the *Desulfovibrio* genus are broadly associated with disease, although some members may provide benefits to their hosts, while members of the *Ruminococcaceae* family are known for breaking down plant material from a host's diet and the production of SCFAs, an important source of energy for colonocytes and a potential regulator of metabolic health (Flint et al., 2007; Wu et al., 2018; Zhou et al., 2024).

Other analyses indicated isolated animals showed increased behaviours associated with anxiety, a greater expression of CRF in the NACC, an increased expression of CRF and brain-derived neurotropic factor in the amygdala, and, in isolated males, increased circulating CORT.

The second, Nuccio et al. (2023), entailed the placement of female prairie voles in either paired or isolated housing for 4 weeks, with faecal collections gathered before the start of this period, followed by weekly collections for the next 4 weeks, as well as collection of faecal content directly from the colon. Emphasized findings included a greater abundance of *Anaerostipes* in paired animals and a greater abundance of *Staphylococcaceae* and *Enterococcaceae* in isolated animals when data from all faecal time points were pooled, as well as greater abundances of *Lactobacillaceae* in paired animals and *Vampirovibrio* in isolated animals when data from the final time point were considered alone. Notably, *Lactobacillaceae* and *Anaerostipes*, respectively, are associated with the regulation of pathogen growth and the greater production of SCFAs, while *Enterococcaceaeus* and *Staphylococcaceae* are families with prominent members associated with disease (Kant et al., 2015; Fiore et al., 2019; Chia et al., 2020; Bui et al., 2021; Zawistowska-Rojek et al., 2022).

This study also reported that isolated animals exhibited behavioural signs of both anxiety and depression. Furthermore, upon examining the faecal and serum metabolomes of their animals, the authors reported several metabolomic differences between paired and isolated animals that they argued were indicative of declining health in isolated animals. Specifically, they suggested that lower serum lactic acid and higher serum sorbitol and glyoxylic acid observed in isolated animals were consistent with the development of pre-diabetes or type-2 diabetes, while increased faecal succinate in isolated animals was consistent with an earlier characterization of colitis in a rodent model (Preston and Calle, 2010; Nikiforova et al., 2014; Osaka et al., 2017; Mora-Ortiz et al., 2019).

Despite the differences in specific bacterial taxa found by the two studies when isolated and paired animals were compared, both studies seemed to reveal isolated animals to have greater abundances of taxa associated with poor health and lower abundances of putatively beneficial taxa, including those associated with SCFA production. The metabolite profiles reported by Nuccio et al. (2023) also indicate that isolated animals were less healthy. However, neither study directly examined the physiological mechanisms that mediated the differences reported. They also did not directly examine whether the microbiome or metabolite profiles observed resulted in gastrointestinal or metabolic disease.

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

Probiotics

Of the two published, peer-reviewed probiotic studies utilizing prairie voles, one focused on the identification of possible probiotic bacteria, while the other focused on the effects of administering what was thought to be a probiotic species (Assefa et al., 2015; Donovan et al., 2023).

The former characterized 30 *Lactobacillus* strains found in the prairie vole gut, assessing them for their probiotic potential (Assefa et al., 2015). Five were found to adhere well to intestinal epithelial cells, tolerate low pH environments and bile, and demonstrate anti-fungal and anti-bacterial properties, inhibiting the growth of *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus.*

The latter study examined how administering *Limosilactobacillus reuteri* to prairie voles impacted their behaviour, neurophysiology, and gut microbiota (Donovan et al., 2023). In this study, however, the researchers did not have a true control condition, instead comparing animals receiving live *Lactobacillus reuteri* to those receiving heat-killed *L. reuteri.* Interestingly, they found animals administered live bacteria exhibited less social behaviour, more CRF, and fewer vasopressin receptors in the PVN, and less CRF and fewer CRF2 receptors in the NACC, while males exhibited more CRF in the amygdala. Upon examining the possible impact of administering live or heat-killed *L. reuteri* on the gut microbiome, the researchers found numerous differences in taxa, including an increase in the potentially beneficial species, *Bifidobacterium boum*, in females administered heat-killed *L. reuteri* and decreased abundances of the potential pathogen, *Capnocytophaga canis.* Additionally, when performing correlational analyses on different neurophysiological measures and gut bacteria, they found in females positive correlations between *Methanobrevibacter oralis* and CRF in the PVN, *Prevotella* and CRF in the PVN, *Desulfovibrio* and vasopressin receptors in the PVN, and *Desulfovibrio* and both V1aRs in the PVN and CRF2 in the NACC.

The authors of this study attributed differences between animals receiving live and heat-killed *L. reuteri* to the administration of the bacterium, although, as with the social isolation studies, to incorporate a microbiome component, a precise mechanism was not identified through the work directly carried out in the study. However, the authors did note that the administration of heat-killed *Lactobacillus* species has been reported to yield physiological and behavioural effects on animals in previous studies, potentially through bacterial proteins, lipids, or metabolites that remain after bacteria are killed. They also suggested that the lower sociality exhibited by animals administered live *L. reuteri* was potentially linked to greater amounts of CRF in the PVN and deficits in CRF and CRF2 in the NACC in these animals, as the actions of CRF on CRF2 in the NACC previously have been linked to social behaviour in prairie voles. Additionally, it is worth noting that, given this study did not have a true control condition, it is unclear whether the administration of live *L. reuteri* led to some of the apparent deficits in these animals, had no effect, or perhaps improved animals compared to an unmeasured baseline but not as much as heat-killed *L. reuteri.*

Microbiological research in prairie voles beyond the gut

Microbiological research utilizing prairie voles for investigations outside the gut has been limited. One study from the social isolation literature that examined the effects of social isolation and aggregate stressors on immune functioning using a bacterial killing assay found that plasma from males housed with same-sex siblings showed greater antibiotic capabilities against *E. coli* than plasma from isolated counterparts (Scotti et al., 2015). It also demonstrated plasma from isolated females to have less antibiotic capability following placement in the RIT than that of paired females, suggesting social stressors, including isolation, can have an aggregate effect in attenuating immune functioning (Scotti et al., 2015). A second study which, to the best of our knowledge, is the only published study to examine any component of the prairie vole microbiome outside of the gut and the only prairie vole microbiome study to use animals housed outside of a standard lab environment, characterized the oral microbiome of prairie voles in a lab setting, as well as that of animals transferred to semi-natural outdoor enclosures

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

(Sabol et al., 2023). This study found Firmicutes to be the dominant phylum in the prairie vole oral microbiome, followed by Proteobacteria, Bacteroidetes, Actinobacteria, and Fusobacteria, regardless of whether animals were housed in a lab or an outdoor enclosure. At the family level, they established what they described as a core oral microbiome comprising 14 families. Upon comparing the oral microbiomes of prairie voles housed in the lab and in the outdoor enclosures, they found prairie voles exhibited greater alpha-diversity when in the outdoor enclosures and speculated this was due to differences in diet or oral contact with soil when burrowing or foraging. Changes in oral communities after animals were placed in outdoor enclosures entailed a decrease in the abundance of core families and an increase in others. Notably, the authors also reported that sociality had no influence on oral microbiome communities and that the oral microbiomes of siblings became more dissimilar as animals spent more time in the outdoor enclosures, suggesting the immediate environment may have a greater influence on the prairie vole oral microbiome than genetic relatedness.

Considerations for future research

Previously proposed directions for future research regarding the prairie vole MGBA include investigating the MGBA's potential role in social behaviours like mate choice and parental care, how this system is altered in paired or parental animals, whether isolation-induced gut microbiome perturbations can be reversed through probiotics, and whether isolation-induced gut microbiota changes broadly associated with metabolic disease are indicative of disease development in these animals (Assefa et al., 2015; Donovan et al., 2020b ; Nuccio et al., 2023). Moving forward, certain considerations should be taken into account by researchers, although it should be noted that many of the matters to which these considerations pertain are not unique to the use of prairie voles.

Procedural considerations in microbiome research

In microbiome research, there are numerous decisions researchers must make that can impact the results and interpretation of their work. These include how samples are collected and stored, the means by which bacterial cells are lysed, which hypervariable regions of the 16S rRNA gene are selected for amplification, which sequencing method is implemented, and how quality control measures are set before taxonomic assignment (Robinson et al., 2016; Gloor et al. 2017; Nearing et al., 2022).

Differences in such decisions regarding protocol may, in fact, account for some of the discrepancies in the composition of the prairie vole faecal microbiome seen across studies in which the general compositions reported were similar, but specific percentages for the proportional abundance of even major taxa were quite different (Curtis et al., 2018; Donovan et al., 2020b, 2023; Nuccio et al., 2023). Such considerations were also highlighted in one prairie vole microbiome study in which multiple sequencing techniques were used on the same samples, but yielded different results (Donovan et al., 2023).

Similarly, the tools and analyses used for statistical comparison can influence one's results, as such tools and analyses may differ in their false discovery rates and their compatibility with the compositional nature of microbiome datasets (Gloor et al. 2017; Nearing et al., 2022). Potentially, differences such as tools and analyses may help explain the inconsistencies in findings from different microbiome studies, such as those of the two social isolation studies that examined the prairie vole microbiome (Donovan et al., 2020b; Nuccio et al., 2023).

Animal models

Despite the noted value of animal models in biomedical research, there is growing concern over conflicting results across studies using animal models and the implications this can have for translating findings from lab animals to their wild counterparts or to humans in clinical settings (Bleich and Fox, 2015; Omary et al., 2016; Rosshart et al., 2019). Suggested remedies include stricter and more

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

standardized reporting requirements for variables like age, sex, genetic background, bedding composition, and diet (Omary et al., 2016).

Of the variables enumerated above, diet is of particular importance for MGBA research, as it can impact gut anatomy, physiology, and microbiome composition, as well as behaviour, cognition, and metabolic health (Pellizzon and Ricci, 2020; Thigpen et al. 2004). However, despite its importance, the authors of relevant reviews highlight that information regarding diet composition, nutrient concentration, and the possible inclusions of non-nutritive components (e.g., phytoestrogens, heavy metals, mycotoxins, and endotoxins), to the extent such details can be known, are generally omitted from published research reports. Moreover, the authors of such reviews note how even commonly used laboratory diets purchased from manufacturers can vary considerably and affect animal phenotype (Pellizzon and Ricci, 2020). Specifically, such authors note how grain-based diets can vary in the concentration of the ingredients, nutrients, and non-nutritive components present, while purified diets, although more consistent and less prone to contamination, may be deficient in the kinds of fibres used by gut microbes for fermentation (Pellizzon and Ricci, 2020).

Additionally, for work examining the microbiome, researchers have highlighted that free-living animals, including humans, evolved in a "microbial world," and that those living in "sanitized environments" are ecologically and microbially different (Rosshart et al., 2019). This has been repeatedly demonstrated, including in studies examining the microbiomes of different rodents (Rosshart et al., 2019; Schmidt et al., 2019; Sabol et al., 2023). It has also been suggested that failure to take this into account can have devastating results for human participants in clinical research, in part, due to differences in the immune functioning of humans and standard lab mice that are downstream of the latter having spent their entire lives in sanitized environments (Rosshart et al., 2019).

Suitability of prairie voles for MGBA research and comparison to other models

The extent to which different concerns about the use of more standard lab animals, such as mice, apply to the use of prairie voles is largely unknown, given the dearth of research on this topic. Animal age and sex are routinely reported in prairie vole research, while possible sex differences are regularly discussed, if not examined directly. Genetically, animals are usually reported as being descended from wild prairie voles initially captured in central Illinois and regularly outbred to maintain genetic diversity within colonies.

Possible retention of wild features

Given the findings of research using "wilding" mice, the fact that prairie voles are regularly outbred may lend additional support for their use in MGBA and microbiome research. Wilding mice are created via the transfer of embryos from lab mice to wild mice. They can possess the genetic background desired by a researcher, but retain a more natural and less easily perturbed microbiome, as well as more natural immune gene expression (Rosshart et al., 2019).

Subsequently, we argue, it is reasonable to hypothesize that prairie voles retain more "wild" gut microbiomes and immune gene expression profiles. If this holds true, standard practices in prairie vole husbandry may facilitate the utilization of animals with more natural microbiomes and immune gene expression under controlled conditions.

However, we also acknowledge work with deer mice in which wild individuals were transferred to a lab setting has shown that the gut microbiomes of these animals become more similar to those of lab-born animals over time (Schmidt et al., 2019), suggesting prairie voles, once brought into the lab, may lose the features of a "wild" gut microbiome due to changes in diet, environment, and stress.

Prairie vole diet

Research pertaining to the effects of diet on prairie voles is limited. Early work on this topic demonstrated that prairie voles prefer dicotyledons such as alfalfa and clover to monocotyledons of comparatively lower nutritional value, but will still eat monocotyledons, and sometimes supplement their diet with

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

seeds and insects, depending on what food items are available (Cole and Batzli, 1979). Prairie voles with access to preferred higher quality food exhibit greater life expectancy and reproductive success than conspecifics in habitats dominated by lower quality food items (Cole and Batzli, 1979). When fed more fibrous, less digestible grass instead of alfalfa, gastrointestinal changes occur (e.g., increased gastrointestinal tract size), presumably as a compensatory mechanism (Young Owl and Batzli, 1998). Additionally, when fed rabbit chow, they exhibit greater reproductive success and greater weight after weaning compared to animals fed a more natural diet of alfalfa (Cole and Batzli, 1979). Given that rabbit chows are routinely fed to prairie voles used in laboratory environments, this may suggest the baseline health of prairie voles used in research might be better than that of their wild counterparts. However, to the best of our knowledge, the physiological reasons and broader implications of these findings remain unexplored, as does the effect of diet and lab-housing on the prairie vole gut microbiome.

Comparison with other rodent models

As for the suitability of prairie voles as subjects for MGBA and microbiome research compared to other rodent models, we hold that these animals are a viable option for MGBA or microbiome research with a social component intended to have relevance to humans, most notably due to similarities in their social systems and behaviours (Lee and Beery, 2019). We also suggest that the applicability of prairie vole microbiome research to humans is likely comparable to the applicability of microbiome research utilizing other rodent models. Although direct comparisons of the human microbiome to those of various models are limited, such research suggests the microbiomes of humans and lab-housed mammals, including mice and rats, qualitatively share a large number of taxa, but that the proportional abundances of these taxa vary considerably (Krych et al., 2013; Nagpal et al. 2018). This has been suggested to likely be due to the evolutionary distance between species and differences in diet (Krych et al., 2013; Nagpal et al. 2018).

Although, to the best of our knowledge, direct comparisons of the human and prairie vole microbiomes have not been performed, previous descriptions of the prairie vole microbiome indicate it is reasonable to hypothesize similar patterns would emerge if direct comparisons were made (Curtis et al., 2018; Donovan et al., 2020b, 2023; Nuccio et al., 2023).

With that stated, we also acknowledge there are certain drawbacks to the use of prairie vole in MGBA and microbiome research. Much more is known about the MGBAs and microbiomes of mice and rats, which can make the development of future research questions and interpretation of subsequent results easier. Also, more is known about how the gastrointestinal systems of mice and rats compare to those of humans. Furthermore, the genetic and environmental distance of such animals from their wild counterparts helps reduce genetic variability, as well as microbial variability. However, once more, this can introduce different questions regarding how applicable one's results are outside of a lab or beyond a specific strain of lab rodent (Rosshart et al., 2019).

Future opportunities

Moving forward, there are ample opportunities for further exploring both basic and applied questions pertaining to the prairie vole MGBA. At present, it is unknown if and how the prairie vole gut microbiome varies between subpopulations or changes in females based on reproductive factors. Additionally, further investigation is required to determine the extent to which the prairie vole microbiome differs between wild and lab-housed animals, as well as the effect of such potential differences on prairie vole immune functioning.

As discussed, prairie voles offer relatively unique opportunities for researchers looking to examine social components of the MGBA. The utilization of the standard design implemented in social isolation studies in conjunction with measures of gut permeability offers researchers the opportunity to examine social stress's effects on gut integrity (Donovan et al., 2020b; Nuccio et al., 2023). By also measuring the presence of inflammatory markers such as LPS and proinflammatory molecules, researchers can

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

examine whether social isolation is associated with systemic inflammation, as has been done in the CUMS literature (Zhang et al., 2023). Additionally, given that elevated LPS in circulation and systemic inflammation are associated with poor metabolic health, one could test for indicators of declining metabolic health associated with LPS, such as increased fasted glycaemia and insulinaemia (Cani et al., 2007). One could also test whether the administration of specific probiotics can attenuate those or other negative health effects spurred by social isolation.

Conclusion

The highly social nature of prairie voles, along with the large bodies of work concerning the biological basis of their social behaviours and the effects of social isolation on these animals, makes prairie voles ideal model organisms for investigating how the MGBA influences the social behaviour of social mammals, as well as how it is influenced by the social environment. Moreover, given that social isolation generally is viewed as a form of chronic stress for social mammals, and that chronic stress has been linked to gut microbiome perturbations, signs of increased gut permeability, and indicators of metabolic disease and systemic inflammation in other rodent species (Zhang et al., 2023), we argue that prairie voles could serve as an excellent rodent model for the exploration of how the stress of social isolation may act through the MGBA to impact metabolic health. However, given that the prairie vole microbiome is not as well characterized as that of other rodent models, further research is needed to establish what approximates a baseline or core prairie vole microbiome. Furthermore, researchers will need to explore how the prairie vole microbiome may differ between wild and lab-housed animals, and what implications this has on immune functioning when translating some basic research findings to clinical settings. They will also have to determine how factors such as subpopulation, sex, age, and diet may influence both the MGBA and gut microbiome. Yet, it is worth pointing out that these problems are not unique to those working with prairie voles, as there are comparable if not identical challenges researchers are still working to overcome, even when using more common animal models such as mice.

Acknowledgements. The authors would like to thank Dr. Richard Ortiz for his insights and feedback on an early version of this article.

Author contribution. Conceptualization: D.A.N., P.S.; Compiling data: D.A.N.; Funding acquisition: P.S., A.G.; Supervision: P.S., A.G.; Writing – original draft: D.A.N., P.S.; Writing – review and editing: D.A.N., P.S., A.G.

Funding. This project was funded in part by the National Institutes of Health grants R15 DK140841 and HL179691.

Disclosure statement. The authors have no relevant interests to declare.

References

Anderson MT and **Armstrong SK** (2006) The *Bordetella* bfe system: Growth and transcriptional response to siderophores, catechols, and neuroendocrine catecholamines. *Journal of Bacteriology* **188**(16), 5731–5740. https://doi.org/10.1128/JB.00495-06.

Aragona BJ, **Liu Y**, **Yu YJ**, **Curtis JT**, **Detwiler JM**, **Insel TR** and **Wang Z** (2006) Nucleus accumbens dopamine differentially mediates the formation and maintenance of monogamous pair bonds. *Nature Neuroscience* **9**(1), 133–139. https://doi.org/10.1038/nn1613.

Assefa S, **Ahles K**, **Bigelow S**, **Curtis JT** and **Köhler GA** (2015) *Lactobacilli* with probiotic potential in the prairie vole (*Microtus ochrogaster*). *Gut Pathogens* **7**, 35. https://doi.org/10.1186/s13099-015-0082-0.

Barrett CE, **Keebaugh AC**, **Ahern TH**, **Bass CE**, **Terwilliger EF** and **Young LJ** (2013) Variation in vasopressin receptor (*Avpr1a*) expression creates diversity in behaviors related to monogamy in prairie voles. *Hormones and Behavior* **63**(3), 518–526.

Berendzen KM, **Sharma R**, **Mandujano MA**, **Wei Y**, **Rogers FD**, **Simmons TC**, **Seelke AM**, **Bond JM**, **Larios R**, **Goodwin NL**, **Sherman M**, **Parthasarthy S**, **Espineda I**, **Knoedler JR**, **Beery A**, **Bales KL**, **Shah NM** and **Manoli DS** (2023) Oxytocin receptor is not required for social attachment in prairie voles. *Neuron* **111**(6), 787–796.

Bleich A and **Fox JG** (2015) The mammalian microbiome and its importance in laboratory animal research. *ILAR Journal* **56**(2), 153–158. https://doi.org/10.1093/ilar/ilv031.

Bui T, **Mannerås-Holm L**, **Puschmann R**, **Wu H**, **Troise AD**, **Nijsse B**, **Boeren S**, **Bäckhed F**, **Fiedler D** and **deVos WM** (2021) Conversion of dietary inositol into propionate and acetate by commensal *Anaerostipes* associates with host health. *Nature Communications* **12**(1), 4798. https://doi.org/10.1038/s41467-021-25081-w.

Burkett JP, **Spiegel LL**, **Inoue K**, **Murphy AZ** and **Young LJ** (2011) Activation of μ-opioid receptors in the dorsal striatum is necessary for adult social attachment in monogamous prairie voles. *Neuropsychopharmacology* **36**(11), 2200–2210. https://doi.org/10.1038/npp.2011.117.

Cacioppo JT, **Cacioppo S**, **Capitanio JP** and **Cole SW** (2015a) The neuroendocrinology of social isolation. *Annual Review of Psychology* **66**, 733–767. https://doi.org/10.1146/annurev-psych-010814-015240.

Cacioppo S, **Grippo AJ**, **London S**, **Goossens L** and **Cacioppo JT** (2015b) Loneliness: Clinical import and interventions. *Perspectives on Psychological Science* **10**(2), 238–249. https://doi.org/10.1177/1745691615570616.

Cani PD, **Amar J**, **Iglesias MA**, **Poggi M**, **Knauf C**, **Bastelica D**, **Neyrinck AM**, **Fava F**, **Tuohy KM**, **Chabo C**, **Waget A**, **Delmée E**, **Cousin B**, **Sulpice T**, **Chamontin B**, **Ferrières J**, **Tanti JF**, **Gibson GR**, **Casteilla L**, **Delzenne NM**, **Alessi MC** and **Burcelin R** (2007) Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **56**(7), 1761–1772. https://doi.org/10.2337/db06-1491.

Carabotti M, **Scirocco A**, **Maselli MA** and **Severi C** (2015) The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology* **28**(2), 203–209.

Carter CS and **Getz LL** (1993) Monogamy and the prairie vole. *Scientific American* **268**(6), 100–106. https://doi.org/10.1038/scientificamerican0693-100.

Carter CS, **Getz LL**, **Gavish L**, **McDermott JL** and **Arnold P** (1980) Male-related pheromones and the activation of female reproduction in the prairie vole (*Microtus ochrogaster*). *Biology of Reproduction* **23**(5), 1038–1045. https://doi.org/10.1095/biolreprod23.5.1038.

Carter CS, **Witt DM**, **Schneider J**, **Harris ZL** and **Volkening D** (1987) Male stimuli are necessary for female sexual behavior and uterine growth in prairie voles (*Microtus ochrogaster*). *Hormones and Behavior* **21**(1), 74–82.

Careaga M, **Schwartzer J** and **Ashwood P** (2015) Inflammatory profiles in the BTBR mouse: How relevant are they to autism spectrum disorders? *Brain, Behavior, and Immunity* **43**, 11–16. https://doi.org/10.1016/j.bbi.2014.06.006.

Chia LW, **Mank M**, **Blijenberg B**, **Aalvink S**, **Bongers RS**, **Stahl B**, **Knol J** and **Belzer C** (2020) *Bacteroides thetaiotaomicron* fosters the growth of butyrate-producing *Anaerostipes caccae* in the presence of lactose and total human milk carbohydrates. *Microorganisms* **8**(10), 1513. https://doi.org/10.3390/microorganisms8101513.

Cogan TA, **Thomas AO**, **Rees LE**, **Taylor AH**, **Jepson MA**, **Williams PH**, **Ketley J** and **Humphrey TJ** (2007) Norepinephrine increases the pathogenic potential of *campylobacter jejuni*. *Gut* **56**(8), 1060–1065. https://doi.org/10.1136/gut.2006.114926.

Cohen S, **Janicki-Deverts D**, **Doyle WJ**, **Miller GE**, **Frank E**, **Rabin BS** and **Turner RB** (2012) Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proceedings of the National Academy of Sciences* **109**(16), 5995–5999.

Cole FR and **Batzli GO** (1979) Nutrition and population dynamics of the prairie vole, *Microtus ochrogaster*, in Central Illinois. *Journal of Animal Ecology* **48**(2), 455–470. https://doi.org/10.2307/4172.

Costa CFFA, **Ferreira-Gomes J**, **Barbosa F**, **Sampaio-Maia B** and **Burnet PWJ** (2024) Importance of good hosting: Reviewing the bi-directionality of the microbiome-gut-brain-axis. *Frontiers in Neuroscience* **18**, 1386866. https://doi.org/10.3389/fnins.2024.1386866.

Curtis JT, **Assefa S**, **Francis A** and **Köhler GA** (2018) Fecal microbiota in the female prairie vole (*Microtus ochrogaster*). *PLoS One* **13**(3), e0190648. https://doi.org/10.1371/journal.pone.0190648.

Cushing BS, **Martin JO**, **Young LJ** and **Carter CS** (2001) The effects of peptides on partner preference formation are predicted by habitat in prairie voles. *Hormones and Behavior* **39**(1), 48–58. https://doi.org/10.1006/hbeh.2000.1633.

Cushing, B. S., **Razzoli, M.**, **Murphy, A. Z.**, **Epperson, P. M.**, **Le, W. W.**, **& Hoffman, G. E.** (2004). Intraspecific variation in estrogen receptor alpha and the expression of male sociosexual behavior in two populations of prairie voles. *Brain Research*, 1016, **2**, 247–254. https://doi.org/10.1016/j.brainres.2004.05.010

de Jonge N, **Carlsen B**, **Christensen MH**, **Pertoldi C** and **Nielsen JL** (2022) The gut microbiome of 54 mammalian species. *Frontiers in Microbiology* **13**, 886252. https://doi.org/10.3389/fmicb.2022.886252.

Delzenne NM and **Cani PD** (2011) Gut microbiota and the pathogenesis of insulin resistance. *Current Diabetes Reports* **11**(3), 154–159. https://doi.org/10.1007/s11892-011-0191-1.

Devaraj S, **Hemarajata P** and **Versalovic J** (2013) The human gut microbiome and body metabolism: Implications for obesity and diabetes. *Clinical Chemistry* **59**(4), 617–628. https://doi.org/10.1373/clinchem.2012.187617.

DeVries AC, **DeVries MB**, **Taymans S** and **Carter CS** (1995) Modulation of pair bonding in female prairie voles (*Microtus ochrogaster*) by corticosterone. *Proceedings of the National Academy of Sciences* **92**(17), 7744–7748. https://doi.org/10.1073/pnas.92.17.7744.

Donovan M, **Lynch M**, **Mackey CS**, **Platt GN**, **Washburn BK**, **Vera DL**, **Trickey DJ**, **Charles TC**, **Wang Z** and **Jones KM** (2020a) Metagenome-assembled genome sequences of five strains from the *Microtus ochrogaster* (prairie vole) fecal microbiome. *Microbiology Resource Announcements* **9**(2), e01310-19. https://doi.org/10.1128/MRA.01310-19.

Donovan M, **Mackey CS**, **Lynch MDJ**, **Platt GN**, **Brown AN**, **Washburn BK**, **Trickey DJ**, **Curtis JT**, **Liu Y**, **Charles TC**, **Wang Z** and **Jones KM** (2023) Limosilactobacillus reuteri administration alters the gut-brain-behavior axis in a sex-dependent

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

manner in socially monogamous prairie voles. *Frontiers in Microbiology* **14**, 1015666. https://doi.org/10.3389/fmicb.2023.1015666.

Donovan M, **Mackey CS**, **Platt GN**, **Rounds J**, **Brown AN**, **Trickey DJ**, **Liu Y**, **Jones KM** and **Wang Z** (2020b) Social isolation alters behavior, the gut-immune-brain axis, and neurochemical circuits in male and female prairie voles. *Neurobiology of Stress* **13**, 100278. https://doi.org/10.1016/j.ynstr.2020.100278.

Fiore E, **Van Tyne D** and **Gilmore MS** (2019) Pathogenicity of *enterococci*. *Microbiology Spectrum* **7**, 4. https://doi.org/10.1128/microbiolspec.GPP3-0053-2018.

Flint HJ, **Duncan SH**, **Scott KP** and **Louis P** (2007) Interactions and competition within the microbial community of the human colon: Links between diet and health. *Environmental Microbiology* **9**(5), 1101–1111. https://doi.org/10.1111/j.1462-2920.2007.01281.x.

Fukuda S and **Ohno H** (2014) Gut microbiome and metabolic diseases. *Seminars in Immunopathology* **36**(1), 103–114. https://doi.org/10.1007/s00281-013-0399-z.

Getz LL, **Carter CS** and **Gavish L** (1981) The mating system of the prairie vole, *Microtus ochrogaster*: Field and laboratory evidence for pair-bonding. *Behavioral Ecology and Sociobiology* **8**(3), 189–194.

Getz LL and **Hofmann JE** (1986) Social organization in free-living prairie voles, *Microtus ochrogaster*. *Behavioral Ecology and Sociobiology* **18**, 275–282. https://doi.org/10.1007/BF00300004.

Gilbert JA, **Blaser MJ**, **Caporaso JG**, **Jansson JK**, **Lynch SV** and **Knight R** (2018) Current understanding of the human microbiome. *Nature Medicine* **24**(4), 392–400. https://doi.org/10.1038/nm.4517.

Gjerstad JK, **Lightman SL** and **Spiga F** (2018) Role of glucocorticoid negative feedback in the regulation of HPA axis pulsatility. *Stress* **21**(5), 403–416. https://doi.org/10.1080/10253890.2018.1470238.

Gloor GB, **Macklaim JM**, **Pawlowsky-Glahn V** and **Egozcue JJ** (2017) Microbiome datasets are compositional: And this is not optional. *Frontiers in Microbiology* **8**. https://doi.org/10.3389/fmicb.2017.02224.

Greenberg GD, **van Westerhuyzen JA**, **Bales KL** and **Trainor BC** (2012) Is it all in the family? The effects of early social structure on neural-behavioral systems of prairie voles (Microtus ochrogaster). *Neuroscience* **216**, 46–56. https://doi.org/10.1016/j.neuroscience.2012.04.063.

Grippo AJ, **Beltz TG** and **Johnson AK** (2003) Behavioral and cardiovascular changes in the chronic mild stress model of depression. *Physiology & Behavior* **78**(4–5), 703–710. https://doi.org/10.1016/s0031-9384(03)00050-7.

Grippo AJ, **Cushing BS** and **Carter CS** (2007a) Depression-like behavior and stressor-induced neuroendocrine activation in female prairie voles exposed to chronic social isolation. *Psychosomatic Medicine* **69**(2), 149–157. https://doi.org/10.1097/PSY.0b013e31802f054b.

Grippo AJ, **Gerena D**, **Huang J**, **Kumar N**, **Shah M**, **Ughreja R** and **Carter CS** (2007b) Social isolation induces behavioral and neuroendocrine disturbances relevant to depression in female and male prairie voles. *Psychoneuroendocrinology* **32**(8–10), 966–980. https://doi.org/10.1016/j.psyneuen.2007.07.004.

Grippo AJ, **Lamb DG**, **Carter CS** and **Porges SW** (2007c) Social isolation disrupts autonomic regulation of the heart and influences negative affective behaviors. *Biological Psychiatry* **62**(10), 1162–1170. https://doi.org/10.1016/j.biopsych.2007.04.011.

Grippo AJ, **Moffitt JA** and **Johnson AK** (2002) Cardiovascular alterations and autonomic imbalance in an experimental model of depression. *American Journal of Physiology* **282**(5), R1333–R1341. https://doi.org/10.1152/ajpregu.00614.2001.

Grippo AJ, **Wu KD**, **Hassan I** and **Carter CS** (2008) Social isolation in prairie voles induces behaviors relevant to negative affect: Toward the development of a rodent model focused on co-occurring depression and anxiety. *Depression and Anxiety* **25**(6), E17–E26. https://doi.org/10.1002/da.20375.

Halfvarson J, **Brislawn CJ**, **Lamendella R**, **Vázquez-Baeza Y**, **Walters WA**, **Bramer LM**, **D'Amato M**, **Bonfiglio F**, **McDonald D**, **Gonzalez A**, **McClure EE**, **Dunklebarger MF**, **Knight R** and **Jansson JK** (2017) Dynamics of the human gut microbiome in inflammatory bowel disease. *Nature Microbiology* **2**, 17004. https://doi.org/10.1038/nmicrobiol.2017.4.

Hawkley LC, **Cole SW**, **Capitanio JP**, **Norman GJ** and **Cacioppo JT** (2012) Effects of social isolation on glucocorticoid regulation in social mammals. *Hormones and Behavior* **62**(3), 314–323. https://doi.org/10.1016/j.yhbeh.2012.05.011.

Henriksen RE, **Nilsen RM** and **Strandberg RB** (2023) Loneliness increases the risk of type 2 diabetes: A 20 year follow-up – results from the HUNT study. *Diabetologia* **66**(1), 82–92. https://doi.org/10.1007/s00125-022-05791-6.

Holt-Lunstad J (2018) Why social relationships are important for physical health: A systems approach to understanding and modifying risk and protection. *Annual Review of Psychology* **69**, 437–458. https://doi.org/10.1146/annurev-psych-122216-011902.

Hume ID, **Karasov WH** and **Darken BW** (1993) Acetate, butyrate and proline uptake in the caecum and colon of prairie voles (*Microtus ochrogaster*). *Journal of Experimental Biology* **176**(1), 285–297. https://doi.org/10.1242/jeb.176.1.285.

Ilchmann-Diounou H and **Menard S** (2020) Psychological stress, intestinal barrier dysfunctions, and autoimmune disorders: An overview. *Frontiers in Immunology* **11**, 1823. https://doi.org/10.3389/fimmu.2020.01823.

Inoue K, **Burkett JP** and **Young LJ** (2013) Neuroanatomical distribution of μ-opioid receptor mRNA and binding in monogamous prairie voles (*Microtus ochrogaster*) and non-monogamous meadow voles (*Microtus pennsylvanicus*). *Neuroscience* **244**, 122–133. https://doi.org/10.1016/j.neuroscience.2013.03.035.

Jianguo L, **Xueyang J**, **Cui W**, **Changxin W** and **Xuemei Q** (2019) Altered gut metabolome contributes to depression-like behaviors in rats exposed to chronic unpredictable mild stress. *Translational Psychiatry* **9**(1), 40. https://doi.org/10.1038/s41398-019-0391-z.

Johnson KV and **Foster KR** (2018) Why does the microbiome affect behaviour? *Nature Reviews. Microbiology* **16**(10), 647–655. https://doi.org/10.1038/s41579-018-0014-3.

Johnson KV, **Watson KK**, **Dunbar RIM** and **Burnet PWJ** (2022) Sociability in a non-captive macaque population is associated with beneficial gut bacteria. *Frontiers in Microbiology* **13**, 1032495. https://doi.org/10.3389/fmicb.2022.1032495.

Kant R, **Rasinkangas P**, **Satokari R**, **Pietilä TE** and **Palva A** (2015) Genome sequence of the butyrate-producing anaerobic bacterium *Anaerostipes hadrus* PEL 85. *Genome Announcements* **3**(2), e00224–e00215. https://doi.org/10.1128/genomeA.00224-15.

Keebaugh AC and **Young LJ** (2011) Increasing oxytocin receptor expression in the nucleus accumbens of pre-pubertal female prairie voles enhances alloparental responsiveness and partner preference formation as adults. *Hormones and Behavior* **60**(5), 498–504. https://doi.org/10.1016/j.yhbeh.2011.07.018.

Kenkel WM, **Gustison ML** and **Beery AK** (2021) A neuroscientist's guide to the vole. *Current Protocols* **1**(6), e175. https://doi.org/10.1002/cpz1.175.

Kenkel WM, **Kingsbury MA**, **Reinhart JM**, **Cetinbas M**, **Sadreyev RI**, **Carter CS** and **Perkeybile AM** (2023) Lasting consequences on physiology and social behavior following cesarean delivery in prairie voles. *Hormones and Behavior* **150**, 105314. https://doi.org/10.1016/j.yhbeh.2023.105314.

Kenkel WM, **Perkeybile AM** and **Carter CS** (2017) The neurobiological causes and effects of alloparenting. *Developmental Neurobiology* **77**(2), 214–232. https://doi.org/10.1002/dneu.22465.

Kostic AD, **Xavier RJ** and **Gevers D** (2014) The microbiome in inflammatory bowel disease: Current status and the future ahead. *Gastroenterology* **146**(6), 1489–1499. https://doi.org/10.1053/j.gastro.2014.02.009.

Krych L, **Hansen CH**, **Hansen AK**, **van den Berg FW** and **Nielsen DS** (2013) Quantitatively different, yet qualitatively alike: A meta-analysis of the mouse core gut microbiome with a view towards the human gut microbiome. *PLoS One* **8**(5), e62578. https://doi.org/10.1371/journal.pone.0062578.

Lee NS and **Beery AK** (2019) Neural circuits underlying rodent sociality: A comparative approach. *Current Topics in Behavioral Neurosciences* **43**, 211–238. https://doi.org/10.1007/7854_2018_77.

Lim MM, **Liu Y**, **Ryabinin AE**, **Bai Y**, **Wang Z** and **Young LJ** (2007) CRF receptors in the nucleus accumbens modulate partner preference in prairie voles. *Hormones and Behavior* **51**(4), 508–515. https://doi.org/10.1016/j.yhbeh.2007.01.006.

Lim MM, **Nair HP** and **Young LJ** (2005) Species and sex differences in brain distribution of corticotropin-releasing factor receptor subtypes 1 and 2 in monogamous and promiscuous vole species. *Journal of Comparative Neurology* **487**(1), 75–92. https://doi.org/10.1002/cne.20532.

Lim MM, **Wang Z**, **Olazábal DE**, **Ren X**, **Terwilliger EF** and **Young LJ** (2004) Enhanced partner preference in a promiscuous species by manipulating the expression of a single gene. *Nature* **429**(6993), 754–757. https://doi.org/10.1038/nature02539.

Liu Y and **Wang ZX** (2003) Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. *Neuroscience* **121**(3), 537–544. https://doi.org/10.1016/S0306-4522(03)00555-4.

Liu L and **Zhu G** (2018) Gut-brain axis and mood disorder. *Frontiers in Psychiatry* **9**, 223. https://doi.org/10.3389/fpsyt.2018.00223.

Lonstein JS and **De Vries GJ** (2000) Sex differences in the parental behavior of rodents. *Neuroscience and Biobehavioral Reviews* **24**(6), 669–686. https://doi.org/10.1016/s0149-7634(00)00036-1.

Loth MK and **Donaldson ZR** (2021) Oxytocin, dopamine, and opioid interactions underlying pair bonding: Highlighting a potential role for microglia. *Endocrinology* **162**(2), bqaa223. https://doi.org/10.1210/endocr/bqaa223.

Martel J, **Chang SH**, **Ko YF**, **Hwang TL**, **Young JD** and **Ojcius DM** (2022) Gut barrier disruption and chronic disease. *Trends in Endocrinology and Metabolism* **33**(4), 247–265. https://doi.org/10.1016/j.tem.2022.01.002.

McEwen BS (2007) Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews* **87**(3), 873–904. https://doi.org/10.1152/physrev.00041.2006.

McGraw LA and **Young LJ** (2010) The prairie vole: An emerging model organism for understanding the social brain. *Trends in Neurosciences* **33**(2), 103–109. https://doi.org/10.1016/j.tins.2009.11.006.

McGuire B and **Bemis WE** (2007) Litter size influences maternal but not paternal care in three species of voles, as measured by nest attendance. *Journal of Mammalogy* **88**(6), 1420–1426.

Misiak B, **Łoniewski I**, **Marlicz W**, **Frydecka D**, **Szulc A**, **Rudzki L** and **Samochowiec J** (2020) The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota? *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **102**, 109951. https://doi.org/10.1016/j.pnpbp.2020.109951.

Molinero N, **Antón-Fernández A**, **Hernández F**, **Ávila J**, **Bartolomé B** and **Moreno-Arribas MV** (2023) Gut microbiota, an additional hallmark of human aging and neurodegeneration. *Neuroscience* **518**, 141–161. https://doi.org/10.1016/j.neuroscience.2023.02.014.

Mora-Ortiz M, **Nuñez Ramos P**, **Oregioni A** and **Claus SP** (2019) NMR metabolomics identifies over 60 biomarkers associated with type II diabetes impairment in db/db mice. *Metabolomics* **15**(6), 89. https://doi.org/10.1007/s11306-019-1548-8.

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

Nagpal R, **Wang S**, **Solberg Woods LC**, **Seshie O**, **Chung ST**, **Shively CA**, **Register TC**, **Craft S**, **McClain DA** and **Yadav H** (2018) Comparative microbiome signatures and short-chain fatty acids in mouse, rat, non-human primate, and human feces. *Frontiers in Microbiology* **9**. https://doi.org/10.3389/fmicb.2018.02897.

Nearing JT, **Douglas GM**, **Hayes MG**, **MacDonald J**, **Desai DK**, **Allward N**, **Jones CMA**, **Wright RJ**, **Dhanani AS**, **Comeau AM** and **Langille MGI** (2022) Microbiome differential abundance methods produce different results across 38 datasets. *Nature Communications* **13**(1), 342. https://doi.org/10.1038/s41467-022-28034-z.

Nikiforova VJ, **Giesbertz P**, **Wiemer J**, **Bethan B**, **Looser R**, **Liebenberg V**, **Ruiz Noppinger P**, **Daniel H** and **Rein D** (2014) Glyoxylate, a new marker metabolite of type 2 diabetes. *Journal of Diabetes Research* **2014**, 685204. https://doi.org/10.1155/2014/685204.

Normann MC, **Cox M**, **Akinbo OI**, **Watanasriyakul WT**, **Kovalev D**, **Ciosek S**, **Miller T** and **Grippo AJ** (2021) Differential paraventricular nucleus activation and behavioral responses to social isolation in prairie voles following environmental enrichment with and without physical exercise. *Social Neuroscience* **16**(4), 375–390. https://doi.org/10.1080/17470919.2021.1926320.

Noureldein M, **Nawfal R**, **Bitar S**, **Maxwell SS**, **Khurana I**, **Kassouf HK**, **Khuri FR**, **El-Osta A** and **Eid AA** (2022) Intestinal microbiota regulates diabetes and cancer progression by IL-1β and NOX4 dependent signaling cascades. *Cellular and Molecular Life Sciences: CMLS* **79**(9), 502. https://doi.org/10.1007/s00018-022-04485-x.

Nuccio DA, **Normann MC**, **Zhou H**, **Grippo AJ** and **Singh P** (2023) Microbiome and metabolome variation as indicator of social stress in female prairie voles. *International Journal of Molecular Sciences* **24**(2), 1677. https://doi.org/10.3390/ijms24021677.

Omary MB, **Cohen DE**, **El-Omar EM**, **Jalan R**, **Low MJ**, **Nathanson MH**, **Peek RM** and **Turner JR** (2016) Not all mice are the same: Standardization of animal research data presentation. *Cellular and Molecular Gastroenterology and Hepatology* **2**(4), 391–393. https://doi.org/10.1016/j.jcmgh.2016.04.001.

Ophir AG, **Phelps SM**, **Sorin AB** and **Wolff JO** (2007) Morphological, genetic, and behavioral comparisons of two prairie vole populations in the field and laboratory. *Journal of Mammalogy* **88**(4), 989–999.

Osaka T, **Moriyama E**, **Arai S**, **Date Y**, **Yagi J**, **Kikuchi J** and **Tsuneda S** (2017) Meta-analysis of fecal microbiota and metabolites in experimental colitic mice during the inflammatory and healing phases. *Nutrients* **9**(12), 1329. https://doi.org/10.3390/nu9121329.

Page MJ, **Kell DB** and **Pretorius E** (2022) The role of lipopolysaccharide-induced cell signalling in chronic inflammation. *Chronic Stress* **6**, 24705470221076390. https://doi.org/10.1177/24705470221076390.

Pasolli E, **Asnicar F**, **Manara S**, **Zolfo M**, **Karcher N**, **Armanini F**, **Beghini F**, **Manghi P**, **Tett A**, **Ghensi P**, **Collado MC**, **Rice BL**, **DuLong C**, **Morgan XC**, **Golden CD**, **Quince C**, **Huttenhower C** and **Segata N** (2019) Extensive unexplored human microbiome diversity revealed by over 150,000 genomes from metagenomes spanning age, geography, and lifestyle. *Cell* **176**(3), 649–662.e20. https://doi.org/10.1016/j.cell.2019.01.001.

Pellizzon MA and **Ricci MR** (2020) Choice of laboratory rodent diet may confound data interpretation and teproducibility. *Current Developments in Nutrition* **4**(4), nzaa031. https://doi.org/10.1093/cdn/nzaa031.

Preston GM and **Calle RA** (2010) Elevated serum sorbitol and not fructose in type 2 diabetic patients. *Biomarker Insights* **5**, 33–38. https://doi.org/10.4137/bmi.s4530.

Resendez SL, **Dome M**, **Gormley G**, **Franco D**, **Nevárez N**, **Hamid AA** and **Aragona BJ** (2013) *M*-Opioid receptors within subregions of the striatum mediate pair bond formation through parallel yet distinct reward mechanisms. *The Journal of Neuroscience* **33**(21), 9140–9149. https://doi.org/10.1523/JNEUROSCI.4123-12.2013.

Resendez SL, **Kuhnmuench M**, **Krzywosinski T** and **Aragona BJ** (2012) *κ*-Opioid receptors within the nucleus accumbens shell mediate pair bond maintenance. *The Journal of Neuroscience* **32**(20), 6771–6784. https://doi.org/10.1523/JNEUROSCI.5779-11.2012.

Ritz NL, **Brocka M**, **Butler MI**, **Cowan CSM**, **Barrera-Bugueño C**, **Turkington CJR**, **Draper LA**, **Bastiaanssen TFS**, **Turpin V**, **Morales L**, **Campos D**, **Gheorghe CE**, **Ratsika A**, **Sharma V**, **Golubeva AV**, **Aburto MR**, **Shkoporov AN**, **Moloney GM**, **Hill C**, **Clarke G**, **Slattery DA**, **Dinan TG** and **Cryan JF** (2024) Social anxiety disorder-associated gut microbiota increases social fear. *Proceedings of the National Academy of Sciences of the United States of America* **121**(1), e2308706120. https://doi.org/10.1073/pnas.2308706120.

Roberts RL, **Williams JR**, **Wang AK** and **Carter CS** (1998) Cooperative breeding and monogamy in prairie voles: Influence of the sire and geographical variation. *Animal Behaviour* **55**(5), 1131–1140.

Robinson CK, **Brotman RM** and **Ravel J** (2016) Intricacies of assessing the human microbiome in epidemiologic studies. *Annals of Epidemiology* **26**(5), 311–321. https://doi.org/10.1016/j.annepidem.2016.04.005.

Rosshart SP, **Herz J**, **Vassallo BG**, **Hunter A**, **Wall MK**, **Badger JH**, **McCulloch JA**, **Anastasakis DG**, **Sarshad AA**, **Leonardi I**, **Collins N**, **Blatter JA**, **Han SJ**, **Tamoutounour S**, **Potapova S**, **Claire MB**, **Yuan W**, **Sen SK**, **Dreier MS**, **Hild B**, **Hafner M**, **Wang D**, **Iliev ID**, **Belkaid Y**, **Trinchieri G** and **Rehermann B** (2019) Laboratory mice born to wild mice have natural microbiota and model human immune responses. *Science* **365**(6452), eaaw4361. https://doi.org/10.1126/science.aaw4361.

Ruscio MG, **Sweeny T**, **Hazelton J**, **Suppatkul P** and **Sue Carter C** (2007) Social environment regulates corticotropin releasing factor, corticosterone and vasopressin in juvenile prairie voles. *Hormones and Behavior* **51**(1), 54–61. https://doi.org/10.1016/j.yhbeh.2006.08.004.

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

Sabol AC, **Close WL**, **Petrullo L**, **Lambert CT**, **Keane B**, **Solomon NG**, **Schloss PD** and **Dantzer B** (2023) Sociality does not predict oral microbiome composition or diversity in free-living prairie voles. *Animal Behaviour* **200**, 167–182.

Sadagopan A, **Mahmoud A**, **Begg M**, **Tarhuni M**, **Fotso M**, **Gonzalez NA**, **Sanivarapu RR**, **Osman U**, **Latha Kumar A** and **Mohammed L** (2023) Understanding the role of the gut microbiome in diabetes and therapeutics targeting leaky gut: A systematic review. *Cureus* **15**(7), e41559. https://doi.org/10.7759/cureus.41559.

Salas-Venegas V, **Flores-Torres RP**, **Rodríguez-Cortés YM**, **Rodríguez-Retana D**, **Ramírez-Carreto RJ**, **Concepción-Carrillo LE**, **Pérez-Flores LJ**, **Alarcón-Aguilar A**, **López-Díazguerrero NE**, **Gómez-González B**, **Chavarría A** and **Konigsberg M** (2022) The obese brain: Mechanisms of systemic and local inflammation, and interventions to reverse the cognitive deficit. *Frontiers in Integrative Neuroscience* **16**, 798995. https://doi.org/10.3389/fnint.2022.798995.

Schmidt E, **Mykytczuk N** and **Schulte-Hostedde AI** (2019) Effects of the captive and wild environment on diversity of the gut microbiome of deer mice (*Peromyscus maniculatus*). *The ISME Journal* **13**(5), 1293–1305. https://doi.org/10.1038/s41396-019-0345-8.

Scotti MA, **Carlton ED**, **Demas GE** and **Grippo AJ** (2015) Social isolation disrupts innate immune responses in both male and female prairie voles and enhances agonistic behavior in female prairie voles (Microtus ochrogaster). *Hormones and Behavior* **70**, 7–13. https://doi.org/10.1016/j.yhbeh.2015.01.004.

Sender R, **Fuchs S** and **Milo R** (2016) Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell* **164**(3), 337–340. https://doi.org/10.1016/j.cell.2016.01.013.

Solomon NG, **Keane B**, **Knoch LR** and **Hogan PJ** (2004) Multiple paternity in socially monogamous prairie voles (*Microtus ochrogaster*). *Canadian Journal of Zoology* **82**(10), 1667–1671. https://doi.org/10.1139/z04-142.

Strekalova T, **Spanagel R**, **Bartsch D**, **Henn FA** and **Gass P** (2004) Stress-induced anhedonia in mice is associated with deficits in forced swimming and exploration. *Neuropsychopharmacology* **29**(11), 2007–2017. https://doi.org/10.1038/sj.npp.1300532.

Sutin AR, **Stephan Y**, **Luchetti M** and **Terracciano A** (2020) Loneliness and risk of dementia. *The Journals of Gerontology* **75**(7), 1414–1422. https://doi.org/10.1093/geronb/gby112.

Supeck DJ, **Assefa S**, **Meek W**, **Curtis JT** and **Köhler GA** (2018) Postnatal maturation of the intestinal epithelial barrier in prairie voles. *Tissue and Cell* **54**, 30–37. https://doi.org/10.1016/j.tice.2018.08.001

Terleph TA, **Jean-Baptiste N** and **Bamshad M** (2004) Mechanisms and time course for induction of paternal behavior in prairie voles (*Microtus ochrogaster*). *Journal of Mammalogy* **85**(6), 1124–1129. https://doi.org/10.1644/BNS-108.1.

Thigpen JE, **Setchell KDR**, **Saunders HE**, **Haseman JK**, **Grant MG** and **Forsythe DB** (2004) Selecting the appropriate rodent diet for endocrine disruptor research and testing studies. *Institute for Laboratory Animal Research Journal* **45**(4), 401–416. https://doi.org/10.1093/ilar.45.4.401.

Valtorta NK, **Kanaan M**, **Gilbody S**, **Ronzi S** and **Hanratty B** (2016) Loneliness and social isolation as risk factors for coronary heart disease and stroke: Systematic review and meta-analysis of longitudinal observational studies. *Heart* **102**(13), 1009–1016. https://doi.org/10.1136/heartjnl-2015-308790.

Walf AA and **Frye CA** (2007) The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. *Nature Protocols* **2**(2), 322–328. https://doi.org/10.1038/nprot.2007.44.

Williams JR, **Insel TR**, **Harbaugh CR** and **Carter CS** (1994) Oxytocin administered centrally facilitates formation of a partner preference in female prairie voles (*Microtus ochrogaster*). *Journal of Neuroendocrinology* **6**(3), 247–250. https://doi.org/10.1111/j.1365-2826.1994.tb00579.x.

Winslow JT, **Hastings N**, **Carter CS**, **Harbaugh CR** and **Insel TR** (1993) A role for central vasopressin in pair bonding in monogamous prairie voles. *Nature* **365**(6446), 545–548. https://doi.org/10.1038/365545a0.

Witt DM, **Carter CS**, **Carlstead K** and **Read LD** (1988) Sexual and social interactions preceding and during male-induced oestrus in prairie voles. *Microtus ochrogaster. Animal Behaviour* **36**(5), 1465–1471.

Wolfe W, **Xiang Z**, **Yu X**, **Li P**, **Chen H**, **Yao M**, **Fei Y**, **Huang Y**, **Yin Y** and **Xiao H** (2023) The challenge of applications of probiotics in gastrointestinal diseases. *Advanced Gut & Microbiome Research*, 1984200. https://doi.org/10.1155/2023/1984200.

Wu J, **Wang K**, **Wang X**, **Pang Y** and **Jiang C** (2021) The role of the gut microbiome and its metabolites in metabolic diseases. *Protein & Cell* **12**(5), 360–373. https://doi.org/10.1007/s13238-020-00814-7.

Wu X, **Wu Y**, **He L**, **Wu L**, **Wang X** and **Liu Z** (2018) Effects of the intestinal microbial metabolite butyrate on the development of colorectal cancer. *Journal of Cancer* **9**(14), 2510–2517. https://doi.org/10.7150/jca.25324.

Young Owl M and **Batzli GO** (1998) The integrated processing response of voles to fibre content of natural diets. *Functional Ecology* **12**(1), 4–13. https://doi.org/10.1046/j.1365-2435.1998.00151.x.

Zawistowska-Rojek A, **Kośmider A**, **Stępień K** and **Tyski S** (2022) Adhesion and aggregation properties of *Lactobacillaceae* strains as protection ways against enteropathogenic bacteria. *Archives of Microbiology* **204**, 285. https://doi.org/10.1007/s00203-022-02889-8.

Zhang S, **Cai Y**, **Meng C**, **Ding X**, **Huang J**, **Luo X**, **Cao Y**, **Gao F** and **Zou M** (2021) The role of the microbiome in diabetes mellitus. *Diabetes Research and Clinical Practice* **172**, 108645. https://doi.org/10.1016/j.diabres.2020.108645.

Zhang M, **Li A**, **Yang Q**, **Li J**, **Zheng L**, **Wang G**, **Sun Y**, **Huang Y**, **Zhang M**, **Song Z** and **Liu L** (2023) Matrine alleviates depressive-like behaviors via modulating microbiota-gut-brain axis in CUMS-induced mice. *Journal of Translational Medicine* **21**(1), 145. https://doi.org/10.1186/s12967-023-03993-z.

https://doi.org/10.1017/gmb.2026.10021 Published online by Cambridge University Press

Zhou H, **Huang D**, **Sun Z** and **Chen X** (2024) Effects of intestinal *Desulfovibrio* bacteria on host health and its potential regulatory strategies: A review. *Microbiological Research* **284**, 127725. https://doi.org/10.1016/j.micres.2024.127725.
Zynel CA and **Wunder BA** (2002) Limits to food intake by the prairie vole: Effects of time for digestion. *Functional Ecology* **16**(1), 58–66. https://doi.org/10.1046/j.0269-8463.2001.00601.x.

Cite this article: Nuccio DA, Grippo A and Singh P 2026. The prairie vole gut–brain–microbiota-axis: a narrative review. *Gut Microbiome,* **7**, e4, 1–19. https://doi.org/10.1017/gmb.2026.10021