

Evolution in reproductive tempo and investment across the *Peromyscus* radiation

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Abstract

Mammals display diverse reproductive strategies, however, the ultimate and proximate mechanisms that underlie this diversity and its composite traits remain poorly understood from both evolutionary and physiological perspectives. The *Peromyscus* genus of rodents, which is found throughout the north and central Americas, has diversified along life history gradients, varying both within and among species in reproductive strategies. This variation provides a useful model for studying reproductive diversity. Here, we combine a literature review with new analyses of captive colony breeding records from six *Peromyscus* species to assess our current understanding of how plasticity and local adaptation contribute to diversity in two classes of reproductive traits: phenology and litter investment. There is substantial evidence that many traits underlying phenology and litter investment have diverged among populations in ways that are likely to be locally adaptive, though plasticity in these traits remains common. However, these conclusions are largely based on data collected from the two most widespread *Peromyscus* species: *P. maniculatus* and *P. leucopus*. The majority of *Peromyscus* species diversity remains understudied regarding reproductive phenology and litter traits. We conclude by discussing key challenges and considerations relevant to using *Peromyscus* as a mammalian model for reproductive trait diversity and evolution moving forward.

KEYWORDS

deer mice, female reproduction, gestation, inter-birth interval, litter size, phenology

1 | INTRODUCTION

The origin and basis of diversity in life history strategies continue to be a major area of interest in integrating subfields across biology. Which selective pressures drive life history diversity across animal lineages, what factors constrain its evolution, and how linked are life history traits? Reproductive traits comprise a major axis of variation in life history strategy: life history strategies often differ in the number of offspring produced per reproductive attempt, investment

per offspring, and age of reproductive maturity (among other traits). Understanding the ecological, physiobehavioral, and genetic basis of variation in these reproductive traits is thus critical to understanding the evolution and diversification of life history strategies.

One challenge to studying diversity in reproductive traits is that these traits tend to be flexible—for example, litter size varies among reproductive attempts within an individual, and phenology (the timing of life cycle events such as reproduction) can vary through time (e.g., across years) as well as among individuals within a population.

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Plasticity in reproductive traits, and lack thereof, is thus a fundamental piece of their evolution and diversification. The degree to which plasticity and/or local adaptation explain variation in reproductive traits can inform both how we think about the genetic basis of trait diversity as well as the ecological and evolutionary processes that may drive changes in these traits among populations and species.

Historically, birds have been a major study group for investigating life history evolution especially as it relates to reproductive traits and their flexibility (e.g., Charmantier & Gienapp, 2014; Forchhammer et al., 1998; Lack, 1947; Martin, 2014; Ricklefs & Wikelski, 2002; Ricklefs, 1980; Visser & Gienapp, 2019). Some of this interest reflects the diversity found among avian species, but much of it also reflects the ease of studying reproductive traits including reproductive timing and clutch size in birds. However, because reproductive mode fundamentally differs between birds and mammals, where reproduction involves unique physiology and trade-offs related to gestation (e.g., Hayssen & Orr, 2017; Scanes, 2020), avian models are unlikely to provide comprehensive explanations for reproductive trait evolution and diversity in mammals. Thus, mammalian model systems are essential to understanding mammalian reproductive trait diversity and the importance of plasticity and local adaptation to its evolution.

In this review, we focus on *Peromyscus*, a genus of rodents commonly referred to as deer mice, as a useful and accessible model for studying reproductive trait diversity and evolution within mammals. We reviewed the literature on reproductive trait diversity across *Peromyscus*, with a particular focus on studies that provide evidence for the degree to which trait variation is driven by plasticity and/or local adaptation. First, we briefly review diversity in the *Peromyscus* lineage and discuss the advantages of the system, though it has been discussed in more detail elsewhere (e.g., Bedford & Hoekstra, 2015; Bester-Meredith et al., 2017; Borniger & Nelson, 2017; Hu & Hoekstra, 2017). Second, we review what is known about flexibility and local adaptation within traits involved in reproductive phenology and litter investment among *Peromyscus* species. We complement the literature review with data on litter size and inter-birth interval (the time between consecutive births) from 18 captive colonies of *Peromyscus* representing 15 strains within 6 species (Supporting Information: Table 1). By summarizing flexibility and local adaptation in reproductive traits within these lineages, we highlight multiple dimensions along which many reproductive traits are plastic. Finally, we suggest opportunities for future work and development of the system.

2 | SPECIES DIVERSITY WITHIN PEROMYSCUS

The *Peromyscus* radiation contains over 50 extant species ranging in size from 8 g to over 50 g (respectively, Old Field Mouse [*Peromyscus polionotus*] and the California deer mouse [*Peromyscus californicus*]). The genus emerged approximately 8 million years ago (MYA), and most species diversity in the genus is estimated to have evolved 2–6 MYA

(Platt et al., 2015). *Peromyscus* species have colonized every terrestrial habitat found throughout north and central America, from arid deserts in Death Valley, to coastal rainforests in the north pacific, up to oxygen-poor peaks in the Rocky and White Mountains in the western United States. Across this wide variety of habitats, *Peromyscus* species display a range of life history strategies in combination with physiological, morphological, and mating system diversity (Modi, 1984). Finally, *Peromyscus* contains both habitat generalists that occupy a large range (e.g., *P. maniculatus* which can be found from Alaska, USA to Mexico) and species with extremely restricted ranges, including species found on a single island or mountain range (e.g., *P. slevini*).

This diversity combined with the genus's amenability to experimental research (*Peromyscus* species are readily trapped in the wild and can be easily maintained in lab colonies) has facilitated important advances particularly within evolutionary ecology (e.g., Hoekstra et al., 2006; Steiner et al., 2007), physiology (e.g., Cheviron et al., 2012; Schweizer et al., 2019; Storz et al., 2007, 2019), and behavior or sociality (e.g., Fisher & Hoekstra, 2010; Gubernick & Teferi, 2000; Turner et al., 2010).

Peromyscus has also been historically used to study physiological and ecological diversity in reproductive traits (e.g., Demas et al., 1996; Dunmire, 1960; Forger & Zucker, 1985; Haigh, 1983; Modi, 1984). More recent work on sperm competition and cooperation (H. S. Fisher et al., 2014, 2016; D. N. Fisher et al., 2018; Hook et al., 2021) has begun to incorporate evolutionary theory, genomics, and genetics into our understanding of the core traits that shape reproductive strategy and life history. However, the basis of variation (i.e., genetic and environmental) in reproductive traits beyond sperm competition remains essentially unknown.

3 | REPRODUCTIVE DIVERSITY IN PEROMYSCUS

In this review, we focus on reproductive traits that comprise reproductive timing (phenology) and traits related to litter investment, including litter size. This focus is motivated by the fact that these two categories roughly reflect two independent axes of reproductive diversity within mammalian reproductive diversity (Bielby et al., 2007). We do not address reproductive behaviors, including mating systems or parental care, here.

Reproductive phenology is a function of both the onset and duration of reproductive activity. Duration of the reproductive season includes gestation and rearing of young and may include consecutive breeding attempts. Plasticity in reproductive phenology refers to an individual's ability to express variation in these traits in response to variation in biotic and abiotic cues. Local adaptation in reproductive phenology or litter size can arise as an absolute shift in trait values without a change in plasticity, or it may arise as a loss or gain in plasticity depending on local selective pressure. Regardless, local adaptation reflects a consistent, population-level responsivity to cues that can be detected using experimental approaches such as common gardens.

For the purposes of this review, we primarily focus on *P. leucopus* and *P. maniculatus*, the two most broadly distributed *Peromyscus* species. This focus is a practical one: most published work relevant to phenology and litter investment use *P. leucopus* and *P. maniculatus*, and thus these are the only species in which there are sufficient data to draw conclusions about the degree to which traits display plasticity and/or evidence of local adaptation. However, we include discussion of data from other *Peromyscus* species for comparison and as an overview for future work. These species tend to occupy more restricted ranges and more semi-tropical or tropical habitats, but most published data are derived from sampling a single population or strain of the species, and thus they are difficult to generalize from.

3.1 | *P. maniculatus* and *P. leucopus*

3.1.1 | Natural history and phenology

There is substantial variation in phenology at the landscape level for *P. maniculatus* and *P. leucopus*. For both species, the onset of the reproductive season for a given population tends to occur later in the year with increasing distance from the equator (Lackey, 1978; McLean & Guralnick, 2021). At the most southern latitudes of their respective ranges, populations of both species tend to breed more or less continuously (Lackey, 1978; McLean & Guralnick, 2021). Shifts in breeding phenology tend to correspond to physiological changes in the reproductive system (as opposed to behavioral regulation alone or seasonal litter loss). For example, in the field, more southern populations of *P. leucopus* had a shorter period of winter gonadal regression compared with northern *P. leucopus* populations (Pierce & Vogt, 1993).

Despite these broad similarities, *P. maniculatus* and *P. leucopus* do differ in their population-level variation in breeding patterns. *P. maniculatus* display a unimodal reproductive pattern in most of their western and northern range (Brown, 1966; Kenagy & Barnes, 1988; Long, 1964; McLean & Guralnick, 2021; Millar & Innes, 1985), which tends to be most intense in the late spring and early summer. Coastal and eastern populations of *P. maniculatus* more often display a bimodal breeding pattern (Dunmire, 1960; Fairbairn, 1977; McLean & Guralnick, 2021), where pregnancies occur throughout the spring, summer, and fall but are concentrated into an initial peak in the spring and a second in the fall. In contrast, *P. leucopus* display a bimodal pattern throughout the vast majority of their range (Adler & Tamarin, 1984; Brown, 1964; Cornish & Bradshaw, 1978; Drickamer, 1978; McMurry et al., 1996; Pratt & Barrett, 2012; Rintamaa et al., 1976) but see (Millar, 1978). In some populations, the summer lull in breeding for *P. leucopus* may be associated with gonadal regression (Terman, 1999) but see (Pierce & Vogt, 1993). *P. leucopus* populations on the most southern edge of their range (e.g., in the southeastern US) may display a unimodal winter breeding period (Pratt & Barrett, 2012). Thus, although the onset of reproduction in populations of *P. maniculatus* and *P. leucopus* vary in similar ways along ecological gradients, there appear to be

species-level differences in the cessation or tempo of breeding across the season.

3.1.2 | Phenology and reproductive diversity

Animals often use environmental cues to effectively time reproductive activity, and thus variation in sensitivity to cues or reliance on different cues can be associated with population- or species-level differences in phenology (e.g., Bronson, 1989). Photoperiod is unique among cues for its stability and long-term predictive power, and substantial work has focused on understanding mechanisms and variations in how animals use photoperiod to organize their reproductive activity (reviewed in Nelson et al., 2010). In temperate rodents, long photoperiod is often a requirement for reproductive activity, and it is also often sufficient on its own to drive reproductive competency (Dardente et al., 2019). However, the absolute day length requisite to trigger reproductive activity or drive cessation can vary, and the sensitivity to changes in day length often varies among populations and species.

Other cues, including temperature, food, water, and social cues, are also used to coordinate reproductive activity with permissible conditions locally, allowing populations to adjust their timing or effort with annual environmental variation. Such cues must play an important role in modulating timing to explain variation in phenology among microhabitats (e.g., *P. maniculatus* nesting in rocky areas initiated breeding earlier than those in a nearby forested area; Sharpe & Millar, 1991) and elevational clines (altitude leads to a shortening of the breeding season; Dunmire, 1960; Millar & Innes, 1985). These other cues can also be dominant drivers of reproductive timing in areas where permissible conditions are not readily anticipated by photoperiodic cycles.

Photoperiod

As expected, both experimental and observational data from *Peromyscus* species confirm that photoperiod is an important driver of variation in reproductive phenology among populations. Both *P. maniculatus* and *P. leucopus* populations display latitudinal-variation in photoperiodic responses such that more northern populations require longer experimental photoperiods to stimulate reproductive activity relative to populations from more tropical latitudes (Carlson et al., 1989; Dark et al., 1983; Dunbar Gram et al., 1982; Lynch et al., 1981). Moreover, photoperiod is the strongest predictor of breeding likelihood among female *P. maniculatus* across North America (McLean & Guralnick, 2021). Photoperiod also influences the cessation of breeding, at least in female *P. leucopus*: short photoperiods suppress the likelihood of post-partum estrus (Beasley et al., 1981). In both species, some of the most southern populations appear to have lost or severely curtailed photoperiodic responses in that their reproductive system no longer responds to photoperiodic cues in isolation (Demas et al., 1996; Scarlett, 2004; Younger, 2002). In line with this, male non-responders, a phenomenon in which some animals in the population do not regress their gonads under short

photoperiods, are increasingly abundant at more equatorial latitudes, at least within *P. maniculatus* (Dark et al., 1983). Non-responders also occur in *P. leucopus* populations (Johnston & Zucker, 1980), though a latitudinal gradient in abundance has not been demonstrated for this species.

When population-level differences in photoperiodism persist under common garden conditions, this is evidence for clinal variation or local adaptation in reproductive timing tied to photoperiodic systems. There is ample evidence that photoperiodic responses are genetically based in *Peromyscus*: photoperiod responsiveness and lack thereof can be readily selected for in the lab, demonstrating that genetic variation underlying photoperiod sensitivity is segregating in wild populations (Heideman et al., 1999, 2005). Still, the degree to which latitudinal variation in photoperiodism reflects selection on shared genetic variation underlying the photoperiodic response remains unclear. To date, all experiments demonstrating a genetic basis to photoperiodism focus on selection for the presence or absence of a response, as opposed to a shift in the threshold photoperiod required for a gonadal response or sensitivity to photoperiod per se. In exploring sensitivity, square versus natural (i.e., gradual) changes in day length may be important to consider in experimental approach; the rate and extent of physiological responses to day length can differ when changes are simulated using gradual photoperiods versus when animals are subjected to abrupt shifts in photoperiod (e.g., Gorman et al., 1997).

Temperature

Temperature can be used as a predictive cue similar to photoperiod, though it contains substantially more noise. *P. maniculatus* appear to use temperature to modulate photoperiod-dependent breeding likelihood, whereas there is limited evidence for the effects of temperature on reproductive activity in *P. leucopus*. At the landscape level, the likelihood of *P. maniculatus* breeding is impacted by monthly average temperature before breeding, but this effect is modulated by the local amplitude of temperature change across the year (i.e., seasonality of temperature; McLean & Guralnick, 2021). Thus, the monthly average of temperature before breeding is more predictive of breeding status in areas that have greater annual variation in temperature. Indeed, cold temperatures can drive small reductions in testes and epididymal size independent of day length in *P. maniculatus* (Demas & Nelson, 1998), and thus may contribute to seasonal suppression of breeding, especially in northern populations of the species. In contrast, temperature apparently has no effect on gonad size in male *P. leucopus* (Lynch, 1973).

Resource availability

Environmental resources, including food and water, can provide both predictive and immediate cues. In both *P. maniculatus* and *P. leucopus*, food availability may shape reproductive timing through either mechanism. Whereas food abundance appears to advance breeding onset for the following spring, food restriction tends to have relatively acute, suppressive effects on reproduction in both species.

Increased food availability often leads to increased body condition in lab *P. maniculatus* and field *P. leucopus* (Cronin &

Bradley, 1988; Scarlett, 2004; Vandegrift et al., 2008; Yunger, 2002), and it tends to result in increased rates of reproduction within these same populations (Cronin & Bradley, 1988; Yunger, 2002) but see (Sharpe & Millar, 1991; Vandegrift et al., 2008). In *P. maniculatus*, seed-masting events were associated with a marginal increase in total reproductive output across the year (Gashwiler, 1979). More strikingly, masting events lengthened the breeding season for *P. maniculatus* such that breeding was more staggered across the population, which contrasted with shorter and more coordinated periods of reproduction during years when tree seed is scarcer (Gashwiler, 1979).

In *P. leucopus*, increasing food availability through supplementation or natural acorn masting events has been associated with an earlier spring onset of breeding (Scarlett, 2004; Yunger, 2002). However, there is no evidence that *P. leucopus* alter total reproduction in anticipation of natural increases in food availability (Scarlett, 2004; Yunger, 2002). Indeed, increasing acorn abundance through deer exclosures do not affect breeding rates in *P. leucopus* experimental plots (Vandegrift et al., 2008). Furthermore, in *P. leucopus*, increased food abundance does not appear to modify the early summer suppression of reproduction: animals that experienced food supplementation retained small gonads and did not breed during the summer lull (Terman, 1999). These patterns suggest either that another factor, such as water, is critically limiting for early summer breeding, or that physiological systems underlying early summer suppression in *P. leucopus* are insensitive to food abundance.

Food scarcity or restriction similarly impacts reproductive output in temperate *Peromyscus* species. In *P. maniculatus*, food restriction drove regression in male gonadal tissues (Nelson et al., 1992), and it tended to decrease the number of viable sperm male *maniculatus* produce (Blank & Desjardins, 1984). Restriction-dependent reductions in gonadal size occur regardless of photoperiod (Nelson et al., 1992). Food restriction also drove gonadal regression in male *P. leucopus*; however, the effects were only significant under short days (Young et al., 2000). Interestingly, this effect persists in otherwise-photoinensitive *P. leucopus* males—food restriction resulted in testes regression, but only under short days (Reilly et al., 2006). Food restriction or caloric deficiencies also reduced breeding likelihood in females from both *P. maniculatus* and *P. leucopus* (Merson & Kirkpatrick, 1981; Perrigo, 1987). In either case, suppression of breeding occurred without loss of body condition, and in *P. leucopus*, food-restricted animals actually increased fat storage (Merson & Kirkpatrick, 1981). Photoperiod-dependent effects of food restriction on reproductive condition have not been explored in females.

Water availability can also be an important cue, especially in arid or semi-tropical regions. Precipitation does contribute to landscape-level variation in breeding phenology of *P. maniculatus*, but is only important in arid regions (McLean & Guralnick, 2021). Earlier work suggested that drought curtailed the breeding season in *P. maniculatus* populations in the White Mountains in California (Morton et al., 1995), and experimental water restriction has been associated with a cessation of spermatogenesis in *P. maniculatus* (Nelson &

Desjardins, 1987). However, in either case, the impact of water on reproductive activity and phenology could be an indirect response to changes in individual body condition—mice experiencing water restriction in the lab lost body mass (Nelson & Desjardins, 1987). Furthermore, about 25% of deer mice held under water restriction maintained spermatogenesis even in the face of body mass loss (Nelson, 1993). These mice tended to be heavier than other mice at the start of the restriction period, suggesting that suppression of spermatogenesis in response to water restriction may occur via an absolute mass threshold that these mice in better body condition did not reach.

Social cues

Substantial research has focused on how social environment can shape reproductive behavior in rodents, particularly with respect to pheromonal cues and breeding intensity. For *P. maniculatus* and *P. leucopus*, evidence for social effects on reproduction are mixed.

There is some suggestion that co-housing reproductively active females or housing females in high-density environments suppress reproductive activity in both *P. maniculatus* and *P. leucopus* females (Haigh, 1987; Helmreich, 1960; Pasley & Christian, 1972). In the case of high-density housing, activation of the stress axis appears physiologically relevant (Helmreich, 1960; Pasley & Christian, 1972). However, pheromones released by dominant or older females may also contribute to this suppression (Haigh et al., 1985), although these effects did not hold in other populations of *P. maniculatus* (Terman, 1968).

For males, exposure to female cues, including urine-soaked bedding, tends to stimulate testicular growth in both *P. maniculatus* and *P. leucopus* (Creigh & Terman, 1988; Pyter et al., 2005; Terman, 1979, 1980), and this has been associated with higher testosterone in *P. leucopus* (Pyter et al., 2005). In contrast, pairing with a female was associated with lower testosterone in male *P. maniculatus* (Trainor et al., 2006). In both cases, circulating testosterone was compared to singly-housed males, so while this difference could reflect species-specific differences in physiological responses to conspecifics, it could also be a function of complex interactions with stress activation associated with single housing. Even though these species are often not considered social (i.e., often display aggression towards unfamiliar conspecifics), social housing alongside enrichment reduces stereotypical behavior in *P. maniculatus* (Hadley et al., 2006). The reduction in stereotypical behavior suggests that social interactions or housing, especially with familiar conspecifics, reduces stress and is important for normal individual behavior.

3.1.3 | Reproductive maturation and phenology

Our discussion of reproductive timing thus far has ignored an important distinction between reproductive activation associated with the onset of a breeding season (an annual event) and puberty (a developmental event that can occur in the fall or spring, depending

on the population). Flexibility in pubertal timing in young-of-the-year is likely to be dependent on sufficient duration of the breeding season.

Photoperiod impacts the rate of vaginal opening and reproductive organ growth in young *P. maniculatus*—in the lab, females born into short photoperiods or moved into short photoperiods at weaning were less likely to be reproductively mature up to 24 weeks after birth when compared with females exposed to long photoperiods (Mal Whitsett & Miller, 1982). Similarly, male *P. maniculatus* raised under longer photoperiods in the lab displayed greater gonadal development during the first 6 weeks of life relative to mice raised under short photoperiods (Whitsett et al., 1984). Similar phenomena occur in *P. leucopus*—animals born under simulated fall photoperiods in the lab delayed gonadal development until at least 120 days of age, whereas those born under simulated spring photoperiods reproductively matured before 60 days of age (Forger & Zucker, 1985).

Food availability also influences pubertal timing in young-of-the-year. Food supplementation in the field increased the proportion of *P. maniculatus* breeding in their first year (Teferi & Millar, 1993), presumably due to increases in individual condition; females that bred in their first year grew faster than those that did not (Teferi & Millar, 1993). Indeed, in another field study where mature females were experimentally removed from the population, young-of-the-year females were more likely to breed coincident with greater growth, which could reflect lower competition for food resources (Lusk & Millar, 1989). In the field, protein supplementation also increased the proportion of *P. maniculatus* young-of-the-year that breed in their first fall (McAdam & Millar, 1999). However, this effect did not appear to occur via faster growth or mass gain—litters from protein-supplemented populations were no larger than conspecifics without supplementation (McAdam & Millar, 1999).

Removing females from the population may also impact breeding by young-of-the-year through pheromonal influence. A series of studies by Gale R. Haigh, suggests that, in both *P. maniculatus* and *P. leucopus*, maternal urine contains pheromones that delay reproduction in female offspring by affecting the ability of these individuals to implant blastocysts (Haigh, 1983; Haigh et al., 1985, 1988). However, this effect has not held up in other studies. In another lab, young female *P. leucopus* housed with older females were more likely to breed than if they were housed alone with a male (Terman, 1992), and delayed dispersal of females in the field did not affect pubertal timing in *P. leucopus* (Wolff, 1994). In *P. maniculatus*, field studies suggest that the presence of adult females has no effect on pubertal timing (Teferi & Millar, 1993; Wolff, 1994) but see (Lusk & Millar, 1989). Finally, removal of males from field populations of *P. maniculatus* suppressed breeding by young-of-the-year (Teferi & Millar, 1993), yet it is not clear whether this was because males were less available or because yearling females actually delayed puberty.

Taken together, these studies suggest that social regulation of pubertal timing in *P. leucopus* and *P. maniculatus* is unlikely to be of major importance in most wild populations. On the other hand, food availability and photoperiodic cues do appear to influence puberty onset in *Peromyscus*.

3.1.4 | Litter investment and other gestational traits

Within the bounds of the breeding season, individuals can vary their reproductive investment and strategy by modifying the number of offspring they produce per litter (litter size), the growth rates of those litters, and/or the number of litters produced in a season. All of these traits vary within and among populations of *P. maniculatus* and *P. leucopus*, though the degree to which this reflects adaptive plasticity and/or local adaptation remains largely undetermined.

Generally, litter size tends to increase with latitude in *P. maniculatus* and *P. leucopus* (McLean et al., 2019; Smith & McGinnis, 1968) but see (Lackey, 1978). However, litter sizes also vary across the breeding season within latitudes. In *P. maniculatus*, litter size tends to increase across the summer (Brown, 1966; Stewart & McAdam, 2017). In more southern populations of *P. leucopus*, where populations display two breeding peaks in the spring and later summer, litters tend to be larger in the fall (Havelka & Millar, 2004; McMurry et al., 1996). In contrast, litters are the largest in the spring in northern populations (Millar, 1978). This landscape-level variation could be explained by demographic differences in maternal age at reproduction or parity: in the field, litters born to younger mothers or as first litters tend to have fewer pups than litters born to older or multi-parous mothers (Havelka & Millar, 2004) but see (Jacquot & Vessey, 1998). Using data derived from captive *Peromyscus* colonies (see Supporting Information), we similarly find that litter size increases with parity across species (Figure 1, Supporting Information: Table 2). Nonetheless, fine-scale demographic work is still needed to resolve the degree to which demographic changes across the year might contribute to broad patterns in litter size.

Litter size could theoretically be modified in anticipation of resource conditions, including food or water availability. Indeed, litter sizes vary with resource abundance among microhabitats for both *P. maniculatus* and *P. leucopus* (Cramer & Chapman, 1992; Morris, 1992). However, most evidence suggests that individuals from these species do not modify reproductive traits other than phenology in response to such cues. Food supplementation in free-living *P. leucopus* has no effect on litter size (Morris, 1992), and working for food (i.e., more effort per calorie) does not modify litter size in *P. maniculatus* (Perrigo, 1987). Extended drought also has no effect on free-living *P. maniculatus* in the White Mountains in California, USA (Morton et al., 1995). Thus, although experimental tests are limited, there is no good evidence for resource-dependent plasticity in litter size.

In contrast, there is substantial evidence for local adaptation or, at the very least, local genetic constraint in litter size that correlates with environmental variation at the landscape-level. For example, the number of frost-free days is negatively correlated with *P. maniculatus* litter size *in utero* across North America—this pattern holds true across both altitudinal and latitudinal gradients (McLean et al., 2019; but see Sawin, 1970). Number of frost-free days presumably impacts the length of the breeding season, with shorter seasons (fewer frost-free days) leading to larger litter sizes.

Population-level differences in litter size also persist in the lab for wild-derived *P. maniculatus* strains, suggesting that these differences

are to some degree genetically determined (Figure 1, Supporting Information: Table 2). However, this variation does not correlate with environmental variables from their source populations (Figure 2, Supporting Information: Table 3). Unfortunately, we found no data sets where we could pair data on litter sizes from wild populations with litter sizes from lab colonies derived from the same population, and thus we cannot determine whether this contradiction reflects population-specific flexibility in litter size, founder effects in the lab lines, or some other spurious effect. Although studies to-date do not show substantial flexibility in litter size among populations (see above), these studies are very few in number and focus only on resource manipulation.

Litter size is often tied to other traits or aspects of an organism's life history, including investment in current versus future litters, which is related to longevity and senescence. Thus, we might expect other reproductive traits tied to litter size to consistently vary among populations of *Peromyscus*. For example, population-level differences in inter-birth intervals may reflect differences in maternal investment in current versus future litters, and it is often correlated on a broad comparative scale with litter size (with smaller litters being associated with longer inter-birth intervals). Because *Peromyscus* species experience post-partum estrous, simultaneous gestation and lactation are the norm, at least in the lab; the degree to which this occurs in the wild is less clear. For lab-maintained populations of *P. maniculatus*, inter-birth interval varies as a function of parity, *in utero* litter size, and lactating litter size (see Supporting Information: Table 5). When controlling for these effects, consistent differences in inter-birth interval among *P. maniculatus* strains remain (Figure 3, Supporting Information: Table 5). In contrast, *P. leucopus* inter-birth intervals do not differ between strains (Figure 3, Supporting Information: Table 5). Small sample size may limit the strength of the analysis in *P. leucopus* (Supporting Information: Table 1).

3.2 | Other *Peromyscus* species

3.2.1 | Natural history and distribution

In this section, we summarize the handful of studies that address phenology and litter traits of other *Peromyscus* species. Roughly speaking, other *Peromyscus* species tend to have more restricted latitudinal ranges at the species level, with northern range limits that tend to occur at lower latitudes relative to *P. maniculatus* and *P. leucopus*. However, there are exceptions to this general characterization. For example, *P. keeni* is the second most northerly species (behind *P. maniculatus*), and this species can be found across nearly 20 latitudinal degrees (Verts & Carraway, 1998). As another exception, *P. truei* only reaches a northern latitude of 44°, but it reaches almost 30° to the south (the third largest latitudinal range of any *Peromyscus* species; Hoffmeister, 1981). Unfortunately, no population-level comparative data on breeding phenology or reproductive traits exist for either of these species. The remaining species can be roughly separated into two subclades (1) a central American subclade including *P. difficilis*, *P. mexicanus*, *P. aztecus*, *P. nudipes*, *P. melanocarpus*, and *P.*

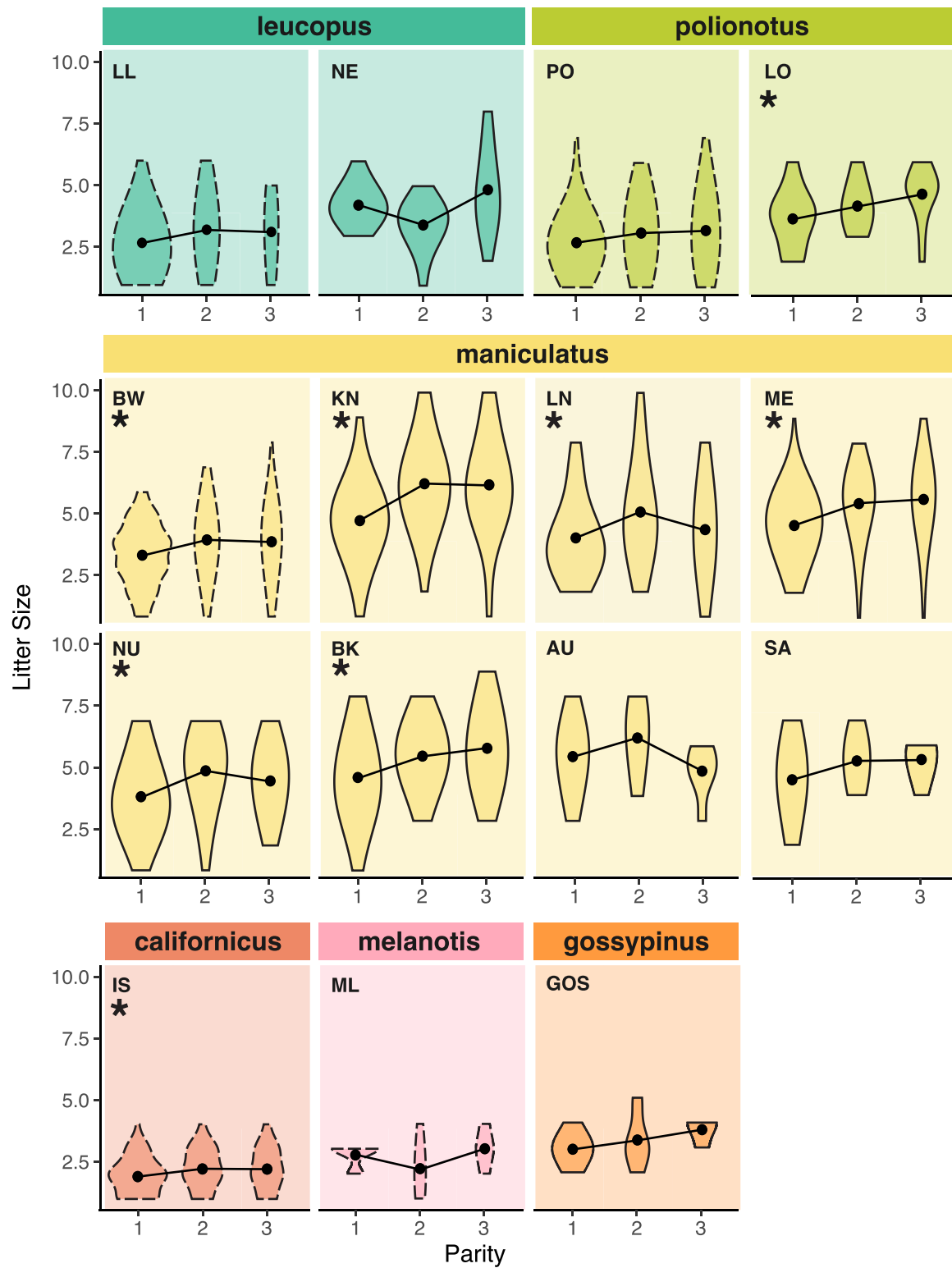


FIGURE 1 Litter size across parities of *Peromyscus* species maintained in laboratory colonies. Each plot contains a violin plot of litter sizes among the first three parities for females from each strain. Black dots connected by lines show the change in mean litter size with increasing parity. Strains available through the *Peromyscus* Stock Center are indicated by dashed outlines in each violin plot; wild-derived mice are indicated by solid outlines. Asterisks (*) indicate significant changes in mean litter size across parities (Supporting Information: Table 2). Specific information on the origin and current location of each strain as well as samples sizes can be found in Supporting Information: Table 1.

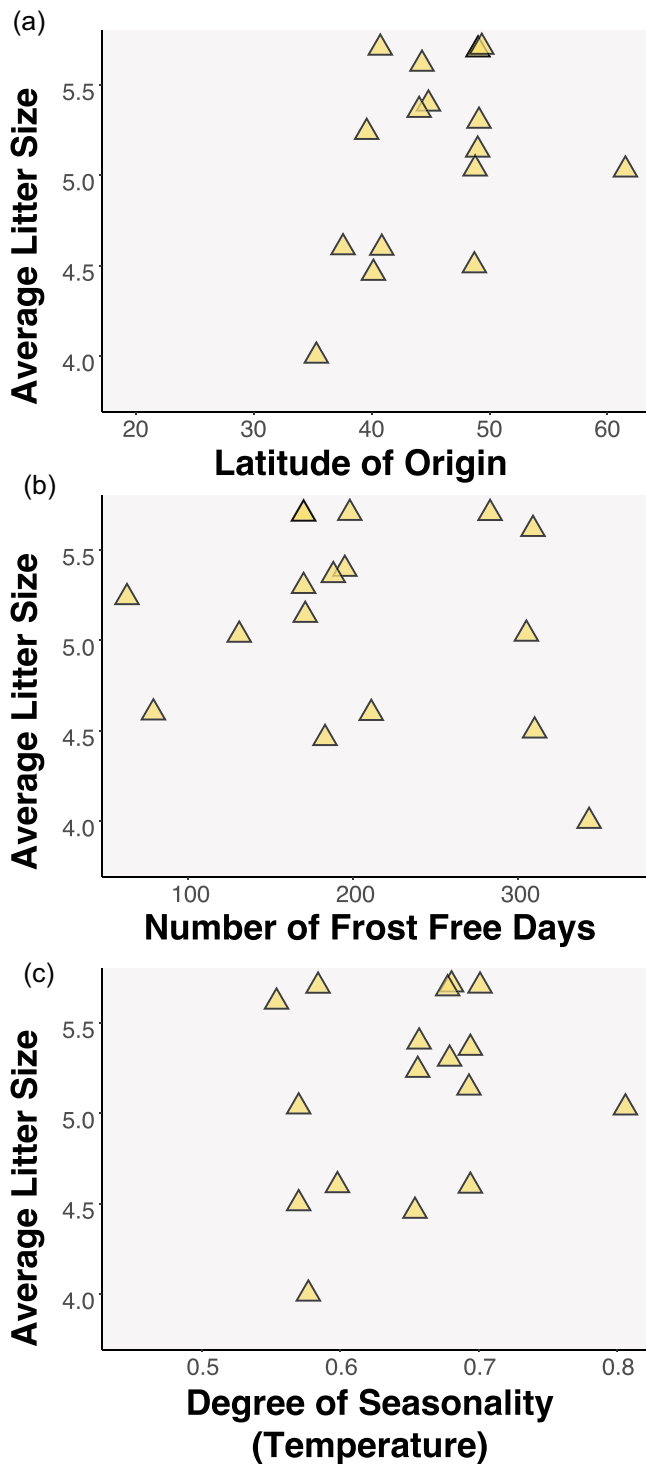


FIGURE 2 Mean litter size in captive colonies of *Peromyscus maniculatus* derived from different locales is not explained by latitude, degree of seasonality in temperature, or number of frost-free days of origin locations (Supporting Information: Tables 3 and 4). Each point represents the average litter size for each strain. Degree of seasonality in temperature was taken from data from Lisovski et al. (2017).

melanophrys, and (2) a more temperate subclade that is also more closely related to *P. maniculatus* and *P. leucopus*, which includes *P. polionotus*, *P. gossypinus*, *P. californicus*, and *P. eremicus*. Although the phylogenetic relationships among *Peromyscus* species are not definitive, these clades generally form monophyletic groups (Platt et al., 2015; but see Natarajan et al., 2013). These subclades differ in their distributional ranges. Species in the central American subclade have northern latitudinal limits at or below 25°N, and a species range center near 20°N, whereas the temperate subclade tends to contain species with a northern latitudinal limit above 30°N, and a species range center near 30° N. However, within the temperate species subclade, *P. eremicus* has a substantially larger latitudinal range relative to other species in the temperate grouping (about 17° vs. 7–10°), and both *P. eremicus* and *P. californicus* have more extensive altitudinal ranges relative to *P. polionotus* and *P. gossypinus*, which are restricted to low elevations in the southeastern US.

In theory, we expect *Peromyscus* species with more subtropical ranges to display reduced seasonality in breeding phenology, in line with the clinal patterns seen in broadly distributed species like *P. maniculatus* and *P. leucopus*. For the subtropical species, year-round breeding is indeed common. Mexican cloud forest *Peromyscus* (*P. melanocarpus* and *P. mexicanus* aka *P. nudipes*) generally lack seasonal breeding patterns, breeding throughout the year across most of their ranges (Rickart, 1977; Rickart & Robertson, 1985; Trujano-Alvarez & Alvarez-Castañeda, 2010); *P. melanocarpus* may display a peak in breeding intensity at the beginning of the wet season (Rickart & Robertson, 1985). Of note, there is some evidence for phenotypic plasticity in age of maturity and litter frequency in *P. mexicanus*—animals in captivity became reproductive significantly earlier and produced litters twice as often compared with free-living counterparts (Heideman & Bronson, 1993).

Year-round breeding can also be found in more temperate species, but patterns still vary based on ecosystem resource pulses. *P. polionotus* in the southern part of their range tend to breed across the year (Wilson et al., 1999), however the season in which an individual breed was driven by birth cohort—females born in the fall delayed puberty longer than spring and summer females (Dapson, 1979). In more northern populations of *P. polionotus* in South Carolina, populations tend to display two breeding peaks across the year with a nadir in the summer (Caldwell & Gentry, 1965), similar to what occurs in *P. leucopus*. In contrast, *P. californicus* appear to maintain moderate seasonality in breeding across their range (Merritt, 1978).

3.2.2 | Plasticity and local adaptation of phenology and litter traits

Reductions in seasonal breeding patterns can occur via reduced sensitivity to photoperiodic cues, as seen in *P. maniculatus* and *P. leucopus*. Alternatively or in addition, populations with some

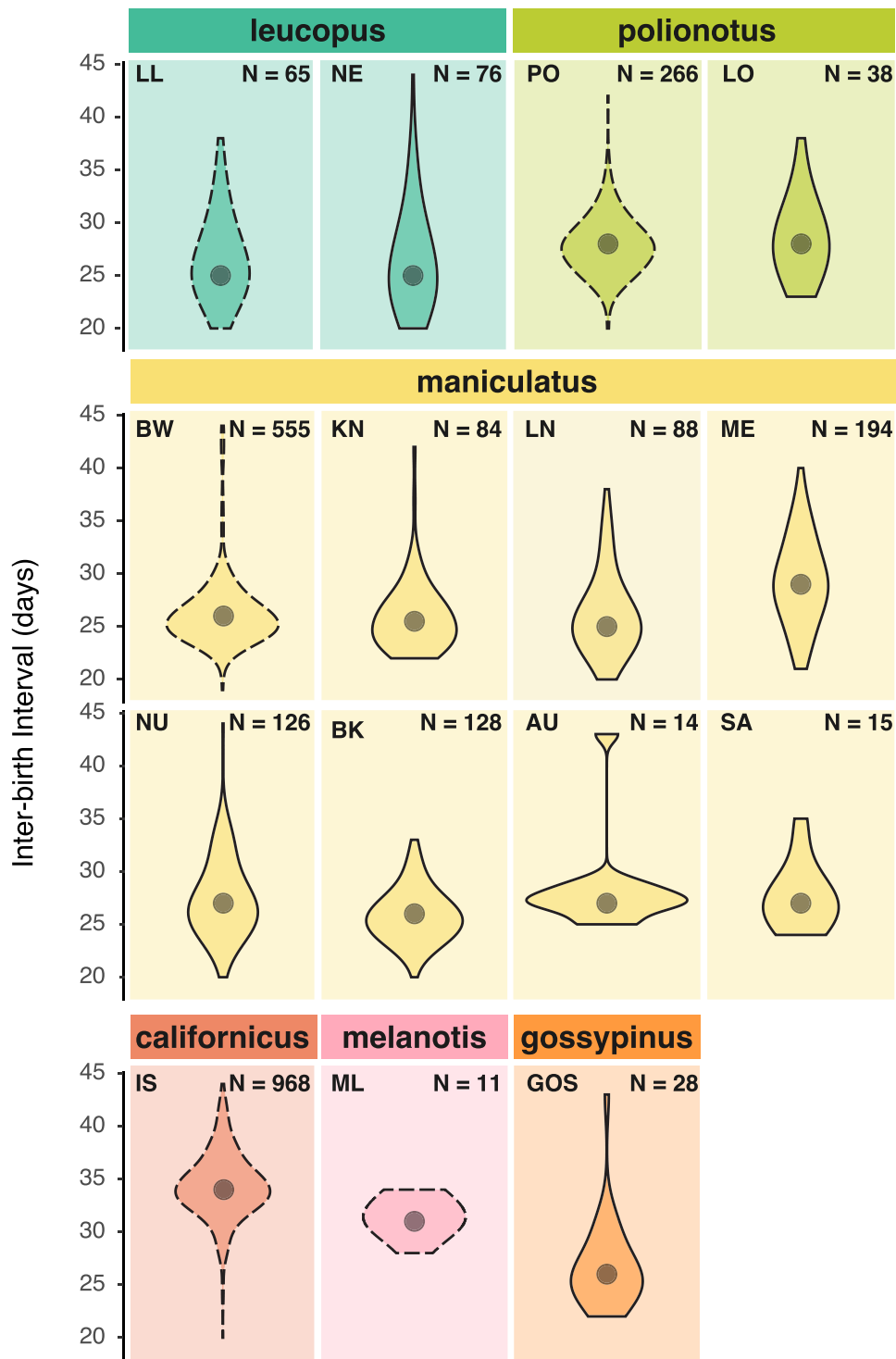


FIGURE 3 Inter-birth interval consistently differs among populations of *Peromyscus* maintained in lab colonies. Dash outlines on violin plots indicate strains available through the Peromyscus Stock Center. The gray dot within each violin plot indicates the median inter-birth interval. Sample size is indicated in the top right of each plot. Further details on the origin and current location of each strain can be found in Supporting Information: Table 1.

seasonality at more tropical latitudes may display increased sensitivity to cues that correspond to rainy seasons (i.e., precipitation) and/or social cues. Photoperiod nearer the equator displays significantly reduced amplitude across the year, and thus photoperiod becomes a

less useful predictor for permissive breeding conditions. Loss of photoperiodic sensitivity can be found in both subtropical and more temperate *Peromyscus* species: *P. aztecus*, *P. californicus*, and *P. eremicus* do not show any change in testes mass relative to body size

in response to changing photoperiods (Demas et al., 1996; Nelson et al., 1995; Trainor et al., 2006), and photoperiod had no effect on likelihood of *P. nudipes* becoming pregnant (Heideman & Bronson, 1992). However, even though photoperiod does not affect testes size in male *P. californicus*, short photoperiods were associated with a small increase in circulating luteinizing hormone, which may suggest that the reproductive system is still sensitive to photoperiod in this species (Nelson et al., 1995). Photoperiodism is retained in other species in each group: both *P. melanophrys* and *P. polionotus* show photoperiod-dependent decreases in testes (Trainor et al., 2006).

Similar variation in sensitivity to food availability appears among temperate and subtropical species of *Peromyscus*, though food availability generally has limited effects on phenology. Food supplementation increased the likelihood of females breeding for *P. mexicanus*, and *P. difficilis*, as well as the more temperate *P. gossypinus* (Duquette & Millar, 1995; Galindo-Leal & Krebs, 1998; Morris et al., 2011). However, in *P. mexicanus*, inter-birth interval remained unaltered (Duquette & Millar, 1995), meaning that reproduction was not more efficient or fast-paced with greater food availability. In *P. nudipes*, food availability does not appear to gate reproductive activity per se, but females only implanted blastocysts and proceeded with pregnancy when food was abundant (Heideman & Bronson, 1992). Conversely, food supplementation did not appear to affect likelihood of breeding in male or female *P. polionotus* or male *P. difficilis* (Galindo-Leal & Krebs, 1998; Morris et al., 2011). Food deprivation reduced reproductive tract size in *P. californicus* (Steinman et al., 2012), but supplementation had no effect (Nelson et al., 1995). Although one would expect water to be particularly important to temperate and subtropical species of *Peromyscus* occupying arid habitats, we only found one study that addressed this possibility; in *P. californicus*, moderate water deprivation caused a small reduction in accessory organ size (Nelson et al., 1995).

Finally, social cues appear to be important to breeding phenology in temperate and subtropical *Peromyscus* species. Access to a mate increased total testosterone and testes size in *P. polionotus* and *P. aztecus*, respectively (Demas et al., 1996; Trainor et al., 2006). Conversely, pairing female offspring with mom reduced reproductive likelihood in *P. eremicus* and *P. californicus* (Gubernick & Nordby, 1992; Skryja, 1978). However, testosterone and testes sizes were unaffected by the presence of a mate in *P. eremicus*, *P. melanophrys*, and *P. aztecus* (Trainor et al., 2006).

Altogether, these data present little in the way of species-level or genus-level patterns. Other than a broad trend towards loss of photoperiodism at latitudes closer to the equator, there is no consistent pattern of cue use or importance among these *Peromyscus* species regardless of their latitudinal range or locale. However, the degree of confidence in this absence of pattern is low, primarily because the data are so sparse. In addition to being few in number, these data sets tend to focus on single, lab-maintained strains from each species. Thus, many of these studies inevitably miss natural variation in ecologically-sensitive traits.

4 | CONNECTING ECOLOGICAL VARIATION TO MECHANISM

The diversity within and among *Peromyscus* offers many opportunities to study local adaptation, parallel adaptation, and life history evolution of mammalian reproductive traits. Indeed, *Peromyscus* has historically been an important model system for studying the physiological mechanisms behind photoperiodic responses (e.g., Borniger & Nelson, 2017; Demas et al., 1996; Heath & Lynch, 1981; Margolis & Lynch, 1981; Petterborg & Reiter, 1981; Prendergast et al., 2001), and our literature review further suggests that reproductive traits display both local adaptation and variation in plasticity across the genus. However, beyond changes in photoperiod sensitivity, the ultimate and proximate bases of reproductive variation among *Peromyscus* species and populations remain unknown. We suggest two areas of focus to broaden the utility of the *Peromyscus* system for studying reproductive diversity and evolution: (1) attention to a broader set of linked life-history traits and (2) careful use of tandem lab and field studies.

4.1 | Integrated life-history traits

Life history traits (including most reproductive traits) tend to vary or evolve as a unit (i.e. life history syndromes), and they are strongly influenced by phylogeny (Blomberg et al., 2003; Freckleton et al., 2002; Végvári et al., 2010) such that lineages differ in their capacity to evolve variation in reproductive traits. Although *Peromyscus* is distinct for its diversity within relatively closely-related species, considering both connections among reproductive traits and diversity with a phylogenetic framework will still be important to consider and control for in comparative and experimental studies. For example, because *P. maniculatus* and *P. leucopus* come from the same subclade within the *Peromyscus* radiation (Bradley et al., 2007; Platt et al., 2015), our current view of the diversity and "evolvability" of reproductive traits may not predict or explain the trajectory or plasticity of reproductive traits in central American *Peromyscus* species.

To understand the degree to which reproductive traits are linked traits (e.g., correlated, modular, or pleiotropic), attention to traits beyond gonadal size will be important. For example, selection for maintaining reproductive activity under short days in *P. leucopus* also results in increased food consumption regardless of light conditions (Heideman et al., 2005), suggesting that changes to reproductive phenology or seasonality are tied to seasonal metabolic or energetic physiology (Moffatt et al., 1993). In a similar vein, litter mass covaries with maternal body size, at least within *P. maniculatus* (Earle & Lavigne, 1990a), however litter size (i.e., pup number), growth rate, interbirth interval, and maternal metabolic rate only correlate with maternal body mass in some populations (Earle & Lavigne, 1990b; Myers & Master, 1983), suggesting that selective pressures differ among populations and that genetic diversity linking traits in some populations may have been severed in others. Furthermore, data from North American *Peromyscus* colonies show that, across species, inter-birth interval is similarly affected by parity, *in utero* litter size,

and lactating litter size: higher parity (i.e., later litters) and larger *in utero* litter size are associated with shorter inter-birth intervals, whereas larger lactating litters are associated with longer inter-birth intervals. However, the effect size of lactating litter size on inter-birth interval is twice as large in *Peromyscus* species with less seasonal reproduction (*polionotus* and *californicus*) relative to *P. maniculatus* (Supporting Information: Table 5), suggesting a stronger link between the two traits in these species.

Finally, behavioral diversity and sex-specific differences in how animals use cues to regulate reproductive phenology are important to consider. Behavior may be a key gatekeeper for reproductive activity in equatorial populations that maintain reproductive competence year-round, and changes in behavior or physiology of a single sex could control reproductive bouts independent of the other sex.

4.2 | Combining field and lab-based approaches

In combination, lab and field studies offer the opportunity to generate deep insight into the mechanisms and forces shaping reproductive diversity. Lab studies and lab-maintained lines of *Peromyscus* have been essential to quantifying the extent to which natural variation in reproductive traits reflects population-level differentiation versus plasticity. However, closed breeding programs, like at the *Peromyscus* Stock Center, have led to consistent changes in reproductive traits, meaning that these strains are not suitable or of limited value for studying reproductive diversity in the genus. Specifically, the common lab strains of several *Peromyscus* species have smaller litters and tend to decrease interbirth-interval relative to strains more recently derived from wild populations (See Figures 1 and 3, Supporting Information: Table 6). This pattern may be the result of either inadvertent lab-selection or epistasis related to inbreeding. It is almost certainly not the result of captivity-related plasticity based on two primary pieces of evidence. First, in early generations of captivity, *P. leucopus* produced similar litter sizes in captivity as in the wild (Millar, 1978). Second, other studies explicitly focused on domesticated versus wild-derived populations have shown similar reductions in litter size in captive *P. maniculatus* strains (Price, 1967; but see Forrester, 1975) and in experimental breeding in captive populations of *P. polionotus* (Lacy et al., 1996). Captive breeding experiments in *P. maniculatus* and *P. polionotus* have also documented changes to offspring weight, especially near birth (Lacy et al., 1996; Millar & Threadgill, 1987). Captive strains regularly outbred to wild populations are thus likely necessary to study reproductive trait and life history diversity in *Peromyscus*—diversity of reproductive traits in stock strains is confounded by inbreeding and/or unavoidable selection on these traits.

5 | CONCLUSIONS

Reproductive variation in mammals is thought to vary along two largely independent axes—one focused on the balance between litter size and mass, and a second related to the “tempo” of reproduction

(Bielby et al., 2007). However, this theory does not address how physiological plasticity contributes to the evolution of reproductive physiology. Additionally, the biological reality underlying these distinct axes and their evolution remains largely unknown within any group of mammals, and there is limited experimental work testing the degree to which these traits evolve independently.

Peromyscus is likely to be useful for testing these ideas because species in this genus vary in inter-birth interval and litter size as well as seasonality or phenology. Moreover, *Peromyscus* species and populations within those species appear to display trait-level convergence on seasonal organization of breeding and in latitudinal clines in cue sensitivity. These patterns have the potential to inform our basic understanding of how life history strategies in mammals evolve and diversify.

To test questions about the mammalian evolution of life history diversity and to understand the genetic or physiological basis of variation in these traits, both experimental and observational data on a wider range of *Peromyscus* populations are needed. Collecting such field data and carefully maintaining stock lines for experimental study together will be important for generating these fundamental advances in our understanding of life history in mammals.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in GitHub at https://github.com/kwilsterman/Peromyscus_ReproFlexibility.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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