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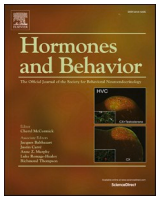

Review article

Frank Beach Award Winner: The centrality of the hypothalamic-pituitary-adrenal axis in dealing with environmental change across temporal scales

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ABSTRACT

Understanding if and how individuals and populations cope with environmental change is an enduring question in evolutionary ecology that has renewed importance given the pace of change in the Anthropocene. Two evolutionary strategies of coping with environmental change may be particularly important in rapidly changing environments: adaptive phenotypic plasticity and/or bet hedging. Adaptive plasticity could enable individuals to match their phenotypes to the expected environment if there is an accurate cue predicting the selective environment. Diversifying bet hedging involves the production of seemingly random phenotypes in an unpredictable environment, some of which may be adaptive. Here, I review the central role of the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoids (GCs) in enabling vertebrates to cope with environmental change through adaptive plasticity and bet hedging. I first describe how the HPA axis mediates three types of adaptive plasticity to cope with environmental change (evasion, tolerance, recovery) over short timescales (e.g., 1–3 generations) before discussing how the implications of GCs on phenotype integration may depend upon the timescale under consideration. GCs can promote adaptive phenotypic integration, but their effects on phenotypic co-variation could also limit the dimensions of phenotypic space explored by animals over longer timescales. Finally, I discuss how organismal responses to environmental stressors can act as a bet hedging mechanism and therefore enhance evolvability by increasing genetic or phenotypic variability or reducing patterns of genetic and phenotypic co-variance. Together, this emphasizes the crucial role of the HPA axis in understanding fundamental questions in evolutionary ecology.

1. Introduction

A pressing question in the face of unprecedented changes in the natural environment is if and how organisms can persist through this change. All organisms experience or have experienced environmental instability where one or more key aspects of the biotic or abiotic environment varies across time and/or space. The signatures of the importance of these environmental fluctuations can be observed in the numerous characteristics of organisms that enable them to cope or buffer themselves from environmental change. Of many examples to choose from, these would include the reorganization of ion transport across the gills of teleost fish as they transition from freshwater to oceanic environments, sensitivity to food or temperature cues that enable adjustments in the phenology of key life history decisions (e.g., when to emerge from hibernation, when to breed) that are observed across organisms experiencing seasonal environments, or behavioral adjustments in response to changes in ambient temperatures or predation risk. Organisms need to be *flexible* in response to the environmental changes they experience, yet this need for flexibility is balanced by its potential costs. In many cases, there are benefits to *inflexibility* or *stability* through environmental change, such as the oft-mentioned example of the maintenance of body temperature within a narrow range to ensure optimal enzyme function.

This trade-off between flexibility and stability manifests itself across biological scales of organization. From the perspective of an individual, they may either be flexible (phenotypic plasticity) or robust (canalization) to an environmental change. Across longer timescales, populations or even species face a trade-off between evolvability and robustness

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through environmental change: too much change in response to environmental perturbations is problematic, but so is too little. The same can be said of the genome when it comes to its sensitivity to environmental or mutational perturbations.

One proposed solution that balances the costs and benefits of flexibility is a "bow tie network" where many environmental inputs are processed centrally (core or hub: Fig. 1A) and there are many outputs that are in turn affected by this central processing system (Fig. 1A). This has been proposed as a solution whereby an organism can balance the need to be both flexible and stable through environmental change (Kitano, 2004; Csete and Doyle, 2004). The hypothalamic-pituitary-adrenal (HPA) axis, also called the vertebrate neuroendocrine stress axis, has been proposed to function as a bow tie network (del Giudice, 2015). This is because HPA axis activity is affected by many inputs from extrinsic and intrinsic sources (predation risk, individual state, ambient food availability, weather patterns, competitive interactions, parasitism or disease), these inputs or information about the environment are processed centrally, and activation of the HPA axis results in the production of the metabolic steroid hormones, glucocorticoids (GCs), which can influence many cell types and, in turn, phenotypes (Fig. 1A). Interestingly, the HPA axis itself may act as a "bow tie of bow ties" as its inputs and targets include other endocrine systems such as nutrient sensing pathways (hypothalamic-pituitary-somatotrophic axis) or the endocrine axis coordinating reproduction in vertebrates (hypothalamic-pituitary-gonadal axis). GCs or other products of the HPA axis can influence the activity of these other endocrine systems (Fig. 1B), thereby exhibiting high centrality (or acting as a hub) in how this physiological network coordinates animal responses to environmental cues.

Given the bow tie nature of the HPA axis in addition to its connection with other bow tie physiological networks (Fig. 1), it is no surprise that it seems central for coordination of phenotypic responses to environmental change in vertebrate animals, including balancing the need to be flexible but not too unstable through change. Here, I discuss how the HPA axis is central to understand how vertebrate animals cope with environmental change and/or stressors across temporal scales. I first briefly describe the evolutionary strategies organisms can use to cope with environmental change and define how stress at the environmental and individual level is defined and measured. I then review the how the HPA axis and GCs coordinate the ability of vertebrate animals to cope with environmental change across short and long timescales. My central point is that the HPA axis and GCs in particular can enable individual vertebrate animals to be flexible to short-term environmental changes through phenotypic plasticity in single phenotypes or integrated suites of phenotypes, but also enable populations of (related) individuals to be stable across longer term environmental changes through bet hedging. I first point out that others have made similar points about the key role of the HPA axis in enabling individuals to cope with short-term environmental change by inducing plasticity (e.g., Wingfield, 2002; Dantzer et al., 2013; Wingfield, 2013; Angelier and Wingfield, 2013; Taff and Vitousek, 2016; Wingfield et al., 2017) or perhaps over longer-time scales through the generation of novel genetic and phenotypic variation or the level of integration among different traits (Badyaev, 2005a; Badyaev, 2005b). Here, I gather these different contributions together for a comprehensive review of this subject about how the HPA axis induces adaptive plasticity to cope with short-term environmental change. I then expand this perspective to think about how the role of the HPA axis in enabling or retarding the ability of populations to cope with environmental change across longer timescales through its effects on phenotypic integration and bet hedging.

I first review how GCs promote three types of plasticity (evasion, tolerance, resistance: *sensu* Bradshaw, 1972; Huey, 2002) to deal with an environmental change/stressor. Because the phenotypic response to an

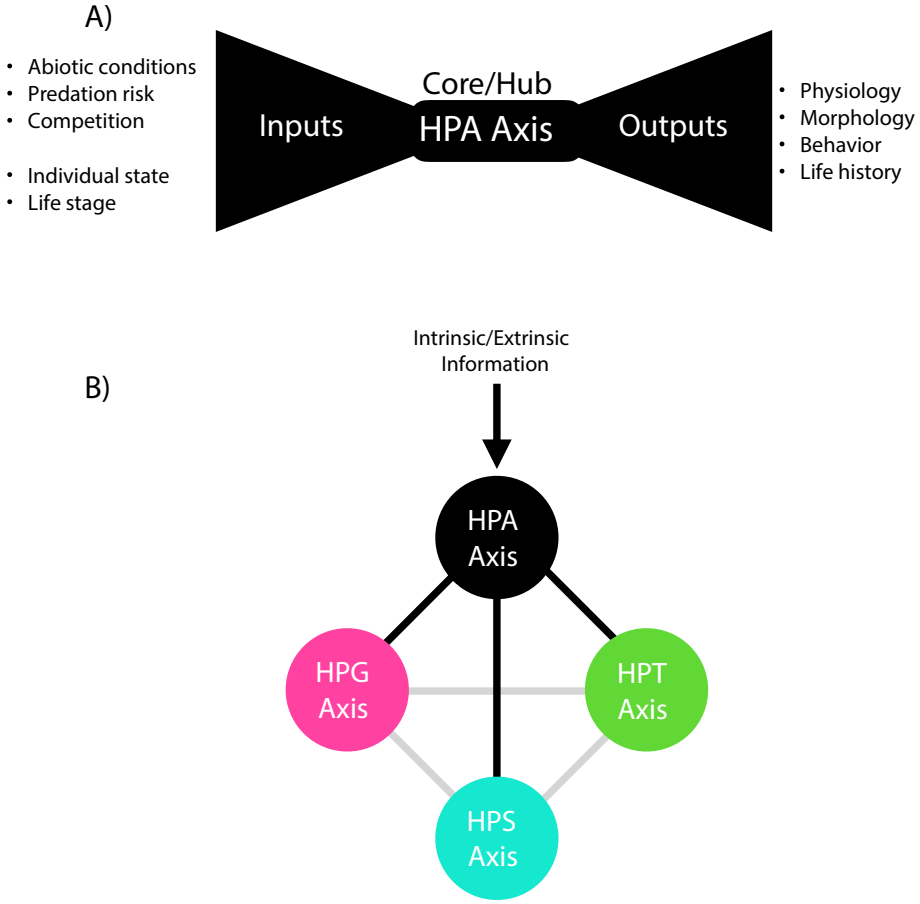

Fig. 1. Bowtie structures are expected to be the outcome of the need for organisms to balance the costs and benefits of flexibility in the face of environmental change. A) The hypothalamic-pituitary-adrenal (HPA) axis exhibits a bowtie type structure in the sense that the HPA axis is the core (or hub) and receives information from the external environment and internal environment that in turn has manifold effects on organismal phenotypes. The activity of the HPA axis is often quantified using measures of glucocorticoid (GCs). GC production can be influenced by external environmental features such as abiotic conditions (season, temperature, precipitation), predation risk, and the degree of competition. Internal environmental conditions, such as individual state (age, level of nutrition, body condition) and life stage (ontogenetic state, reproductive condition) can also affect GCs. In turn, elevations in GCs can have diverse effects on organismal phenotypes from physiological to life history traits. B) The HPA axis could be viewed as being a "bowtie of bowties" or central hub in physiological networks. Information from the internal or external environment can modify HPA axis activity that in turn influences the hypothalamic-pituitary-gonadal axis (HPG Axis), hypothalamic-pituitary-thyroid axis (HPT Axis), and the hypothalamic-pituitary-somatotrophic axis (HPS Axis), each of which could be considered as exhibiting a bowtie structure itself. Note that these conceptual diagrams are an oversimplification for the many components of the HPA axis (hormone, receptors, carrier proteins, etc.) and the cross-talk envisioned in panel B can vary among species (see text).

environmental change/stress is multifaceted, involving complementary changes to physiological, morphological, behavioral, and life history traits, I then focus on how activation of the HPA axis affects phenotypic integration, or patterns of co-variation among different traits. The effects of GCs on phenotypic integration during environmental change could be adaptive over short temporal scales, but potentially maladaptive over longer timescales because of the ability of GCs to structure patterns of phenotypic co-variation, which could theoretically constrain the dimensions of phenotypic space explored by animals over longer timescales. Finally, I focus on the potential role of the HPA axis on coping with environmental change/stress over longer timescales in the context of evolvability, which I define as the ability of populations to rapidly adapt (exhibit an evolutionary response to selection) to new environments due to the emergence of novel heritable phenotypic variation (sensu Wagner and Altenberg, 1996; Kirschner and Gerhart, 1998; West-Eberhard, 1998). "*Novel phenotypic variation that is heritable*" is challenging to define but here it is meant to refer to heritable phenotypes or phenotypic combinations that have not before been exposed to selection. Activation of the HPA axis could function as a bet hedging mechanism that enhances population persistence through environmental change (and therefore evolvability) because exposure to environmental stress can enhance genetic and phenotypic variation or alter genetic and phenotypic co-variation to produce novel combinations of traits. Because little work has been done on this topic with specific focus on the HPA axis, I discuss how organisms respond to environmental stress writ large. My focus is on vertebrate animals, but I also discuss other organisms including plants and microbes to make specific points about plasticity, bet hedging, and responses to environmental stressors. I note that below I focus on how activation of the HPA axis can be associated with plasticity in adulthood or during development, but I do not focus on some of the possible epigenetic mechanisms that might contribute to the inter-generational transfer of such plasticity given that this has been covered extensively elsewhere (e.g., Champagne, 2013; Anacker et al., 2014; Matthews and McGowan, 2019; Cao-Lei et al., 2020).

2. Evolutionary strategies to cope with environmental change

Organisms are invariant in that all of them experience environmental change and exhibit specific responses to cope with such change. The types of environmental change experienced are various, but the responses to deal with the change can largely be grouped under four different types of "strategies" that I discuss below. These strategies could be used to deal with environmental change both from the perspective of short temporal scales (e.g., within the lifetime of a single individual or across two generations such as from parents to offspring) and over longer time periods (e.g., population or species persistence). Although I briefly describe all four strategies, I focus the rest of this contribution on phenotypic plasticity and bet hedging.

The first way to respond to an environmental change is to exhibit phenotypic robustness, do not let the environmental change alter your phenotype (Wagner et al., 2007; Masel and Siegal, 2009). This is often referred to as canalization and is often considered to be a by-product of stabilizing selection (Waddington, 1942; Schmalhausen, 1949; Flatt, 2005). For example, organisms may experience profound fluctuations in nutrient availability during development, which can influence body size, the size of specific morphological structures, or the allometric relationships between body size and some specific morphological trait (Emlen, 1997). However, some traits, such as genital size in many insects, exhibit canalization where they do not respond to variability in the developmental environment (Eberhard et al., 1998; House and Simmons, 2003; Shingleton et al., 2009). The robustness of insect genitalia should be adaptive given that the potential cost of scaling your genitals with your overall body size is a lack of fit with the genitals of opposite-sex conspecifics (Eberhard, 1985).

Second, organisms may exhibit an evolutionary or genetic response to the environmental change (i.e., adapt to it: Darwin, 1859), which is also called "adaptive tracking" (Simons, 2011). Here, selection of beneficial phenotypes that are heritable leads to a shift in the genetic composition of a population. Populations with higher levels of standing genetic variation, such as when there are larger populations sizes, are expected to have greater potential to mount an evolutionary response to environmental change (Fisher, 1930; Houle, 1992; Lande and Shannon, 1996). Populations may also be "rescued" from extinction due to a sudden environmental change by the evolutionary response to selection (Gonzalez et al., 2013; Bell, 2017). This can take time, so it is often viewed to not be involved in coping with rapid environmental change (Botero et al., 2015), but there are some examples where adaptation is occurring over short (ecological) timescales (Hairston et al., 2005) in the context of global climate change (Donelson et al., 2019) or even within-season changes in weather patterns or predation risk in species with large population sizes (Yoshida et al., 2003; Rudman et al., 2022).

Third, organisms may exhibit adaptive (or predictive or anticipatory) phenotypic plasticity in response to the environmental change. I define phenotypic plasticity as a situation where a phenotype is conditionally expressed depending upon the environment where the organism either responds to the environment or the environment induces plasticity, with special emphasis made on being inclusive with respect to both "response" vs. "induce" (*sensu* Sultan, 2021). Adaptive plasticity is expected to evolve in organisms that experience heterogeneous environments (which often cause fluctuating selection) where there is no one phenotype that is "best" for all environments, but where individuals have access to a reliable cue with which to predict the selective environment as well as the sensory capabilities to detect the cue (Levins, 1968; Gavrilets and Scheiner, 1993; Scheiner, 1993; Chevin et al., 2010; Reed et al., 2010; Bonamour et al., 2019). Plasticity exhibited by an individual can be reversible, which has also been called phenotypic flexibility or activational or contextual plasticity: (Piersma and Drent, 2003; Snell-Rood, 2013; Stamps, 2016). Plasticity may also be irreversible, which is often a consequence of plasticity that occurs during development either from the individuals own environmental experience or the environment/phenotype provided by the parent or even grandparent (Uller, 2008; Snell-Rood, 2013; Burton and Metcalfe, 2014; Nettle and Bateson, 2015). Adaptive developmental plasticity (or intergenerational plasticity) in the context of parental effects comes with more names than can be listed here (anticipatory parental effects, predictive adaptive responses, adaptive transgenerational phenotypic plasticity, etc.: Engqvist and Reinhold, 2016). Acclimation may also be used to describe activational plasticity when it is adaptive, but activational and developmental plasticity can also decrease the match between the phenotype and environment (Ghalambor et al., 2007). Whether plasticity is reversible or irreversible likely depends upon its costs (potentially being lower for reversible/activational plasticity: Snell-Rood, 2013), but also the temporal scale (and autocorrelation) of environmental changes experienced by an organism (Botero et al., 2015; Leimar and McNamara, 2015). Activational (reversible plasticity) may be expected in organisms that experience fine grained environments (e.g., multiple environments experienced during the lifetime of an individual: Levins, 1968; Botero et al., 2015) whereas developmental (irreversible) plasticity may be likely to be observed in organisms that experience coarse grained environments (minimal environmental variation during the lifetime of an individual: Levins, 1968; Snell-Rood, 2013; Botero et al., 2015). Phenotypic plasticity can play an important role in the ability of populations to cope with natural environmental fluctuations (e.g., temperature, food availability), but also through abrupt environmental changes, such as those caused by global climate change, in addition to its ability to increase the ability of individuals to colonize and populations to persist in novel environments (Yeh and Price, 2004; Miner et al., 2005; Lande, 2009; Chevin et al., 2010; Chevin and Lande, 2011; Merilä and Hendry, 2014; O'Dea et al., 2016; Snell-Rood et al., 2018; Fox et al., 2019; Kelly, 2019). Plasticity occurring early in life may result in stable changes in offspring phenotypes through

epigenetic mechanisms (Champagne, 2013; Anacker et al., 2014; Matthews and McGowan, 2019; Cao-Lei et al., 2020).

The fourth way of dealing with environmental change is through bet hedging, which is expected to maximize geometric mean fitness in an unpredictable environment as it is expected to reduce the temporal variation in fitness (Cohen, 1966; Slatkin, 1974; Seger and Brockmann, 1987). Bet hedging is a form of risk reduction (the risk here being zero fitness) that may evolve in organisms that experience unpredictable environments (Slatkin, 1974) or those experiencing temporal fluctuations in selection (Simons, 2009). Unlike adaptive phenotypic plasticity, bet hedging is expected to be exhibited by organisms that do not have predictive cues about the selective environment. Diversifying bet hedging (also called "adaptive coin-flipping": Cooper and Kaplan, 1982) involves "spreading the risk" where a group of related individuals or those with the same genotype to exhibit enhanced phenotypic variability, increasing the likelihood that one individual exhibits the optimal phenotype in that environment (Cohen, 1966; Seger and Brockmann, 1987; Philippi and Seger, 1989). For example, plants may hedge their bets by producing seeds that germinate in different subsequent years (Cohen, 1966; Philippi and Seger, 1989) or animals may produce offspring that vary in some continuous (e.g., body size: Crump, 1981; Marshall et al., 2008; Crean and Marshall, 2009) or discrete/discontinuous (polyphenic) trait. Diversifying bet hedging and the corresponding increase in phenotypic variability should promote population viability and persistence through periods of environmental change. This is most evident in studies of microbes where there is evidence suggesting that groups exhibit an adaptive bet hedging strategy where individual cells in the group differ in their phenotypes and the enhanced phenotypic variability can increase population persistence through an environmental stressor (Balaban et al., 2004; Veening et al., 2008; Ratcliff and Denison, 2010).

There is overlap in these different strategies, such as plasticity in response to an environmental change that increases population sizes and therefore allows new genetic variants to emerge, which can "buy time" for evolutionary adaptation to occur (Chevin et al., 2010; Chevin et al., 2010; Kelly, 2019). Plasticity could "lead" adaptation (West-Eberhard, 2003; Levis and Pfennig, 2016), for example enhancing phenotypic variability that in turn promotes adaptation to extreme environments (Bódi et al., 2017). It is also possible that plasticity could hinder adaptation because individuals can buffer themselves from the environment and shield the genome from selection (Huey et al., 2003; Donelson et al., 2019). There is also some degree of overlap between plasticity and diversifying bet hedging, such as in situations where the parental phenotype or environment induces higher levels of phenotypic

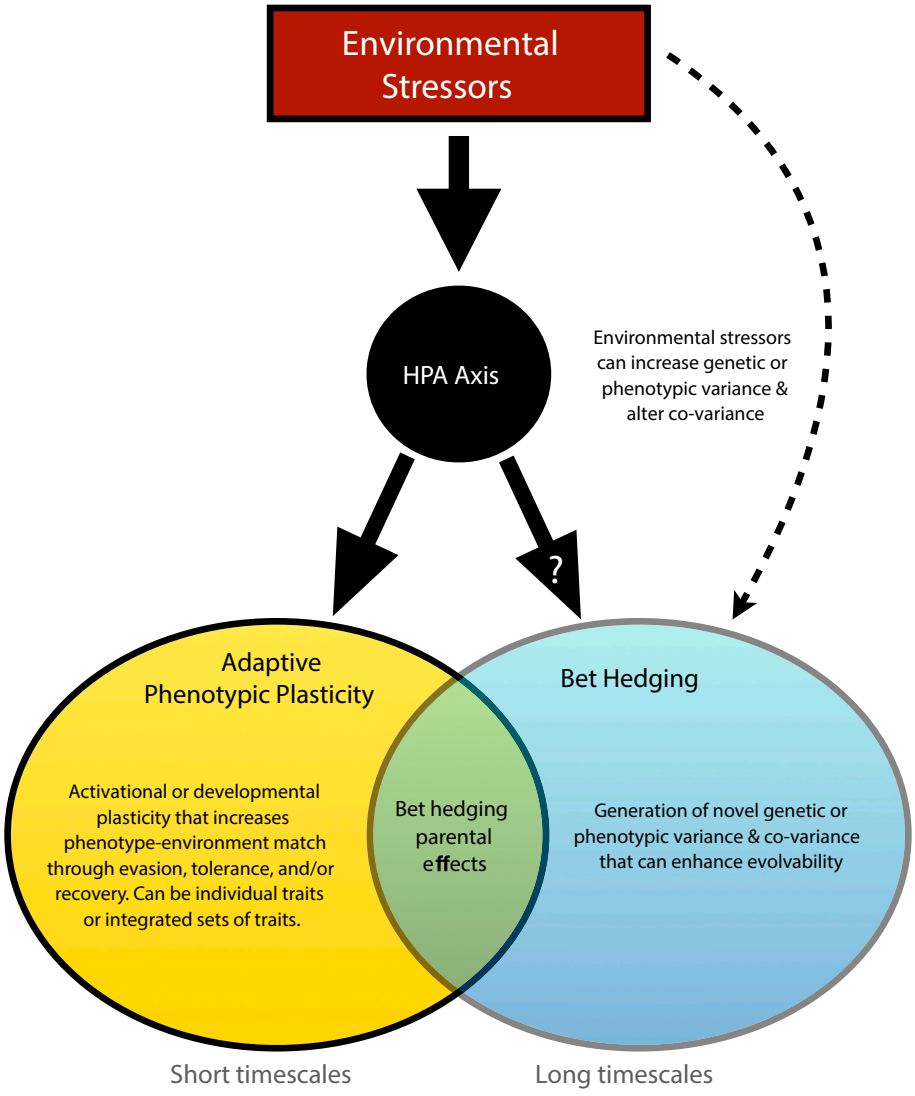

Fig. 2. Two evolutionary strategies organisms use to respond to environmental stressors are adaptive phenotypic plasticity and bet hedging. Adaptive phenotypic plasticity can be reversible (also called activational) or irreversible (often occurring during development) where a phenotype is modified due to exposure to some environmental cue experienced early in life. Adaptive plasticity can increase the match between the phenotype and the environment. Diversifying bet hedging can involve the increased production of genetic and phenotypic variation or modify genetic/phenotypic co-variation to produce novel combinations of phenotypes. This is sometimes immediately detrimental (reducing phenotype-environment match) but can enhance evolvability of organisms inhabiting unpredictable environments by increasing population persistence over longer timescales. Bet hedging parental effects occur where the environment experienced by a breeding individual increases the total phenotypic variability present within all the offspring produced in that litter or clutch (essentially inducing developmental plasticity but not necessarily increasing phenotype-environment match). The HPA axis appears to play an important role in mediating adaptive plasticity to environmental stressors occurring across relatively short temporal scales, such as a pregnant female mammal exhibiting behavioral plasticity in response to elevated predation risk and her offspring being exposed to maternally derived GCs that induce changes in an integrated set of phenotypes in her offspring that increase the ability of them to survive (tolerate) environments with high predation risk. In other organisms, exposure to an environmental stressor may increase genetic or phenotypic variation or patterns of genetic and phenotypic co-variance, providing new phenotypes or combinations of phenotypes, that could be favored in the stressful environment. Relatively little is known about how the HPA axis or increases in GCs affect genetic/phenotypic variation and co-variation (indicated by the question mark), but some studies suggest exposure to developmental stressors or elevated GCs early in life can modify the degree of phenotypic co-variance (Careau et al., 2014; Merrill and Grindstaff, 2018; Dantzer et al., 2020b).

variability among offspring (called "bet hedging parental effects" in Fig. 2: Crean and Marshall, 2009). Simulations also suggest that both bet hedging and developmental plasticity could be used to cope with environmental fluctuations on the same temporal scale (Botero et al., 2015). However, here I split them up and refer to them as adaptive phenotypic plasticity (both activational and developmental) and bet hedging, respectively, because I focus on how the former may be important for coping with environmental change across shorter timescales (e.g., within 13– generations: Fig. 2) whereas the latter may be important over longer timescales (e.g., >3 generations: Fig. 2). Below, I discuss how exposure to environmental change and/or activation of the HPA axis induces adaptive plasticity that enables vertebrate animals to cope with environmental change across short time scales and, secondly, how it elicits a bet hedging strategy to cope with change across longer time scales, thereby increasing evolvability.

3. Environmental stress, the HPA Axis, and glucocorticoids

Many of the environmental changes experienced by organisms are stressful, which can be quantified at the level of a population or an individual organism. At a population level and from the perspective of an evolutionary ecologist, environments are defined as stressful if there is a reduction in population mean fitness, such as a broad reduction in survival or reproductive success of individuals in the population (Hoffmann and Parsons, 1991; Schulte, 2014). This reduction in fitness may be caused by a "sudden reduction in the availability of any fundamental factor" (Schlichting and Pigliucci, 1998), for example oxygen, water, and food in vertebrates. At the level of a vertebrate animal and from multiple perspectives (organismal biologist, physiological ecologist, behavioral neuroendocrinologist or neuroscientist), environmental change is usually considered stressful if there is some measurable increase in nervous system activity that is indicative of heightened arousal of components of the nervous system that are associated with fear, stress, and anxiety (e.g., amygdala, nucleus accumbens, hippocampus, ventromedial hypothalamus, insular cortex, etc.). Because detection of the activity or arousal of this neurocircuitry is non-trivial, these types of data are usually only collected from laboratory animals. Instead, an animal is often considered "stressed" based upon behavioral or physiological indicators, which often, but not always, are reflective of stress and anxiety. These could be behavioral indices, such as an enhanced startle response or freezing to some conditioned stimulus in rodents or increased self-directed behavior in non-human primate species. Because arousal of the nervous system may occur without an outward behavioral manifestation, whole-animal stress is often inferred from the physiological manifestation such as an increased heart rate, reduction in heart rate variability, or increase in some physiological biomarker like monamine neurotransmitters (catelcholamines) or the steroid hormones GCs (cortisol and/or corticosterone).

Most work on this topic focuses on measuring the activity of the HPA axis, which needs little introduction given multiple reviews on this subject (Sapolsky et al., 2000; Romero, 2004; Charmandari et al., 2005; Romero and Wingfield, 2015; McEwen and Akil, 2020) so I will not do so here. Although there are other methods to quantify activation of the HPA axis, they are often more challenging to measure in free-living animals or require more invasive methods to do so (Gaidica and Dantzer, 2020). Most studies quantify HPA axis activity using a diversity of measures of GCs (Sheriff et al., 2011), such as mean fecal glucocorticoid metabolite concentrations (Dantzer et al., 2010) or mean plasma GCs (van Kesteren et al., 2019) or the reactivity of the HPA axis to pharmacological agents that suppress and stimulate the HPA axis (van Kesteren et al., 2019; Westrick et al., 2021).

GCs can be elevated due to a variety of intrinsic and extrinsic variables, namely abiotic conditions (temperature, precipitation, extreme weather), predation risk, competition, parasitism, and nutrition (Fig. 1A). Elevated GCs are often assumed to be indicative of "stress" even though they can be elevated for other reasons, such as seasonal changes in GCs associated with reproduction (Romero, 2002; Boonstra, 2005; Fletcher et al., 2015) or be elevated at specific times of the day (e.g., immediately prior to the start the active part of the day) due to GC production exhibiting a circadian rhythm (Dickmeis, 2009). These elevations in GCs in the absence of exposure to some stressor like adverse weather or increased predation risk can reflect the metabolic role of GCs in coordinating energetic demands such as mobilizing energetic resources needed for reproduction (Dallman et al., 1993; Romero, 2002). Thus, it is important to emphasize (or stress!) that although "stress" can be associated with elevated GCs, an elevation of GCs may not reflect exposure to some physical or psychological challenge and instead highlights the metabolic functions that GCs can play especially in terms of energy balance and how energy is allocated within an organism (Herman et al., 2016; MacDougall-Shackleton et al., 2019).

GCs can in turn have manifold effects on diverse phenotypes (Sapolsky et al., 2000; Hau et al., 2016). Their numerous effects are congruent with viewing the HPA axis as a bow tie network (described above) where many inputs (intrinsic and extrinsic) influence its activity and its products that in turn have many phenotypic targets (Fig. 1A). For instance, elevated GCs can affect numerous phenotypes given that most tissues have cells with GC receptors (GRs: Rousseau and Baxter, 1979; Bamberger et al., 1996; Lattin et al., 2012), although this does not always mean cells expressing GRs will respond to increased GCs (Bamberger et al., 1996). As such, GCs have been viewed as a type of "integrator" that links the environment, genotype, and phenotype because the circulating concentrations of GCs are affected by both internal and external processes and they can coordinate phenotypic responses to stimuli through genomic or non-genomic mechanisms (Martin et al., 2011a, 2011b; Cohen et al., 2012). This centrality of the HPA axis and GCs in coordinating responses to environmental change is especially evident if we consider how the HPA axis is a "first responder" to different sources of intrinsic and extrinsic information (Fig. 1B) and how it engages in cross-talk with the other endocrine axes responsible for major life history traits (growth, development, reproduction, and lifespan: Fig. 1B). Specifically, the HPA axis appears highly sensitive to extrinsic (predation risk) or intrinsic (individual or nutritional state) cues that reliably signal environmental harshness (Fig. 1B). It can then relay or transduce this information through crosstalk with the other endocrine axes through the production of corticotropin releasing hormone, GCs, or through adjustments in the production or metabolism of other products of these other endocrine axes. For instance, environmental stressors that cause chronic activation of the HPA axis can suppress reproduction by reducing HPG activity (e.g., Kirby et al., 2009; Tsutsui et al., 2010) or suppress growth of individuals after birth/hatching by inhibiting or lowering the activity of the HPS and/or HPT axes (Kühn et al., 1998; Singleton et al., 2000; Charmandari et al., 2005).

Obviously, these hypothesized relationships among the different endocrine axes (Fig. 1B) represent a series of oversimplifications and there are many exceptions. For example, some have hypothesized that the phenotypic responses of plants and animals to environmental stress is "generalized" or stereotypical (Parsons, 1987; Chapin, 1991; Petrullo et al., 2022), such as specific environmental features always causing the cessation of growth in plants (Chapin, 1991). However, organismal biologists show that there is no consistent phenotypic manifestation of "chronic stress" (Dickens and Romero, 2013). They also show that the effects of HPA axis activation due to exposure to an environmental stressor can depend upon the ecological environment that shaped the life history of the vertebrate species (Ricklefs and Wikelski, 2002; Bókony et al., 2009; Hau et al., 2010). This is evident when we consider how chronic activation of the HPA axis or chronically elevated GCs is expected to cause the cessation of reproduction and growth (Sapolsky et al., 2000) where the animal goes into a state of waiting and maximizes self-maintenance, but this is not always the case (Wingfield and Sapolsky, 2003). Animals that could be characterized as exhibiting a "fast" life history, namely semelparous animals, can have extraordinarily high

GCs while engaged in mating (Boonstra, 2005). Additionally, although elevated HPA axis activity might suppress growth and development during larval or adult stages (Kühn et al., 1998), it can instead accelerate growth and development during larval/fetal stages (Crespi and Denver, 2005) or in some taxonomic groups where the adaptive response to the environmental stressor causing HPA axis activation is to leave the area (e.g., in larval amphibians experiencing a drying pond: Denver, 1997). Thus, there is much more complexity in how and when the HPA axis is activated by an environmental stressor (it may not respond depending upon their life history) and if and how elevated GCs affect phenotypes (phenotypes need not respond if there are no receptors). Here, I gloss over this complexity and simply indicate that the HPA axis is responsive to many extrinsic factors (e.g., Petrullo et al., 2022) and in turn affects many phenotypes, some of which is due to crosstalk with other endocrine axes.

4. HPA axis and three types of phenotypic plasticity to cope with environmental change: mediation of evasion, tolerance, and recovery

The different types of adaptive plasticity that organisms may exhibit in response to environmental change were put into a helpful organizational framework by Bradshaw (1972) and Huey (2002). In response to an environmental change, organisms could *evade* it, *tolerate* or *resist* it, or, if they are damaged by exposure to the environmental change, they could exhibit an increased *recovery* rate (Bradshaw, 1972; Huey, 2002). These three solutions to dealing with environmental change are non-mutually exclusive. For example, animals are sensitive to predation risk during foraging and may alter where or when they forage or reduce foraging/activity in the presence of predators. Below, I classify this as *evasion* from the environmental change (predation risk) as it enables the animal to avoid the danger, but it could also be classified as *tolerance/resistance* as it is essentially an example of behavioral plasticity that enables an individual to tolerate increased predation risk. Here, I discuss the central importance of the HPA axis in mediating the adaptive response to short term environmental change and/or stressors in vertebrates by facilitating evasion, tolerance/resistance, and perhaps recovery to stressors. This is in the context of within an individual, such as reversible (activational) behavioral plasticity of mainly adult individuals (Snell-Rood, 2013), or among individuals or generations, such as in the case of early life environments, parental phenotypes or environments inducing developmental plasticity in offspring that is usually irreversible (Uller, 2008; Nettle and Bateson, 2015). Notably, the latter could involve developmental or inter-generational plasticity, where the parental phenotype or environment induces or elicits plasticity in the phenotypes of F_1 or F_2 or even F_3 offspring (Skinner, 2008; Burton and Metcalfe, 2014; Dias and Ressler, 2014), that is induced through epigenetic mechanisms (Champagne, 2013; Anacker et al., 2014; Matthews and McGowan, 2019; Cao-Lei et al., 2020). The maternal HPA axis response or perinatal stress more broadly has been implicated in inducing such inter-generational plasticity in offspring behavior or physiology and some of the epigenetic mechanisms have been identified (Champagne, 2013; Anacker et al., 2014; Matthews and McGowan, 2019; Cao-Lei et al., 2020). Given that this has been reviewed extensively elsewhere, I do not devote too much space on this topic below.

4.1. Evasion

Behavioral responses to environmental change may be an animals first response to environmental change that enables them to evade a stressor either in space or time (Bartholomew, 1987). In mobile organisms, this can include movement away from a specific area containing the stressor (temporary or permanent dispersal or recurrent migratory behavior), but it can also include different types of dormancy in mobile or less mobile organisms (e.g., hibernation, torpor, or aestivation during harsh conditions). Organisms may also respond through temporal evasion of the stressor, such as modifying when they are active to avoid the stressor (e.g., Kohl et al., 2018).

The HPA axis seems intricately involved in many of these evasive responses, especially those associated with movement away from an environmental stressor (Wada, 2008). For example, individuals with elevated movement or restlessness often exhibit higher GCs (Buttemer et al., 1991; Landys et al., 2004; Eikenaar et al., 2014). Causality cannot be determined in these latter studies, but other studies that experimentally elevated GCs show that increased GCs also elevates movement and escape behavior (e.g., Belliure and Clobert, 2004). The effects of GCs on movement behavior may also occur in a non-linear fashion where moderate levels of GCs cause the highest levels of movement (Dallman et al., 1993; Breuner et al., 1998). Individuals who are more active, bold, and/or exploratory (and therefore potentially more likely to disperse: Cote et al., 2010) can also exhibit different HPA axis dynamics or increased GCs (Carere et al., 2003; Atwell et al., 2012; Westrick et al., 2019, 2021). Individuals often exhibit elevated GCs during natal or adult dispersal or recurrent migratory behavior (Heath, 1997; Belthoff and Dufty Jr, 1998; Landys-Ciannelli et al., 2002; Romero, 2002; Landys et al., 2006; Cease et al., 2007; Hamann et al., 2007; Young and Monfort, 2009; Maag et al., 2019; Piersma et al., 2000; Bauer and Watts, 2021). However, elevated GCs during migration is not universal in passerine birds (Bauer et al., 2016). Nonetheless, elevated GCs during these time periods or life history stages is frequently interpreted because of the "stress" associated with these long-distance movements, but it could also be due to the role that GCs may play in mobilizing energy that is needed for dispersal/migration (Sapolsky et al., 2000). For example, individuals with elevated GCs during dispersal events may exhibit longer dispersal distances due to increased stamina (Miles et al., 2007) or increased energetic resources because of the effects of GCs on motivating food-seeking behavior (Santana et al., 1995; Dallman, 2010). Finally, elevated GCs in response to sudden extreme weather conditions can trigger the well-documented "emergency life history stage" associated with the abandonment and dispersal away from a nest and/or territory (Wingfield et al., 1998; Wingfield and Kitaysky, 2002).

Direct connections have also been made between GCs and developmental plasticity in dispersal behavior by assessing how early life exposure to heightened GCs influences offspring dispersal behavior. Like most biological phenomenon, the effects of activation of the HPA axis on offspring dispersal are context dependent. For example, in willow tits (*Parus montanus*), experimental elevations in corticosterone levels were associated with higher juvenile but not adult dispersal (Silverin, 1997). In common lizards (*Lacerta vivipara*), experimental application of synthetic GCs to breeding females reduced movement behavior of offspring (Belliure et al., 2004), but its effects on offspring dispersal behavior depended upon maternal body condition (de Fraipont et al., 2000; Meylan et al., 2002). Offspring from heavier mothers who were treated with GCs prenatally were significantly less likely to disperse than heavier control mothers whereas those from lighter mothers who were treated with GCs tended to be more likely to disperse than lighter control mothers (de Fraipont et al., 2000; Meylan et al., 2002). The effects of maternal GCs on offspring dispersal behavior can also depend upon offspring sex and maternal age. For instance, yearling male but not female yellow-bellied marmots (*Marmota flaviventris*) were more likely to disperse away from their natal burrow if their mother was older and had elevated GCs, but yearling males from younger mothers with elevated GCs were less likely to disperse (Monclús et al., 2011). Although there are exceptions (e.g., Stumpf et al., 2009; Akinyi et al., 2017), these studies together illustrate that individuals with elevated GCs exhibit higher movement, activity, escape behavior, and are more likely to disperse or leave an area, though those from mothers treated with GCs are less likely to disperse.

Animals may not necessarily need to leave an area to avoid the challenge/stressor as they could also alter their daily or seasonal behavioral patterns or rhythms to enable escape from the stressor (e.g., temporal niche partitioning exhibited by prey species). The HPA axis

interfaces with biological clocks and the adrenal cortex itself expresses clock genes that seem to regulate GC production (Oster et al., 2006; Son et al., 2008, 2011). GCs may also to play an important role in ultradian and circadian rhythms (Dickmeis, 2009; Jaikumar et al., 2020) as well as circannual (seasonal) rhythms (Romero, 2002; Landys et al., 2006; Dickmeis et al., 2013), and they can help entrain biological clocks in peripheral tissues expressing GRs (e.g., liver: Reddy et al., 2007). This alone helps to establish the possibility that the HPA axis can play a role in establishing adaptive behavioral rhythms across different temporal scales (days or seasons). For example, adjustments in peak GC production could increase arousal during periods of the day when the stressor (such as a predator) is least active. Elevated GC production in response to exposure to a stressor could also alter or entrain biological clocks in such a way that produces adaptive adjustments in behavioral rhythmicity to avoid the stressor. Because relatively little is known on how the HPA axis might modify biological rhythms to cope with environmental stressors (but see Spencer et al., 2018), I focus my attention instead on examples that suggest that acute HPA axis activation facilitates evasion of environmental stressors through the induction of antipredator behavior (a type of behavioral plasticity).

In mammals and fish, exposure to predators or their cues can enhance HPA axis activity, as evidenced by increased GCs, and this activation of the HPA axis seems to cause an increase in freezing or quiescent behavior (Apfelbach et al., 2005; Remage-Healey et al., 2006; Roseboom et al., 2007; Kondoh et al., 2016), which should be beneficial when predators are nearby. However, exposure to predator cues can also elicit evasion of the risk of predation by changes in prey behavior by *inhibiting* the HPA axis. For instance, wood frog (*Rana sylvatica*) tadpoles exposed to cues of simulated predation of conspecifics (macerated skin cells from other tadpoles) exhibit a rapid reduction in swimming activity (i.e., they freeze) and an inhibition of the HPA axis (Fraker et al., 2009). Whole body corticosterone levels of tadpoles exposed to these predator cues are significantly lower than controls 2–4 h (but not 1 h) after the cues were added to an aquarium (Fraker et al., 2009). If exogenous corticosterone was added to the aquarium at the same time as the predator cues, swimming activity was not reduced as much as in controls, indicating that this decrease in corticosterone production in response to exposure to these predator cues was at least partially responsible for this evasive behavior (reduction in swimming) that should be beneficial in the presence of these predators (Fraker et al., 2009). Although these studies suggest that exposure to predators initiates either an increase or decrease in HPA axis activity that in turn facilitates behavioral evasion from predators, at least one study suggests that the hormonal response to predator cues may be sufficient but not necessary to elicit the antipredator behavioral response. Specifically, volatile predator odors activate neurons in the olfactory cortex (amygdalo-piriform transition area: AmPir) in mice that in turn initiates an increase in the production of GCs through activation of corticotropin releasing hormone neurons (Kondoh et al., 2016). Although chemogenetic silencing the activity of the AmPir when mice were exposed to predator cues prevents the increase in GCs compared to controls, these mice still exhibited increased freezing behavior (Kondoh et al., 2016), suggesting a decoupling of the behavioral and hormonal response to predator cues.

There is also evidence that early life exposure to environmental stressors or increased GCs can promote adaptive developmental plasticity that enables offspring to evade predators in space or time. For example, birds with experimentally increased yolk corticosterone exhibit better flight performance (Chin et al., 2009), which may increase their ability to evade direct predation attempts. GCs may interact with thyroid hormones in larval amphibians to accelerate metamorphosis (Denver, 2013; Sachs and Buchholz, 2019), which could decrease their amount of time spent in vulnerable life stages. Perhaps the best studied and most widespread pattern is where mothers exposed to increased predation risk produce offspring that exhibit elevated anti-predator behavior (e.g., reduced movement or activity in the presence of predators) that may enable them to better evade predators (Giesing et al., 2011; Storm and Lima, 2010; St-Cyr and McGowan, 2015; Bell et al., 2016; Donelan and Trussell, 2018; Ensminger et al., 2018). In some cases, the epigenetic mechanisms contributing to these changes in offspring characteristics have been identified (reviewed by Matthews and McGowan, 2019). It has been hypothesized that these changes in offspring anti-predator behavior are due to elevations in maternal GCs in response to them experiencing increased predation risk (Love et al., 2013; Sheriff and Love, 2013). This has been supported in some studies (St-Cyr and McGowan, 2015, St-Cyr et al., 2017; Ensminger et al., 2018), but studies in fish suggest that the mechanisms by which elevated predation risk in the parental environment affects offspring anti-predator behavior are independent of maternal GCs (Sopinka et al., 2014; Bell et al., 2016).

A final way that the HPA axis is involved in evading stressors is through its role in the regulation of on-body energy stores in species that engage in temporary dormancy that enables individuals to evade some stressor. Torpor and hibernation are both strategies to minimize energetic expenditure during harsh environments with the most obvious difference (of many) between the two being the length of time an animal spends in torpor or hibernation (torpor < hibernation). Hibernation is thought to be an adaptive response to seasonal environments that enables some species to escape environments that are associated with low availability of energy sources, such as the winter or dry seasons. In the case of torpor, birds with naturally higher or experimental elevations in GCs can exhibit longer torpor bouts (Hiebert et al., 2000). During preparation and entry into hibernation, GCs are elevated in a variety of mammalian species (Shivatcheva et al., 1988; Armitage, 1991; Boswell et al., 1994; Nunes et al., 2006; Willis and Wilcox, 2014) and this may serve as a potential motivator of food-seeking behavior or by altering other mechanistic pathways to increase fattening prior to hibernation (Willis and Wilcox, 2014). Although these studies are few in number (especially in the case of torpor), they illustrate that GCs and the HPA axis plays a central role in enabling organisms to enter behavioral states (torpor or hibernation) that facilitates their ability to cope with and escape seasons with low resource availability or that are otherwise harsh.

4.2. Tolerance/resistance

Organisms exposed to environmental changes that are stressful need not escape them in space or time. They could instead exhibit plasticity that enables them to stay put, but be more tolerant or resistant to the stressor. Below I discuss some examples where activation of the HPA axis by different environmental stressors induces plasticity that seems to enable the individuals to better tolerate or at least resist its effects. For instance, individuals experiencing low food availability can exhibit an increase in GCs that increases motivation to seek food (Dallman, 2010). This would be a type of adaptive behavioral plasticity that increases the resilience of that individual in a low food area instead of the individual fleeing the area. As I indicated above, increased anti-predator behavior exhibited by individuals in response to increased predation risk is considered here to be a type of *evasion* from the stressor, though it could equally be viewed as a way to *tolerate* the negative effects of predators.

Research on larval amphibians has played a central role in our understanding of the intimate relationship between the HPA axis and mediation of tolerance/resistance to predation risk. Pre-metamorphic larval amphibians do not have the option to exhibit immediate dispersal away from a pond or ephemeral body of water containing predators. They may accelerate metamorphosis and growth to escape predators more quickly, or they could adjust their behavior (as discussed above for *evasion*), but they also exhibit morphological plasticity that enables them to better resist predators *in situ*. In response to increased predation risk, larval amphibians often exhibit pronounced changes to the head/trunk shape and tail depth (Relyea, 2001; Benard, 2004) that increases their ability to evade predators (van Buskirk et al., 1997; Van

Buskirk and McCollum, 2000). In wood frogs, tadpoles collected from ponds with more predators have higher whole-body corticosterone and tadpoles exposed to predator cues (caged predators who were consuming wood frog tadpoles) in the laboratory exhibited higher whole-body corticosterone (Middlemis Maher et al., 2013). Exposure to these predator cues caused increases in tail depth and reductions in trunk length, which have both been repeatedly shown to be an example of adaptive morphological plasticity in larval amphibians that increases the ability of tadpoles to escape predators, perhaps by increasing swimming performance (Calsbeek and Kuchta, 2011). Larval amphibians exposed to exogenous GCs also exhibited a similar increase in tail height and reduction in trunk length as those that were exposed to predator cues whereas if the tadpoles were exposed to predator cues and were treated with a GC receptor antagonist (metyrapone), it blocked the expression of this morphological plasticity (Middlemis Maher et al., 2013). This well-documented example (in addition to previous studies: Denver, 1997, Denver, 2009) illustrates the central role of the HPA axis in the induction of adaptive morphological plasticity that enables stationary (at least temporarily during the larval stage) vertebrate animals to tolerate and resist an environmental stressor like increased predation risk.

Elevations in GCs in response to social stressors may also promote resistance rather than evasion. Rank in a social dominance hierarchy affects GCs with sometimes the socially dominant individual having higher GCs than subordinates and sometimes subordinates have higher GCs than dominants (Sapolsky, 2005; Creel, 2022; Dantzer and Newman, 2022). The increases in subordinate GCs are primarily caused by restricted food access or receiving physical aggression or psychological intimidation from dominant individuals (Sapolsky, 2005; Dantzer and Newman, 2022). In laboratory rats, social defeat in a dyadic interaction promotes an acute increase in GCs in both the eventual winner and loser, but often only a prolonged increase in GCs in the loser (Dantzer and Newman, 2022). These elevations in GCs in the loser of the antagonistic interaction can in turn promote a type of adaptive behavioral plasticity, submissiveness, that may enable them to reduce the likelihood of continued assaults from the dominant individual (Weger et al., 2018). Chronic elevations in GCs observed in subordinates in group-living species may therefore promote submissiveness that enables them to stay within the social group and reduce their likelihood of being evicted from the social group, which could be quite costly. In contrast to the above examples where elevations in GCs are associated with behavioral plasticity that enables an individual to *evade* a stressor, in group-living species, elevations in GCs may promote behavioral plasticity (submissiveness) that enables them to resist or tolerate this social stressor.

Life history plasticity can also enable animals to cope with environmental change or stressor. For example, birds experiencing a specific environmental stressor (harsh weather) exhibit a pronounced increase in GCs that shifts their investment towards self-maintenance/survival and away from reproduction (i.e., enter the "emergency life history stage": Wingfield et al., 1998; Wingfield and Kitaysky, 2002), indicating the important role of the HPA axis in mediating plasticity in this major life history trade-off but also in terms of affecting the timing of breeding. More recent work has revealed how elevated GCs suppress reproduction through suppression of the HPG axis (Kirby et al., 2009). However, an elevation in HPA axis activity or increased GCs is not necessarily always a trigger that shunts investment towards survival and self-maintenance and away from reproduction (Wingfield and Sapolsky, 2003; Boonstra, 2013). For example, seasonal breeders exhibit elevated GCs during the breeding season, perhaps to enable the mobilization of energetic resources (Romero, 2002; Fletcher et al., 2015). Moreover, short-lived or semelparous species can exhibit pronounced increases in GCs while breeding (Carruth et al., 2000; Barry et al., 2001; Boonstra, 2005; Boonstra, 2013; Fletcher et al., 2015), indicating the potential for the HPA axis to mediate this major life history trade-off but in a nuanced and species-specific manner.

GC responses to environmental stressors may also mediate other (lesser) life history trade-offs, such as that between offspring size and number (Stearns, 1992). For instance, individuals breeding under harsh conditions (high predation risk, low food availability, high conspecific competition) are often expected to produce fewer but larger offspring (offspring quantity vs. quality trade-off: Lima, 1987; Stearns, 1992; Martin, 1995; Roff, 2002). Some field studies that exposed breeding birds to cues of increased predation risk support these predictions as they show that individuals experiencing heightened predation risk produce smaller clutches (Eggers et al., 2006; Hua et al., 2014), smaller clutches of heavier eggs (Zanette et al., 2011), or no change in clutch size, but larger eggs (LaManna and Martin, 2016) or offspring that are initially smaller at hatching and who grow faster after hatching (Coslovsky and Richner, 2011). Note that the effects of predation risk on clutch size and egg mass are not entirely uniform among different bird species (Fontaine and Martin, 2006; Martin and Briskie, 2009; LaManna and Martin, 2016), but these selected studies illustrate how an increased risk of predation induces plasticity in the trade-off between litter size and offspring size or growth.

Given that predation risk can elicit increase GCs in prey (Clinchy et al., 2013), if these changes in GCs occur in breeding females, do they induce shifts in the number or size of offspring? Ideally, these studies in birds described above would have also quantified the GC responses of females to increased cues of predation risk and if the elevation in GCs caused changes in clutch size or egg/offspring size, but they did not do so. However, other studies show that the GC responses of breeding females to cues predicting that their offspring will encounter a harsh environment affect the trade-off between the number and size of offspring (Travers et al., 2010; Dantzer et al., 2013). For example, in North American red squirrels (*Tamiasciurus hudsonicus*) in the Yukon, Canada, conspecific densities vary due to temporal fluctuations in the availability of their major food source (Dantzer et al., 2020a). When densities are elevated, overwinter survival of offspring is reduced because there are no or few territories available for juveniles to acquire (Taylor et al., 2014). Consequently, breeding female squirrels can experience reductions in reproductive success when conspecific densities are increased (Dantzer et al., 2013), which emphasizes that high conspecific densities in this species is analogous to a harsh environment or characteristic of environmental stress. Adult squirrels do not evade these elevations in density because they rarely disperse away from their territory where they have accumulated a cache of food (Berteaux and Boutin, 2000). Dispersal to evade these increases in density is also unlikely to be beneficial because temporal/spatial synchrony in food availability causes little variation in conspecific densities across large spatial scales. In other words, squirrels experiencing high densities at their territory are very likely to experience high densities elsewhere if they dispersed. Instead of evading this stressor (conspecific density), most pregnant females exhibit an increase in GCs due to experiencing elevated conspecific densities and these elevations in maternal GCs promote increases in offspring postnatal growth rates that can result in offspring being better able to acquire a territory under high density conditions (Dantzer et al., 2013; Guindre-Parker et al., 2019; Dantzer et al., 2020a, 2020b). This example illustrates how GC responses can enable *resistance* to environmental fluctuations by inducing adaptive developmental plasticity: without the change in offspring growth rates, individuals would be expected to experience reduced reproductive success.

This developmental plasticity induced in offspring growth rates in red squirrels should be beneficial for both mothers and offspring (Dantzer et al., 2013), but there are also examples where the fitness benefits of developmental plasticity are less obvious. For example, in cooperatively breeding meerkats (*Suricata suricatta*), socially dominant females who were treated with GCs produced daughters that exhibited significantly slower postnatal growth, which should reduce their ability to breed independently later in life (Dantzer et al., 2019). However, these slower growing daughters also exhibit elevated cooperative (pup-rearing) behavior later in life that aids their mother in rearing offspring,

which was likely due to changes in the daughter's HPA axis (Dantzer et al., 2017, 2019). Here, the developmental plasticity in offspring growth rates in daughters appears to reduce the chances of their direct fitness but could enhance their indirect fitness if their elevated cooperative behavior helps their mother produce more relatives.

4.3. Recovery

A final way by which the HPA axis may facilitate the ability of animals to cope with an environmental change or stressor is through enhancing *recovery* following exposure to the change/stressor. This differs from evasion or tolerance/resistance by the fact that animals do not leave the area where they experience the stressor (*evasion*) and do not stay in the area and adjust their easily observable characteristics (behavior, morphology, life history traits) to deal with it (*tolerance/evasion*). Instead, the HPA axis may facilitate recovery after being exposed to the stressor through physiological means, which are of course less easily observed. Studies on this topic are somewhat rare except in the realm of biomedical research, so I largely focus on these studies below.

Recovery following exposure to a stressor is most often discussed in the context of how quickly individuals can terminate the increase in GCs in response to the stressor (i.e., exhibit strengthened negative feedback: Romero et al., 2009; Lattin and Kelly, 2020). This is often related to individual differences in mineralcorticoid (MRs) and glucocorticoid receptors (GRs) in specific parts of the HPA axis, such as individuals having more GRs in the hippocampus, pituitary gland, or paraventricular nucleus exhibiting a quicker return to baseline GCs (Ladd et al., 2004). This focus on recovery of the HPA axis, especially through the binding of GCs to GRs, has been reviewed at length elsewhere (de Kloet et al., 1998, 2005; de Kloet, 2022; Herman et al., 2012, 2016; van Bodegom et al., 2017). Consequently, I instead focus on how activation of the HPA axis that results in a measurable increase in GCs has other physiological effects (that is other than how quickly GCs return to baseline levels) on an individual that promotes recovery from the stressor.

Most of the studies on this topic illustrate how the duration of the increase in GCs impacts their consequences, finding that acute or short-duration increases in GCs can enhance recovery but long/chronic elevations in GCs decrease organismal function. This is very similar to the hypothesis that acute increases in GCs are adaptive whereas chronic elevations in GCs are maladaptive (McEwen, 1998; Sapolsky et al., 2000; McEwen and Wingfield, 2003; Romero et al., 2009; McEwen and Akil, 2020; but see Boonstra, 2013). This inverted u-shaped relationship (or Yerkes-Dodson phenomenon: Yerkes and Dodson, 1908) where moderate elevations in GCs have hormetic effects is often best illustrated by the effects of GCs on stimulating recovery from an acute immune attack. For instance, Dhabhar and McEwen (1999) showed how exposure to stress of short durations can enhance delayed-type hypersensitivity reactions, which may be beneficial for wild animals in the form of enhancing cell-mediated immunity by increasing resistance to different pathogens. Chronic exposure to stressors or chronic elevations in GCs (which are not necessarily synonymous) may reduce immune function and be detrimental (Munck et al., 1984; Sapolsky et al., 2000; Glaser and Kiecolt-Glaser, 2005), but acute increases in GCs may promote cell-mediated immunity towards pathogens, at least at the level of the skin (Dhabhar et al., 1996; Dhabhar and McEwen, 1999). As such, acute increases in GCs could promote recovery from exposure to physical stressors (e.g., wounding due to some antagonistic interaction with a conspecific or heterospecific) or pathogenic agents through their immunoenhancing effects, thereby once again facilitating the ability of an animal to cope with an environmental change or stressor but without evasion or tolerance/resistance.

A second way in which moderate or acute elevations in GCs may enhance recovery is through their effects on telomerase production. Exposure to stress is thought to be costly by accelerating biological aging or increasing the risk of mortality (Cohen et al., 2007; Monaghan, 2014; Lin and Epel, 2022). One way it may do so is through elevations in GCs (due to exposure to stressors) that may cause oxidative damage to telomeres, which may themselves directly contribute to the rate of aging (Shalev, 2012; Shalev et al., 2013; Monaghan, 2014; Haussmann and Heidinger, 2015; Reichert and Stier, 2017; Lin and Epel, 2022). For example, previous studies illustrate that individuals with a higher GC response have shorter telomeres or find a negative association between basal or stress-induced GCs and telomere lengths (Tomiyama et al., 2012; Jiang et al., 2019; Bae et al., 2021). Telomerase, an enzyme that can maintain or even enhance telomere lengths (Blackburn et al., 2015; Criscuolo et al., 2018), is also affected by exposure to GCs. For example, T lymphocytes in cell culture exposed to synthetic GCs exhibited reductions in telomerase levels 3 days after continuous exposure (Choi et al., 2008) and higher levels of cortisol in the urine in humans was associated with lower telomerase activity (Epel et al., 2006).

On the other hand, more recent studies about the effects of increased exposure to stress or GCs on telomerase have provided a potentially new way to view how the HPA axis affects recovery from exposure to environmental stressors (see also Epel, 2009; Smith et al., 2021; Marasco et al., 2022). This was largely spurred by the observational study in elderly women showing that 50- and 90-min after exposure to an acute stressor, there was a significant increase in telomerase levels measured in leukocytes that was independent of any change in leukocyte composition in the blood samples (Epel et al., 2010). Additionally, women with the highest increase in salivary cortisol following the acute stressor had the largest increase in leukocyte telomerase levels 90 min after exposure to the stressor (Epel et al., 2010). Depressed individuals, who often exhibit disruptions to HPA axis function, have higher telomerase levels (Wolkowitz et al., 2012; Chen et al., 2014; Deng et al., 2016), although there is some evidence that this pattern is gender specific (Simon et al., 2015). In a meta-analysis, Deng et al. (2016) showed that of the nine studies reporting an association between major depressive disorder (MDD) and telomerase, five reported individuals with MDD had higher telomerase levels. A subsequent study in humans did not find that an acute stressor increased maximal telomerase levels following a mitogen challenge (de Punder et al., 2018). Similar studies in non-human animals are increasing in number and are supportive of the hypothesis that telomerase levels are *elevated* in response to exposure to stressors or increased GCs. For example, male laboratory rats exposed to 3 months of a chronic stress experimental paradigm (seven types of randomized stressors, 5 days per week) had higher telomerase levels than controls (Beery et al., 2012). A previous study in wild North American red squirrels showed that females with increased GCs either during pregnancy or lactation did not produce offspring with shortened telomeres, potentially due to offspring (or mothers) exhibiting elevated telomerase levels (Dantzer et al., 2020b). In support of the latter, subsequent studies in wild gulls that injected GCs into eggs showed that offspring had elevated telomerase levels and no attenuation of telomere lengths (Noguera et al., 2020). Collectively, these studies about the effects of exposure to stressors, elevated GCs, and telomere lengths provide divergent results, with some studies suggestive of elevated GCs being associated or causing a reduction in telomere lengths (e.g., Tomiyama et al., 2012; Jiang et al., 2019; Bae et al., 2021) and telomerase production (e.g., Epel et al., 2006; Choi et al., 2008) or actually enhancing telomere lengths due to their stimulative effects on telomerase (Epel et al., 2010; Beery et al., 2012; Noguera et al., 2020). How to reconcile these divergent findings is challenging and must be the subject of future study, but once again they may reflect the hormetic effects of stress and HPA axis activation where there is a dose-dependent effect of stress and/or elevated GCs on telomerase levels and telomere lengths, as described above.

The HPA axis and GCs may also facilitate recovery from an environmental change/stressor that increases their movement or aerobic activity. This is often illustrated in human athletes, but non-human animals are also athletes when it comes to competing for life and

death (Killen et al., 2017). For example, in male side-blotched lizards (*Uta stansburiana*) that were exercised to exhaustion, those that received implants of corticosterone exhibited enhanced recovery as measured by the time it took them reach resting oxygen consumption rate following the exercise. We can also integrate the above section on telomerase as studies in both humans and non-human animals show that telomerase levels are increased following exercise (Deng et al., 2016). For instance, in lab mice, 21 days or ~6 months of voluntary wheel running exercise was associated with increased telomerase levels in cardiac cells, leukocytes, or skeletal muscle (Werner et al., 2008, 2009; Ludlow et al., 2012). These studies illustrate the potential for increased GCs in response to an environmental change/stressor that increases movement of individuals to promote recovery from the increased activity levels.

5. HPA Axis & phenotypic integration

The effects of HPA axis activation (or GCs themselves) on phenotypes are often studied from a unidimensional perspective where an increase in GCs due to an environmental change is expected to influence the expression a single trait that in turn affects animal performance or fitness. This is true of many of the examples discussed above, which is reflective of both reductionism and a logistical constraint that researchers face as they try to identify causality in terms of hormone- > trait- > fitness. However, how selection operates in nature and the phenotypic and genetic response to selection in nature emphasize the need for a more dimensional view of the effects of the HPA axis on how animals cope with environmental change and stressors. Environmental change can induce *multifarious* selection, where multiple environmental features that induce selection on phenotypes will change simultaneously resulting in selection along many different axes of environmental variation. For instance, as predation risk increases in wild guppies, so too do numerous features of the abiotic environment (stream width, openness of tree canopy, light intensity, water temperature, etc.) and these may also induce selection on guppy phenotypes (Endler, 1995). Additionally, adaptive phenotypic responses to environmental change are often *multidimensional* where the optimal phenotype for a given environment is an integrated phenotype involving suites of traits (physiological, morphological, behavioral, life history) that work well together and respond to a shift in the environment in a coordinated fashion (Fischer et al., 2016).

An additional (and more dimensional) way that the HPA axis can affect vertebrate animal responses to environmental change on relatively short temporal scales is by promoting *phenotypic integration* (Fig. 2). Phenotypic integration can be defined and characterized in many ways (Armbruster et al., 2014), but it is usually discussed in reference to patterns of co-variation (or inter-dependency) among multiple traits that make up a complex characteristic of an organism. These can be broken down to the degree of co-variance both within and across units (modules) that make up the complex trait (Klingenberg, 2008). For example, the "rattle" possessed by some viperid snakes is a complex trait made up of a highly correlated set of physiological, morphological, and behavioral traits. Each of these units (physiological, morphological, and behavioral) has a different function and can be referred to as a module. Within each module, there is strong co-variation among different traits that comprises it, reflective of within-module phenotypic integration. For instance, within the physiological module, oxygen consumption and enzymatic activity of tail shaker muscles are correlated with one another (Moon, 2001). Integration can also be present across modules where rattlesnakes exhibit a complex trait (rattling) composed of a morphological structure (the rattle composed of hollow modified keratin scales at the end of the tail), anti-predator behavioral response (vibrating the tail), and a suite of physiological traits that enable fast twitching of the tail-shaker muscles for long periods of time (Schaeffer et al., 1996).

In this snake example, there may be strong co-variation (integration) within and among the modules, which would suggest that the modules are not independent from one another (i.e., a lack of modularity: West-Eberhard, 2003; Wagner et al., 2007). In other cases, there may be strong co-variation (integration) among component traits within a module, but not across modules (i.e., modularity: West-Eberhard, 2003; Wagner et al., 2007). A different way to view this is that each module or functional unit is composed of many highly connected nodes (traits), organisms have multiple modules (physiological, morphological, behavioral), and biological networks often show a lack of connection (autonomy) among these different modules (nodes in module 1 are unlinked to nodes in module 2). This is the essence of the concept of modularity (Wagner et al., 2007) or community structure in biological or engineered networks (Girvan and Newman, 2002), which is important to consider when discussing how HPA axis activation coordinates the phenotypic response to environmental change and whether these changes are adaptive or maladaptive.

Here, I discuss the role of the HPA axis in phenotypic integration within modules, such as behavioral syndromes where multiple behavioral traits are correlated with one another (Sih et al., 2004). I also discuss the effects of the HPA axis on integration across modules, such as "coping styles" where behavioral and physiological traits (modules) are hypothesized to correlate with one another (Koolhaas et al., 1999, 2010) or "pace-of-life syndromes" where behavioral, physiological (including metabolic traits), and life history traits (three different modules) are hypothesized to correlate with one another (Ricklefs and Wikelski, 2002; Careau et al., 2008; Biro and Stamps, 2008, 2010; Réale et al., 2010; Careau and Garland Jr., 2012). This is largely descriptive as many of these studies describing how the HPA axis response to an environmental change affects integration within- or across-modules do not investigate how it affects individual fitness in that specific environment. However, the assumption of many of the studies discussed below is that the integration induced by HPA axis activation is adaptive.

5.1. Causes of phenotypic integration

Strong correlations among different phenotypic traits (either within or across modules) are a statistical representation of the degree of phenotypic integration and are quite common across organisms (Clausen and Hiesey, 1958; Olson and Miller, 1958; Berg, 1960; Murren, 2012; Conner et al., 2014). For example, reproductive traits in self-fertilizing plants often exhibit strong positive phenotypic and genetic correlations between corolla tube and filament length (Conner, 2003). In most organisms, the sizes of different morphological traits (legs, organs, etc.) scale allometrically with total body size to such a degree that they can be predicted by relatively simple equations (Shingleton, 2010a). These patterns of phenotypic co-variation could reflect some non-adaptive process due to a shared developmental or genetic mechanism (Wagner and Altenberg, 1996; West-Eberhard, 2003; Wagner et al., 2007; Klingenberg, 2008). In the case of the latter, phenotypic co-variation can be caused by genetic pleiotropy or linkage disequilibrium (Lynch and Walsh, 1998; Wagner et al., 2007; Wagner and Zhang, 2011; Saltz et al., 2017). Environmental co-variance can also cause phenotypic co-variation, such as when a feature of the environment causes the co-expression of two or more traits (Price et al., 1988; Rausher, 1992; Dantzer et al., 2016). Alternatively, or in combination with the above mechanisms (pleiotropy, linkage disequilibrium, or both), phenotypic integration could be adaptive and reflect correlational selection where individuals with specific combinations of traits (or integrated phenotypes) were favored for specific environments (Armbruster and Schwaegerle, 1996; Cheverud, 1996; Sinervo and Svensson, 2002; McGlothlin et al., 2005). This is evident when one looks at what happens to whole organismal function if there is an environmental perturbation that disrupts these patterns of phenotypic co-variation. For example, a perturbation in the size of one craniofacial bone (Olson and Miller, 1958; Cheverud, 1996) or organ (Shingleton, 2010b) can result in a reduction in whole-organism function unless the other bones/organs change in a coordinated manner thereby maintaining the integrated

phenotype. In self-fertilizing plants, a lack of strong positive co-variation between corolla tube and filament length can result in an inability to secure reproduction. Other studies in plants that can measure phenotypic integration at a comprehensive level confirm that phenotypic integration is under positive selection in the wild (e.g., Damián et al., 2020).

Although the concept of phenotypic integration has been a topic of discussion in ecology and evolution for decades (Darwin, 1872; Clausen and Hiesey, 1958; Olson and Miller, 1958; Berg, 1960; Pigliucci, 2003; Pigliucci and Preston, 2004; Murren, 2012), the ability of endocrine axes or hormones to act as a mediator of phenotypic integration did not really arrive on the scene until pivotal work led by Barry Sinervo (Sinervo and Licht, 1991a, 1991b), and Ellen Ketterson (Ketterson and Nolan Jr, 1992, 1999; Ketterson et al., 2005, 2009), among others (Hinde, 1970; Marler and Moore, 1988, 1989; Finch and Rose, 1995; Rose and Bradley, 1998). These studies have largely focused on the pleiotropic effects of hormones and how the phenotypic correlations they can generate may influence the response to selection or phenotypic evolution (Sinervo and Svensson, 1998; McGlothlin and Ketterson, 2008; Cox et al., 2016; Dantzer and Swanson, 2017; Cox, 2020). For the most part, these studies have focused on a two-trait paradigm where they aim to identify the mechanistic basis of negative phenotypic or genetic correlations between two traits. These negative correlations are indicative of trade-offs that are themselves a type of phenotypic integration (Agrawal et al., 2010). These studies also tend to focus on the degree of co-variation among traits within specific modules (among life history or among behavioral traits). For example, Sinervo and Licht (1991a, 1991b) examined the mechanistic basis of the trade-off between egg size and number by manipulating follicle-stimulating hormone whereas Ketterson and colleagues (Ketterson and Nolan Jr, 1992, 1999; Ketterson et al., 2005) have focused on how testosterone affects the trade-off between reproduction and self-maintenance/survival (especially from a behavioral perspective). More recent studies have focused on identifying how hormones might impact phenotypic integration, such as how the degree of insulin-signaling affects multivariate life history phenotypes (Dantzer and Swanson, 2012; Swanson and Dantzer, 2014) or the relationship among different physiological, immune, and life history traits (Sparkman et al., 2009; Robert and Bronikowski, 2010). There has also been a related but broader focus examining how physiological, behavioral, and life history traits co-evolve to form a pace-of-life syndrome (Ricklefs and Wikelski, 2002; Réale et al., 2010; Dammhahn et al., 2018; Mathot and Frankenhuis, 2018) and how physiological and/or metabolic traits co-evolve with multiple behavioral traits (Careau et al., 2008; Royauté et al., 2015; Biro et al., 2018). Studies specifically testing if hormones affect statistical estimates of phenotypic integration, the strength of genetic correlations, the matrix of genetic variances and co-variances, or gene expression itself have only recently arrived and have focused exclusively on testosterone (Cox et al., 2016, 2017, 2022; Lipshutz et al., 2019; Wittman et al., 2021).

5.2. HPA axis & phenotypic integration

Does the HPA axis coordinate phenotypic integration such that animals can mount an adaptive multidimensional response to environmental change? GCs do appear to play an important role in affecting patterns of phenotypic integration, both from a perspective of within-module integration (correlations among life history traits or among behavioral traits) or among-module integration (correlations among life history, behavioral, and physiological traits). Once again, this is often viewed from a two-trait paradigm that focuses on asking if GCs mediate trade-offs between two traits (i.e., cause negative phenotypic correlations). For example, elevations in GCs in response to an environmental stressor are expected to be an adaptive shift of investment away from current reproduction in populations or species where individuals have a high probability of reproducing again in the future (due to being young, iteroparous, experiencing low predation risk, etc.: Wingfield et al., 1998; Boonstra, 2004; Bókony et al., 2009; Hau et al., 2010). Other studies document how GCs affect life history trade-offs at lower hierarchical levels, such as Lancaster et al. (2007) showing that female lizards treated with GCs exhibited a lessening of the trade-off between offspring size and number. In red squirrels, there is also evidence of a lessening of the trade-off between litter size and offspring postnatal growth rate in mothers exposed to conspecific territorial vocalizations that were meant to simulate high density conditions (Dantzer et al., 2013). These females experiencing increased density cues also had higher fecal GC metabolites (Dantzer et al., 2013). These studies illustrate how the HPA axis may adaptively modulate the degree of covariance between two life history traits, either magnifying the trade-off (current vs. future reproduction) or lessening it (offspring size/growth vs. number).

Other studies focus on the potential role of the HPA axis (or exposure to developmental stress) in generating patterns of co-variation among different behavioral traits (Sih, 2011) or among behavioral and physiological traits to form a coping style (Groothuis and Carere, 2005; Korte et al., 2005; Koolhaas et al., 1999, 2010). Here, multiple behavioral traits are integrated (co-vary) into a "behavioral module" (or syndrome: Sih et al., 2004) and different physiological traits are integrated (co-vary) into a "physiological module" with higher-level integration (significant co-variation suggestive of a lack of modularity) between the behavioral and physiological modules to form a coping style (Koolhaas et al., 1999, 2007, 2010). For instance, individuals exhibiting a proactive coping style are expected to exhibit higher levels of aggression, activity, and HPA axis reactivity, suggestive of both within and across module integration (Koolhaas et al., 1999, 2007; Cockrem, 2007; Carere et al., 2010). Despite much interest in coping styles, there is little evidence of integration between the behavioral and physiological modules (Westrick et al., 2019). Other studies emphasize that exposure to developmental stress can cause a specific (and often consistent) constellation of traits in offspring, including specific physiological and behavioral traits (Meaney, 2001; Harris and Seckl, 2011; Guenther et al., 2018), such as birds in urban areas (which may experience higher exposure to environmental stressors) exhibiting higher exploration, aggressiveness, and breathing rates (Caizergues et al., 2022). In red squirrels, there is evidence of integration within relatively simple (two trait) behavioral modules (activity and aggression exhibit significant positive phenotypic and genetic correlations: Taylor et al., 2012; Westrick et al., 2019; Martinig et al., 2022) and physiological modules (baseline GCs and stress-responsiveness to a pharmaceutical challenge [ACTH] exhibit significant positive phenotypic correlations: Westrick et al., 2021). When the degree of association between the behavioral and physiological modules was examined, the results depended upon the developmental stage (adult vs. juvenile) and method used to quantify the HPA axis. Specifically, there was no significant association between fecal GC metabolites and activity, aggression, or docility in adult red squirrels (Westrick et al., 2019) whereas juvenile red squirrels from specific treatment groups that exhibited a stronger GC response to ACTH were less active and aggressive (Westrick et al., 2021). These two studies conducted in the same population but at different developmental stages and methods to quantify HPA axis activity illustrate the inherent complexities of trying to identify how hormones affect phenotypic integration. Just as Schlichting and Pigliucci (1998) emphasized how the environment can affect the degree of phenotypic integration, this study shows that that ontogenetic stage at which the traits are measured does so as well.

Researchers have also started to examine the degree of phenotypic integration among GCs, body condition, biomarkers of oxidative damage and antioxidants, telomeres, immune function, and behavior (Costantini et al., 2011; Buehler et al., 2012; Hau et al., 2015; Ouyang et al., 2016; Angelier et al., 2018). These studies are revealing in that GCs (or other attributes of the HPA axis) can co-vary with some of these other traits, but they still largely operate in a bi-variate (or two dimensional) world that focuses on the effects of GCs on mediating trade-offs between two traits (usually assessed using pairwise correlations). Recently,

several studies have gotten us closer to understanding the effects of GCs on phenotypic integration by studying if exposure to developmental stressors or direct treatment with GCs early in life shaped the strength of phenotypic correlations among different traits. Careau et al. (2014) showed that exposure of juvenile birds to nutritional stress reduced the degree of both positive and negative phenotypic correlations between two traits for multiple physiological and behavioral attributes that were measured. For instance, control birds who exhibited a higher basal metabolic rate (BMR) exhibited significantly less activity in a novel environment, whereas this association was substantially lessened in birds who were exposed to nutritional stress during the nestling stage (Careau et al., 2014). By contrast, Merrill and Grindstaff (2018) found that offspring treated with GCs early in life exhibited stronger phenotypic correlations both within specific clusters of traits (morphological, baseline and stress-induced GCs, immune measures) and also among them (e.g., baseline GCs and bacterial killing ability). In studies of red squirrels, treatment of mothers with GCs during pregnancy or lactation had minimal effects on the degree of co-variation between behavioral and physiological traits (Westrick et al., 2021) or between a life history trait (growth), physiological condition (hematocrit) and measures of oxidative damage or antioxidants (Dantzer et al., 2020b). These three studies illustrate the diversity of organismal responses to exposure to an environmental stressor or increases in GCs showing that it can increase, decrease, or have no effect on the strength of phenotypic correlations within- or among-modules.

In nearly all these examples, the fitness consequences of the effects of GCs on phenotypic integration largely remain untested, especially from the perspective of the animal exhibiting an increase in GCs that alters patterns of phenotypic integration in response to an environmental cue that is adaptive for the selective environment predicted by that cue. It is still unclear if phenotypic integration induced within or across modules is adaptive. Interestingly, Merrill and Grindstaff (2018) showed that captive juvenile birds treated with GCs early in life had stronger phenotypic correlations among traits and those with enhanced integration among these traits exhibited reduced survival, suggesting an immediate cost to phenotypic integration. Although enhanced phenotypic integration caused by GCs could be adaptive, it may also be maladaptive if the expected environment is not met in reality or when the effects are considered over longer timescales, which I now turn to below.

5.3. HPA axis & evolvability: coping with environmental change across longer timescales

> "Extreme stress can be regarded as an environmental probe which increases genetic variability revealing associations among life-history and stress traits that are difficult to perceive under more benign conditions."
>
> Parsons, 1993

Most work on the HPA axis has focused on how activation of the HPA axis induces adaptive plasticity to cope with environmental change over relatively short timescales. For instance, many studies have examined if elevations in maternal GCs induce adaptive developmental or intergenerational plasticity in offspring characteristics that prepares them for a harsh environment (Dantzer et al., 2013; Sheriff et al., 2017). Some studies in animal models in the laboratory or in humans have extended this work by focusing on epigenetic mechanisms that cause the persistence of offspring phenotypes induced by being produced by mothers with elevated GCs or by being exposed to perinatal stress (Champagne, 2013; Matthews and McGowan, 2019; Cao-Lei et al., 2020; Anacker et al., 2014), though notably most of these studies are only concerned with F_1 offspring and, as such, are still focused on relatively short timescales. By contrast, evolutionary ecologists and other researchers have studied for some time how environmental stressors can have important macroevolutionary consequences or evolutionary phenomena that happen over longer timescales than those considered above (Belyaev and Borodin, 1982; Belyaev, 1983; Parsons, 1987; Hoffmann and Parsons, 1991; Poole et al., 2003; Badyaev, 2005a, 2005b). By "*longer timescales*", I mean the impacts beyond an individual offspring or the effects of developmental stress on F_1 of F_2 offspring. Here, I use insight gained from their studies and focus on how responses to environmental stressors (including activation of the HPA axis and increased GCs) affect evolvabilty. I do so from a broad perspective because of the lack of research on this topic specifically focused on the HPA axis or in vertebrates.

Evolvability is defined and quantified in various ways and at various levels of biological organization from the genome to the individual organism, and to populations (Wagner and Altenberg, 1996; Kirschner and Gerhart, 1998; West-Eberhard, 1998, 2003; Pigliucci, 2008; Brookfield, 2009; Brown, 2014; Hansen and Pélabon, 2021; Hansen et al., 2022). Here, I define it as the ability of populations to adapt (exhibit an evolutionary response to selection) to new environments due to the emergence of novel heritable phenotypic variation (Wagner and Altenberg, 1996; Kirschner and Gerhart, 1998; West-Eberhard, 1998; Schlichting and Murren, 2004; Pigliucci, 2008). Although this definition of evolvability is an abstract description of a population, it ultimately starts with if and how individual organisms can produce novel phenotypic variation that is heritable (or eventually heritable due to genetic assimilation: Waddington, 1953; Pigliucci and Murren, 2003; West-Eberhard, 2003; Crispo, 2007). What is and is not "novel phenotypic variation that is heritable" is also challenging to define, but here I refer to it as phenotypes or phenotypic combinations that have not before been exposed to selection. This often occurs during development where the environment modifies the effects of genotype on phenotype (Wagner and Altenberg, 1996; West-Eberhard, 2003; Klingenberg, 2008). I characterize populations as exhibiting "higher evolvability" if they produce higher quantities of genetic and phenotypic variation (perhaps due to higher rates of mutation or recombination or the "release" of cryptic genetic variation) and/or produce greater variability in the number of trait combinations available for selection to act upon because the environment modifies the degree of integration among phenotypes by enhancing or dissolving phenotypic correlations between traits. In all cases, these may be caused by some epigenetic mechanism, but I do not focus on these. Finally, I will note that the concept of evolvability, as defined here, can be controversial (Brookfield, 2001; Poole et al., 2003; Pigliucci, 2008) because it suggests that selection acts at levels higher than an individual (group, population, species, clade, etc.) to increase evolvability or because it suggests that evolution through natural selection acts in a teleological fashion where it favors traits that offers some benefit in the future (Kirschner and Gerhart, 1998, Sniegowski and Murphy, 2006; Lynch, 2007; Brookfield, 2009).

Below, I discuss the effects of environmental stressors and, where possible, the HPA axis on evolvability. I do so by describing the effects of stress on the generation of novel genotypic and phenotypic variation and genetic and phenotypic co-variance. This encompasses several related concepts (phenotypic integration, modularity, cryptic genetic variation, evolutionary constraints), but ultimately these are distilled into similar concepts under the heading of how environmental stressors affect genetic and phenotypic variation and co-variation. As described above, organismal responses to environmental change or stress that increases genetic or phenotypic variance or increases the number of combinations of phenotypic traits could act as a diversifying bet hedging mechanism where total phenotypic variability is enhanced that in turn increases the geometric mean fitness of a population.

5.4. Effects of stress on phenotypic & genetic variation

The amount of additive genetic variation is expected to determine the rapidity of an evolutionary response to selection (Fisher, 1930; Houle, 1992; Lande and Shannon, 1996) and higher levels of phenotypic variability could provide a greater number of targets of selection, both of which could facilitate the ability of a population to persist through a

severe environmental stressor. The responses of individual organisms to environmental stressors may therefore enhance evolvability through the production of novel genetic and phenotypic variability. Genetic variation may increase during periods of environmental stress for a variety of reasons, such as increased mutation, recombination, or transposition rates (Holloway et al., 1990; Hoffmann and Parsons, 1991; Pigliucci et al., 1995; Badyaev, 2005a; Zhong and Priest, 2011; Rowiński and Rogell, 2017). The evidence of the effect of environmental stress on genetic variation is mixed (Hoffmann and Parsons, 1991; Blows and Sokolowski, 1995; Merilä and Fry, 1998; Hoffmann and Merilä, 1999; Fowler and Whitlock, 2002; Charmantier and Garant, 2005; Paaby and Rockman, 2014), with differences observed in studies measuring heritability of traits in laboratory animals versus those in natural populations (Charmantier and Garant, 2005). However, a meta-analysis that directly quantified a measure of genetic variation (coefficient of genetic variation) showed an increase in genetic variance for life history traits (but not morphological traits) under stressful conditions (Rowiński and Rogell, 2017). This could be because exposure to stress releases cryptic genetic variation (Rutherford, 2000; Siegal and Bergman, 2002; Gibson and Dworkin, 2004; Badyaev, 2005a; Schlichting, 2008; McGuigan and Sgrò, 2009; Ledón-Rettig et al., 2014). Mechanistically, cryptic genetic variation exposed by stressful environments could be the outcome of epigenetic modifications that alters gene expression or the generation of new genetic variation due to changes in mutation rates (among other possibilities). Cryptic genetic variation appears common (Paaby and Rockman, 2014), for example as has been shown to occur during exposure to an environmental stressor that disrupts the availability of heat shock proteins (Hsp90) to resist environmental or mutational perturbations revealing genetic variation that is usually hidden by the activity of Hsp90 (Jarosz and Lindquist, 2010). This ability of stressful environments to reveal cryptic genetic variation may have important effects on the ability of populations to persist through environmental change or to colonize novel environments (McGuigan and Sgrò, 2009; Paaby and Rockman, 2014), such as freshwater fish colonizing caves (Rohner et al., 2013).

Exposure to a stressful environment can also enhance evolvability through the production of novel phenotypic variants or expose "hidden reaction norms" some of which are beneficial for novel or stressful environments (Schlichting and Pigliucci, 1998; Schlichting, 2004; West-Eberhard, 2003; Pfennig et al., 2010; Moczek et al., 2011). This can manifest itself in terms of an increase in phenotypic variance within a population when organisms are exposed to an environmental stressor, as in many studies about wing shape in *Drosophila* (e.g., Fowler and Whitlock, 2002). This could be the outcome of "phenotypic accommodation" where the developmental environment results in a change in one trait that causes a change in other traits (West-Eberhard, 2003, 2005). Recent meta-analyses show that this is a widespread phenomenon: organisms exposed to developmental stressors exhibit heightened phenotypic variance (Sánchez-Tójar et al., 2020; but see Moran et al., 2021). For instance, fish in thermally stressful environments (increased temperatures) exhibit higher levels of total phenotypic variability (O'Dea et al., 2019) and animals experiencing nutritional stress during development exhibit increased variance in longevity (Senior et al., 2017). This increase in phenotypic variability could enable the production of novel phenotypic variants that enable the population to persist through the environmental change or "buy time" until the population can build up enough genetic variation to mount an evolutionary response to the new selective environment (Gavrilets and Scheiner, 1993; Ghalambor et al., 2007; Moran et al., 2016; O'Dea et al., 2016; Fox et al., 2019; Thompson et al., 2022). If some of these phenotypic variants were adaptive for the stressful or novel environment and the environment remains somewhat consistent, they could undergo genetic assimilation where the formerly plastic trait that was sensitive to an environmental cue becomes constitutively expressed due to genetic differences (Waddington, 1953; Pigliucci and Murren, 2003; West-Eberhard, 2003; Crispo, 2007).

Turning to the HPA axis, there are very few studies that can address if activation of the HPA axis and increased GCs in individuals have an influence on genetic or phenotypic variability within a group or population. There are no studies on genetic variation that I am aware of and most studies examining the effects of endocrine responses on phenotypes assess them through their effects on measures of central tendency in some treatment group (means and medians) rather than their influence on variance among the treated groups (Bennett, 1987; Williams, 2008). For instance, the numerous studies that have addressed how developmental stress impacts offspring traits, including direct manipulation of circulating GCs, focus on the effects of a treatment on the means and medians of offspring traits (Harris and Seckl, 2011). This focus on means and medians is also true in most meta-analyses (Sánchez-Tójar et al., 2020). For example, recent meta-analyses on the effects of developmental stress or GC manipulations on animal phenotypes do not report how their effects on the variance in the phenotypes considered (Eyck et al., 2019; Bonier and Cox, 2020). Other meta-analyses have started to focus on how exposure to stress affects phenotypic variance (O'Dea et al., 2019; Sánchez-Tójar et al., 2020; Moran et al., 2021). When the phenotypic data from Eyck et al. (2019) were re-analyzed to look at the effects of developmental stress on phenotypic variance, Sánchez-Tójar et al. (2020) reported that developmental stress did indeed enhance phenotypic variance. Finally, although rare, there are some studies that manipulate GCs and show that offspring have higher levels of phenotypic variance. For instance, in cavies (*Cavia aperea*), groups treated with exogenous GCs during adolescence had higher among-individual variance in physiological and behavioral traits than a control group (Guenther et al., 2018). This lack of examples emphasizes opportunities for researchers to identify if exposure to an environmental stressor that activates the HPA axis promotes phenotypic variation, as studies in other taxonomic groups have shown.

5.5. *Effects of stress on phenotypic & genetic co-variation*

Not only might exposure to environmental stressors generate the production of genetic and phenotypic variation, but it may also influence the ability of populations to cope with environmental change over evolutionary (long) timescales by affecting the degree of phenotypic integration. The effects of hormones on phenotypic integration represents a sort of double-edged sword. Strong phenotypic integration promoted by hormones (or another mechanism) can be adaptive in relatively constant environments by promoting the expression of adaptive combinations of traits (discussed above). An environmental change that alters hormone titers could alter multiple phenotypes in an adaptive direction, such as changes in insulin-signaling in response to changes in food availability or competition promoting an adaptive increase in the pace of life (Dantzer and Swanson, 2012; Swanson and Dantzer, 2014). The integration of different physiological, behavioral, and life history traits into a "syndrome" could be adaptive for specific types of environments that are predictable (Hämäläinen et al., 2021). In both cases, there is integration within- and among-modules (i.e., multiple behaviors are strongly correlated with one another and also strongly correlated with life history traits), indicating strong integration and a lack of modularity.

On the other hand, phenotypic integration and/or lack of modularity should theoretically reduce the evolvability of populations by limiting the independent evolution of parcels of traits or acting as a constraint to population or species persistence in the face of environmental change because the required diversity in form and function (or specific combination of phenotypes) is not present (Wagner and Altenberg, 1996). Modularity or compartmentalization can reflect "weak linkages" among the component parts (or modules) of an organism and is expected to enhance evolvability (Kirschner and Gerhart, 1998; Wagner et al., 2007; Pigliucci, 2008) because each module of an organism can respond to new environmental challenges separately rather than as a whole. If integration within- and across-modules (i.e., a lack of modularity) is

caused by genetic co-variance, it could theoretically limit the multidimensional phenotypic space that can be explored during evolutionary change. Genetic co-variance between two traits is thought to act as a type of constraint on their independent evolution because a response to selection on one trait causes a correlated response in another trait (Lande, 1979; Cheverud, 1984; Lynch and Walsh, 1998; Conner, 2002; Chenoweth et al., 2010). Populations may evolve along "genetic lines of least resistance" where the co-variance between two traits is largely stable even if there are shifts in the mean trait value over evolutionary timescales (Lande, 1976; Schluter, 1996; McGuigan et al., 2005; McGlothlin et al., 2018). For example, two morphological traits may exhibit strong positive genetic co-variance whereby they are also positively phenotypically correlated. If the major axis of genetic co-variation is congruent with the direction of selection (such as favoring an increase in the size of trait 1 and trait 2), it can facilitate an adaptive response to selection. If the major axis of genetic variation is orthogonal to the direction of selection (such as favoring an increase in size of trait 1 but a decrease in the size of trait 2), the response to selection could be blunted. As such, phenotypic integration and genetic co-variation could constrain the total amount of phenotypic variability that can be exposed to selection or blunt the evolutionary response to selection, thereby lowering evolvability. Greater phenotypic integration, perhaps caused by genetic co-variance, may also limit the total amount of phenotypic plasticity mounted by an organism in response to environmental change (Gianoli and Palacio-López, 2009). Alternatively, if different traits can exhibit differential plasticity to the same environmental cue, it may reduce phenotypic integration and expose novel combinations of phenotypes to selection (Schlichting, 1986, 1989). Note that these are types of "local constraints" rather than "universal constraints" (sensu Maynard Smith et al., 1985) given that the local constraints posed by modularity or integration are expected to be dissolved given enough time or pressure from selection.

The evidence for genetic co-variance to act as an evolutionary constraint is mixed (Chenoweth et al., 2010; Bolstad et al., 2014; Hansen and Pélabon, 2021). Examples from the fossil record provide some support for the hypothesis that strong morphological integration can constrain divergence or variation in morphological phenotypes (Firmat et al., 2014; Goswami et al., 2014; Voje et al., 2014). Other studies using morphological data from extant bird species also show that the response to selection can be reduced by 28 % by genetic co-variance among morphological traits (Teplitsky et al., 2014). Yet, genetic co-variance can also facilitate responses to selection (Agrawal and Stinchcombe, 2009) and empirical studies using artificial selection highlight that observed patterns of phenotypic co-variation among morphological traits in plants and animals can be broken if selection is strong enough (e.g., Beldade et al., 2002; Conner, 2003; Frankino et al., 2005; Agrawal et al., 2010). It seems that if selection is strong enough, the genetic architecture underlying the phenotypes under selection can be reshaped by selection (e.g., Arnold et al., 2008; Doroszuk et al., 2008; Eroukhmanoff, 2009; Eroukhmanoff and Svensson, 2011; Wood and Brodie, 2015). This may be because even in situations where two traits are highly functionally related to one another, these two traits are heavily influenced by two separate gene regulatory networks (described in Wagner et al., 2007), suggesting that they can evolve independently from one another due to this modularity.

Leaving aside this issue of whether genetic co-variance acts as an evolutionary constraint and/or reduces evolvability, how might environmental stress or activation of the HPA axis affect evolvability by influencing genetic and phenotypic co-variation? We can first look at this from the responses of plants and animals to environmental stressors. Exposure to a severe environmental stressor may enhance evolvability by lessening phenotypic integration and/or the genetic covariance among traits (Parsons, 1987, 1994; Hoffmann and Parsons, 1991; Badyaev, 2005a). For instance, different traits could exhibit differential plasticity to the same environmental cue, thereby reducing phenotypic integration and expose novel combinations of phenotypes to selection (Schlichting, 1986, 1989). Despite the interesting potential, few studies find that exposure to stress enhances evolvability by decreasing phenotypic integration. Matesanz et al. (2021) did find that plants exposed to a stressor (drought) did have lower integration. Additionally, the overall degree of integration among phenotypes is expected to be reduced by stress, as reflected in the fluctuating asymmetry literature (Parsons, 1990; Hoffmann and Woods, 2003). For example, developmental stress could promote instability in the development of phenotypes or the dissolution of phenotypic canalization, producing novel phenotypic combinations of traits by causing fluctuating asymmetry in different traits that are usually related to one another in a consistent manner (Siegal and Bergman, 2002; Hoffmann and Woods, 2003; Badyaev, 2005a). Some studies also find that the negative genetic correlation between two life history traits is reduced in the stress treatment group. For instance, in *Drosophila* the negative genetic correlation between early life fecundity and starvation resistance was −0.913 in the standard environment, but −0.453 in the novel (stressful) environment (Gebhardt and Stearns, 1988).

By contrast, many studies find that environmental stress actually enhances phenotypic integration (Schlichting, 1986; Waitt and Levin, 1993; Donohue and Schmitt, 1999; Gianoli, 2004; Gianoli and Palacio-López, 2009; Benavides et al., 2021). This is evident when viewing how the trade-off between traits that compete for the same pool of resources being increased under stressful conditions. For instance, studies investigating life history trade-offs find that nutritional stress exacerbates the trade-off (increases the negative phenotypic correlation between two traits) exhibited by two life history traits that compete for the same resources (current vs. future reproduction, offspring size vs. number, etc.: Merilä et al., 2000; Reznick et al., 2000). Finally, novel environments encountered by organisms are expected to be stressful (although not necessarily), yet they do not seem to alter patterns of genetic covariance among multiple traits (Wood and Brodie, 2015). Thus, there is mixed evidence for the hypothesis that activation of the stress response can relieve evolutionary constraints by increasing the number of combinations of phenotypes that selection can act upon. This could be because the types of environmental stressors that are often used in these studies are not entirely novel to the organism from the perspective of its evolutionary history. For example, plants and animals may have specific adaptive patterns of trait combinations to deal with nutritional stress or water restriction that they have undoubtedly experienced over evolutionary timescales so it may not be surprising that exposure to one of these stressors enhances integration. On the other hand, exposure to a truly novel environment or stressor (such as the panoply of stressors present in urbanized landscapes) may dissolve the patterns of phenotypic and genetic co-variance and therefore promote evolvability.

To date, there are no studies about how activation of the HPA axis or increased GCs affects statistical characterizations of phenotypic and genetic co-variance. As described above, there are three studies about how early life nutritional stress or increased GCs affects phenotypic (pairwise) correlations with one study showing an enhancement of pairwise correlations between two traits both within- and across-modules (Merrill and Grindstaff, 2018), another showing a reduction in pairwise correlations between traits across modules (Careau et al., 2014), and the other suggesting no change (Dantzer et al., 2020b). Other studies described above have described how developmental stress might promote the co-variation among behavioral traits (syndromes) or between physiological and behavioral traits (Meaney, 2001; Harris and Seckl, 2011; Guenther et al., 2018). Clearly a future area of research is to investigate how activation of the HPA axis affects patterns of phenotypic co-variation and, if sample size permits, quantifying how elevations in GCs affects patterns of genetic co-variance. By doing so, this would help reveal if the HPA axis promotes adaptive phenotypic integration to cope with predictable environmental change over short timescales, but also how its effects on integration may constrain or facilitate coping with environmental change across longer timescales.

6. Some future directions

Moving forward, there are many research opportunities when it comes to understanding if and how the HPA axis mediates adaptive plasticity, but also if and how it affects evolvability by modifying patterns of phenotypic integration or inducing bet hedging. First, it will be interesting to consider if individuals experience trade-offs in these different types of plastic responses to environmental change. For example, do individuals that employ evasion to deal with an environmental stressor also exhibit a reduction in the ability to recover from stressors? Furthermore, given that GCs can promote recovery from stressors (even chronic stressors: Beery et al., 2012), rather than only inflict damage, it may require a revaluation of models exploring the respective roles of damage and repair in the evolution of the vertebrate stress response (Taborsky et al., 2022). Second, we need studies of how GCs affect statistical estimates of phenotypic and genetic co-variance. Some of the studies described above demonstrate the potential for how exposure to environmental stressors or increases in GCs can alter patterns of phenotypic integration, but they are still analyses of pairwise associations. We still have poor knowledge on how the HPA axis affects statistical patterns of phenotypic or genetic co-variance among different traits (i.e., statistical estimates of integration as in studies with other hormones: Cox et al., 2017; Wittman et al., 2021). This is surprising given that the classic review on the HPA axis (Sapolsky et al., 2000) emphasized how GCs coordinate adaptive phenotypic integration, causing a cavalcade of physiological responses that facilitate evasion from dangerous situations. Other studies examining the pleiotropic effects of testosterone provide an organizational framework to carry out this type of work and they largely support the hypothesis that testosterone can have important impacts on the evolutionary trajectories of species by affecting the genetic response to selection or patterns of phenotypic/genetic variance and co-variance (Cox et al., 2016; Cox, 2020). Third, there is a need to consider how the plastic responses of different traits are related to one another. This concept of "whole organism plasticity" (Steiner and Van Buskirk, 2008) or "plasticity integration" (Schlichting, 1986; Schlichting and Pigliucci, 1998; Gianoli and Palacio-López, 2009; Plaistow and Collin, 2014; Ellers and Liefting, 2015) focuses on understanding how an individual organism integrates plastic responses in suites of traits (similar to phenotypic accommodation: West-Eberhard, 2005). How does the whole organism or complex trait stay functional if one trait is responding to an environmental cue? If one trait exhibits plasticity to an environmental stressor, how do the other traits respond? Are the patterns of phenotypic co-variance plastic or static when exposed to an environmental change? These outstanding questions have implications for the evolution of plasticity induced by the HPA axis (Schlichting, 1989; Schlichting and Pigliucci, 1998; Pigliucci, 2003) and addressing them will require more sophisticated statistical approaches. Luckily, many of these are already used in other taxonomic groups besides vertebrates (Schlichting and Pigliucci, 1998; Gianoli and Palacio-López, 2009). Fourth, measures of the HPA axis such as GCs may exhibit co-variation with other traits (physiological, morphological, behavioral), but does the HPA axis mediate this integration or does it merely reflect another biomarker of some life history stage or strategy that is associated with all these other coordinated trait changes? That is, is the HPA axis a *hub* on a phenotypic network where if it is activated, it results in changes in all the other nodes (Fig. 1B)? Or, is it just a *node* in the phenotypic network where all nodes are jointly influenced by some environmental factor? Similar discussions have occurred around linkages between telomeres and lifespan regarding whether telomere lengths or rates of telomere attrition are a cause or symptom of aging (Simons, 2015; Casagrande and Hau, 2019). Here, it is quite possible that the response of the HPA axis to an environmental change acts as a hub in the phenotypic network or, said differently, acts as an "integrator" between the environment and the multidimensional phenotypic response (Martin et al., 2011a, 2011b). Empirical tests of these possibilities requires testing how GCs affect patterns of trait covariation (e.g., through experimental manipulation of the hormone: Cox et al., 2017) and/or identifying if specific "supergenes" associated with HPA axis function contribute to a multifaceted phenotypic response similar to those chromosomal inversion polymorphisms that influence other steroid hormones or their receptors (Maney and Küpper, 2022). Fifth, we do not yet know if these patterns of integration that are observed (such as the presence of coping styles or pace-of-life syndromes) are adaptive or reflect some pleiotropic constraint where GCs constrain the independent expression of two traits. The latter is thought to be unlikely given that different parts of endocrine systems (production, transport, reception) can evolve independently from one another (Hau, 2007; Adkins-Regan, 2008; Ketterson et al., 2009; Dantzer and Swanson, 2017). On the other hand, there is evidence that component parts of the HPA axis (GC receptors and mineralcorticoid receptors) are correlated with one another across tissues (Lattin et al., 2015) and, for other hormones, some level of macroevolutionary stasis in the relationships between ligand production and suites of life history traits (Swanson and Dantzer, 2014). The HPA axis also seems to be closely connected with other endocrine axes affecting growth, reproduction, and lifespan (Fig. 1B), which is suggestive of a lack of "weak linkages" among these physiological networks, could reduce evolvability (Kirschner and Gerhart, 1998; Kitano, 2004). The interconnectedness of the HPA axis with other endocrine axes suggests some coordinated rather than compartmentalized (or parcellated) response to environmental change is possible, potentially lowering both modularity and evolvability (Kirschner and Gerhart, 1998; Kitano, 2004). It seems plausible that future studies will show that the sequalae of phenotypes or the pattern of integration that are induced by activation of the HPA axis or exposure to developmental stress are beneficial for those specific environments if the individual encounters the expected environment (i.e., observed in animals with short lifespans: Nettle and Bateson, 2015), but what are the consequences of this integration and the potential for a lack of modularity across longer timescales? Finally, there is a desperate need to consider how the HPA axis has evolved to not only promote adaptive responses of individual organisms across short timescales, but also longer/evolutionary timescales. More than 15 years ago, Williams (2008) brought back Bennet's (Bennett, 1987) concepts about the "tyranny of the golden mean" and yet there is still a lack of reporting when it comes to the phenotypic variance within treatment groups or meta-analyses on the effects of environmental stressors or GCs on phenotypic variance (Sánchez-Tójar et al., 2020). This is changing but there is a need for more of these studies focusing on the magnitude of genetic and phenotypic variance and co-variance within groups to better understand how responses to environmental stressors (during development or another life stage) could act as a bet hedging mechanism.

7. Synthesis

The HPA axis serves as a bow tie network that balances the need for organisms and populations to be flexible, but not too flexible, in response to environmental change. Above I have discussed how the HPA axis can coordinate organismal responses to environmental change by promoting adaptive phenotypic plasticity in terms of evasion, tolerance, and recovery and in terms of coordinating adaptive phenotypic integration. This univariate and multivariate plasticity induced by the HPA axis can enable individuals to cope with environmental change across short timescales, namely at the level of the individual or from parents to offspring or grand offspring (13– generations). At the same time, organismal responses to environmental change, including activation of the HPA axis, seem to play an important role in their ability to cope with environmental change across longer timescales (>3 generations) by affecting evolvability through their effects on genetic and phenotypic variation and co-variation.

In the field of evolutionary endocrinology, which combines evolutionary ecology and behavioral neuroendocrinology (Zera et al., 2007; Cox et al., 2016), there may have been a tendency to shy away from

considering how environmental changes over long timescales have shaped the evolution of the HPA axis or how organismal responses to environmental stressors affect evolvability (but see Badyaev, 2005a, 2005b). This is evident in the many studies that are primarily focused on asking if the parental HPA axis induces adaptive developmental plasticity in offspring that enables offspring to evade or tolerate environmental stressors (heightened predation risk, low food, high competition: Dantzer et al., 2013; Love et al., 2013; Sheriff et al., 2017). Although informative, this is a narrow view about the selective factors that shape the HPA axis. For instance, for this type of developmental plasticity to evolve, it requires some level of environmental stability in the environment experienced by offspring (Kuijper and Hoyle, 2015; McNamara et al., 2016) where the parental phenotype (e.g., elevated maternal GCs) provided offspring with a predictive cue that the environment they would encounter would be harsh, it caused developmental plasticity, and offspring exhibiting that plasticity did indeed encounter a harsh environment that increased their fitness relative to offspring that did not exhibit this plasticity (Nettle and Bateson, 2015). Thus, while these studies attempt to illustrate how maternal hormonal responses to ecological cues induce adaptive developmental plasticity, this is potentially only applicable to species that exhibit high temporal autocorrelation between parental and offspring environments, which may only apply over short time scales.

The perspective I have advocated here is to consider how the HPA axis facilitates coping with environmental change across *both* short and long timescales from the evolutionary strategies of plasticity to bet hedging, respectively. Doing so can help us fully understand the causes of HPA axis activation and its consequences (or lack thereof) and may illuminate new interpretations for common and seemingly anomalous observations. For example, in red squirrels, some individuals exposed to the same cues of environmental harshness (high conspecific density) do not exhibit an increase in GCs (Guindre-Parker et al., 2019) and/or their offspring do not exhibit developmental plasticity in response to those cues that would be adaptive (Dantzer et al., 2013, 2020a). This could be because some individuals do not have equal access to those cues or because they value them differently according to their individual state, the amount of resources they have on hand, or their residual reproductive value. Alternatively, this individual-variation in the responsiveness of the HPA axis to conspecific density may be shaped by environmental fluctuations across larger temporal scales than is usually considered. For instance, the lack of response to these cues exhibited by some individuals could be reflective of a bet hedging strategy that was favored because it enhances evolvability. Another example illustrating the potential value of widening the temporal scope of the selective factors shaping the HPA axis comes from studies of the effects of perinatal stress in laboratory rodents (Harris and Seckl, 2011). They have been kept in captivity for numerous generations, yet they still exhibit a stereotypical response to perinatal stress where their offspring exhibit plasticity in their characteristics that should be adaptive for high predation risk environments (Harris and Seckl, 2011). Instead of the maintenance of this response being maladaptive given their present environment, it could reflect a bet hedging strategy to avoid making the costliest error (Sheriff et al., 2018; Petrullo et al., 2023). These types of observations are common and incorporating a perspective focused on bet hedging can help us better understand the selective forces shaping the HPA axis.

Understanding how the HPA axis has been shaped by selective factors over both short (plasticity) and long (bet hedging) timescales is pressing due to the need to understand how animals will cope with human-induced rapid environmental change (HIREC: Sih et al., 2011). HIREC is expected to be stressful for animals because these are often novel and unpredictable environmental changes. Moreover, bow tie type networks like the HPA axis may exhibit fragility when they encounter unanticipated environmental perturbations (Kitano, 2004), such as HIREC activating the HPA axis and potentially inducing maladaptive plasticity (Donelan et al., 2020). Even though results from meta-analyses regarding the effects of anthropogenic factors on GCs in wild vertebrates is mixed and some studies find a reduction in the GC response for those in urban environments (Atwell et al., 2012), many animals exposed to HIREC do indeed exhibit elevated GCs (Dantzer et al., 2014; Iglesias-Carrasco et al., 2020; Injaian et al., 2020). However, these elevations in GCs may be adaptive over short timescales, such as the developmental plasticity that is induced when parental GCs are elevated being adaptive for offspring living in harsh environments (Dantzer et al., 2014). More importantly, the increase in GCs due to HIREC could also be adaptive over longer timescales, such as inducing novel phenotypic variation or combinations of phenotypes that act as a bet hedging mechanism to enhance population persistence under HIREC (see also Donelan et al., 2020). Although there is much focus on the negative consequences of HPA axis activation of animals experiencing HIREC, there could also be hope when we consider how the HPA axis has evolved to deal with environmental fluctuations over longer timescales than is typically considered.

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References

Adkins-Regan, E., 2008. Do hormonal control systems produce evolutionary inertia? Phil. Trans. Roy. Soc. B Biol. Sci. 363, 1599–1609.

Agrawal, A.F., Stinchcombe, J.R., 2009. How much do genetic covariances alter the rate of adaptation? Proc. Roy. Soc. B Biol. Sci. 276, 1183–1191.

Agrawal, A.A., Conner, J.K., Rasmann, S., 2010. Tradeoffs and negative correlations in evolutionary ecology. In: Bell, M.A., Eanes, W.F., Futuyma, D.J., Levinton, J.S. (Eds.), Evolution Since Darwin: The First 150 Years. Sinaeur, Sunderland, MA, pp. 243–268.

Akinyi, M.Y., Gesquiere, L.R., Franz, M., Onyango, P.O., Altmann, J., Alberts, S.C., 2017. Hormonal correlates of natal dispersal and rank attainment in wild male baboons. Horm. Behav. 94, 153–161. https://doi.org/10.1016/j.yhbeh.2017.07.005.

Anacker, C., O'Donnell, K.J., Meaney, M.J., 2014. Early life adversity and the epigenetic programming of hypothalamic-pituitary-adrenal function. Dialogues Clin. Neurosci. 16, 321–333. https://doi.org/10.31887/DCNS.2014.16.3/canacker.

Angelier, F., Wingfield, J.C., 2013. Importance of the glucocorticoid stress response in a changing world: theory, hypotheses and perspectives. Gen. Comp. Endocrinol. 190, 118–128. https://doi.org/10.1016/j.ygcen.2013.05.022.

Angelier, F., Costantini, D., Blévin, P., Chastel, O., 2018. Do glucocorticoids mediate the link between environmental conditions and telomere dynamics in wild vertebrates? A review. Gen. Comp. Endocrinol. 256, 99–111.
Apfelbach, R., Blanchard, C.D., Blanchard, R.J., Hayes, R.A., McGregor, I.S., 2005. The effects of predator odors in mammalian prey species: a review of field and laboratory studies. Neurosci. Biobehav. Rev. 29, 1123–1144. https://doi.org/10.1016/j.neubiorev.2005.05.005.
Armbruster, W.S., Schwaegerle, K.E., 1996. Causes of covariation of phenotypic traits among populations. J. Evol. Biol. 9, 261–276.
Armbruster, W.S., Pélabon, C., Bolstad, G.H., Hansen, T.F., 2014. Integrated phenotypes: understanding trait covariation in plants and animals. Philos. Trans. R. Soc. B Biol. Sci. 369, 20130245. https://doi.org/10.1098/rstb.2013.0245.
Armitage, K.B., 1991. Factors affecting corticosteroid concentrations in yellow-bellied marmots. Comp. Biochem. Physiol. A Physiol. 98, 47–54. https://doi.org/10.1016/0300-9629(91)90576-X.
Arnold, S.J., Bürger, R., Hohenlohe, P.A., Ajie, B.C., Jones, A.G., 2008. Understanding the evolution and stability of the G-matrix. Evol. Int. J. Org. Evol 62, 2451–2461.
Atwell, J.W., Cardoso, G.C., Whittaker, D.J., Campbell-Nelson, S., Robertson, K.W., Ketterson, E.D., 2012. Boldness behavior and stress physiology in a novel urban environment suggest rapid correlated evolutionary adaptation. Behav. Ecol. 23, 960–969. https://doi.org/10.1093/beheco/ars059.
Badyaev, A.V., 2005a. Stress-induced variation in evolution: from behavioural plasticity to genetic assimilation. Proc. R. Soc. B Biol. Sci. 272, 877–886. https://doi.org/10.1098/rspb.2004.3045.
Badyaev, A.V., 2005b. Role of stress in evolution: From individual adaptability to evolutionary adaptation. In: Hallgrimsson, B., Hall, B.K. (Eds.), Variation. Academic Press, pp. 277–302.
Bae, J., Bertucci, E.M., Bock, S.L., Hale, M.D., Moore, J., Wilkinson, P.M., Rainwater, T. R., Bowden, J.A., Koal, T., PhamTuan, H., Parrott, B.B., 2021. Intrinsic and extrinsic factors interact during development to influence telomere length in a long-lived reptile. Mol. Ecol. mec.16017 https://doi.org/10.1111/mec.16017.
Balaban, N.Q., Merrin, J., Chait, R., Kowalik, L., Leibler, S., 2004. Bacterial persistence as a phenotypic switch. Science 305, 1622–1625. https://doi.org/10.1126/science.1099390.
Bamberger, C.M., Schulte, H.M., Chrousos, G.P., 1996. Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. Endocr. Rev. 17 (3), 245–261.
Barry, T.P., Unwin, M.J., Malison, J.A., Quinn, T.P., 2001. Free and total cortisol levels in semelparous and iteroparous Chinook salmon. J. Fish Biol. 59, 1673–1676. https://doi.org/10.1111/j.1095-8649.2001.tb00230.x.
Bartholomew, G.A., 1987. Interspecific comparison as a tool for ecological physiologists. In: Feder, M.E., Bennett, A.F., Burggren, W.W., Huey, R.B. (Eds.), New Directions in Ecological Physiology. Cambridge University Press, Cambridge, pp. 11–35.
Bauer, C.M., Watts, H.E., 2021. Corticosterone's roles in avian migration: assessment of three hypotheses. Horm. Behav. 135, 105033 https://doi.org/10.1016/j.yhbeh.2021.105033.
Bauer, C.M., Needham, K.B., Le, C.N., Stewart, E.C., Graham, J.L., Ketterson, E.D., Greives, T.J., 2016. Hypothalamic-pituitary-adrenal axis activity is not elevated in a songbird (*Junco hyemalis*) preparing for migration. Gen. Comp. Endocrinol. 232, 60–66. https://doi.org/10.1016/j.ygcen.2015.12.020.
Beery, A.K., Lin, J., Biddle, J.S., Francis, D.D., Blackburn, E.H., Epel, E.S., 2012. Chronic stress elevates telomerase activity in rats. Biol. Lett. 8, 1063–1066. https://doi.org/10.1098/rsbl.2012.0747.
Beldade, P., Koops, K., Brakefield, P.M., 2002. Developmental constraints versus flexibility in morphological evolution. Nature 416, 844–847.
Bell, G., 2017. Evolutionary rescue. Annu. Rev. Ecol. Evol. Syst. 48, 605–627. https://doi.org/10.1146/annurev-ecolsys-110316-023011.
Bell, A.M., McGhee, K.E., Stein, L.R., 2016. Effects of mothers' and fathers' experience with predation risk on the behavioral development of their offspring in threespined sticklebacks. Curr. Opin. Behav. Sci. 7, 28–32. https://doi.org/10.1016/j.cobeha.2015.10.011.
Belliure, J., Clobert, J., 2004. Behavioral sensitivity to corticosterone in juveniles of the wall lizard, *Podarcis muralis*. Physiol. Behav. 81, 121–127. https://doi.org/10.1016/j.physbeh.2004.01.008.
Belliure, J., Meylan, S., Clobert, J., 2004. Prenatal and postnatal effects of corticosterone on behavior in juveniles of the common lizard, *Lacerta vivipara*. J. Exp. Zool. 301A, 401–410. https://doi.org/10.1002/jez.a.20066.
Belthoff, J.R., Dufty Jr., A.M., 1998. Corticosterone, body condition and locomotor activity: a model for dispersal in screech-owls. Anim. Behav. 55, 405–415. https://doi.org/10.1006/anbe.1997.0625.
Belyaev, D.K., 1983. Stress as a factor of genetic variation and the problem of destabilizing selection. Folia Biol. (Praha) 29, 177–187.
Belyaev, D.K., Borodin, P.M., 1982. The influence of stress on variation and its role in evolution. Biologisches Zentralblatt 100, 705–714.
Benard, M.F., 2004. Predator-induced phenotypic plasticity in organisms with complex life histories. Annu. Rev. Ecol. Evol. Syst. 35, 651–673. https://doi.org/10.1146/annurev.ecolsys.35.021004.112426.
Benavides, R., Carvalho, B., Matesanz, S., Bastias, C.C., Cavers, S., Escudero, A., Fonti, P., Martínez-Sancho, E., Valladares, F., 2021. Phenotypes of *Pinus sylvestris* are more coordinated under local harsher conditions across Europe. J. Ecology 109, 2580–2596.
Bennett, A.F., 1987. Interindividual variability: an under-utilized resource. In: Feder, M. E., Bennett, A.F., Burggren, W.W., Huey, R.B. (Eds.), New Directions in Ecological Physiology. Cambridge University Press, Cambridge, U.K., pp. 147–169
Berg, R.L., 1960. The ecological significance of correlation pleiades. Evolution 14, 171–180.
Berteaux, D., Boutin, S., 2000. Breeding dispersal in female North American red squirrels. Ecology 81, 1311–1326. https://doi.org/10.1890/0012-9658(2000)081[1311:BDIFNA]2.0.CO;2.
Biro, P.A., Stamps, J.A., 2008. Are animal personality traits linked to life-history productivity? Trends Ecol. Evol. 23, 361–368.
Biro, P.A., Stamps, J.A., 2010. Do consistent individual differences in metabolic rate promote consistent individual differences in behavior? Trends Ecol. Evol. 25 (11), 653–659.
Biro, P.A., Garland Jr., T., Beckmann, C., Ujvari, B., Thomas, F., Post, J.R., 2018. Metabolic scope as a proximate constraint on individual behavioral variation: effects on personality, plasticity, and predictability. Am. Nat. 192, 142–154.
Blackburn, E.H., Epel, E.S., Lin, J., 2015. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. Science 350, 1193–1198. https://doi.org/10.1126/science.aab3389.
Blows, M.W., Sokolowski, M.B., 1995. The expression of additive and nonadditive genetic variation under stress. Genetics 140, 1149–1159.
Bódi, Z., Farkas, Z., Nevozhay, D., Kalapis, D., Lázár, V., Csörgő, B., Nyerges, Á., Szamecz, B., Fekete, G., Papp, B., Araújo, H., 2017. Phenotypic heterogeneity promotes adaptive evolution. PLoS Biol. 15 (5), e2000644.
Bókony, V., Lendvai, Á.Z., Liker, A., Angelier, F., Wingfield, J.C., Chastel, O., 2009. Stress response and the value of reproduction: are birds prudent parents? Am. Nat. 173, 589–598. https://doi.org/10.1086/597610.
Bolstad, G.H., Hansen, T.F., Pélabon, C., Falahati-Anbaran, M., Pérez-Barrales, R., Armbruster, W.S., 2014. Genetic constraints predict evolutionary divergence in Dalechampia blossoms. Phil. Trans. Roy. Soc. B 369, 20130255.
Bonamour, S., Chevin, L.-M., Charmantier, A., Teplitsky, C., 2019. Phenotypic plasticity in response to climate change: the importance of cue variation. Philos. Trans. R. Soc. B Biol. Sci. 374, 20180178. https://doi.org/10.1098/rstb.2018.0178.
Bonier, F., Cox, R.M., 2020. Do hormone manipulations reduce fitness? A meta-analytic test of the optimal endocrine phenotype hypothesis. Molec. Cell Endocrinol. 500, 110640.
Boonstra, R., 2004. Coping with changing northern environments: the role of the stress axis in birds and mammals. Integr. Comp. Biol. 44, 95–108.
Boonstra, R., 2005. Equipped for life: the adaptive role of the stress axis in male mammals. J. Mammal. 86, 236–247. https://doi.org/10.1644/BHE-001.1.
Boonstra, R., 2013. Reality as the leading cause of stress: rethinking the impact of chronic stress in nature. Funct. Ecol. 27, 11–23. https://doi.org/10.1111/1365-2435.12008.
Boswell, T., Woods, S.C., Kenagy, G.J., 1994. Seasonal changes in body mass, insulin, and glucocorticoids of free-living Golden-Mantled Ground Squirrels. Gen. Comp. Endocrinol. 96, 339–346. https://doi.org/10.1006/gcen.1994.1189.
Botero, C.A., Weissing, F.J., Wright, J., Rubenstein, D.R., 2015. Evolutionary tipping points in the capacity to adapt to environmental change. Proc. Natl. Acad. Sci. 112, 184–189. https://doi.org/10.1073/pnas.1408589111.
Bradshaw, A.D., 1972. Some of the evolutionary consequences of being a plant. Evol. Biol. 5, 25–47.
Breuner, C.W., Greenberg, A.L., Wingfield, J.C., 1998. Noninvasive corticosterone treatment rapidly increases activity in Gambel's White-Crowned Sparrows (*Zonotrichia leucophrys gambelii*). Gen. Comp. Endocrinol. 111, 386–394. https://doi.org/10.1006/gcen.1998.7128.
Brookfield, J.F.Y., 2001. Evolution: the evolvability enigma. Curr. Biol. 11, PR106–PR108. https://doi.org/10.1016/S0960-9822(01)00041-0.
Brookfield, J.F.Y., 2009. Evolution and evolvability: celebrating Darwin 200. Biol. Lett. 5, 44–46. https://doi.org/10.1098/rsbl.2008.0639.
Brown, R.L., 2014. What evolvability really is. Brit. J. Phil. Sci. 65, 549–572.
Buehler, D.M., Vézina, F., Goymann, W., Schwabl, I., Versteegh, M., Tieleman, B.I., Piersma, T., 2012. Independence among physiological traits suggests flexibility in the face of ecological demands on phenotypes. J. Evol. Biol. 25, 1600–1613.
Burton, T., Metcalfe, N.B., 2014. Can environmental conditions experienced in early life influence future generations? Proc. R. Soc. B Biol. Sci. 281, 20140311. https://doi.org/10.1098/rspb.2014.0311.
Buttemer, WilliamA, Astheimer, LeeB, Wingfield, JohnC, 1991. The effect of corticosterone on standard metabolic rates of small passerine birds. J. Comp. Physiol. B. 161 https://doi.org/10.1007/BF00260804.
Caizergues, A.E., Grégoire, A., Choquet, R., Perret, S., Charmantier, A., 2022. Are Behaviour and Stress-Related Phenotypes in Urban Birds Adaptive? J. Anim, Ecol (In press).
Calsbeek, R., Kuchta, S., 2011. Predator mediated selection and the impact of developmental stage on viability in wood frog tadpoles (*Rana sylvatica*). BMC Evol. Biol. 11, 353. https://doi.org/10.1186/1471-2148-11-353.
Cao-Lei, L., De Rooij, S.R., King, S., Matthews, S.G., Metz, G.A.S., Roseboom, T.J., Szyf, M., 2020. Prenatal stress and epigenetics. Neurosci. Biobehav. Rev. 117, 198–210. https://doi.org/10.1016/j.neubiorev.2017.05.016.
Careau, V., Garland Jr., T., 2012. Performance, personality, and energetics: correlation, causation, and mechanism. Phys. Biochem. Zool. 85, 543–571.
Careau, V., Thomas, D., Humphries, M.M., Réale, D., 2008. Energy metabolism and animal personality. Oikos 117, 641–653.
Careau, V., Buttemer, W.A., Buchanan, K.L., 2014. Developmental stress can uncouple relationships between physiology and behaviour. Biol. Lett. 10, 20140834.
Carere, C., Groothuis, T.G.G., Möstl, E., Daan, S., Koolhaas, J.M., 2003. Fecal corticosteroids in a territorial bird selected for different personalities: daily rhythm and the response to social stress. Horm. Behav. 43, 540–548. https://doi.org/10.1016/S0018-506X(03)00065-5.
Carere, C., Caramaschi, D., Fawcett, T.W., 2010. Covariation between personalities and individual differences in coping with stress: converging evidence and hypotheses. Curr. Zool. 56, 728–740.

Carruth, L.L., Dores, R.M., Maldonado, T.A., Norris, D.O., Ruth, T., Jones, R.E., 2000. Elevation of plasma cortisol during the spawning migration of landlocked kokanee salmon (*Oncorhynchus nerka kennerlyi*). Comp. Biochem. Physiol. C Pharmacol. Toxicol. Endocrinol. 127, 123–131. https://doi.org/10.1016/S0742-8413(00)00140-7.

Casagrande, S., Hau, M., 2019. Telomere attrition: metabolic regulation and signalling function? Biol. Lett. 15, 20180885.

Cease, A.J., Lutterschmidt, D.I., Mason, R.T., 2007. Corticosterone and the transition from courtship behavior to dispersal in male red-sided garter snakes (*Thamnophis sirtalis parietalis*). Gen. Comp. Endocrinol. 150, 124–131. https://doi.org/10.1016/j.ygcen.2006.07.022.

Champagne, F., 2013. Early environments, glucocorticoid receptors, and behavioral epigenetics. Behav. Neurosci. 127, 628–636. https://doi.org/10.1037/a0034186.

Chapin, F.S., 1991. Integrated responses of plants to stress. BioScience 41, 29–36. https://doi.org/10.2307/1311538.

Charmandari, E., Tsigos, C., Chrousos, G., 2005. Endocrinology of the stress response. Annu. Rev. Physiol. 67, 259–284. https://doi.org/10.1146/annurev.physiol.67.040403.120816.

Charmantier, A., Garant, D., 2005. Environmental quality and evolutionary potential: lessons from wild populations. Proc. Roy. Soc. B 272, 1415–1425.

Chen, S.H., Epel, E.S., Mellon, S.H., Lin, J., Reus, V.I., Rosser, R., Kupferman, E., Burke, H., Mahan, L., Blackburn, E.H., Wolkowitz, O.M., 2014. Adverse childhood experiences and leukocyte telomere maintenance in depressed and healthy adults. J. Affect. Disord. 169, 86–90. https://doi.org/10.1016/j.jad.2014.07.035.

Chenoweth, S.F., Rundle, H.D., Blows, M.W., 2010. The contribution of selection and genetic constraints to phenotypic divergence. Am. Nat. 175, 186–196.

Cheverud, J.M., 1984. Quantitative genetics and developmental constraints on evolution by selection. J. Theor. Biol. 110, 155–171.

Cheverud, J.M., 1996. Developmental integration and the evolution of pleiotropy. Am. Zool. 36, 44–50.

Chevin, L.-M., Lande, R., 2011. Adaptation to marginal habitats by evolution of increased phenotypic plasticity: evolving plasticity in marginal populations. J. Evol. Biol. 24, 1462–1476. https://doi.org/10.1111/j.1420-9101.2011.02279.x.

Chevin, L.-M., Lande, R., Mace, G.M., 2010. Adaptation, plasticity, and extinction in a changing environment: towards a predictive theory. PLoS Biol. 8, e1000357 https://doi.org/10.1371/journal.pbio.1000357.

Chin, E.H., Love, O.P., Verspoor, J.J., Williams, T.D., Rowley, K., Burness, G., 2009. Juveniles exposed to embryonic corticosterone have enhanced flight performance. Proc. R. Soc. B Biol. Sci. 276, 499–505. https://doi.org/10.1098/rspb.2008.1294.

Choi, J., Fauce, S.R., Effros, R.B., 2008. Reduced telomerase activity in human T lymphocytes exposed to cortisol. Brain Behav. Immun. 22, 600–605. https://doi.org/10.1016/j.bbi.2007.12.004.

Clausen, J., Hiesey, W.M., 1958. Experimental Studies on the Nature of Species. IV. "Genetic Structure of Ecological Races". Experimental Studies on the Nature of Species. IV. Genetic Structure of Ecological Races.

Clinchy, M., Sheriff, M.J., Zanette, L.Y., 2013. Predator-induced stress and the ecology of fear. Funct. Ecol. 27, 56–65. https://doi.org/10.1111/1365-2435.12007.

Cockrem, J.F., 2007. Stress, corticosterone responses and avian personalities. J. Ornithol. 148, 169–178.

Cohen, D., 1966. Optimizing reproduction in a randomly varying environment. J. Theor. Biol. 12, 119–129. https://doi.org/10.1016/0022-5193(66)90188-3.

Cohen, S., Janicki-Deverts, D., Miller, G.E., 2007. Psychological stress and disease. JAMA 298, 1685. https://doi.org/10.1001/jama.298.14.1685.

Cohen, A.A., Martin, L.B., Wingfield, J.C., McWilliams, S.R., Dunne, J.A., 2012. Physiological regulatory networks: ecological roles and evolutionary constraints. Trends Ecol. Evol. 27, 428–435. https://doi.org/10.1016/j.tree.2012.04.008.

Conner, J.K., 2002. Genetic mechanisms of floral trait correlations in a natural population. Nature 420, 407–410.

Conner, J.K., 2003. Artificial selection: a powerful tool for ecologists. Ecology 84, 1650–1660.

Conner, J.K., Cooper, I.A., La Rosa, R.J., Pérez, S.G., Royer, A.M., 2014. Patterns of phenotypic correlations among morphological traits across plants and animals. Phil. Trans. R. Soc. A 369, 20130246.

Cooper, W.S., Kaplan, R.H., 1982. Adaptive "coin-flipping": a decision-theoretic examination of natural selection for random individual variation. J. Theor. Biol. 94, 135–151. https://doi.org/10.1016/0022-5193(82)90336-8.

Coslovsky, M., Richner, H., 2011. Predation risk affects offspring growth via maternal effects: maternal effects due to predation risk. Funct. Ecol. 25, 878–888. https://doi.org/10.1111/j.1365-2435.2011.01834.x.

Costantini, D., Marasco, V., Møller, A.P., 2011. A meta-analysis of glucocorticoids as modulators of oxidative stress in vertebrates. J. Comp. Physiol. B. 181, 447–456.

Cote, J., Clobert, J., Brodin, T., Fogarty, S., Sih, A., 2010. Personality-dependent dispersal: characterization, ontogeny and consequences for spatially structured populations. Philos. Trans. R. Soc. B Biol. Sci. 365, 4065–4076. https://doi.org/10.1098/rstb.2010.0176.

Cox, R.M., 2020. Sex steroids as mediators of phenotypic integration, genetic correlations, and evolutionary transitions. Molec. Cell Endocrinol. 502, 110668.

Cox, R.M., McGlothlin, J.W., Bonier, F., 2016. Hormones as mediators of phenotypic and genetic integration: an evolutionary genetics approach. Integ. Comp. Biol. 56, 126–137.

Cox, R.M., Cox, C.L., McGlothlin, J.W., Card, D.C., Andrew, A.L., Castoe, T.A., 2017. Hormonally mediated increases in sex-biased gene expression accompany the breakdown of between-sex genetic correlations in a sexually dimorphic lizard. Am. Nat. 189, 315–332.

Cox, R.M., Hale, M.D., Wittman, T.N., Robinson, C.D., Cox, C.L., 2022. Evolution of hormone-phenotype couplings and hormone-genome interactions. Horm. Behav. 144, 105216.

Crean, A.J., Marshall, D.J., 2009. Coping with environmental uncertainty: dynamic bet hedging as a maternal effect. Philos. Trans. R. Soc. B Biol. Sci. 364, 1087–1096. https://doi.org/10.1098/rstb.2008.0237.

Creel, S., 2022. A retrospective view of early research on dominance, stress and reproduction in cooperatively breeding carnivores. Horm. Behav. 140, 105119 https://doi.org/10.1016/j.yhbeh.2022.105119.

Crespi, E.J., Denver, R.J., 2005. Ancient origins of human developmental plasticity. Am. J. Hum. Biol. 17, 44–54. https://doi.org/10.1002/ajhb.20098.

Criscuolo, F., Smith, S., Zahn, S., Heidinger, B.J., Haussmann, M.F., 2018. Experimental manipulation of telomere length: does it reveal a corner-stone role for telomerase in the natural variability of individual fitness? Philos. Trans. R. Soc. B Biol. Sci. 373, 20160440. https://doi.org/10.1098/rstb.2016.0440.

Crispo, E., 2007. The Baldwin effect and genetic assimilation: revisiting two mechanisms of evolutionary change mediated by phenotypic plasticity. Evolution 61, 2469–2479.

Crump, M.L., 1981. Variation in propagule size as a function of environmental uncertainty for tree frogs. Am. Nat. 117 (5), 724–737.

Csete, M., Doyle, J., 2004. Bow ties, metabolism and disease. Trends Biotechnol. 22, 446–450. https://doi.org/10.1016/j.tibtech.2004.07.007.

Dallman, M.F., 2010. Stress-induced obesity and the emotional nervous system. Trends Endocrinol. Metab. 21, 159–165. https://doi.org/10.1016/j.tem.2009.10.004.

Dallman, M.F., Strack, A.M., Akana, S.F., Bradbury, M.J., Hanson, E.S., Scribner, K.A., Smith, M., 1993. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. Front. Neuroendocrinol. 14, 303–347. https://doi.org/10.1006/frne.1993.1010.

Damián, X., Ochoa-López, S., Gaxiola, A., Fornoni, J., Domínguez, C.A., Boege, K., 2020. Natural selection acting on integrated phenotypes: covariance among functional leaf traits increases plant fitness. New Phytol. 225, 546–557.

Dammhahn, M., Dingemanse, N.J., Niemelä, P.T., Réale, D., 2018. Pace-of-life syndromes: a framework for the adaptive integration of behaviour, physiology and life history. Behav. Ecol. Sociobiol. 72, 1–8.

Dantzer, B., Newman, A.E.M., 2022. Expanding the frame around social dynamics and glucocorticoids: from hierarchies within the nest to competitive interactions among species. Horm. Behav. 144, 105204 https://doi.org/10.1016/j.yhbeh.2022.105204.

Dantzer, B., Swanson, E.M., 2012. Mediation of vertebrate life histories via insulin-like growth factor-1. Biol. Rev. 87, 414–429. https://doi.org/10.1111/j.1469-185X.2011.00204.x.

Dantzer, B., Swanson, E.M., 2017. Does hormonal pleiotropy shape the evolution of performance and life history traits? Integr. Comp. Biol. 57, 372–384. https://doi.org/10.1093/icb/icx064.

Dantzer, B., McAdam, A.G., Palme, R., Fletcher, Q.E., Boutin, S., Humphries, M.M., Boonstra, R., 2010. Fecal cortisol metabolite levels in free-ranging North American red squirrels: assay validation and the effects of reproductive condition. Gen. Comp. Endocrinol. 167, 279–286. https://doi.org/10.1016/j.ygcen.2010.03.024.

Dantzer, B., Newman, A.E.M., Boonstra, R., Palme, R., Boutin, S., Humphries, M.M., McAdam, A.G., 2013. Density triggers maternal hormones that increase adaptive offspring growth in a wild mammal. Science 340, 1215–1217. https://doi.org/10.1126/science.1235765.

Dantzer, B., Fletcher, Q.E., Boonstra, R., Sheriff, M.J., 2014. Measures of physiological stress: a transparent or opaque window into the status, management and conservation of species? Conserv. Physiol. 2, cou023. https://doi.org/10.1093/conphys/cou023.

Dantzer, B., Westrick, S.E., van Kesteren, F., 2016. Relationships between endocrine traits and life histories in wild animals: insights, problems, and potential pitfalls. Integr. Comp. Biol. 56, 185–197. https://doi.org/10.1093/icb/icw051.

Dantzer, B., Goncalves, I.B., Spence-Jones, H.C., Bennett, N.C., Heistermann, M., Ganswindt, A., Dubuc, C., Gaynor, D., Manser, M.B., Clutton-Brock, T.H., 2017. The influence of stress hormones and aggression on cooperative behaviour in subordinate meerkats. Proc. R. Soc. B Biol. Sci. 284, 20171248. https://doi.org/10.1098/rspb.2017.1248.

Dantzer, B., Dubuc, C., Goncalves, I.B., Cram, D.L., Bennett, N.C., Ganswindt, A., Heistermann, M., Duncan, C., Gaynor, D., Clutton-Brock, T.H., 2019. The development of individual differences in cooperative behaviour: maternal glucocorticoid hormones alter helping behaviour of offspring in wild meerkats. Philos. Trans. R. Soc. B Biol. Sci. 374, 20180117. https://doi.org/10.1098/rstb.2018.0117.

Dantzer, B., McAdam, A.G., Humphries, M.M., Lane, J.E., Boutin, S., 2020a. Decoupling the effects of food and density on life-history plasticity of wild animals using field experiments: insights from the steward who sits in the shadow of its tail, the North American red squirrel. J. Anim. Ecol. 89, 2397–2414. https://doi.org/10.1111/1365-2656.13341.

Dantzer, B., van Kesteren, F., Westrick, S.E., Boutin, S., McAdam, A.G., Lane, J.E., Gillespie, R., Majer, A., Haussmann, M.F., Monaghan, P., 2020b. Maternal glucocorticoids promote offspring growth without inducing oxidative stress or shortening telomeres in wild red squirrels. J. Exp. Biol. 223, jeb212373. https://doi.org/10.1242/jeb.212373.

Darwin, C., 1859. On the Origin of Species, 1st ed. John Murray, London.

Darwin, C., 1872. On the Origin of Species, 6th ed. John Murray, London.

de Fraipont, M., Clobert, J., John, H., Alder, Meylan, S., 2000. Increased pre-natal maternal corticosterone promotes philopatry of offspring in common lizards *Lacerta vivipara*. J. Anim. Ecol. 69, 404–413. https://doi.org/10.1046/j.1365-2656.2000.00405.x.

De Kloet, E.R., 2022. Brain mineralocorticoid and glucocorticoid receptor balance in neuroendocrine regulation and stress-related psychiatric etiopathologies. Curr. Opin.

Endocrinol. Metabol. Res. 24, 100352 https://doi.org/10.1016/j.coemr.2022.100352.
De Kloet, E.R., Vreugdenhil, E., Oitzl, M.S., Joëls, M., 1998. Brain corticosteroid receptor balance in health and disease. Endocr. Rev. 19, 269–301. https://doi.org/10.1210/edrv.19.3.0331.
De Kloet, E.R., Joëls, M., Holsboer, F., 2005. Stress and the brain: from adaptation to disease. Nat. Rev. Neurosci. 6, 463–475. https://doi.org/10.1038/nrn1683.
de Punder, K., Heim, C., Przesdzing, I., Wadhwa, P.D., Entringer, S., 2018. Characterization in humans of *in vitro* leucocyte maximal telomerase activity capacity and association with stress. Philos. Trans. R. Soc. B Biol. Sci. 373, 20160441. https://doi.org/10.1098/rstb.2016.0441.
Del Giudice, M., 2015. Plasticity as a developing trait: exploring the implications. Front. Zool. 12, S4. https://doi.org/10.1186/1742-9994-12-S1-S4.
Deng, W., Cheung, S.T., Tsao, S.W., Wang, X.M., Tiwari, A.F.Y., 2016. Telomerase activity and its association with psychological stress, mental disorders, lifestyle factors and interventions: a systematic review. Psychoneuroendocrinology 64, 150–163. https://doi.org/10.1016/j.psyneuen.2015.11.017.
Denver, R.J., 1997. Environmental stress as a developmental cue: corticotropin-releasing hormone is a proximate mediator of adaptive phenotypic plasticity in amphibian metamorphosis. Horm. Behav. 31 (2), 169–179.
Denver, R.J., 2009. Stress hormones mediate environment-genotype interactions during amphibian development. Gen. Comp. Endocrinol. 164, 20–31. https://doi.org/10.1016/j.ygcen.2009.04.016.
Denver, R.J., 2013. Neuroendocrinology of amphibian metamorphosis. In: Current Topics in Developmental Biology. Elsevier, pp. 195–227. https://doi.org/10.1016/B978-0-12-385979-2.00007-1.
Dhabhar, F.S., McEwen, B.S., 1999. Enhancing versus suppressive effects of stress hormones on skin immune function. Proc. Natl. Acad. Sci. 96, 1059–1064. https://doi.org/10.1073/pnas.96.3.1059.
Dhabhar, F.S., Miller, A.H., McEwen, B.S., Spencer, R.L., 1996. Stress-induced changes in blood leukocyte distribution. Role of adrenal steroid hormones. J. Immunol. Baltim. Md 1950 (157), 1638–1644.
Dias, B.G., Ressler, K.J., 2014. Parental olfactory experience influences behavior and neural structure in subsequent generations. Nat. Neurosci. 17, 86–96. https://doi.org/10.1038/nn.3594.
Dickens, M.J., Romero, L.M., 2013. A consensus endocrine profile for chronically stressed wild animals does not exist. Gen. Comp. Endocrinol. 191, 177–189. https://doi.org/10.1016/j.ygcen.2013.06.014.
Dickmeis, T., 2009. Glucocorticoids and the circadian clock. J. Endocrinol. 200, 3–22. https://doi.org/10.1677/JOE-08-0415.
Dickmeis, T., Weger, B.D., Weger, M., 2013. The circadian clock and glucocorticoids – interactions across many time scales. Mol. Cell. Endocrinol. 380, 2–15. https://doi.org/10.1016/j.mce.2013.05.012.
Donelan, S.C., Trussell, G.C., 2018. Parental and embryonic experiences with predation risk affect prey offspring behaviour and performance. Proc. R. Soc. B Biol. Sci. 285, 20180034. https://doi.org/10.1098/rspb.2018.0034.
Donelan, S.C., Hellmann, J.K., Bell, A.M., Luttbeg, B., Orrock, J.L., Sheriff, M.J., Sih, A., 2020. Transgenerational plasticity in human-altered environments. Trends Ecol. Evol. 35, 115–124. https://doi.org/10.1016/j.tree.2019.09.003.
Donelson, J.M., Sunday, J.M., Figueira, W.F., Gaitán-Espitia, J.D., Hobday, A.J., Johnson, C.R., Leis, J.M., Ling, S.D., Marshall, D., Pandolfi, J.M., Pecl, G., Rodgers, G.G., Booth, D.J., Munday, P.L., 2019. Understanding interactions between plasticity, adaptation and range shifts in response to marine environmental change. Philos. Trans. R. Soc. B Biol. Sci. 374, 20180186. https://doi.org/10.1098/rstb.2018.0186.
Donohue, K., Schmitt, J., 1999. The genetic architecture of plasticity to density in *Impatiens capensis*. Evolution 53, 1377–1386.
Doroszuk, A., Wojewodzic, M.W., Gort, G., Kammenga, J.E., 2008. Rapid divergence of genetic variance-covariance matrix within a natural population. Am. Nat. 171, 291–304.
Eberhard, W.G., 1985. Sexual Selection and Evolution of Animal Genitalia. Harvard University Press, Cambridge, MA, USA.
Eberhard, W.G., Huber, B.A., S., R.L.R., Briceño, R.D., Salas, I., Rodriguez, V., 1998. One size fits all? Relationships between the size and degree of variation in genitalia and other body parts in twenty species of insects and spiders. Evolution 52, 415–431. https://doi.org/10.1111/j.1558-5646.1998.tb01642.x.
Eggers, S., Griesser, M., Nystrand, M., Ekman, J., 2006. Predation risk induces changes in nest-site selection and clutch size in the Siberian jay. Proc. Biol. Sci. 273, 701–706. https://doi.org/10.1098/rspb.2005.3373.
Eikenaar, C., Klinner, T., Szostek, K.L., Bairlein, F., 2014. Migratory restlessness in captive individuals predicts actual departure in the wild. Biol. Lett. 10, 20140154. https://doi.org/10.1098/rsbl.2014.0154.
Ellers, J., Liefting, M., 2015. Extending the integrated phenotype: covariance and correlation in plasticity of behavioural traits. Curr. Opin. Insect Sci. 9, 31–35.
Emlen, D.J., 1997. Alternative reproductive tactics and male-dimorphism in the horned beetle *Onthophagus acuminatus* (*Coleoptera*: *Scarabaeidae*). Behav. Ecol. Sociobiol. 41, 335–341. https://doi.org/10.1007/s002650050393.
Endler, J.A., 1995. Multiple-trait coevolution and environmental gradients in guppies. Trends Ecol. Evol. 10, 22–29. https://doi.org/10.1016/S0169-5347(00)88956-9.
Engqvist, L., Reinhold, K., 2016. Adaptive trans-generational phenotypic plasticity and the lack of an experimental control in reciprocal match/mismatch experiments. Methods Ecol. Evol. 7, 1482–1488. https://doi.org/10.1111/2041-210X.12618.
Ensminger, D.C., Langkilde, T., Owen, D.A.S., MacLeod, K.J., Sheriff, M.J., 2018. Maternal stress alters the phenotype of the mother, her eggs and her offspring in a wild-caught lizard. J. Anim. Ecol. 87, 1685–1697. https://doi.org/10.1111/1365-2656.12891.
Epel, E.S., 2009. Telomeres in a life-span perspective: a new "psychobiomarker"? Curr. Dir. Psychol. Sci. 18, 6–10. https://doi.org/10.1111/j.1467-8721.2009.01596.x.
Epel, E., Lin, J., Wilhelm, F., Wolkowitz, O., Cawthon, R., Adler, N., Dolbier, C., Mendes, W., Blackburn, E., 2006. Cell aging in relation to stress arousal and cardiovascular disease risk factors. Psychoneuroendocrinology 31, 277–287. https://doi.org/10.1016/j.psyneuen.2005.08.011.
Epel, E.S., Lin, J., Dhabhar, F.S., Wolkowitz, O.M., Puterman, E., Karan, L., Blackburn, E. H., 2010. Dynamics of telomerase activity in response to acute psychological stress. Brain Behav. Immun. 24, 531–539. https://doi.org/10.1016/j.bbi.2009.11.018.
Eroukhmanoff, F., 2009. Just how much is the G-matrix actually constraining adaptation? Evol. Biol. 36, 323–326.
Eroukhmanoff, F., Svensson, E.I., 2011. Evolution and stability of the G-matrix during the colonization of a novel environment. J. Evol. Biol. 24, 1363–1373.
Eyck, H.J., Buchanan, K.L., Crino, O.L., Jessop, T.S., 2019. Effects of developmental stress on animal phenotype and performance: a quantitative review. Biol. Rev. 94, 1143–1160.
Finch, C.E., Rose, M.R., 1995. Hormones and the physiological architecture of life history evolution. Q. Rev. Biol. 70, 1–52.
Firmat, C., Lozano-Fernández, I., Agusti, J., Bolstad, G.H., Cuenca-Bescós, G., Hansen, T. F., Pélabon, C., 2014. Walk the line: 600000 years of molar evolution constrained by allometry in the fossil rodent *Mimomys savini*. Phil. Trans. Roy. Soc. B 369, 20140057.
Fischer, E.K., Ghalambor, C.K., Hoke, K.L., 2016. Plasticity and evolution in correlated suites of traits. J. Evol. Biol. 29, 991–1002. https://doi.org/10.1111/jeb.12839.
Fisher, R.A., 1930. The Genetical Theory of Natural Selection. Oxford University Press, Oxford, U. K.
Flatt, T., 2005. The evolutionary genetics of canalization. Q. Rev. Biol. 80, 287–316. https://doi.org/10.1086/432265.
Fletcher, Q.E., Dantzer, B., Boonstra, R., 2015. The impact of reproduction on the stress axis of free-living male northern red backed voles (*Myodes rutilus*). Gen. Comp. Endocrinol. 224, 136–147. https://doi.org/10.1016/j.ygcen.2015.07.004.
Fontaine, J.J., Martin, T.E., 2006. Parent birds assess nest predation risk and adjust their reproductive strategies. Ecol. Lett. 9, 428–434. https://doi.org/10.1111/j.1461-0248.2006.00892.x.
Fowler, K., Whitlock, M.C., 2002. Environmental stress, inbreeding, and the nature of phenotypic and genetic variance in Drosophila melanogaster. Proc. R. Soc. Lond. Ser. B Biol. Sci. 269 (1492), 677–683.
Fox, R.J., Donelson, J.M., Schunter, C., Ravasi, T., Gaitán-Espitia, J.D., 2019. Beyond buying time: the role of plasticity in phenotypic adaptation to rapid environmental change. Philos. Trans. R. Soc. B Biol. Sci. 374, 20180174. https://doi.org/10.1098/rstb.2018.0174.
Fraker, M.E., Hu, F., Cuddapah, V., McCollum, S.A., Relyea, R.A., Hempel, J., Denver, R. J., 2009. Characterization of an alarm pheromone secreted by amphibian tadpoles that induces behavioral inhibition and suppression of the neuroendocrine stress axis. Horm. Behav. 55, 520–529. https://doi.org/10.1016/j.yhbeh.2009.01.007.
Frankino, W.A., Zwaan, B.J., Stern, D.L., Brakefield, P.M., 2005. Natural selection and developmental constraints in the evolution of allometries. Science 307, 718–720.
Gaidica, M., Dantzer, B., 2020. Quantifying the autonomic response to stressors—one way to expand the definition of "stress" in animals. Integr. Comp. Biol. 60, 113–125. https://doi.org/10.1093/icb/icaa009.
Gavrilets, S., Scheiner, S.M., 1993. The genetics of phenotypic plasticity. V. Evolution of reaction norm shape. J. Evol. Biol. 6, 31–48.
Gebhardt, M.D., Stearns, S.C., 1988. Reaction norms for developmental time and weight at eclosion in *Drosophila mercatorum*. J. Evol. Biol. 1, 335–354.
Ghalambor, C.K., McKay, J.K., Carroll, S.P., Reznick, D.N., 2007. Adaptive versus non-adaptive phenotypic plasticity and the potential for contemporary adaptation in new environments. Funct. Ecol. 21, 394–407. https://doi.org/10.1111/j.1365-2435.2007.01283.x.
Gianoli, E., 2004. Plasticity of traits and correlations in two populations of *Convolvulus arvensis* (Convolvulaceae) differing in environmental heterogeneity. Int. J. Plant Sci. 165, 825–832.
Gianoli, E., Palacio-López, K., 2009. Phenotypic integration may constrain phenotypic plasticity in plants. Oikos 118, 1924–1928.
Gibson, G., Dworkin, I., 2004. Uncovering cryptic genetic variation. Nat. Rev. Genet. 5, 681–690.
Giesing, E.R., Suski, C.D., Warner, R.E., Bell, A.M., 2011. Female sticklebacks transfer information via eggs: effects of maternal experience with predators on offspring. Proc. R. Soc. B Biol. Sci. 278, 1753–1759. https://doi.org/10.1098/rspb.2010.1819.
Girvan, M., Newman, M.E., 2002. Community structure in social and biological networks. Proc. Natl. Acad. Sci. 99 (12), 7821–7826.
Glaser, R., Kiecolt-Glaser, J.K., 2005. Stress-induced immune dysfunction: implications for health. Nat. Rev. Immunol. 5, 243–251. https://doi.org/10.1038/nri1571.
Gonzalez, A., Ronce, O., Ferriere, R., Hochberg, M.E., 2013. Evolutionary rescue: an emerging focus at the intersection between ecology and evolution. Philos. Trans. R. Soc. B Biol. Sci. 368, 20120404. https://doi.org/10.1098/rstb.2012.0404.
Goswami, A., Smaers, J.B., Soligo, C., Polly, P.D., 2014. The macroevolutionary consequences of phenotypic integration: from development to deep time. Philos. Trans. R. Soc. B Biol. Sci. 369, 20130254.
Groothuis, T.G., Carere, C., 2005. Avian personalities: characterization and epigenesis. Neurosci. Biobehav. Rev. 29, 137–150.
Guenther, A., Groothuis, A.G.G., Krüger, O., Goerlich-Jansson, V.C., 2018. Cortisol during adolescence organises personality traits and behavioural syndromes. Horm. Behav. 103, 129–139.
Guindre-Parker, S., Mcadam, A.G., van Kesteren, F., Palme, R., Boonstra, R., Boutin, S., Lane, J.E., Dantzer, B., 2019. Individual variation in phenotypic plasticity of the stress axis. Biol. Lett. 15, 20190260. https://doi.org/10.1098/rsbl.2019.0260.

Hairston, N.G., Ellner, S.P., Geber, M.A., Yoshida, T., Fox, J.A., 2005. Rapid evolution and the convergence of ecological and evolutionary time: rapid evolution and the convergence of ecological and evolutionary time. Ecol. Lett. 8, 1114–1127. https://doi.org/10.1111/j.1461-0248.2005.00812.x.
Hämäläinen, A.M., Guenther, A., Patrick, S.C., Schuett, W., 2021. Environmental effects on the covariation among pace-of-life traits. Ethology 127, 32–44.
Hamann, M., Jessop, T.S., Schäuble, C.S., 2007. Fuel use and corticosterone dynamics in hatchling green sea turtles (*Chelonia mydas*) during natal dispersal. J. Exp. Mar. Biol. Ecol. 353, 13–21.
Hansen, T.F., Pélabon, C., 2021. Evolvability: a quantitative-genetics perspective. Ann. Rev. Ecol. Evol. Syst. 52, 153–175.
Hansen, T.F., Houle, D., Pavlicev, M., Pélabon, C., 2022. Evolvability: A Unifying Concept in Evolutionary Biology? MIT Press.
Harris, A., Seckl, J., 2011. Glucocorticoids, prenatal stress and the programming of disease. Horm. Behav. 59, 279–289.
Hau, M., 2007. Regulation of male traits by testosterone: implications for the evolution of vertebrate life histories. BioEssays 29, 133–144.
Hau, M., Ricklefs, R.E., Wikelski, M., Lee, K.A., Brawn, J.D., 2010. Corticosterone, testosterone and life-history strategies of birds. Proc. R. Soc. B Biol. Sci. 277, 3203–3212. https://doi.org/10.1098/rspb.2010.0673.
Hau, M., Haussmann, M.F., Greives, T.J., Matlack, C., Costantini, D., Quetting, M., Adelman, J.S., Miranda, A.C., Partecke, J., 2015. Repeated stressors in adulthood increase the rate of biological ageing. Front. Zool. 12, 1–10.
Hau, M., Casagrande, S., Ouyang, J.Q., Baugh, A.T., 2016. Glucocorticoid-mediated phenotypes in vertebrates. In: Advances in the Study of Behavior. Elsevier, pp. 41–115. https://doi.org/10.1016/bs.asb.2016.01.002.
Haussmann, M.F., Heidinger, B.J., 2015. Telomere dynamics may link stress exposure and ageing across generations. Biol. Lett. 11, 20150396. https://doi.org/10.1098/rsbl.2015.0396.
Heath, J., 1997. Corticosterone levels during nest departure of juvenile American kestrels. Condor 99, 806–811.
Herman, J.P., McKlveen, J.M., Solomon, M.B., Carvalho-Netto, E., Myers, B., 2012. Neural regulation of the stress response: glucocorticoid feedback mechanisms. Braz. J. Med. Biol. Res. 45, 292–298. https://doi.org/10.1590/S0100-879X2012007500041.
Herman, J.P., McKlveen, J.M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., Myers, B., 2016. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr. Physiol. 6, 603–621. https://doi.org/10.1002/cphy.c150015.
Hiebert, S.M., Salvante, K.G., Ramenofsky, M., Wingfield, J.C., 2000. Corticosterone and nocturnal torpor in the rufous hummingbird (*Selasphorus rufus*). Gen. Comp. Endocrinol. 120, 220–234.
Hinde, R.A., 1970. Animal Behaviour: A Synthesis of Ethology and Comparative Psychology. McGraw-Hill.
Hoffmann, A.A., Merilä, J., 1999. Heritable variation and evolution under favourable and unfavourable conditions. Trends Ecol. Evol. 14, 96–101.
Hoffmann, A.A., Parsons, P.A., 1991. Evolutionary Genetics and Environmental Stress. Oxford University Press, Oxford, U. K.
Hoffmann, A.A., Woods, R., 2003. Associating environmental stress with developmental stability: Problems and patterns. In: Polak, M. (Ed.), Developmental Instability: Causes and Consequences. Oxford University Press, Oxford, U.K., pp. 387–401
Holloway, G.J., Povey, S.R., Sibly, R.M., 1990. The effect of new environment on adapted genetic architecture. Heredity 64, 323–330.
Houle, D., 1992. Comparing evolvability and variability of quantitative traits. Genetics 130, 195–204. https://doi.org/10.1093/genetics/130.1.195.
House, C.M., Simmons, L.W., 2003. Genital morphology and fertilization success in the dung beetle Onthophagus taurus: an example of sexually selected male genitalia. Proc. R. Soc. Lond. Ser. B Biol. Sci. 270 (1514), 447–455.
Hua, F., Sieving, K.E., Fletcher, R.J., Wright, C.A., 2014. Increased perception of predation risk to adults and offspring alters avian reproductive strategy and performance. Behav. Ecol. 25, 509–519. https://doi.org/10.1093/beheco/aru017.
Huey, R.B., 2002. Plants versus animals: do they deal with stress in different ways? Integr. Comp. Biol. 42, 415–423. https://doi.org/10.1093/icb/42.3.415.
Huey, R.B., Hertz, P.E., Sinervo, B., 2003. Behavioral drive versus behavioral inertia in evolution: a null model approach. Am. Nat. 161 (3), 357–366.
Iglesias-Carrasco, M., Aich, U., Jennions, M.D., Head, M.L., 2020. Stress in the city: meta-analysis indicates no overall evidence for stress in urban vertebrates. Proc. Roy. Soc. B Biol. Sci. 287, 20201754.
Injaian, A.S., Francis, C.D., Ouyang, J.Q., Dominoni, D.M., Donald, J.W., Fuxjager, M.J., Goymann, W., Hau, M., Husak, J.F., Johnson, M.A., Kircher, B.K., 2020. Baseline and stress-induced corticosterone levels across birds and reptiles do not reflect urbanization levels. Conserv. Physiol. 8, coz110.
Jaikumar, G., Slabbekoorn, H., Sireeni, J., Schaaf, M., Tudorache, C., 2020. The role of the glucocorticoid receptor in the regulation of diel rhythmicity. Physiol. Behav. 223, 112991.
Jarosz, D.F., Lindquist, S., 2010. Hsp90 and environmental stress transform the adaptive value of natural genetic variation. Science 330, 1820–1824.
Jiang, Y., Da, W., Qiao, S., Zhang, Q., Li, X., Ivey, G., Zilioli, S., 2019. Basal cortisol, cortisol reactivity, and telomere length: a systematic review and meta-analysis. Psychoneuroendocrinology 103, 163–172.
Kelly, M., 2019. Adaptation to climate change through genetic accommodation and assimilation of plastic phenotypes. Philos. Trans. R. Soc. B Biol. Sci. 374, 20180176. https://doi.org/10.1098/rstb.2018.0176.
Ketterson, E.D., Nolan Jr., V., 1992. Hormones and life histories: an integrative approach. Am. Nat. 140, S33–S62.
Ketterson, E.D., Nolan Jr., V., 1999. Adaptation, exaptation, and constraint: a hormonal perspective. Am. Nat. 154, S4–S25.
Ketterson, E.D., Nolan Jr., V., Sandell, M., 2005. Testosterone in females: mediator of adaptive traits, constraint on sexual dimorphism, or both? Am. Nat. 166, S85–S98.
Ketterson, E.D., Atwell, J.W., McGlothlin, J.W., 2009. Phenotypic integration and independence: hormones, performance, and response to environmental change. Integr. Comp. Biol. 49, 365–379.
Killen, S.S., Calsbeek, R., Williams, T.D., 2017. The ecology of exercise: mechanisms underlying individual variation in behavior, activity, and performance: an introduction to symposium. Integr. Comp. Biol. 57, 185–194. https://doi.org/10.1093/icb/icx083.
Kirby, E.D., Geraghty, A.C., Ubuka, T., Bentley, G.E., Kaufer, D., 2009. Stress increases putative gonadotropin inhibitory hormone and decreases luteinizing hormone in male rats. Proc. Natl. Acad. Sci. 106, 11324–11329. https://doi.org/10.1073/pnas.0901176106.
Kirschner, M., Gerhart, J., 1998. Evolvability. Proc. Natl. Acad. Sci. 95, 8420–8427. https://doi.org/10.1073/pnas.95.15.8420.
Kitano, H., 2004. Biological robustness. Nat. Rev. Genet. 5, 826–837. https://doi.org/10.1038/nrg1471.
Klingenberg, C.P., 2008. Morphological integration and developmental modularity. Annu. Rev. Ecol. Evol. Syst. 39, 115–132. https://doi.org/10.1146/annurev.ecolsys.37.091305.110054.
Kohl, M.T., Stahler, D.R., Metz, M.C., Forester, J.D., Kauffman, M.J., Varley, N., White, P. J., Smith, D.W., MacNulty, D.R., 2018. Diel predator activity drives a dynamic landscape of fear. Ecol. Monogr. 88, 638–652.
Kondoh, K., Lu, Z., Ye, X., Olson, D.P., Lowell, B.B., Buck, L.B., 2016. A specific area of olfactory cortex involved in stress hormone responses to predator odours. Nature 532, 103–106. https://doi.org/10.1038/nature17156.
Koolhaas, J.M., Korte, S.M., de Boer, S.F., van der Vegt, B.J., van Reenen, C.G., Hopster, H., de Jong, I.C., Ruis, M.A.W., Blokuis, H.J., 1999. Coping styles in animals: current status in behavior and stress-physiology. Neurosci. Biobehav. Rev. 23, 925–935. https://doi.org/10.1016/S0149-7634(99)00026-3.
Koolhaas, J.M., de Boer, S.F., Buwalda, B., van Reenen, K., 2007. Individual variation in coping with stress: a multidimensional approach of ultimate and proximate mechanisms. Brain Behav. Evol. 70, 218–226. https://doi.org/10.1159/000105485.
Koolhaas, J.M., de Boer, S.F., Coppens, C.M., Buwalda, B., 2010. Neuroendocrinology of coping styles: towards understanding the biology of individual variation. Front. Neuroendocrinol. 31, 307–321. https://doi.org/10.1016/j.yfrne.2010.04.001.
Korte, S.M., Koolhaas, J.M., Wingfield, J.C., McEwen, B.S., 2005. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci. Biobehav. Rev. 29, 3–38.
Kühn, E.R., Geris, K.L., van der Geyten, S., Mol, K.A., Darras, V.M., 1998. Inhibition and activation of the thyroidal axis by the adrenal axis in vertebrates. Comp. Biochem. Physiol. A Mol. Integr. Physiol. 120, 169–174. https://doi.org/10.1016/S1095-6433(98)10026-0.
Kuijper, B., Hoyle, R.B., 2015. When to rely on maternal effects and when on phenotypic plasticity? Evolution 69, 950–968.
Ladd, C.O., Huot, R.L., Thrivikraman, K.V., Nemeroff, C.B., Plotsky, P.M., 2004. Long-term adaptations in glucocorticoid receptor and mineralocorticoid receptor mRNA and negative feedback on the hypothalamo-pituitary-adrenal axis following neonatal maternal separation. Biol. Psychiatry 55, 367–375. https://doi.org/10.1016/j.biopsych.2003.10.007.
LaManna, J.A., Martin, T.E., 2016. Costs of fear: behavioural and life-history responses to risk and their demographic consequences vary across species. Ecol. Lett. 19, 403–413. https://doi.org/10.1111/ele.12573.
Lancaster, L.T., McAdam, A.G., Wingfield, J.C., Sinervo, B.R., 2007. Adaptive social and maternal induction of antipredator dorsal patterns in a lizard with alternative social strategies. Ecol. Lett. 10 (9), 798–808.
Lande, R., 1976. Natural selection and random genetic drift in phenotypic evolution. Evolution 30, 314–334.
Lande, R., 1979. Quantitative genetic analysis of multivariate evolution, applied to brain: body size allometry. Evolution 33, 402–416.
Lande, R., 2009. Adaptation to an extraordinary environment by evolution of phenotypic plasticity and genetic assimilation. J. Evol. Biol. 22 (7), 1435–1446.
Lande, R., Shannon, S., 1996. The role of genetic variation in adaptation and population persistence in a changing environment. Evolution 50, 434–437. https://doi.org/10.1111/j.1558-5646.1996.tb04504.x.
Landys, M.M., Wingfield, J.C., Ramenofsky, M., 2004. Plasma corticosterone increases during migratory restlessness in the captive white-crowned sparrow *Zonotrichia leucophrys gambelli*. Horm. Behav. 46, 574–581. https://doi.org/10.1016/j.yhbeh.2004.06.006.
Landys, M.M., Ramenofsky, M., Wingfield, J.C., 2006. Actions of glucocorticoids at a seasonal baseline as compared to stress-related levels in the regulation of periodic life processes. Gen. Comp. Endocrinol. 148, 132–149. https://doi.org/10.1016/j.ygcen.2006.02.013.
Landys-Ciannelli, M.M., Ramenofsky, M., Piersma, T., Jukema, J., Group, C.R, Wingfield, J.C., 2002. Baseline and stress-induced plasma corticosterone during long-distance migration in the Bar-tailed godwit, *Limosa lapponica*. Physiol. Biochem. Zool. 75, 101–110. https://doi.org/10.1086/338285.
Lattin, C.R., Kelly, T.R., 2020. Glucocorticoid negative feedback as a potential mediator of trade-offs between reproduction and survival. Gen. Comp. Endocrinol. 286, 113301 https://doi.org/10.1016/j.ygcen.2019.113301.
Lattin, C.R., Waldron-Francis, K., Richardson, J.W., de Bruijn, R., Bauer, C.M., Breuner, C.W., Michael Romero, L., 2012. Pharmacological characterization of intracellular glucocorticoid receptors in nine tissues from house sparrow (*Passer*

domesticus). Gen. Comp. Endocrinol. 179, 214–220. https://doi.org/10.1016/j.ygcen.2012.08.007.
Lattin, C.R., Keniston, D.E., Reed, J.M., Romero, L.M., 2015. Are receptor concentrations correlated across tissues within individuals? A case study examining glucocorticoid and mineralocorticoid receptor binding. Endocrinology 156 (4), 1354–1361.
Ledón-Rettig, C.C., Pfennig, D.W., Chunco, A.J., Dworkin, I., 2014. Cryptic genetic variation in natural populations: a predictive framework. Integr. Comp. Biol. 54, 783–793.
Leimar, O., McNamara, J.M., 2015. The evolution of transgenerational integration of information in heterogeneous environments. Am. Nat. 185, E55–E69. https://doi.org/10.1086/679575.
Levins, R., 1968. Evolution in changing environments: some theoretical exploration. Princeton University Press. https://doi.org/10.2307/j.ctvx5wbbh.
Levis, N.A., Pfennig, D.W., 2016. Evaluating 'plasticity-first' evolution in nature: key criteria and empirical approaches. Trends Ecol. Evol. 31, 563–574. https://doi.org/10.1016/j.tree.2016.03.012.
Lima, S.L., 1987. Clutch size in birds: a predation perspective. Ecology 68, 1062–1070.
Lin, J., Epel, E., 2022. Stress and telomere shortening: insights from cellular mechanisms. Ageing Res. Rev. 73, 101507 https://doi.org/10.1016/j.arr.2021.101507.
Lipshutz, S.E., George, E.M., Bentz, A.B., Rosvall, K.A., 2019. Evaluating testosterone as a phenotypic integrator: from tissues to individuals to species. Mol. Cell. Endocrinol. 96, 110531.
Love, O.P., McGowan, P.O., Sheriff, M.J., 2013. Maternal adversity and ecological stressors in natural populations: the role of stress axis programming in individuals, with implications for populations and communities. Funct. Ecol. 27, 81–92.
Ludlow, A.T., Witkowski, S., Marshall, M.R., Wang, J., Lima, L.C.J., Guth, L.M., Spangenburg, E.E., Roth, S.M., 2012. Chronic exercise modifies age-related telomere dynamics in a tissue-specific fashion. J. Gerontol. A 67, 911–926. https://doi.org/10.1093/gerona/gls002.
Lynch, M., 2007. The frailty of adaptive hypotheses for the origins of organismal complexity. Proc. Natl. Acad. Sci. 104 (suppl_1), 8597–8604.
Lynch, M., Walsh, B., 1998. Genetics and Analysis of Quantitative Traits. Sinaeur, Sunderland, MA.
Maag, N., Cozzi, G., Bateman, A., Heistermann, M., Ganswindt, A., Manser, M., Clutton-Brock, T., Ozgul, A., 2019. Cost of dispersal in a social mammal: body mass loss and increased stress. Proc. Roy. Soc. B 286, 20190033.
MacDougall-Shackleton, S.A., Bonier, F., Romero, L.M., Moore, I.T., 2019. Glucocorticoids and "stress" are not synonymous. Integr. Comp. Biol. 1, 0bz017. https://doi.org/10.1093/iob/obz017.
Marasco, V., Smith, S., Angelier, F., 2022. How does early-life adversity shape telomere dynamics during adulthood? Problems and paradigms. BioEssays 44, 2100184. https://doi.org/10.1002/bies.202100184.
Marler, C.A., Moore, M.C., 1988. Evolutionary costs of aggression revealed by testosterone manipulations in free-living male lizards. Behav. Ecol. Sociobiol. 23, 21–26.
Marler, C.A., Moore, M.C., 1989. Time and energy costs of aggression in testosterone-implanted free-living male mountain spiny lizards (*Sceloporus jarrovi*). Physiol. Zool. 62, 1334–1350.
Marshall, D.J., Boduriansky, R., Bussiere, L.F., 2008. Offspring size variation within broods as a bet-hedging strategy in unpredictable environments. Ecology 89, 2506–2517.
Martin, T.E., 1995. Avian life history evolution in relation to nest sites, nest predation, and food. Ecol. Monogr. 65, 101–127. https://doi.org/10.2307/2937160.
Martin, T.E., Briskie, J.V., 2009. Predation on dependent offspring: a review of the consequences for mean expression and phenotypic plasticity in avian life history traits. Ann. N. Y. Acad. Sci. 1168, 201–217. https://doi.org/10.1111/j.1749-6632.2009.04577.x.
Martin, L.B., Liebl, A.L., Trotter, J.H., Richards, C.L., McCoy, K., McCoy, M.W., 2011a. Integrator networks: illuminating the black box linking genotype and phenotype. Intgr. Comp. Biol. 51, 514–527.
Martin, T.E., Lloyd, P., Bosque, C., Barton, D.C., Biancucci, A.L., Cheng, Y.-R., Ton, R., 2011b. Growth rate variation among passerine species in tropical and temperate sites: an antagonistic interaction between parental food provisioning and nest predation risk. Evolution 65, 1607–1622. https://doi.org/10.1111/j.1558-5646.2011.01227.x.
Martinig, A.R., Karst, H.J., Siracusa, E.R., Studd, E.K., McAdam, A.G., Dantzer, B., Delaney, D.M., Lane, J.E., Pokharel, P., Boutin, S., 2022. Animal personality: a comparison of standardized assays and focal observations in North American red squirrels. Anim. Behav. 190, 221–232.
Masel, J., Siegal, M.L., 2009. Robustness: mechanisms and consequences. Trends Genet. 25, 395–403. https://doi.org/10.1016/j.tig.2009.07.005.
Matesanz, S., Blanco-Sánchez, M., Ramos-Muñoz, M., de la Cruz, M., Benavides, R., Escudero, A., 2021. Phenotypic integration does not constrain phenotypic plasticity: differential plasticity of traits is associated to their integration across environments. New Phytol. 231, 2359–2370.
Mathot, K.J., Frankenhuis, W.E., 2018. Models of pace-of-life syndromes (POLS): a systematic review. Behav. Ecol. Sociobiol. 72, 1–12.
Matthews, S.G., McGowan, P.O., 2019. Developmental programming of the HPA axis and related behaviours: epigenetic mechanisms. J. Endocrinol. 242, T69–T79. https://doi.org/10.1530/JOE-19-0057.
Maynard Smith, J., Burian, R., Kauffman, S., Alberch, P., Campbell, J., Goodwin, B., Lande, R., Raup, D., Wolpert, L., 1985. Developmental constraints and evolution: a perspective from the mountain Lake conference on development and evolution. Q. Rev. Biol. 60, 265–287.
McEwen, B.S., 1998. Stress, adaptation, and disease: allostasis and allostatic load. Ann. N. Y. Acad. Sci. 840, 33–44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x.
McEwen, B.S., Akil, H., 2020. Revisiting the stress concept: implications for affective disorders. J. Neurosci. 40, 12–21. https://doi.org/10.1523/JNEUROSCI.0733-19.2019.
McEwen, B.S., Wingfield, J.C., 2003. The concept of allostasis in biology and biomedicine. Horm. Behav. 43, 2–15. https://doi.org/10.1016/S0018-506X(02)00024-7.
McGlothlin, J.W., Ketterson, E.D., 2008. Hormone-mediated suites as adaptations and evolutionary constraints. Phil. Trans. Roy. Soc. B 363, 1611–1620.
McGlothlin, J.W., Parker, P.G., Nolan, V., Ketterson, E.D., 2005. Correlational selection leads to genetic integration of body size and an attractive plumage trait in dark-eyed juncos. Evolution 59, 658–671.
McGlothlin, J.W., Kobiela, M.E., Wright, H.V., Mahler, D.L., Kolbe, J.J., Losos, J.B., Brodie III, E.D., 2018. Adaptive radiation along a deeply conserved genetic line of least resistance in Anolis lizards. Evol. Lett. 2, 310–322.
McGuigan, K., Sgrò, C.M., 2009. Evolutionary consequences of cryptic genetic variation. Trends Ecol. Evol. 24, 305–311.
McGuigan, K., Chenoweth, S.F., Blows, M.W., 2005. Phenotypic divergence along lines of genetic variance. Am. Nat. 165, 32–43.
McNamara, J.M., Dall, S.R., Hammerstein, P., Leimar, O., 2016. Detection vs. selection: integration of genetic, epigenetic and environmental cues in fluctuating environments. Ecol. Lett. 19, 1267–1276.
Meaney, M.J., 2001. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu. Rev. Neurosci. 24, 1161–1192.
Merilä, J., Fry, J.D., 1998. Genetic variation and causes of genotype-environment interaction in the body size of blue tit (*Parus caeruleus*). Genetics 148, 233–1244.
Merilä, J., Hendry, A.P., 2014. Climate change, adaptation, and phenotypic plasticity: the problem and the evidence. Evol. Appl. 7, 1–14. https://doi.org/10.1111/eva.12137.
Merilä, J., Laurila, A., Laugen, A.T., Räsänen, K., Pahkala, M., 2000. Plasticity in age and size at metamorphosis in *Rana temporaria*-comparison of high and low latitude populations. Ecography 23, 457–465.
Merrill, L., Grindstaff, J.L., 2018. Early life stress strengthens trait covariance: a plastic response that results in reduced flexibility. Am. Nat. 192, 593–604.
Meylan, S., Belliure, J., Clobert, J., de Fraipont, M., 2002. Stress and body condition as prenatal and postnatal determinants of dispersal in the common lizard (*Lacerta vivipara*). Horm. Behav. 42, 319–326. https://doi.org/10.1006/hbeh.2002.1827.
Middlemis Maher, J., Werner, E.E., Denver, R.J., 2013. Stress hormones mediate predator-induced phenotypic plasticity in amphibian tadpoles. Proc. R. Soc. B Biol. Sci. 280 (1758), 20123075.
Miles, D.B., Sinervo, B., Hazard, L.C., Svensson, E.I., Costa, D., 2007. Relating endocrinology, physiology and behaviour using species with alternative mating strategies. Funct. Ecol. 21, 653–665.
Miner, B.G., Sultan, S.E., Morgan, S.G., Padilla, D.K., Relyea, R.A., 2005. Ecological consequences of phenotypic plasticity. Trends Ecol. Evol. 20, 685–692. https://doi.org/10.1016/j.tree.2005.08.002.
Moczek, A.P., Sultan, S., Foster, S., Ledón-Rettig, C., Dworkin, I., Nijhout, H.F., Abouheif, E., Pfennig, D.W., 2011. The role of developmental plasticity in evolutionary innovation. Proc. Roy. Soc. B 278, 2705–2713.
Monaghan, P., 2014. Organismal stress, telomeres and life histories. J. Exp. Biol. 217, 57–66. https://doi.org/10.1242/jeb.090043.
Monclús, R., Tiulim, J., Blumstein, D.T., 2011. Older mothers follow conservative strategies under predator pressure: the adaptive role of maternal glucocorticoids in yellow-bellied marmots. Horm. Behav. 60, 660–665.
Moon, B.R., 2001. Muscle physiology and the evolution of the rattling system in rattlesnakes. J. Herpetol. 35, 497–500. https://doi.org/10.2307/1565969.
Moran, N.P., Sánchez-Tójar, A., Schielzeth, H., Reinhold, K., 2021. Poor nutritional condition promotes high-risk behaviours: a systematic review and meta-analysis. Biol. Rev. 96, 269–288.
Munck, A., Guyre, P.M., Holbrook, N.J., 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr. Rev. 5, 25–44. https://doi.org/10.1210/edrv-5-1-25.
Murren, C.J., 2012. The integrated phenotype. Integr. Comp. Biol. 52, 64–76.
Nettle, D., Bateson, M., 2015. Adaptive developmental plasticity: what is it, how can we recognize it and when can it evolve? Proc. R. Soc. B Biol. Sci. 282, 20151005. https://doi.org/10.1098/rspb.2015.1005.
Noguera, J.C., Silva, A., Velando, A., 2020. Egg corticosterone can stimulate telomerase activity and promote longer telomeres during embryo development. Mol. Ecol. mec.15694 https://doi.org/10.1111/mec.15694.
Nunes, S., Pelz, K.M., Muecke, E.M., Holekamp, K.E., Zucker, I., 2006. Plasma glucocorticoid concentrations and body mass in ground squirrels: seasonal variation and circannual organization. Gen. Comp. Endocrinol. 146, 136–143.
O'Dea, R.E., Noble, D.W.A., Johnson, S.L., Hesselson, D., Nakagawa, S., 2016. The role of non-genetic inheritance in evolutionary rescue: epigenetic buffering, heritable bet hedging and epigenetic traps. Environ. Epigenet. 2, dvv014. https://doi.org/10.1093/eep/dvv014.
O'Dea, R.E., Lagisz, M., Hendry, A.P., Nakagawa, S., 2019. Developmental temperature affects phenotypic means and variability: a meta-analysis of fish data. Fish Fish. 20, 1005–1022.
Olson, E.C., Miller, R.L., 1958. Morphological Integration. The University of Chicago Press, Chicago, IL.
Oster, H., Damerow, S., Kiessling, S., Jakubcakova, V., Abraham, D., Tian, J., Hoffmann, M.W., Eichele, G., 2006. The circadian rhythm of glucocorticoids is regulated by a gating mechanism residing in the adrenal cortical clock. Cell Metab. 4, 163–173. https://doi.org/10.1016/j.cmet.2006.07.002.

Ouyang, J.Q., Lendvai, Á.Z., Moore, I.T., Bonier, F., Haussmann, M.F., 2016. Do hormones, telomere lengths, and oxidative stress form an integrated phenotype? A case study in free-living tree swallows. Intgr. Comp. Biol. 56, 138–145.
Paaby, A.B., Rockman, M.V., 2014. Cryptic genetic variation: evolution's hidden substrate. Nat. Rev. Genet. 15, 247–258.
Parsons, P.A., 1987. Evolutionary rates under environmental stress. In: Hecht, M.K., Wallace, B., Prance, G.T. (Eds.), Evolutionary Biology. Springer US, Boston, MA, pp. 311–347. https://doi.org/10.1007/978-1-4615-6986-2_10.
Parsons, P.A., 1990. Fluctuating asymmetry: an epigenetic measure of stress. Biol. Rev. 65, 131–145.
Parsons, P.A., 1993. The importance and consequences of stress in living and fossil populations: from life-history variation to evolutionary change. Am. Nat. 142, S5–S20.
Parsons, P.A., 1994. Habitats, stress, and evolutionary rates. J. Evol. Biol. 7, 387–397.
Petrullo, L., Delaney, D., Boutin, S., McAdam, A.G., Lane, J.E., Boonstra, R., Palme, R., Dantzer, B., 2022. The glucocorticoid response to environmental change is not specific to agents of natural selection in wild red squirrels. Horm. Behav. 146, 105262 https://doi.org/10.1016/j.yhbeh.2022.105262.
Petrullo, L., Boutin, S., Lane, J.E., McAdam, A.G., Dantzer, B., 2023. Phenotype-environment mismatch errors enhance lifetime fitness in wild red squirrels. Science. http://www.science.org/doi/10.1126/science.abn0665.
Pfennig, D.W., Wund, M.A., Snell-Rood, E.C., Cruickshank, T., Schlichting, C.D., Moczek, A.P., 2010. Phenotypic plasticity's impacts on diversification and speciation. Trends Ecol. Evol. 25, 459–467.
Philippi, T., Seger, J., 1989. Hedging one's evolutionary bets, revisited. Trends Ecol. Evol. 4, 41–44. https://doi.org/10.1016/0169-5347(89)90138-9.
Piersma, T., Drent, J., 2003. Phenotypic flexibility and the evolution of organismal design. Trends Ecol. Evol. 18, 228–233. https://doi.org/10.1016/S0169-5347(03)00036-3.
Piersma, T., Reneerkens, J., Ramenofsky, M., 2000. Baseline corticosterone peaks in shorebirds with maximal energy stores for migration: a general preparatory mechanism for rapid behavioral and metabolic transitions? Gen. Comp. Endocrinol. 120, 118–126. https://doi.org/10.1006/gcen.2000.7543.
Pigliucci, M., 2003. Phenotypic integration: studying the ecology and evolution of complex phenotypes. Ecol. Lett. 6, 265–272.
Pigliucci, M., 2008. Is evolvability evolvable? Nat. Rev. Genet. 9, 75–82.
Pigliucci, M., Murren, C.J., 2003. Perspective: genetic assimilation and a possible evolutionary paradox: can macroevolution sometimes be so fast as to pass us by? Evolution 57, 1455–1464.
Pigliucci, M., Preston, K. (Eds.), 2004. Phenotypic Integration: Studying the Ecology and Evolution of Complex Phenotypes. Oxford University Press, Oxford, U.K.
Pigliucci, M., Schlichting, C.D., Whitton, J., 1995. Reaction norms of *Arabidopsis*. II. Response to stress and unordered environmental variation. Funct. Ecol. 9, 537–547.
Plaistow, S.J., Collin, H., 2014. Phenotypic integration plasticity in D aphnia magna: an integral facet of G× E interactions. J. Evol. Biol. 27, 1913–1920.
Poole, A.M., Phillips, M.J., Penny, D., 2003. Prokaryote and eukaryote evolvability. Biosystems 69 (2-3), 163–185.
Price, T., Kirkpatrick, M., Arnold, S.J., 1988. Directional selection and the evolution of breeding date in birds. Science 240, 798–799.
Ratcliff, W.C., Denison, R.F., 2010. Individual-level bet hedging in the bacterium *Sinorhizobium meliloti*. Curr. Biol. 20, 1740–1744. https://doi.org/10.1016/j.cub.2010.08.036.
Rausher, M.D., 1992. The measurement of selection on quantitative traits: biases due to environmental covariances between traits and fitness. Evolution 46, 616–626.
Réale, D., Garant, D., Humphries, M.M., Bergeron, P., Careau, V., Montiglio, P.O., 2010. Personality and the emergence of the pace-of-life syndrome concept at the population level. Phil. Trans. Roy. Soc. B 365, 4051–4063.
Reddy, A.B., Maywood, E.S., Karp, N.A., King, V.M., Inoue, Y., Gonzalez, F.J., Lilley, K.S., Kyriacou, C.P., Hastings, M.H., 2007. Glucocorticoid signaling synchronizes the liver circadian transcriptome. Hepatology 45, 1478–1488.
Reed, T.E., Waples, R.S., Schindler, D.E., Hard, J.J., Kinnison, M.T., 2010. Phenotypic plasticity and population viability: the importance of environmental predictability. Proc. Roy. Soc. B. 277, 3391–3400.
Reichert, S., Stier, A., 2017. Does oxidative stress shorten telomeres *in vivo*? A review. Biol. Lett. 13, 20170463. https://doi.org/10.1098/rsbl.2017.0463.
Relyea, R.A., 2001. Morphological and behavioral plasticity of larval anurans in response to different predators. Ecology 82, 523–540.
Remage-Healey, L., Nowacek, D.P., Bass, A.H., 2006. Dolphin foraging sounds suppress calling and elevate stress hormone levels in a prey species, the Gulf toadfish. J. Exp. Biol. 209, 4444–4451. https://doi.org/10.1242/jeb.02525.
Reznick, D., Nunney, L., Tessier, A., 2000. Big houses, big cars, superfleas and the costs of reproduction. Trends Ecol. Evol. 15, 421–425.
Ricklefs, R.E., Wikelski, M., 2002. The physiology/life-history nexus. Trends Ecol. Evol. 17, 462–468. https://doi.org/10.1016/S0169-5347(02)02578-8.
Robert, K.A., Bronikowski, A.M., 2010. Evolution of senescence in nature: physiological evolution in populations of garter snake with divergent life histories. Am. Nat. 175, 147–159.
Roff, D., 2002. Life History Evolution. Sinaeur, Sunderland, MA, USA.
Rohner, N., Jarosz, D.F., Kowalko, J.E., Yoshizawa, M., Jeffery, W.R., Borowsky, R.L., Lindquist, S., Tabin, C.J., 2013. Cryptic variation in morphological evolution: HSP90 as a capacitor for loss of eyes in cavefish. Science 342, 1372–1375.
Romero, L.M., 2002. Seasonal changes in plasma glucocorticoid concentrations in free-living vertebrates. Gen. Comp. Endocrinol. 128, 1–24. https://doi.org/10.1016/S0016-6480(02)00064-3.
Romero, L.M., 2004. Physiological stress in ecology: lessons from biomedical research. Trends Ecol. Evol. 19, 249–255. https://doi.org/10.1016/j.tree.2004.03.008.
Romero, L.M., Wingfield, J.C., 2015. Tempests, Poxes, Predators, and People: Stress in Wild Animals and How They Cope. Oxford University Press.
Romero, L.M., Dickens, M.J., Cyr, N.E., 2009. The reactive scope model — a new model integrating homeostasis, allostasis, and stress. Horm. Behav. 55, 375–389. https://doi.org/10.1016/j.yhbeh.2008.12.009.
Rose, M.R., Bradley, T.J., 1998. Evolutionary physiology of the cost of reproduction. Oikos 83, 443–451.
Roseboom, P.H., Nanda, S.A., Bakshi, V.P., Trentani, A., Newman, S.M., Kalin, N.H., 2007. Predator threat induces behavioral inhibition, pituitary-adrenal activation and changes in amygdala CRF-binding protein gene expression. Psychoneuroendocrinology 32, 44–55. https://doi.org/10.1016/j.psyneuen.2006.10.002.
Rousseau, G.G., Baxter, J.D., 1979. Glucocorticoid receptors. In: Baxter, John D., Rousseau, Guy G. (Eds.), Glucocorticoid Hormone Action. Springer, Berlin Heidelberg, Berlin, Heidelberg, pp. 49–77. https://doi.org/10.1007/978-3-642-81265-1_3.
Rowiński, P.K., Rogell, B., 2017. Environmental stress correlates with increases in both genetic and residual variances: a meta-analysis of animal studies. Evolution 71, 1339–1351.
Royauté, R., Greenlee, K., Baldwin, M., Dochtermann, N.A., 2015. Behaviour, metabolism and size: phenotypic modularity or integration in Acheta domesticus? Anim. Behav. 110, 163–169.
Rudman, S.M., Greenblum, S.I., Rajpurohit, S., Betancourt, N.J., Hanna, J., Tilk, S., Yokoyama, T., Petrov, D.A., Schmidt, P., 2022. Direct observation of adaptive tracking on ecological time scales in *Drosophila*. Science 375, eabj7484. https://doi.org/10.1126/science.abj7484.
Rutherford, S.L., 2000. From genotype to phenotype: buffering mechanisms and the storage of genetic information. Bioessays 22, 1095–1105.
Sachs, L.M., Buchholz, D.R., 2019. Insufficiency of thyroid hormone in frog metamorphosis and the role of glucocorticoids. Front. Endocrinol. 10, 287.
Saltz, J.B., Hessel, F.C., Kelly, M.W., 2017. Trait correlations in the genomics era. Trends Ecol. Evol. 32, 279–290.
Sánchez-Tójar, A., Lagisz, M., Moran, N.P., Nakagawa, S., Noble, D.W., Reinhold, K., 2020. The jury is still out regarding the generality of adaptive 'transgenerational'effects. Ecol. Lett. 23, 1715–1718.
Santana, P., Akana, S.F., Hanson, E.S., Strack, A.M., Sebastian, R.J., Dallman, M.F., 1995. Aldosterone and dexamethasone both stimulate energy acquisition whereas only the glucocorticoid alters energy storage. Endocrinology 136, 2214–2222.
Sapolsky, R.M., 2005. The influence of social hierarchy on primate health. Science 308, 648–652. https://doi.org/10.1126/science.1106477.
Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 21, 55–89. https://doi.org/10.1210/edrv.21.1.0389.
Schaeffer, P., Conley, K., Lindstedt, S., 1996. Structural correlates of speed and endurance in skeletal muscle: the rattlesnake tailshaker muscle. J. Exp. Biol. 199, 351–358. https://doi.org/10.1242/jeb.199.2.351.
Scheiner, S.M., 1993. Genetics and evolution of phenotypic plasticity. Annu. Rev. Ecol. Syst. 24, 35–68.
Schlichting, C.D., 1986. The evolution of phenotypic plasticity in plants. Ann. Rev. Ecol. Evol. Syst. 17, 667–693.
Schlichting, C.D., 1989. Phenotypic integration and environmental change. BioScience 39, 460–464.
Schlichting, C.D., 2004. The role of phenotypic plasticity in diversification. In: DeWitt, T. J., Scheiner, S.M. (Eds.), Phenotypic Plasticity: Functional and Conceptual Approaches. Oxford University Press, Oxford, U.K., pp. 191–200
Schlichting, C.D., 2008. Hidden reaction norms, cryptic genetic variation, and evolvability. Ann. N.Y. Acad. Sci. 1133, 187–203.
Schlichting, C.D., Murren, C.J., 2004. Evolvability and the raw materials for adaptation. In: Cronk, Q.C.B., Whitton, J., Ree, R.H., Taylor, I.E.P. (Eds.), Plant Adaptation: Molecular Genetics and Ecology. NRC Research Press, Ottawa, ON, Canada, pp. 18–29.
Schlichting, C.D., Pigliucci, M., 1998. Phenotypic Evolution: A Reaction Norm Perspective. Sinauer, Sunderland, MA.
Schluter, D., 1996. Adaptive radiation along genetic lines of least resistance. Evolution 50, 1766–1774.
Schmalhausen, I.I., 1949. Factors of Evolution: The Theory of Stabilizing Selection. Blakiston.
Schulte, P.M., 2014. What is environmental stress? Insights from fish living in a variable environment. J. Exp. Biol. 217, 23–34.
Seger, J., Brockmann, H.J., 1987. What is bet-hedging? Oxf. Surv. Evol. Biol. 4, 182–211.
Senior, A.M., Nakagawa, S., Raubenheimer, D., Simpson, S.J., Noble, D.W.A., 2017. Dietary restriction increases variability in longevity. Biol. Lett. 13, 20170057.
Shalev, I., 2012. Early life stress and telomere length: investigating the connection and possible mechanisms: a critical survey of the evidence base, research methodology and basic biology. BioEssays 34, 943–952. https://doi.org/10.1002/bies.201200084.
Shalev, I., Entringer, S., Wadhwa, P.D., Wolkowitz, O.M., Puterman, E., Lin, J., Epel, E.S., 2013. Stress and telomere biology: a lifespan perspective. Psychoneuroendocrinology 38 (9), 1835–1842.
Sheriff, M.J., Love, O.P., 2013. Determining the adaptive potential of maternal stress. Ecol. Lett. 16, 271–280. https://doi.org/10.1111/ele.12042.
Sheriff, M.J., Dantzer, B., Delehanty, B., Palme, R., Boonstra, R., 2011. Measuring stress in wildlife: techniques for quantifying glucocorticoids. Oecologia 166, 869–887. https://doi.org/10.1007/s00442-011-1943-y.
Sheriff, M.J., Bell, A., Boonstra, R., Dantzer, B., Lavergne, S.G., McGhee, K.E., MacLeod, K.J., Winandy, L., Zimmer, C., Love, O.P., 2017. Integrating ecological and

evolutionary context in the study of maternal stress. Integr. Comp. Biol. 57, 437–449. https://doi.org/10.1093/icb/icx105.
Sheriff, M.J., Dantzer, B., Love, O.P., Orrock, J.L., 2018. Error management theory and the adaptive significance of transgenerational maternal-stress effects on offspring phenotype. Ecol. Evol. 8, 6473–6482. https://doi.org/10.1002/ece3.4074.
Shingleton, A.W., 2010a. Allometry: the study of biological scaling. Nat. Educ. Knowl. 3, 2.
Shingleton, A.W., 2010b. The regulation of organ size in *Drosophila*: physiology, plasticity, patterning and physical force. Organogenesis 6, 76–87.
Shingleton, A.W., Estep, C.M., Driscoll, M.V., Dworkin, I., 2009. Many ways to be small: different environmental regulators of size generate distinct scaling relationships in *Drosophila melanogaster*. Proc. R. Soc. B Biol. Sci. 276, 2625–2633. https://doi.org/10.1098/rspb.2008.1796.
Shivatcheva, T.M., Ankov, V.K., Hadjioloff, A.I., 1988. Circannual fluctuations of the serum cortisol in the European ground squirrel, *Citellus citellus* L. Comp. Biochem. Physiol. A Physiol. 90, 515–518. https://doi.org/10.1016/0300-9629(88)90229-0.
Siegal, M.L., Bergman, A., 2002. Waddington's canalization revisited: developmental stability and evolution. PNAS 99, 10528–10532.
Sih, A., 2011. Effects of early stress on behavioral syndromes: an integrated adaptive perspective. Neurosci. Biobehav. Rev. 35, 1452–1465.
Sih, A., Bell, A., Johnson, J.C., 2004. Behavioral syndromes: an ecological and evolutionary overview. Trends Ecol. Evol. 19, 372–378. https://doi.org/10.1016/j.tree.2004.04.009.
Sih, A., Ferrari, M.C., Harris, D.J., 2011. Evolution and behavioural responses to human-induced rapid environmental change. Evol. Appl. 4, 367–387.
Silverin, B., 1997. The stress response and autumn dispersal behaviour in willow tits. Anim. Behav. 53, 451–459. https://doi.org/10.1006/anbe.1996.0295.
Simon, N.M., Walton, Z.E., Bui, E., Prescott, J., Hoge, E., Keshaviah, A., Schwarz, N., Dryman, T., Ojserkis, R.A., Kovachy, B., Mischoulon, D., Worthington, J., DeVivo, I., Fava, M., Wong, K.-K., 2015. Telomere length and telomerase in a well-characterized sample of individuals with major depressive disorder compared to controls. Psychoneuroendocrinology 58, 9–22. https://doi.org/10.1016/j.psyneuen.2015.04.004.
Simons, A.M., 2009. Fluctuation natural selection accounts for the evolution of diversification bet hedging. Proc. Roy. Soc. B 276, 1987–1992.
Simons, A.M., 2011. Modes of response to environmental change and the elusive empirical evidence for bet hedging. Proc. Roy. Soc. B 278, 1601–1609.
Simons, M.J., 2015. Questioning causal involvement of telomeres in aging. Ageing Res. Rev. 24, 191–196.
Sinervo, B., Licht, P., 1991a. Proximate constraints on the evolution of egg size, number, and total clutch mass in lizards. Science 252, 1300–1302.
Sinervo, B., Licht, P., 1991b. Hormonal and physiological control of clutch size, egg size, and egg shape in side-blotched lizards (*Uta stansburiana*): constraints on the evolution of lizard life histories. J. Exp. Zool. 257, 252–264.
Sinervo, B., Svensson, E., 1998. Mechanistic and selective causes of life history trade-offs and plasticity. Oikos 83, 432–442.
Sinervo, B., Svensson, E., 2002. Correlational selection and the evolution of genomic architecture. Heredity 89, 329–338.
Singleton, J.R., Baker, B.L., Thorburn, A., 2000. Dexamethasone inhibits insulin-like growth factor signaling and potentiates myoblast apoptosis. Endocrinology 141, 2945–2950.
Skinner, M.K., 2008. What is an epigenetic transgenerational phenotype? F3 or F2? Reprod. Toxicol. 25, 2–6. https://doi.org/10.1016/j.reprotox.2007.09.001.
Slatkin, M., 1974. Hedging ones evolutionary bets. Nature 250, 704–705.
Smith, S., Hoelzl, F., Zahn, S., Criscuolo, F., 2021. Telomerase activity in ecological studies: what are its consequences for individual physiology and is there evidence for effects and trade-offs in wild populations. Mol. Ecol. mec.16233 https://doi.org/10.1111/mec.16233.
Snell-Rood, E.C., 2013. An overview of the evolutionary causes and consequences of behavioural plasticity. Anim. Behav. 85, 1004–1011. https://doi.org/10.1016/j.anbehav.2012.12.031.
Snell-Rood, E.C., Kobiela, M.E., Sikkink, K.L., Shephard, A.M., 2018. Mechanisms of plastic rescue in novel environments. Annu. Rev. Ecol. Evol. Syst. 49, 331–354.
Sniegowski, P.D., Murphy, H.A., 2006. Evolvability. Curr. Biol. 16, R831–R834.
Son, G.H., Chung, S., Choe, H.K., Kim, H.D., Baik, S.M., Lee, H., Lee, H.W., Choi, S., Sun, W., Kim, H., Cho, S., 2008. Adrenal peripheral clock controls the autonomous circadian rhythm of glucocorticoid by causing rhythmic steroid production. PNAS 105, 20970–20975.
Son, G.H., Chung, S., Kim, K., 2011. The adrenal peripheral clock: glucocorticoid and the circadian timing system. Front. Neuroendocrinol. 32, 451–465.
Sopinka, N.M., Hinch, S.G., Middleton, C.T., Hills, J.A., Patterson, D.A., 2014. Mother knows best, even when stressed? Effects of maternal exposure to a stressor on offspring performance at different life stages in a wild semelparous fish. Oecologia 175, 493–500. https://doi.org/10.1007/s00442-014-2915-9.
Sparkman, A.M., Vleck, C.M., Bronikowski, A.M., 2009. Evolutionary ecology of endocrine-mediated life-history variation in the garter snake *Thamnophis elegans*. Ecology 90, 720–728.
Spencer, R.L., Chun, L.E., Hartsock, M.J., Woodruff, E.R., 2018. Glucocorticoid hormones are both a major circadian signal and major stress signal: how this shared signal contributes to a dynamic relationship between the circadian and stress systems. Front. Neuroendocrinol. 49, 52–71.
Stamps, J.A., 2016. Individual differences in behavioural plasticities. Biol. Rev. 91, 534–567. https://doi.org/10.1111/brv.12186.
St-Cyr, S., McGowan, P.O., 2015. Programming of stress-related behavior and epigenetic neural gene regulation in mice offspring through maternal exposure to predator odor. Front. Behav. Neurosci. 9 https://doi.org/10.3389/fnbeh.2015.00145.
Stearns, S.C., 1992. The Evolution of Life Histories. Oxford University Press, London, U.K.
St-Cyr, S., Abuaish, S., Sivanathan, S., McGowan, P.O., 2017. Maternal programming of sex-specific responses to predator odor stress in adult rats. Horm. Behav. 94, 1–12.
Steiner, U.K., Van Buskirk, J., 2008. Environmental stress and the costs of whole-organism phenotypic plasticity in tadpoles. J. Evol. Biol. 21 (1), 97–103.
Storm, J.J., Lima, S.L., 2010. Mothers forewarn offspring about predators: a transgenerational maternal effect on behavior. Am. Nat. 175, 382–390. https://doi.org/10.1086/650443.
Stumpf, R.P., Tomlinson, M.C., Calkins, J.A., Kirkpatrick, B., Fisher, K., Nierenberg, K., Currier, R., Wynne, T.T., 2009. Skill assessment for an operational algal bloom forecast system. J. Mar. Syst. 76, 151–161. https://doi.org/10.1016/j.jmarsys.2008.05.016.
Sultan, S.E., 2021. Plasticity as an intrinsic property of organisms. In: Pfennig, D.W. (Ed.), Phenotypic Plasticity and Evolution: Causes, Consequences, Controversies. CRC Press, Boca Raton, FL, USA, p. 24.
Swanson, E.M., Dantzer, B., 2014. Insulin-like growth factor-1 is associated with life-history variation across Mammalia. Proc. Roy. Soc. B 281, 20132458.
Taborsky, B., Kuijper, B., Fawcett, T.W., English, S., Leimar, O., McNamara, J.M., Ruuskanen, S., 2022. An evolutionary perspective on stress responses, damage and repair. Horm. Behav. 142, 105180 https://doi.org/10.1016/j.yhbeh.2022.105180.
Taff, C.C., Vitousek, M.N., 2016. Endocrine flexibility: optimizing phenotypes in a dynamic world? Trends Ecol. Evol. 31, 476–488. https://doi.org/10.1016/j.tree.2016.03.005.
Taylor, R.W., Boon, A.K., Dantzer, B., Réale, D., Humphries, M.M., Boutin, S., Gorrell, J.C., Coltman, D.W., McAdam, A.G., 2012. Low heritabilities, but genetic and maternal correlations between red squirrel behaviours. J. Evol. Biol. 25, 614–624. https://doi.org/10.1111/j.1420-9101. 2012.02456.x.
Taylor, R.W., Boutin, S., Humphries, M.M., McAdam, A.G., 2014. Selection on female behaviour fluctuates with offspring environment. J. Evol. Biol. 27, 2308–2321. https://doi.org/10.1111/jeb.12495.
Teplitsky, C., Tarka, M., Møller, A.P., Nakagawa, S., Balbontin, J., Burke, T.A., Doutrelant, C., Gregoire, A., Hansson, B., Hasselquist, D., Gustafsson, L., 2014. Assessing multivariate constraints to evolution across ten long-term avian studies. PLoS One 9, e90444.
Thompson, M.J., Capilla-Lasheras, P., Dominoni, D.M., Réale, D., Charmantier, A., 2022. Phenotypic variation in urban environments: mechanisms and implications. Trends Ecol. Evol. 37, 171–182.
Tomiyama, A.J., O'Donovan, A., Lin, J., Puterman, E., Lazaro, A., Chan, J., Dhabhar, F.S., Wolkowitz, O., Kirschbaum, C., Blackburn, E., Epel, E., 2012. Does cellular aging relate to patterns of allostasis? Physiol. Behav. 106, 40–45. https://doi.org/10.1016/j.physbeh.2011.11.016.
Travers, M., Clinchy, M., Zanette, L., Boonstra, R., Williams, T.D., 2010. Indirect predator effects on clutch size and the cost of egg production: Indirect predator effects on clutch size. Ecol. Lett. https://doi.org/10.1111/j.1461-0248.2010.01488.x no-no.
Tsutsui, K., Bentley, G.E., Bedecarrats, G., Osugi, T., Ubuka, T., Kriegsfeld, L.J., 2010. Gonadotropin-inhibitory hormone (GnIH) and its control of central and peripheral reproductive function. Front. Neuroendocrinol. 31, 284–295. https://doi.org/10.1016/j.yfrne.2010.03.001.
Uller, T., 2008. Developmental plasticity and the evolution of parental effects. Trends Ecol. Evol. 23, 432–438. https://doi.org/10.1016/j.tree.2008.04.005.
van Bodegom, M., Homberg, J.R., Henckens, M.J., 2017. Modulation of the hypothalamic-pituitary-adrenal axis by early life stress exposure. Front. Cell. Neurosci. 11, 87. https://doi.org/10.3389/fncel.2017.00087.
Van Buskirk, J., McCollum, S.A., 2000. Influence of tail shape on tadpole swimming performance. J. Exp. Biol. 203, 2149–2158. https://doi.org/10.1242/jeb.203.14.2149.
Van Buskirk, J., McCollum, S.A., Werner, E.E., 1997. Natural selection for environmentally induced phenotypes in tadpoles. Evolution 51, 1983–1992. https://doi.org/10.1111/j.1558-5646.1997.tb05119.x.
Van Kesteren, F., Delehanty, B., Westrick, S.E., Palme, R., Boonstra, R., Lane, J.E., Boutin, S., McAdam, A.G., Dantzer, B., 2019. Experimental increases in glucocorticoids alter function of the HPA axis in wild red squirrels without negatively impacting survival and reproduction. Physiol. Biochem. Zool. 92, 445–458.
Veening, J.-W., Smits, W.K., Kuipers, O.P., 2008. Bistability, epigenetics, and bet-hedging in bacteria. Annu. Rev. Microbiol. 62, 193–210. https://doi.org/10.1146/annurev.micro.62.081307.163002.
Voje, K.L., Hansen, T.F., Egset, C.K., Bolstad, G.H., Pelabon, C., 2014. Allometric constraints and the evolution of allometry. Evolution 68, 866–885.
Wada, H., 2008. Glucocorticoids: mediators of vertebrate ontogenetic transitions. Gen. Comp. Endocrinol. 156, 441–453.
Waddington, C.H., 1942. Canalization of development and the inheritance of acquired characters. Nature 150, 563–565. https://doi.org/10.1038/150563a0.
Waddington, C.H., 1953. Genetic assimilation of an acquired character. Evolution 118–126.
Wagner, G.P., Altenberg, L., 1996. Perspective: complex adaptations and the evolution of evolvability. Evolution 50, 967–976.
Wagner, G.P., Zhang, J., 2011. The pleiotropic structure of the genotype–phenotype map: the evolvability of complex organisms. Nat. Rev. Genet. 12, 204–213.
Wagner, G.P., Pavlicev, M., Cheverud, J.M., 2007. The road to modularity. Nat. Rev. Genet. 8, 921–931. https://doi.org/10.1038/nrg2267.
Waitt, D.E., Levin, D.A., 1993. Phenotypic integration and plastic correlations in *Phlox drummondii* (Polemoniaceae). Am. J. Botany 80, 1224–1233.
Weger, M., Sevelinges, Y., Grosse, J., de Suduiraut, I.G., Zanoletti, O., Sandi, C., 2018. Increased brain glucocorticoid actions following social defeat in rats facilitates the

long-term establishment of social subordination. Physiol. Behav. 186, 31–36. https://doi.org/10.1016/j.physbeh.2018.01.008.
Werner, C., Hanhoun, M., Widmann, T., Kazakov, A., Semenov, A., Pöss, J., Bauersachs, J., Thum, T., Pfreundschuh, M., Müller, P., Haendeler, J., Böhm, M., Laufs, U., 2008. Effects of physical exercise on myocardial telomere-regulating proteins, survival pathways, and apoptosis. J. Am. Coll. Cardiol. 52, 470–482. https://doi.org/10.1016/j.jacc.2008.04.034.
Werner, C., Fürster, T., Widmann, T., Pöss, J., Roggia, C., Hanhoun, M., Scharhag, J., Büchner, N., Meyer, T., Kindermann, W., Haendeler, J., Böhm, M., Laufs, U., 2009. Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. Circulation 120, 2438–2447. https://doi.org/10.1161/CIRCULATIONAHA.109.861005.
West-Eberhard, M.J., 1998. Evolution in the light of developmental and cell biology, and *vice versa*. Proc. Natl. Acad. Sci. 95, 8417–8419. https://doi.org/10.1073/pnas.95.15.8417.
West-Eberhard, M.J., 2003. Developmental Plasticity and Evolution. Oxford University Press, Oxford, U. K.
West-Eberhard, M.J., 2005. Developmental plasticity and the origin of species differences. PNAS 102, 6543–6549.
Westrick, S.E., van Kesteren, F., Palme, R., Boonstra, R., Lane, J.E., Boutin, S., McAdam, A.G., Dantzer, B., 2019. Stress activity is not predictive of coping style in North American red squirrels. Behav. Ecol. Sociobiol. 73, 113. https://doi.org/10.1007/s00265-019-2728-2.
Westrick, S.E., van Kesteren, F., Boutin, S., Lane, J.E., McAdam, A.G., Dantzer, B., 2021. Maternal glucocorticoids have minimal effects on HPA axis activity and behavior of juvenile wild North American red squirrels. J. Exp. Biol. 224, jeb236620. https://doi.org/10.1242/jeb.236620.
Williams, T.D., 2008. Individual variation in endocrine systems: moving beyond the 'tyranny of the Golden mean'. Phil. Trans. Roy. Soc. B 363, 1687–1698.
Willis, C.K.R., Wilcox, A., 2014. Hormones and hibernation: possible links between hormone systems, winter energy balance and white-nose syndrome in bats. Horm. Behav. 66, 66–73. https://doi.org/10.1016/j.yhbeh.2014.04.009.
Wingfield, J.C., 2002. Endocrine responses to unpredictable environmental events: stress or anti-stress hormones? Integr. Comp. Biol. 42, 600–609. https://doi.org/10.1093/icb/42.3.600.
Wingfield, J.C., 2013. Ecological processes and the ecology of stress: the impacts of abiotic environmental factors. Funct. Ecol. 27, 37–44. https://doi.org/10.1111/1365-2435.12039.
Wingfield, J.C., Kitaysky, A.S., 2002. Endocrine responses to unpredictable environmental events: stress or anti-stress hormones? Integr. Comp. Biol. 42, 600–609.
Wingfield, J.C., Sapolsky, R.M., 2003. Reproduction and resistance to stress: when and how: reproduction and resistance to stress. J. Neuroendocrinol. 15, 711–724. https://doi.org/10.1046/j.1365-2826.2003.01033.x.
Wingfield, J.C., Maney, D.L., Breuner, C.W., Jacobs, J.D., Lynn, S., Ramenofsky, M., Richardson, R.D., 1998. Ecological bases of hormone—behavior interactions: The "emergency life history stage.". Am. Zool. 38, 191–206. https://doi.org/10.1093/icb/38.1.191.
Wingfield, J.C., Pérez, J.H., Krause, J.S., Word, K.R., González-Gómez, P.L., Lisovski, S., Chmura, H.E., 2017. How birds cope physiologically and behaviourally with extreme climatic events. Phil. Trans. Roy. Soc. B 372, 20160140.
Wittman, T.N., Robinson, C.D., McGlothlin, J.W., Cox, R.M., 2021. Hormonal pleiotropy structures genetic covariance. Evol. Lett. 5, 397–407.
Wolkowitz, O.M., Mellon, S.H., Epel, E.S., Lin, J., Reus, V.I., Rosser, R., Burke, H., Compagnone, M., Nelson, J.C., Dhabhar, F.S., Blackburn, E.H., 2012. Resting leukocyte telomerase activity is elevated in major depression and predicts treatment response. Mol. Psychiatry 17, 164–172. https://doi.org/10.1038/mp.2010.133.
Wood, C.W., Brodie III, E.D., 2015. Environmental effects on the structure of the G-matrix. Evolution 69, 2927–2940.
Yeh, P.J., Price, T.D., 2004. Adaptive phenotypic plasticity and the successful colonization of a novel environment. Am. Nat. 164 (4), 531–542.
Yerkes, R.M., Dodson, J.D., 1908. The relation of strength of stimulus to rapidity of habit-formation. J. Comp. Neurol. Psychol. 18, 459–482.
Yoshida, T., Jones, L.E., Ellner, S.P., Fussmann, G.F., Hairston, N.G., 2003. Rapid evolution drives ecological dynamics in a predator–prey system. Nature 424, 303–306.
Young, A.J., Monfort, S.L., 2009. Stress and the costs of extra-territorial movement in a social carnivore. Biol. Lett. 5, 439–441.
Zanette, L.Y., White, A.F., Allen, M.C., Clinchy, M., 2011. Perceived predation risk reduces the number of offspring songbirds produce per year. Science 334, 1398–1401. https://doi.org/10.1126/science.1210908.
Zera, A.J., Harshman, L.G., Williams, T.D., 2007. Evolutionary endocrinology: the developing synthesis between endocrinology and evolutionary genetics. Annu. Rev. Ecol. Evol. Syst. 38, 793–817.
Zhong, W., Priest, N.K., 2011. Stress-induced recombination and the mechanism of evolvability. Behav. Ecol. Sociobiol. 65, 493–502. https://doi.org/10.1007/s00265-010-1117-7.