7. Aton, S.J., Seibt, J., Dumoulin, M., Jha, S.K., Steinmetz, N., Coleman, T., Naidoo, N., and Frank, M.G. (2009). Mechanisms of sleep-dependent consolidation of cortical plasticity. Neuron *61*, 454–466.
8. Marcano-Reik, A.J., Prasad, T., Weiner, J.A., and Blumberg, M.S. (2010). An abrupt developmental shift in callosal modulation of sleep-related spindle bursts coincides with the emergence of excitatory-inhibitory balance and a reduction of somatosensory cortical plasticity. Behav. Neurosci. *124*, 600–611.
9. Khazipov, R., Sirota, A., Leinekugel, X., Holmes, G.L., Ben-Ari, Y., and Buzsaki, G. (2004). Early motor activity drives spindle bursts in the developing somatosensory cortex. Nature *432*, 758–761.
10. Mohns, E.J., and Blumberg, M.S. (2010). Neocortical activation of the hippocampus during sleep in infant rats. J. Neurosci. *30*, 3438–3449.
11. Petersen, C.C. (2007). The functional organization of the barrel cortex. Neuron *56*, 339–355.
12. Taepavarapruk, N., McErlane, S.A., and Soja, P.J. (2002). State-related inhibition by GABA and glycine of transmission in Clarke's column. J. Neurosci. *22*, 5777–5788.
13. Brooks, P.L., and Peever, J.H. (2011). Impaired GABA and glycine transmission triggers cardinal features of rapid eye movement sleep behavior disorder in mice. J. Neurosci. *31*, 7111–7121.
14. Brooks, P.L., and Peever, J.H. (2008). Glycinergic and GABA(A)-mediated inhibition of somatic motoneurons does not mediate rapid eye movement sleep motor atonia. J. Neurosci. *28*, 3535–3545.
15. Khazipov, R., and Luhmann, H.J. (2006). Early patterns of electrical activity in the developing cerebral cortex of humans and rodents. Trends Neurosci. *29*, 414–418.
16. Mohns, E.J., and Blumberg, M.S. (2008). Synchronous bursts of neuronal activity in the developing hippocampus: modulation by active sleep and association with emerging gamma and theta rhythms. J. Neurosci. *28*, 10134–10144.
17. Petersson, P., Waldenstrom, A., Fahraeus, C., and Schouenborg, J. (2003). Spontaneous muscle twitches during sleep guide spinal self-organization. Nature *424*, 72–75.

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Aging: Evolution of Life Span Revisited

A new study reports that high rates of extrinsic mortality can lead to the evolution of a longer life — a pattern opposite to that expected under the classic predictions of the evolutionary theory of aging.

Damian K. Dowling

Most people seem to realize that death is an inevitable consequence of life. For those individuals that don't suffer a premature death at the hands of extrinsic hazards of mortality, such as predation (Figure 1), infectious disease or accidents, a slower physiological deterioration invariably awaits. It is this deterioration that is aging — the intrinsic component of mortality — and it has captured widespread interest among evolutionary biologists for well over a century [1]. A new study by Chen and Maklakov in this issue of *Current Biology* [2] has shown that in nematodes life span evolves when populations experience increases in the rate of extrinsic mortality. Remarkably, the direction of this evolutionary response hinges on the type of mortality. These findings help to explain why empirical tests of classic theories of aging have hitherto provided an inconclusive set of results.

Aging in Theory

The suggestion that aging might evolve invokes an immediate paradox: aging will generally decrease Darwinian fitness; that aging exists at all thus runs counter to the expectation that natural selection should favour adaptations that improve survival. The solution to this paradox seems to lie in the fact that the probability of an individual reproducing will typically decline with age [3], simply because the probability of surviving to later age classes is reduced in the face of extrinsic mortality hazards. Thus, the magnitude of natural selection should diminish with age, thereby allowing mutations to accumulate that exert negative effects on late life stages, by mutation accumulation [4] or even by Darwinian selection in cases where the mutations encode beneficial effects in earlier age classes [3].

The evolution of aging should, therefore, be directly tied to the rate of extrinsic mortality experienced by a population. Populations with higher extrinsic mortality rates should evolve accelerated aging and shorter life spans, because higher mortality will shift the reproductive probability distribution such that it peaks at a younger age. Numerous studies have tested this classic prediction. Generally, studies examining patterns of aging in wild populations, across taxa, have provided inconsistent evidence [5], while those harnessing experimental evolution in a laboratory setting have been more supportive of the classic theory [6–10] — in particular an empirical test in the fruit fly *Drosophila melanogaster*, which directly manipulated the mortality rate [7]. Nonetheless, another experimental study comparing natural populations of guppies (*Poecilia reticulata*) failed to support the classic prediction [11].

Such inconsistency between studies raises eyebrows, particularly because we can generally confirm the classic predictions when we pull the strings in the laboratory setting, but struggle to do so when testing the predictions in more realistic, natural environments. Does this mean that the evolutionary theory of aging is not generally applicable to the real world? Or is there some unaccounted factor at play, whose effects run havoc in the wild and alter the trajectories of aging in unpredicted directions, but that we effectively nullify in the laboratory environment? Emerging theoretical studies [12], and the latest empirical evidence mounted by Chen and Maklakov [2], would suggest that the answer to this latter question is 'yes'.

The Reality of Mortality

Chen and Maklakov [2] set out to test the role that extrinsic mortality plays in driving evolutionary trajectories of life span. They report that the evolutionary response of life span to increases in the rate of extrinsic mortality differs according to whether mortality is applied randomly on a population, or in a condition-dependent manner that promotes the survival of the fittest. The authors used thermal heat stress as the source of condition-dependent mortality. Using the nematode *Caenorhabditis remanei*, they showed

Figure 1. Extrinsic mortality in action.

A cheetah chases a Thomson's Gazelle. In natural populations, predators represent important sources of mortality. In many cases it is likely that the predator-induced risk of mortality will be condition-dependent, with the least agile or weakest individuals in a population being the ones most likely to be targeted by predators. Photo: Anup Shah, Getty Images.

that shorter life span evolves under high, but randomly applied, mortality, whereas longer life span evolves under high, but condition-dependent, mortality, after 12 generations of laboratory-based experimental evolution. Strikingly, a switch in the mortality source from random to condition-dependent changed the direction of the trajectory along which life span evolved. How do these results sit in relation to our current understanding of the evolution of aging? Remarkably, they support, and in many ways reconcile, both the classic predictions discussed above [3], with some emerging predictions to arise in more recent years [5,12–15].

The classic prediction essentially assumes that the source of extrinsic mortality within a population will be random, such that all individuals within it will be equally susceptible. This assumption would probably not rest easily with the majority of biologists, and there is much evidence that individuals within populations vary considerably in their susceptibility to a wide range of hazards, such as predation and infectious disease. This susceptibility should be at least partly determined by the condition that individuals are in [5]. And, when this point is factored into theoretical models, predicted associations between the external mortality risk and the evolution of aging can change quite dramatically [5,12–15]. The reason for this is that increasing the mortality rate due to a condition-dependent environmental hazard on a population can result in selection to delay senescence in those traits that are involved in resistance to that specific hazard. The environmental hazard could thus select for the evolution of more robust organisms with age, since selection will weed out more susceptible genotypes [12]. Thus, factoring mortality source interactions into theoretical models of aging can lead to a variety of outcomes, including the evolution of longer life under high condition-dependent mortality [12].

Emerging theory [5,12] and the new findings by Chen and Maklakov [2] thus strongly suggest that variance across populations, or species, in the sources and forces of extrinsic mortality will account for discrepancies in experimental tests of the classic evolutionary predictions of aging. Much, however, must be done before this supposition can be confirmed, and several avenues will benefit from further enquiry. The Chen and Maklakov study [2] is very much a 'proof-of-concept', testing two extreme scenarios (completely random versus near-exclusive condition-dependence), at two ends of the mortality-rate spectrum (very low and very high). Contrary to laboratory conditions, individuals within natural populations will experience multiple sources of mortality, each varying in the rate of mortality that they account for. Moreover, some of these sources will interact with each other, and many (but not all) will interact with intrinsic factors such as individual condition and age. While this will make predicting trajectories of aging difficult in natural environments, laboratory- and field-based approaches should allow for future advances. In the laboratory, valuable insights will be gained from experimental evolution studies of different species that couple various regimes of mortality source (from multiple sources) along an axis of mortality rate. In the field, estimates of aging in the wild [5] can be augmented with information on the identity and the strength of key environmental hazards, and efforts made to determine the strength of condition–environment interactions across a range of common hazards. Populations with a known evolutionary history of condition–environment interactions in the wild can also be screened for aging in a controlled laboratory setting. Previously, a laboratory study of aging in Trinidadian guppies reported that fish sourced from high predation sites lived longer than those from low predation sites [11], consistent with the idea that susceptibility to predation is condition-dependent and perhaps linked to evolutionary trajectories of aging in these fish.

Finally, when formulating predictions about the effects of condition–environment interactions on the evolution of aging, it will be fruitful to factor in the role that genetic correlations between key life history traits have on the evolutionary responses. Of particular interest are correlations between life span and

traits important in resistance to a range of extrinsic environmental hazards. When these genetic correlations are negative, we might expect that condition–environment interactions will accelerate the evolutionary response of aging in the direction of the classic prediction. When positive, condition–environment interactions might act to slow down or even reverse the sign of the classic prediction. Genetic covariance between stress-resistance traits (e.g. resistance to starvation, heat or cold stress) and life span, within populations, generally tends to be positive or absent [16–20], which suggests that increases in extrinsic mortality imposed by environmental stressors might generally promote the evolution of longer life, consistent with the findings by Chen and Maklakov [2]. That said, before we can make conclusions here, we will need to better understand patterns of genetic covariance between susceptibility to predation and infectious disease and intrinsic components of aging, given the pervasiveness of these mortality sources in natural populations. Clearly, the Chen and Maklakov study [2] provides a new insight into the evolution of life span. Ironically, in doing so, it reminds us how much remains to be done if we are to ever fully understand the evolution of aging in natural populations.

References

1. Rose, M.R. (1991). Evolutionary Biology of Aging, 1 Edition (New York: Oxford University Press).
2. Chen, H., and Maklakov, A. (2012). Longer lifespan evolves under high rates of condition-dependent mortality. Curr. Biol. *22*, 2140–2143.
3. Williams, G.C. (1957). Pleiotropy, natural selection, and the evolution of senescence. Evolution *11*, 398–411.
4. Medawar, P.B. (1952). An Unsolved Problem of Biology (London: H. K. Lewis).
5. Williams, P.D., Day, T., Fletcher, Q., and Rowe, L. (2006). The shaping of senescence in the wild. Trends Ecol. Evol. *21*, 458–463.
6. Rose, M.R. (1984). Laboratory evolution of postponed senescence in *Drosophila melanogaster*. Evolution *38*, 1004–1010.
7. Stearns, S.C., Ackermann, M., Doebeli, M., and Kaiser, M. (2000). Experimental evolution of aging, growth, and reproduciton in fruitflies. Proc. Natl. Acad. Sci. USA *97*, 3309–3313.
8. Partridge, L., and Fowler, K. (1992). Direct and correlated responses to selection on age at reproduction in *Drosophila melanogaster*. Evolution *46*, 76–91.
9. Partridge, L., Prowse, N., and Pignatelli, P. (1999). Another set of responses and correlated responses to selection on age at reproduction in Drosophila melanogaster. Proc. R. Soc. Lond. B-Biol. Sci. *266*, 255–261.
10. Zwaan, B., Bijlsma, R., and Hoekstra, R.E. (1995). Direct selection on life-span in *Drosophila melanogaster*. Evolution *49*, 649–659.
11. Reznick, D.N., Bryant, M.J., Roff, D., Ghalambor, C.K., and Ghalambor, D.E. (2004). Effect of extrinsic mortality on the evolution of senescence in guppies. Nature *431*, 1095–1099.
12. Williams, P.D., and Day, T. (2003). Antagonistic pleiotropy, mortality source interactions, and the evolutionary theory of senescence. Evolution *57*, 1478–1488.
13. Bronikowski, A.M., and Promisiow, D.E.L. (2005). Testing evolutionary theories of aging in wild populations. Trends Ecol. Evol. *20*, 271–273.
14. Abrams, P.A. (1993). Does increased mortality favor the evolution of more rapid senescence? Evolution *47*, 877–887.
15. Abrams, P.A. (2004). Evolutionary biology - mortality and life span. Nature *431*, 1048–1049.
16. Lithgow, G.J., White, T.M., Melov, S., and Johnson, T.E. (1995). Thermotolerance and extended life-span conferred by single-gene mutations and induced by thermal-stress. Proc. Natl. Acad. Sci. USA *92*, 7540–7544.
17. Hoffmann, A.A., and Harshman, L.G. (1999). Desiccation and starvation resistance in *Drosophila*: patterns of variation at the species, population and intrapopulation levels. Heredity *83*, 637–643.
18. Ayroles, J.F., Carbone, M.A., Stone, E.A., Jordan, K.W., Lyman, R.F., Magwire, M.M., Rollmann, S.M., Duncan, L.H., Lawrence, F., Anholt, R.R.H., *et al*. (2009). Systems genetics of complex traits in *Drosophila melanogaster*. Nat. Genet. *41*, 299–307.
19. Burke, M.K., and Rose, M.R. (2009). Experimental evolution with Drosophila. Am. J. Physiol.-Regul. Integr. Comp. Physiol. *296*, R1847–R1854.
20. Bubliy, O.A., and Loeschcke, V. (2005). Correlated responses to selection for stress resistance and longevity in a laboratory population of Drosophila melanogaster. J. Evol. Biol. *18*, 789–803.

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Dopamine: On the Threshold of Sleep

A new study examining the neural circuitry regulating sleep in *Drosophila* has identified a pair of dopamine neurons that signal to the fan-shaped body to suppress sleep. These neurons are separate from the dopamine neurons that regulate motivation, memory, and feeding, suggesting that independent populations of dopamine neurons regulate distinct behaviors.

Pavel Masek and Alex C. Keene

The neurotransmitter dopamine plays a central role in motivation, feeding, memory and sleep–wake regulation across phyla. Fruit flies mutant for the dopamine transporter, the primary target for cocaine and methamphetamine, have reduced sleep, revealing dopamine to be a potent suppressor of sleep [1]. Flies with reduced dopamine signaling have deficits in associative memory and feeding behaviors. How does a single transmitter regulate such diverse behavioral and cognitive processes? One possibility is through a diversity of receptors. Alternatively, the distinct effects of dopamine may be mediated through neural connectivity. The fly brain contains approximately 200 dopamine neurons with widespread projections throughout the central brain [2,3]. Identifying the specific dopamine neurons that modulate individual behavioral processes is difficult and limited by the availability of genetic tools capable of labeling individual classes of neurons.

In this issue of *Current Biology*, Liu *et al.* [4] identify two dopamine neurons that suppress sleep. The authors transgenically activate dopamine neurons in a temperature-dependent fashion by genetically expressing the heat-inducible cation channel transient-receptor-potential A1 (TRPA1) in small populations of dopamine neurons. Expressing TRPA1 under control of the Tyrosine Hydroxylase promoter allows for inducible activation of all dopamine neurons and results in a dramatic reduction in sleep [5]. Liu *et al.* generated driver lines using fragments of the Tyrosine Hydroxylase genomic locus to transgenically label and manipulate specific populations of dopamine neurons. One line labeled a single neuron in each of the