ANNUAL REVIEWS

Annual Review of Entomology

The Biology of Aging in Insects: From *Drosophila* to Other Insects and Back

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Annu. Rev. Entomol. 2022. 67:83–103

The *Annual Review of Entomology* is online at ento.annualreviews.org

https://doi.org/10.1146/annurev-ento-061621-064341

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Keywords

insects, *Drosophila*, aging, longevity, life history, natural populations

Abstract

An enormous amount of work has been done on aging in *Drosophila melanogaster*, a classical genetic and molecular model system, but also in numerous other insects. However, these two extensive bodies of work remain poorly integrated to date. Studies in *Drosophila* often explore genetic, developmental, physiological, and nutrition-related aspects of aging in the lab, while studies in other insects often explore ecological, social, and somatic aspects of aging in both lab and natural populations. Alongside exciting genomic and molecular research advances in aging in *Drosophila*, many new studies have also been published on aging in various other insects, including studies on aging in natural populations of diverse species. However, no broad synthesis of these largely separate bodies of work has been attempted. In this review, we endeavor to synthesize these two semi-independent literatures to facilitate collaboration and foster the exchange of ideas and research tools. While lab studies of *Drosophila* have illuminated many fundamental aspects of senescence, the stunning diversity of aging patterns among insects, especially in the context of their rich ecology, remains vastly

understudied. Coupled with field studies and novel, more easily applicable molecular methods, this represents a major opportunity for deepening our understanding of the biology of aging in insects and beyond.

1. INTRODUCTION

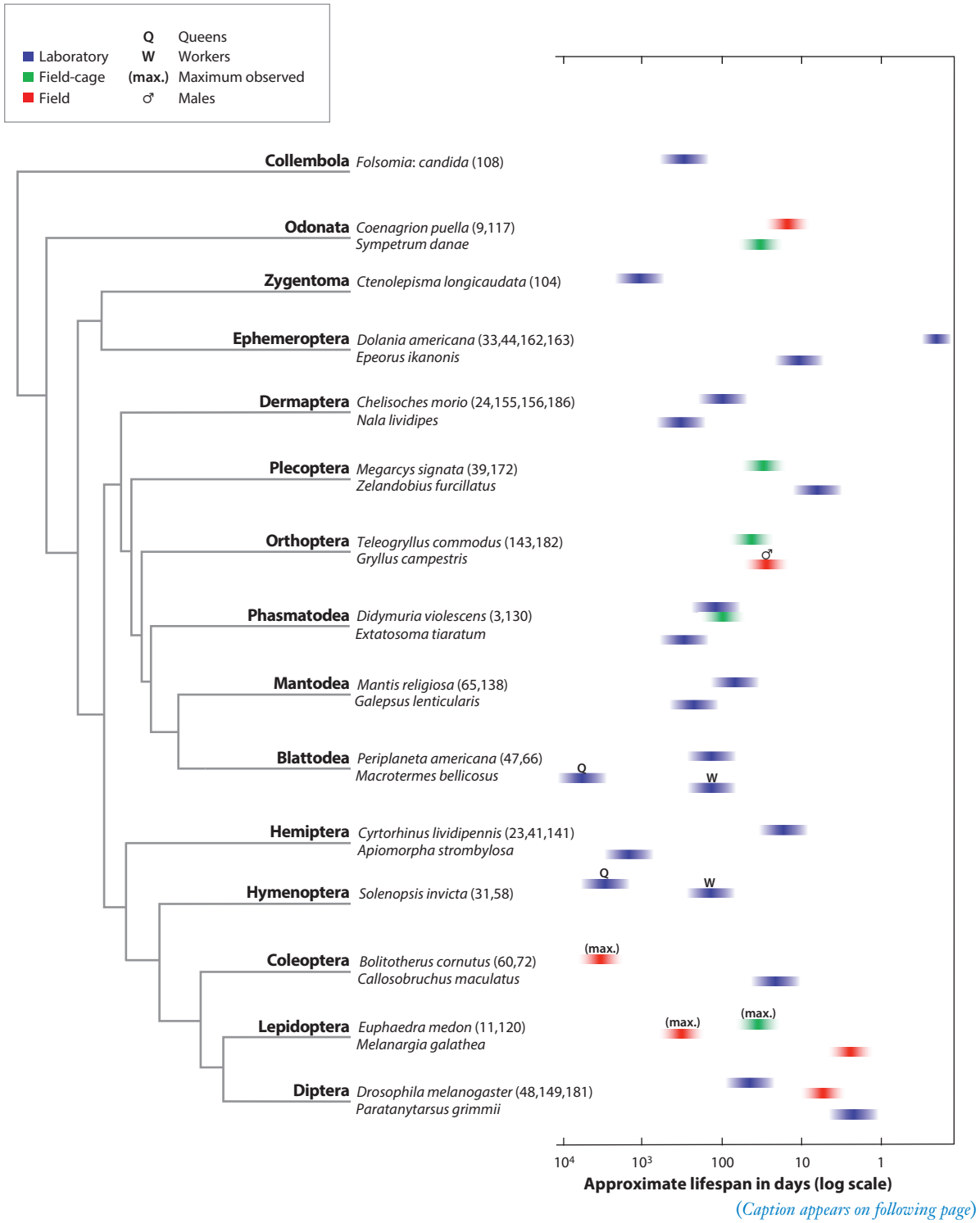
For the past century, biologists have used the vinegar or fruit fly *Drosophila melanogaster* as a model in aging research—that is, as an organism whose physiology, cell biology, and genetics have been studied in great depth in the hope of illuminating biological processes that operate in all animals. A historical account of aging research in *Drosophila* reads much like a history of major advances in evolution, genetics, cell biology, and biochemistry. By aging (or senescence), we mean the age-related decline in intrinsic function, age-specific survival, and reproduction. In parallel with studies of senescence in *Drosophila*, researchers have pursued diverse lines of inquiry into aging in other insect species, not only in species commonly studied in the lab, like *Tribolium* and the bean weevil, *Callosobruchus maculatus*, but also in many nontraditional systems. While a few of these other insect species have contributed substantially to some areas of aging research (as we detail below), no other insect has been studied as broadly or intensively as *D. melanogaster*. In this article, we review the range of aging research in *Drosophila* and other insects and use this review to pursue two broad goals. First, we contrast work in *Drosophila* with aging research in less studied insect species, including those that capture some of the stunning diversity found across the class Insecta (**Figure 1**). By examining this breadth of research against the backdrop of fly studies, we show where studies in nontraditional insect species support discoveries from *Drosophila* and where fly research has yet to be replicated in other systems and outside of the lab. Second, in setting up the juxtaposition of *Drosophila* and other species, we hope to illustrate how nontraditional species offer an opportunity to address questions that are not easily answered in *Drosophila* and the potential for research tools to be transferred across systems. With these two major goals in mind, we aim to highlight the tremendous potential for new directions in aging research, both in *Drosophila* and in nontraditional insect species. We structure our comparison of *Drosophila* and other insect systems by broad intellectual topic.

2. THE DEMOGRAPHY OF INSECT AGING

Measures of age-related changes in demographic processes such as survival and reproduction make up a common thread running through all of aging research. Accordingly, we start with a brief overview of how we define and measure aging demographically and of the concept of demographic trade-offs, which is central to our understanding of aging in insects.

2.1. Measuring Aging

We see clear signs of aging across almost all species and within individuals across diverse traits, including physiology (Section 2.2), behavior (Section 4), body structures, and molecular pathways. These functional senescence changes can result in age-related decline in age-specific reproduction and survival. It is ultimately age-specific survival and reproduction that define fitness (34). Thus, these demographic traits shape the evolution of aging in functional traits and lie at the heart of evolutionary models of aging (34). While both reproduction and survival are obviously critical to fitness, throughout this review we focus primarily on age-specific survival or its inverse, age-specific mortality. The rate of increase in age-specific mortality is known as actuarial aging or



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Variation in insect lifespan. Lifespan varies by four orders of magnitude in the insects. The plot shows lifespan variation within and between some major insect orders and Collembola. For each group, one or two species are shown for comparison, with approximate mean or maximum lifespan in days (log-transformed) based on lab, field, or field-cage studies. Although some species exhibit considerable sexual dimorphism in lifespan, all lifespans shown are for females unless otherwise indicated. For social insects, lifespans are shown separately for queens and workers. Note that lifespan can be strongly affected by environmental factors such as diet, temperature, and crowding, and small differences between species in estimated mean lifespan should therefore be interpreted with caution. References are listed in parentheses to the right of Order name. Phylogeny is based on Reference 175. Photos courtesy of R. Bonduriansky.

demographic aging. Mortality rates are measurable, at least in principle, in all populations, including those that do not reproduce, like sterile hymenopteran workers. Moreover, mortality rates are comparable between species with diverse reproductive strategies.

Two often-used measures of aging are mean and maximum lifespan, but these do not actually measure actuarial aging (**Figure 2**). To understand how a species ages, we need to measure individual ages at death. Even with a modest sample size, age-at-death data allow us not only to measure rates of aging, but also to identify factors associated with survival, using Kaplan-Meier or Cox Proportional Hazard models (99).

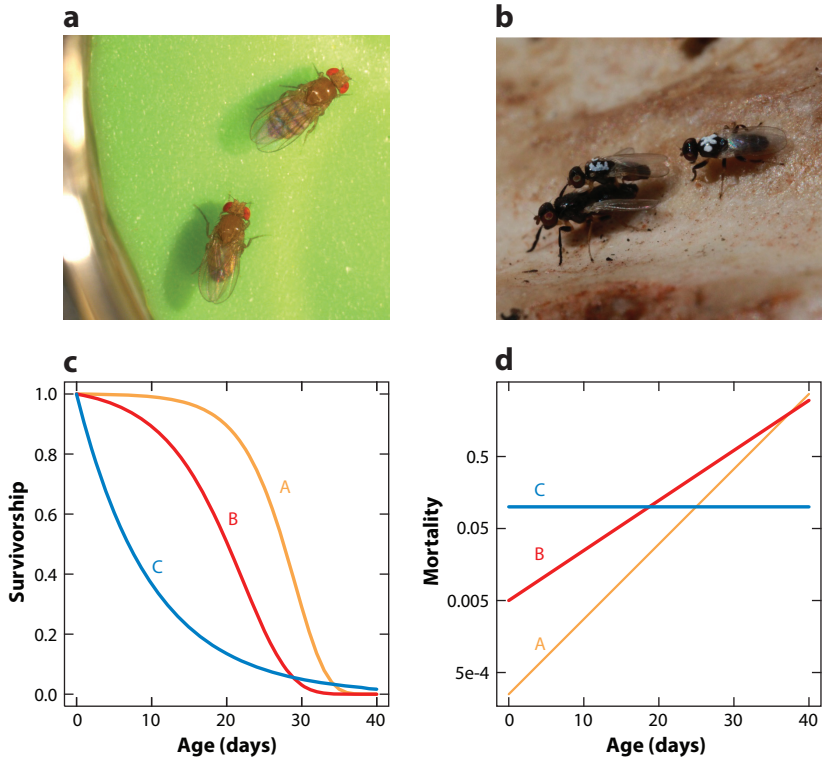


Figure 2

Insect mortality in the lab and the wild. (*a*) *Drosophila melanogaster* male courting a female in a vial in the lab. (*b*) A marked male antler fly (*Protopiophila litigata*) guarding a female while being pursued by a marked rival male on a moose antler in a forest in Algonquin Park, Ontario. (*c*) Survivorship (proportion alive) as a function of age. (*d*) Age-specific mortality rate, plotted on a log10 scale. Curves A and B are representative of mortality patterns typically observed in lab-housed insects. Curve C (*blue*) shows a population in which mortality rates are constant (i.e., no sign of demographic aging), a pattern more commonly seen in the wild.

Age-specific mortality curves across diverse vertebrate and invertebrate taxa exhibit a common pattern, with low rates in early adult life that then increase with age, often following the exponential increase described by the Gompertz equation (64):

$$\mu_x = \alpha e^{\beta x}, \quad 1.$$

where μ_x is the instantaneous mortality rate at age x, and α and β are constants. Taking the logarithm of both sides, we obtain

$$\ln(\mu_x) = \ln(\alpha) + \beta x, \quad 2.$$

where $\ln(\alpha)$ and β represent the intercept and slope, respectively, of the plot of log(mortality) versus age (**Figure 2*d***). Many researchers use the Gompertz slope β as a measure of the rate of actuarial aging.

While it was long thought that actuarial aging would be rare in nature, it has been shown to be common among mammals (135) and even in insects by studies using capture–mark–recapture methods. An early use of this approach followed wild *Drosophila* for their entire lifespan (146). Bonduriansky & Brassil (19) provided the first compelling evidence for actuarial and reproductive aging in a wild insect by marking and following male antler flies (*Protopiophila litigata*) living on discarded moose antlers. Molleman et al. (119) captured and marked more than 30,000 butterflies, showing that some butterflies can live for at least 9 months, though even these large numbers were not sufficient to provide estimates of rates of actuarial aging.

Of course, it is not always feasible to track individual insects in the wild longitudinally. An alternative approach has been to measure lifespan in wild-caught insects housed in the lab. Using this approach, Carey (33) found that newly emerged mayflies showed signs of aging over their lifespan of just a few days. While the age of wild-caught adults at capture is typically not known, Carey and colleagues (124) developed methods to estimate mortality curves in Tephritid flies based on duration of life following capture of adults of unknown age, a method that has since been applied to other species (e.g., 13).

2.2. Demographic Trade-Offs

While we often focus on age-specific survival and reproduction in aging research, also of great interest and importance are the trade-offs, or negative correlations, between these fitness traits (155), such as the cost-of-reproduction trade-off between early fecundity and survival (15, 54). These trade-offs make up a central tenet of life-history theory and evolutionary theories of aging (94, 173). Trade-offs can be physiological (e.g., individuals that reproduce more live shorter lives) and/or evolutionary (e.g., evolution of higher reproductive effort causes reduced lifespan) (155). In terms of physiology, trade-offs might arise from competitive resource allocation, as when energy invested into reproduction is not available for maintenance and survival (see below). For example, in male crickets, the same adult diet maximizes both survival and reproduction (107). What really matters evolutionarily is that such trade-offs are genetically based. Negative genetic correlations arise primarily from alleles with antagonistic pleiotropic effects on the traits involved; antagonistic pleiotropy (AP) is thought to be one of the key factors underlying the evolution of aging (173).

Some of the clearest evidence for genetically based trade-offs comes from artificial selection and experimental evolution experiments, mainly in *D. melanogaster*, selecting for late-life fertility and/or postponed senescence (54). While the best-known examples of trade-offs come from fruit flies (for reviews, see 34, 54, 145), there are many studies, both in the field and in the lab, that have looked at trade-offs in other insects, such as crickets (142), water striders (87), and *C. maculatus*

(115). Results have been mixed, however: In some cases, we see clear negative phenotypic correlations between reproduction and survival, while in others, these two traits are positively correlated. In the field cricket, *Gryllus campestris*, for example, males that emerge earlier (and presumably start reproducing sooner) live longer than late-emerging males (for recent reviews, see 54, 142).

Much work has focused on the physiology of costs of reproduction (16, 55, 69). Using genetic or surgical manipulations that curtail reproduction, it has been found that reproductive arrest extends lifespan in *Drosophila* (56) and the grasshopper *Romalea microptera* (45), but not in the bug *Pyrrhocoris apterus* (75). Likewise, mating manipulations in fruit flies and *C. maculatus* have established survival costs of mating (59, 132). In terms of mechanisms, many studies have examined the endocrine underpinnings of trade-offs (55, 57). Ablation of insulin-producing cells in the brain or the corpora allata, the gland producing juvenile hormone (JH), reduces or abolishes fecundity and extends lifespan in *D. melanogaster*, the butterfly *Danaus plexippus*, *P. apterus*, and several grasshoppers (*Anacridium aegyptium*, *Schistocerca gregaria*, *Locusta migratoria*) (for reviews, see 26, 57, 75, 177). This supports the idea that insulin-like peptides and JH have gonadotropic effects that promote senescence (for a review, see 57; see also 157, 167). The lifespan-shortening effects of JH might be due to its negative effects on oxidative stress resistance and immunity, as suggested by results from *Drosophila*; the mealworm beetle, *Tenebrio molitor*; and the damselfly *Calopteryx virgo* (see also 40; for a review, see 57). Similarly, evidence from honey bees (*Apis mellifera*) indicates that the yolk precursor vitellogenin, an endocrine factor downstream of insulin and JH, affects immunity, oxidative stress, and lifespan of workers and might contribute to the long life of queens (5, 43, 128). Remarkably, costs of reproduction can also depend on sensory perception: In female and male *D. melanogaster*, food-derived odors and olfaction affect lifespan (102). Similarly, in male flies, the costs of reproduction seem to be associated with the pheromone perception of females; abolishing pheromone perception abolishes these costs (70).

Because the costs of reproduction might be due to resource allocation trade-offs, several studies have employed diet manipulation in *Drosophila*, *C. maculatus*, butterflies (*Bicyclus anynana*, *Pieris napi*) (51, 54, 165) and other insects (see Section 5). While some studies have found that nutrition might mediate the survival–reproduction trade-off (165), experiments quantifying resource allocation and metabolic stores in grasshoppers and *D. melanogaster* have found only weak or no support for this notion (54). Nonetheless, biochemical and metabolic studies of wing polymorphic crickets (*Gryllus firmus*) have established a resource allocation trade-off between reproduction and investment in flight ability (for a review, see 69). Likewise, manipulation of resource availability during development has shed light on trade-offs between investment in reproduction-related traits and juvenile and adult survival in neriid flies (79). Metabolomic studies are likely to advance our understanding of these issues (for an example in *Drosophila*, see 76), as they are readily applicable to most insects.

The ready availability and rapid improvements of physiological methods (endocrinology, metabolic assays, metabolomics, transcriptomics) mean that many physiological aspects of senescence and trade-offs can now be studied in insects beyond *Drosophila*.

3. INSECT AGING IN THE LAB VERSUS THE WILD

As most work on insect aging takes place in the lab, we need to be mindful of the influence of the lab environment not only on measures of aging in the short term, but also on how populations might evolve in lab culture over the longer term. To understand how senescence evolves and diversifies, we must also study senescence in natural populations. Senescence integrates numerous life-history traits (i.e., fitness components such as fecundity and age-specific survival) that are highly plastic and context dependent in their expression and their effects on fitness (55). Because

the lab environment differs in many ways from natural environments, captive populations are likely to express senescence differently and to experience different patterns of selection on senescence. This means that lab studies could yield misleading results (25).

As we note in Section 2, benign lab environments can mask costs and trade-offs, but not only due to effects of diet. Mortality risk from most biotic and abiotic sources is dramatically reduced under typical lab conditions, meaning that captive animals are likely to experience much weaker selection on traits that affect mortality risk and to survive much longer than they would in the wild (89, 110). For example, in the wild, individuals that reproduce more or earlier might be more vulnerable to mortality from predation, illness, or harsh weather. In contrast, elevated reproductive effort might have little effect on mortality risk in the lab, where such extrinsic mortality risks are absent. For similar reasons, an allele that affects senescence rate in natural populations (e.g., by altering the costs of reproduction or vulnerability to predators or parasites) might have a much weaker effect on age-specific mortality in the lab than it would in the wild (although the controlled lab environment might make allelic effects easier to detect and so amplify narrow-sense heritability). Lab animals are also typically provided with abundant, rich food and plentiful water, reducing selection on foraging ability. Thus, while selection in natural populations might act against an allele that induces earlier or greater investment in reproduction because of the associated risks and costs, the same allele might be under net positive selection in a benign lab environment, where such risks and costs are greatly reduced. At the same time, truncation of reproductive lifespan in lab culture (e.g., by propagating populations from eggs laid early in life) can select for reduced longevity and rapid aging in the lab and result in accelerated aging in lab-adapted flies relative to natural populations (151).

In some cases, environmental or genetic effects on senescence could be not only masked but also altered qualitatively by the lab environment. For example, numerous studies on *D. melanogaster* and other insects have shown that protein restriction increases lifespan (100, 107), a response interpreted as an adaptive reallocation of metabolic resources toward somatic maintenance that enables animals to survive periods of famine (95). However, because dietary protein also enhances physiological capacity to respond to challenges such as infection and injury, protein restriction might increase some mortality risks in natural environments (2).

Another example of how the lab environment could influence results of research on senescence is the role of extrinsic mortality in the evolution of lifespan and senescence. Extrinsic mortality (i.e., mortality that results at least partly from factors external to the organism) can result from a variety of biotic factors (such as predators or pathogens) and abiotic factors (such as harsh weather or accidents). In insects, spikes in ambient temperature could represent especially important abiotic sources of extrinsic mortality (130). Theory and empirical evidence suggest that the evolution of senescence depends not only on the levels but also on age-specific patterns of extrinsic mortality and fecundity. If extra mortality is random but limited to adult ages, then the ability of selection to purge mutations that increase mortality erodes faster with age. If extra mortality is random with respect to all ages, then age-specific selection will not change unless mortality leads indirectly to something else, such as increased density dependence of age-specific fecundity (120, 173). However, if mortality is strongly condition dependent, then alleles that promote survival could be favored, potentially resulting in the evolution of slower senescence (1, 35, 141). Thus, if mortality is more strongly condition dependent in the wild than in the lab, an increased mortality rate could have very different consequences for the evolution of senescence in natural versus lab environments.

Little is known about patterns of senescence in natural populations of *D. melanogaster*, although some studies have compared the longevity of lab- versus wild-adapted lines in the lab (e.g., 151), and a few studies have estimated longevity in the wild using cohort-marking techniques (146) or

field cages (see, e.g., 109). However, some insects are more amenable to longitudinal field studies (180). Such studies suggest that captive animals can exhibit dramatically different rates of senescence from their wild counterparts (89) and that dietary protein might affect senescence differently in lab versus natural environments (110). This evidence supports the need for more research on senescence in natural populations of insects, as well as in seminatural or stressful environments in the lab (25, 180). Research on natural populations might also contribute to our understanding of the diversity of senescence patterns (see 38, 86).

4. AGING, BEHAVIOR, AND COGNITION

The impact of aging is manifest in diverse physiological and behavioral systems. In insects, the ability to perform complex behaviors such as locomotion, foraging, reproduction, and antipredator defense contributes enormously to variation in fitness. Because behavioral performance depends on cognition, a decline in brain or neuronal function with advancing age could contribute substantially to senescent declines in behavioral performance and fitness. While theory predicts that all aspects of performance decline with age (173), behavioral performance might decline especially rapidly because it integrates so many biological systems, relying on the condition and functionality of relevant brain regions, sense organs, motor neurons, muscles, and the cuticle and joints of locomotory appendages (legs, wings). Reduced functionality in any one system could reduce the ability to walk, fly, forage, or perform courtship.

In *Drosophila*, aging is associated with reductions in many aspects of cognitive and behavioral performance, including memory and learning (113, 114, 161), flight performance (97), locomotion and sleep (85), visual acuity and phototactic ability (32), courtship (36), and response to social cues (22). These changes are associated with structural and chemical changes in the nervous system, including loss of neuronal synapses and changes in mushroom bodies in the brain (17, 67, 101, 170), as well as changes in neurotransmitter release (181). Interestingly, age at breeding can affect cognitive and behavioral performance of descendants. For example, offspring and grand-offspring of older flies exhibit reduced memory (29), and both maternal and paternal ages at breeding affect reproductive behavior in offspring (123) (see Section 6).

Studies in other insects suggest that patterns of behavioral senescence can vary markedly among taxonomic groups. For example, older cockroaches exhibit reduced ability to solve mazes (27), but there is little evidence of declining cognitive or behavioral performance in ant or honey bee workers (12, 63, 147). Moreover, senescent declines appear to be reversed when honey bee workers switch tasks (126). Yet, like *D. melanogaster*, old honey bee workers exhibit pronounced changes in brain structure and chemistry (50, 125, 150), suggesting the possibility of more subtle or context-dependent changes in performance (e.g., changes in some forms of learning or memory).

While behavioral performance declines with age in many insects, behavioral interactions could also contribute to senescence. For example, male–male combat can cause wear and tear (e.g., 14). Likewise, intersexual conflict over mating can result in injury or elevated predation risk (68, 139). It remains unclear to what extent such interactions impose immediate versus latent costs, but both types of costs could influence the evolution of senescence.

Understanding the implications of cognitive and behavioral senescence for fitness will require research in natural and seminatural environments. Both the expression of behavioral traits and the fitness consequences of such variation are likely to be strongly environment dependent. The behavior of individual insects in the lab does not necessarily predict their behavior under natural conditions (53). Lab housing can restrict the opportunity to exhibit many types of behavior as a result of limited space to fly, run, or jump. Moreover, without a need to disperse, locate food, or escape from predators, locomotory performance might have much less impact on fitness in captivity

(except perhaps in a sexual context). The lab environment could also affect the rate of decline of cognitive and behavioral traits. For example, flight performance in *D. melanogaster* declines more rapidly with age when flies are prevented from flying (97).

D. melanogaster is very challenging to study in the wild because these tiny and highly mobile animals are difficult to mark and resight over the course of their lives. However, some evidence for behavioral senescence from natural populations of other insects is starting to emerge. For example, in natural populations of *P. litigata*, male reproductive aging involves both increased time-out from mating aggregations and a reduction in the ability to mate twice per day (20). Wild cricket (*G. campestris*) males exhibit declining call rate and reduced ability to dominate rivals as they age but do not show declines in mate searching or mating promptness (143). Nonetheless, while older males attract more females, mating rate still declines with age (143). Very little is known about behavioral senescence in natural populations of most other insects.

5. ENVIRONMENTAL EFFECTS ON AGING AND LIFESPAN

In insects, age-related fitness traits are exquisitely sensitive to diverse environmental factors, including temperature, humidity, diet, and oxygen levels. In this section, we focus on two of the most commonly studied environmental factors affecting lifespan—temperature and diet.

5.1. Temperature

Some of the earliest work on the biology of insect aging focused on the effect of temperature on lifespan. Over a century ago, Baumberger (10), in a study of wild-caught individuals from diverse orders of insects, showed not only that chronic exposure to high temperature was negatively associated with longevity, but also that a brief early exposure to high temperature was positively associated with longevity.

The negative correlation between chronic high temperature and lifespan has been demonstrated in numerous subsequent studies, starting with a review of diverse insects by Alpatov & Pearl (4); then in greater detail in other *Drosophila* species [e.g., Maynard Smith (111, 112) recapitulated the effects of brief and chronic heat exposure in *Drosophila subobscura*]; and later in a diverse range of other systems, from grasshoppers (116, 172) to bedbugs (80, 184) and more (see 90). Just as warm temperatures shorten lifespan, cool temperatures lengthen it (106, 111), and in some cases, cold-induced diapause can dramatically slow aging (e.g., 166).

The observation by Baumberger (10) and Maynard Smith (112) that early-life exposure to high temperature might increase lifespan (a phenomenon known as hormesis) generated much excitement when it was rediscovered in *D. melanogaster* (92) and some other Drosophilids (148). Numerous mechanisms have been suggested for this hormetic temperature effect. High temperature induces expression of heat shock proteins, key molecules in maintaining proteostasis, providing long-term benefits to individuals that are primed with a nonlethal heat stress (74).

The compelling effects of temperature on aging raise an important question: How might climate change alter life history strategies in general, and aging in particular (30)? The tremendous diversity of insects provides a powerful framework with which to address this question. Numerous studies (28, 93) have shown that warming climate over the past decades has changed insect life histories. With warming climate, through direct and indirect effects, insects often emerge earlier in the season; breed earlier; and, in the case of multivoltine species, go through more generations each year. These warming patterns can also lead to changes in overwinter survival and fitness. Thus, we might also expect changes in selection on aging due to shorter generation times and age-specific responses to changes in temperature or resources. On a shorter timescale, extreme

weather events, including temperature spikes and natural disasters, could lead to mass mortality events with longer-term consequences on life histories. Although this is beyond the scope of this discussion, changes in CO_2 levels might also affect insect lifespans (131). A key issue is whether natural populations of insects will be able to adapt to these environmental changes (77). To address this, moving the focus back to the lab and studies of *D. melanogaster* might provide invaluable insight into natural populations (77).

5.2. Diet

As with temperature, the first studies of the effects of diet on survival began a century ago (106), and numerous studies have established the ability of both intermittent feeding and dilute or chemically defined diets [dietary restriction (DR)] to extend lifespan in *Drosophila* (133). There is considerable debate regarding the generality of the effects of DR on increasing lifespan. Some have argued that the phenomenon is an artifact of the benign lab environment (i.e., absence of factors such as predation or temperature stress that might elevate risk for diet-restricted individuals) and suggested that DR might have no or even a negative effect on lifespan in a natural environment where individuals are exposed to many stresses and risk factors (2). We see considerable genetic variation in the response to DR in *Drosophila* (84), with some genotypes living shorter lives under DR. Among other insects and spiders, one can find examples of DR leading to increased lifespan (e.g., 8, 49, 71), leading to decreased lifespan (42, 118), or having no effect. Given this considerable variation, in-depth analyses of insects other than *Drosophila* might shed critical light on the evolutionary and molecular mechanisms that underlie the DR effect on lifespan.

Both diet- and temperature-related stressors, as well as changes in photoperiod, can provide cues indicating upcoming stressful environments. In response, many insects can enter diapause, a state of developmental arrest associated with increased stress resistance and somatic maintenance. For example, numerous adult insects (e.g., *Drosophila*, *Phormia*, grasshoppers, butterflies, bugs) undergo reproductive diapause or dormancy, a state of reproductive arrest that promotes somatic persistence and adult survival (for a review, see 168). Reproductive diapause can thus be viewed as a case of phenotypic plasticity of lifespan and associated life-history traits (168). Similar to larval diapause in *Caenorhabditis elegans*, which is also connected to the regulation of adult lifespan, insect reproductive diapause is under neuroendocrine control (52, 55, 168).

5.3. Biotic Interactions

Age-specific mortality and fecundity rates determine how selection shapes life-history strategies in general and senescence in particular. Moreover, the literature on the evolution of aging not only distinguishes between the effects of extrinsic versus intrinsic mortality (156), but also investigates whether mortality depends on population density (1), individual condition (174), and frequency-dependent selection (122). These different types of responses to mortality risk might affect how aging evolves.

However, typically missing from these discussions is the consideration of how biotic factors might generate different evolutionary responses to mortality risk. Perhaps this is not surprising given that most studies are carried out in the lab. In the wild, insects might die as a result of interspecific interactions with predators (149), micro- and macroparasites (127), and plant-derived toxins (81). Insects also underscore the importance of intraspecific causes of mortality, including cannibalism (6), mate competition (105), and sexual conflict (21, 136). Natural populations of insects offer a powerful resource for exploring these very diverse sources of mortality and their demographic and evolutionary consequences.

6. THE GENETICS OF INSECT LONGEVITY

6.1. Quantitative Genetics

Quantitative genetics is concerned with the generation, evolution, and maintenance of genetic variation for phenotypes of interest. We can show this mathematically as the simple equation $P = G + E + \text{cov}(G,E)$, which states that phenotypic variance P is the sum of genetic variance G, environmental variance E, and the interaction (covariance) between the two. Genetic variance in turn can be broken down into component parts, including contributions due to alleles with additive or dominant effects, epistasis, maternal and paternal genetic effects, and inbreeding. Genetic variance components influence not only how variable traits are among individuals, but also how they evolve. Researchers have sought to parse genetic variance for aging into its various components in an effort to describe the underlying architecture of aging in genetically variable populations and thereby to test theories of aging (for a review, see 54). While the vast majority of molecular genetic studies of aging in insects have focused on *D. melanogaster*, the quantitative genetic literature is replete with examples from other insect species (e.g., 7, 18, 87, 138). This literature includes not only tests of predictions arising from the evolutionary genetic theories of aging, but also studies asking more broadly how genetic and environmental variation affects aging.

Drosophila researchers have invested considerable effort into testing for the relative importance of the two major evolutionary genetic theories of aging—AP and mutation accumulation (for reviews, see 34, 54). Some of the earliest studies, on the effects of inbreeding on longevity, were carried out in the 1950s using *D. subobscura* (78). The following two decades saw relatively little work until a series of independent studies showing that artificial selection for long lifespan led to reduced early-age fecundity, in support of the AP or trade-off model for the evolution of aging (for a review, see 145). This work sparked decades of research on the quantitative genetics of aging not only in *Drosophila*, but also in other insects such as *C. maculatus*.

Maternal age effects have long been of interest to researchers working on aging in insects. While maternal age effects have not been a formal component of classical evolutionary models of aging until recently (121), Lansing (98) showed in rotifers that older mothers produced short-lived offspring, inspiring numerous studies on parental age effects. The Lansing effect is sometimes recapitulated in insects, for example, in butterflies (46) or ladybirds (154), but other studies have found that older mothers produce longer-lived offspring, as in *C. maculatus* (61), or have found no effect of maternal age, as in burying beetles (83). This lack of consistency raises the interesting challenge of identifying the biological or environmental factors that determine the nature of parental age effects among species. To date, very few studies have investigated whether age at breeding can affect the longevity of descendants over more than one generation, but some intriguing findings have come to light. For example, in *Drosophila serrata*, maternal and grand-maternal ages at breeding have interactive effects on the viability of descendants (73). In the neriid fly *Telostylinus angusticollis*, age-at-breeding effects interact over two generations in both matrilines and patrilines, with large effects on descendants' mortality rate and longevity (176). The potential for maternal and paternal age effects to persist and interact across multiple generations suggests that such effects could represent a substantial source of aging-related variation among individuals. Likewise, the potential for parental environments (e.g., temperature or diet) to influence the longevity and senescence rate of descendants warrants investigation.

6.2. Molecular Genetics of Lifespan in Insects

Even though the evolutionary geneticist John Maynard Smith (111) had already investigated a long-lived mutant of the *grandchildless* gene in *D. subobscura* in 1958, the molecular genetic study of lifespan in multicellular organisms only began in earnest with the discovery of long-lived mutants

in the nematode worm *C. elegans* in the early 1980s (for a review, see 91). The corresponding longevity genes were later cloned and characterized by the Ruvkun and Kenyon labs. Several of these genes turned out to belong to the conserved insulin/insulin-like growth factor signaling (IIS) pathway (91). These groundbreaking discoveries paved the way for molecular studies of longevity in other metazoans, mainly in *D. melanogaster* and the mouse *Mus musculus* (134, 163, 164).

The first longevity mutant to be studied in *D. melanogaster* was a mutation in the *methuselah* (*mth*) gene, which encodes a G protein–coupled receptor (103). Mutations that extend fly lifespan were also found in a gene that encodes a tricarboxylic acid–cycle transporter and is named *I am not dead yet* (*Indy*) (144). Around the same time, the first transgenic studies of fly lifespan showed that overexpression of antioxidant enzymes and heat shock proteins extends lifespan (for a review, see 162). Most notably, work by the laboratories of Marc Tatar and Linda Partridge in the early 2000s found that mutations in IIS genes homologous to those identified in *C. elegans* markedly extend lifespan in the fly, suggesting that the effects of this pathway on longevity are evolutionarily conserved (37, 164, 167). Downregulation of the target of rapamycin (TOR) pathway, which closely interacts with the IIS pathway, was also found to promote longevity in *Drosophila* (88).

By leveraging the powerful genetic toolbox in the fly, subsequent work identified numerous other genes and pathways impacting longevity, including the histone deacetylase Sir2, first discovered as a factor affecting aging in yeast; JNK signaling; the Imd and Toll immune pathways; the energy sensor AMPK and the amino acid sensor GCN2/ATF4; Ras-Erk-ETS signaling; the transcription factor Myc; the DNA repair factor dPRP19; steroid hormone (ecdysone) signaling; and others (e.g., see 134 and references therein). Many of these genes and pathways interact with each other, and they often converge onto the IIS/TOR network. This body of work has also revealed how lifespan is correlated with other fitness-related traits such as stress resistance and fecundity, often revealing the existence of trade-offs between lifespan and other fitness components (54).

Unfortunately, much less is known about the molecular genetics of longevity in insects other than *D. melanogaster*, mainly due to the unavailability of genetic tools, with a few notable exceptions. For example, RNA interference (RNAi) has been leveraged to show that the yolk precursor gene *vitellogenin* (*Vg*) and the *insulin receptor substrate* gene affect worker lifespan in the honeybee (*A. mellifera*) (82, 128). Similarly, RNAi knockdown of *Vg* has been found to extend lifespan in the lubber grasshopper (*Romalea microptera*) (171). While progress in insects outside *Drosophila* has been slow, the rapid improvements of genetic tools such as transgenesis, RNAi, and—most importantly—CRISPR/Cas9 genome editing hold the promise that the mechanisms of aging can soon be studied in a variety of insects, at least in those that can be bred easily in the lab (62, 158). Such tools are now applicable to many insects, including the silk moth (*Bombyx mori*) and other lepidopterans, the flour beetle (*Tribolium castaneum*), mosquitoes (*Aedes aegypti*, *Anopheles stephensi*), the linden bug (*Pyrrhocoris apterus*), and the clonal raider ant (*Ooceraea biroi*). Notably, recent work in the brown planthopper (*Nilaparvata lugens*) has employed CRISPR/Cas9 to induce mutations in the *insulin-like receptor* gene, showing that heterozygous mutants are long-lived and suggesting that the effects of reduced IIS upon lifespan are conserved between planthoppers and *Drosophila* (182). There is also much scope for research on the potential roles of epigenetic factors (such as DNA methylation and chromatin structure) in shaping variation in lifespan and aging rate in insects and mediating the effects of environmental factors on these traits.

7. CONCLUSIONS

Among the millions of insect species that exist, we have barely scratched the surface of the diversity in patterns and mechanisms of aging. This diversity provides us with a fantastic opportunity to learn how ecology and physiology shape patterns of aging and about its underlying mechanisms,

from evolutionarily conserved traits to those found in a single taxon. We now have molecular tools to explore this realm of aging far beyond *Drosophila* and indeed beyond traditional lab-based studies. In this section, we highlight five research areas likely to prove especially fruitful in the coming years.

First, scientific discovery starts with observation. We urge the next generation of researchers to explore the full diversity of aging and life-history strategies found in insects (e.g., **Figure 1**). How is the evolution of aging affected by whether a species is semelparous or iteroparous, a capital versus an income breeder (e.g., *C. maculatus* versus *D. melanogaster*), hemimetabolous versus holometabolous, aposematic versus cryptic, winged versus wingless, and so forth? Similarly, how is aging influenced by the extraordinary range of environments in which insects are found, in terms of both plastic responses within species and long-term evolutionary responses across taxa?

Second, to better understand how selection shapes aging and the entire life history, we need to investigate how genes and physiological systems interact with key environmental variables such as nutrients, temperature, and parasites or symbionts. Such research is very challenging to do with *D. melanogaster* because these animals have low site fidelity (i.e., they do not form stable aggregations and lack a defined home range). However, such work can be done using field systems such as antler flies, which have a high degree of site fidelity that makes it possible to observe individually marked insects throughout their lives in the wild. Many other insects, including *Drosophila*, can be studied in seminatural enclosures such as field cages and under controlled stressful environments in the lab.

Third, comparative phylogenetic studies of aging have highlighted the enormous diversity of lifespans among species, ecological factors associated with this diversity, and even potential genetic determinants (96). While comparative studies of aging have focused largely on vertebrates, the phenomenal genetic, ecological, and life-history diversity of insects is a powerful resource for understanding the evolution of longevity and senescence. *Drosophila melanogaster* has been enormously fruitful as a research model for understanding highly conserved processes in aging, but rigorous phylogenetic studies are needed to achieve a full understanding of how natural selection shapes aging.

Fourth, many molecular and genomic tools—previously limited to *D. melanogaster* and a few other animals—are becoming increasingly available for use with other insects. Conversely, techniques developed for field research (e.g., mark–recapture studies) could be applied to *D. melanogaster* to better understand the natural ecology of this lab model. We believe that such transfer of tools and approaches harbors great potential for enhancing our understanding of the ecology and evolution of senescence. These tools will make it possible to investigate aging at physiological, cellular, genetic, and ecological scales in a diverse range of insect species exhibiting distinct ecological niches and vast differences in body size, morphology, physiology, and longevity. The transfer of tools between species will make it possible to take full advantage of insect diversity in aging research.

Finally, in Section 5, we discuss the potential impact of climate change on patterns of aging in insects. Researchers have already begun to consider the effect of global warming on insect phenology (28). This area is particularly rich with important research opportunities. Research on a diverse range of insect species, especially those found in climate change hotspots, will provide us with critically important biotic indicators of the speed with which this change is occurring and its short-term (demographic) and long-term (evolutionary) impacts on aging in insects.

Aging is a conceptual hub with the potential to link diverse realms of biological inquiry, from ecology and evolution, to physiology and behavior, to biophysics and molecular and systems biology. In our effort to improve aging research by bridging these disciplines, these bridges can inform broad areas of research. What better way to pursue this agenda than against the backdrop

of the stunning diversity of insects, including the diversity in patterns of aging that we are only beginning to discover?

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We are grateful to Angela Douglas for her invitation to contribute this paper and to Marc Tatar for helpful comments on a previous version of the manuscript. We apologize that, due to space limitations, we often had to cite reviews and could not always give proper credit to original research. R.B. was supported by a Discovery Grant from the Australian Research Council (DP170102449). T.F. was supported by grants from the Swiss National Science Foundation (SNSF 31003A_182262); the Novartis Foundation for Medical-Biological Research; and a Mercator Visiting Professor Fellowship from the German Research Foundation (DFG) held at the Institute for Evolution and Biodiversity, University of Münster. D.P. was supported in part by National Institutes of Health grants AG049494 and AG063371.

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