CHAPTER TWO

Glucocorticoid-Mediated Phenotypes in Vertebrates: Multilevel Variation and Evolution

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1. GLUCOCORTICOIDS AS MEDIATORS OF PHENOTYPIC ADJUSTMENTS

Fluctuations in abiotic and biotic conditions exist in almost all habitats (Dunlap, Loros, & DeCoursey, 2004; Stevenson et al., 2015). Some fluctuations like the alternation between day and night or between seasons are regular and predictable, while others like severe climatic events, abundance of ephemeral food sources and social interactions may be erratic and unpredictable. Hormonal systems are powerful physiological mechanisms by which organisms can flexibly adjust behavioral, physiological, and morphological phenotypes to variation in environmental conditions (Nelson, 2011). Glucocorticoid (GC) hormones (cortisol, corticosterone) are of particular importance in this context for vertebrates, as they serve diverse functions revolving around maintaining the energy balance of an organism according to its needs. The role of GCs includes coordinating organismal responses to regular and predictable, but also to acute, unpredictable circumstances (Sapolsky, Romero, & Munck, 2000; Wingfield, 2013b). Hence, GCs are crucial mediators of individual phenotypic flexibility and are involved in coordinating adjustments to variation in climate, resource abundance, social and internal conditions.

Although the role of GCs in mediating phenotypic adjustments has now been demonstrated in a large variety of taxa, it has become apparent that large variation exists in circulating concentrations within individuals as well as among individuals, populations, and species (Bókony et al., 2009; Bonier, Martin, Moore, & Wingfield, 2009; Goymann & Wingfield, 2004; Hau & Goymann, 2015; Korte, Koolhaas, Wingfield, & McEwen, 2005; Lema & Kitano, 2013; Williams, 2008; Wingfield, 2013a). These findings have motivated an interest in improving our understanding of

the pathways and phenotypic effects of GCs as well as the evolutionary processes that optimize their functioning in different ecological settings (Crespi, Williams, Jessop, & Delehanty, 2013; Hau & Goymann, 2015; Landys, Ramenofsky, & Wingfield, 2006; Romero et al., 2015; Wingfield, 2013a). The field of evolutionary endocrinology is still in its infancy and a large number of questions have remained unanswered (Hau, 2007; Hau & Goymann, 2015; Ketterson, Atwell, & McGlothlin, 2009; Ketterson & Nolan, 1999; Zera, Harshman, & Williams, 2007). For example, to what extent are hormonal mechanisms involved in mediating repeatable variation in behavior among individuals? Can we assign hormonal phenotypes to individuals, and what fraction of phenotypic variance is determined by genetic, environmental, and internal factors? Are different aspects of a hormonal phenotype, like circulating concentrations, receptor distributions, and plastic responses to external and internal information, equivalently relevant for fitness? How might selection act on hormonal signaling cascades and the phenotypes they mediate? Which forces of evolution are most relevant? And finally, at what rates may diverse components of hormonal cascades evolve?

Addressing such evolutionary questions for GCs and many other hormones will be of great importance in the near future. Since hormonal signals provide an interactive interface between the organism and its environment, advances in our understanding of the scope for evolution in this intricate system will be critically important for evaluating whether major changes in environmental conditions will pose a threat to populations. Human–induced environmental change has brought on particularly rapid and drastic alteration in habitats and climate on a global scale, raising the question whether ancient mechanisms like hormonal systems can keep up with the pace and the ongoing multifaceted changes in the environment (Wingfield, 2015).

To highlight these issues, in this review we first provide a brief introduction of the synthesis, regulation, and functions of GCs. In Section 2, we discuss evidence for individual consistency of hormonal traits, and why we should carefully parse hormone-behavior phenotypes into within- and among–individual variation to make progress in our understanding of evolutionary patterns. Next, in Section 3, we review studies estimating the heritability of GC traits and their responses to selection, also discussing the potential for selection to act by highlighting the fitness implications of hormonally mediated phenotypes. In Section 4, we introduce and discuss reaction norm approaches that will aid our understanding of flexible traits like

GCs, outline environmental and internal factors that are known to cause GC flexibility, and contrast the costs and benefits of hormonally mediated phenotypic flexibility. Finally, in Section 5, and throughout this review, we aim at providing suggestions for promising research avenues that we think will shed light on the evolution of hormonally mediated phenotypes.

We concentrate our review on hormonal traits that can be easily measured in intact animals, circulating plasma concentrations, because most studies in ecological and evolutionary endocrinology are aimed at linking an individual's hormone profile to its expressed phenotype and the resulting fitness. Circulating hormone concentrations also are systemic signals that likely affect many tissues simultaneously and thereby exert pleiotropic effects on the phenotype. It is important to note, however, that circulating hormone concentrations are just one aspect of an individual's hormonal phenotype; therefore, where relevant, we discuss other components of hormonal signaling cascades including binding proteins, enzymatic processes and receptors. Because of our own expertise, we particularly highlight studies from bird species, but also include examples from other taxa to illustrate general patterns. Finally, given space constraints we narrow our focus to GC phenotypes and flexibility during adulthood. It is well known that GC phenotypes of individuals are influenced by experiences during early life (maternal and/or developmental effects) and epigenetic effects (Adkins-Regan, Banerjee, Correa, & Schweitzer, 2013; MacDougall–Shackleton, Schmidt, Furlonger, & MacDougall–Shackleton, 2013; Weaver et al., 2004). We summarize some of these effects in Section 1.2, but refrain from discussing developmental effects further in this review.

1.1 Functions of Glucocorticoids

The main GC in many mammals including humans and teleost fish is cortisol, while birds, amphibians, reptiles, and some small mammals primarily have corticosterone—although species can also have both (and elasmobranch fishes have 1-hydroxycorticosterone; Bentley, 1998). GCs are synthesized from cholesterol through the action of several enzymes (Denver, 2009; Nelson, 2011). The main sources of circulating GCs are the adrenal cortices. The release of GCs begins with the integration of stimuli in the brain, leading to the secretion of neuropeptides, such as corticotropin-releasing hormone (CRH). CRH (but also arginine vasopressin, oxytocin, and mesotocin) then stimulate the secretion of the peptide adrencorticotropin (ACTH) from the pituitary (Fig. 1; Wingfield & Romero, 2001), which in turn acts on enzymes in adrenocortical cells to synthesize GCs. There is
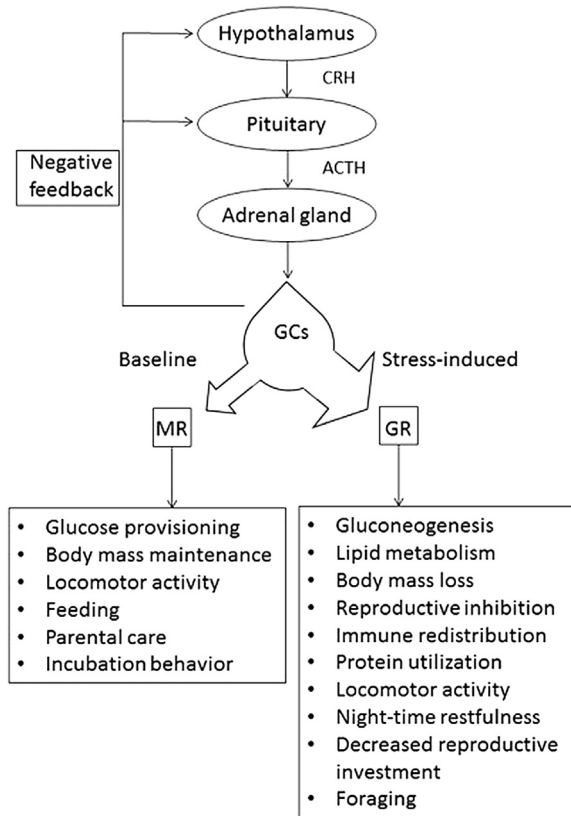
Figure 1 Schematic representation of glucocorticoid (GC) production pathways resulting from activation of the hypothalamic-pituitary-adrenal axis and relevant phenotypic actions of GCs in vertebrates. *CRH*, corticotropin-releasing hormone; *ACTH*, adrenocorticotropin; *MR*, mineralocorticoid receptor; *GR*, glucocorticoid receptor. Negative feedback might occur via both receptors, including in the hippocampus.

evidence that other tissues including the brain, lymph nodes, intestines, skin, and perhaps the heart can also synthesize GCs (Rensel & Schlinger, 2015; Taves, Gomez–Sanchez, & Soma, 2011).

Like other steroid hormones, GCs are small, lipophilic hormones that can easily diffuse through cell membranes to and from the blood stream, thus obviating the need for specific release or uptake mechanisms. In the blood, GC hormones likely are bound to large carrier proteins (corticosteroid–binding globulins, CBGs), although the precise role of CBGs in the functioning of GCs is still under debate (Breuner, Delehanty, & Boonstra, 2013; Schoech, Romero, Moore, & Bonier, 2013; see also Section 4.2). GC–responsive cells in central and peripheral tissues can express one or

both intracellular GC receptors: the mineralocorticoid (MR, or type I) or glucocorticoid (GR, or type II) receptor. Once GCs bind to MR or GR, changes in cell function can occur as a result of transcriptional effects within minutes, but also for longer timescales (Nelson, 2011). The MR has a high affinity to GCs, and is thus saturated at lower circulating concentrations than the low affinity GR. This difference in affinities has implications for their functions (see below). There is evidence for a third GC receptor located in the cell membrane (mGR), which exerts its effects through second-messenger systems and can lead to much faster changes (Breuner & Orchinik, 2009; Tasker, Di, & Malcher-Lopes, 2006). The time lag in change of cell function following the activation of the two intracellular receptors highlights that GCs (like other steroid hormones) primarily modulate the properties of cells or tissues, thereby changing the likelihood with which a phenotypic trait like behavior may be expressed (see also discussion in: Hau & Goymann, 2015). The transcriptional effects of steroid hormones can further be modified by a variety of molecules inside the cell; a topic that is discussed elsewhere (Wingfield, 2013b).

The deactivation of GC-induced actions constitutes another important part of their regulation and can occur via two pathways. First, GCs can be enzymatically converted into inactive compounds (Wingfield, 2013b; see also Section 4.2). Second, a negative feedback process can be activated through the binding of GCs to their receptors in hypothalamus, hippocampus, and pituitary (Nelson, 2011; though exact mechanisms and location of feedback still need to be clarified), shutting down increased production rates and allowing elevated levels to return to baseline.

GCs have been of special interest for behavioral endocrinologists because their actions differ at baseline versus stress-induced levels (Landys et al., 2006; Romero, 2004; Sapolsky et al., 2000). An undisturbed individual typically has low baseline concentrations of GCs, which support basic processes associated with energy metabolism and ongoing behavior including modulating glucose availability in a tissue-dependent manner, maintaining body mass, and mediating foraging and locomotor activity (Fig. 1; Beerling et al., 2011; Landys et al., 2006). In vertebrates, baseline concentrations of GCs show variation on a diel basis, often decreasing toward the end of the activity period and increasing at the end of the resting period before the individual resumes its daily activities (Breuner, Wingfield, & Romero, 1999; Krieger & Hauser, 1978; Rich & Romero, 2001). At baseline levels, GCs also increase moderately with the degree of energetic demands that an individual faces, for example, with increased workload, thermoregulatory

demands, reproductive investment, and immune responses (Landys et al., 2006; Romero, Dickens, & Cyr, 2009; see also Section 1.3). Effects of baseline GCs are typically mediated through the MR (Landys et al., 2006; Romero, 2004; Sapolsky et al., 2000; Fig. 1), although elevated baseline GC concentrations may also begin to bind to GR and mGR (Landys et al., 2006).

On top of such regular variation in baseline concentrations, GCs can show acute, large increases in circulating concentrations (Fig. 1), which occur typically within 2—3 min after an individual has experienced an unpredictable challenging stimulus (Romero, 2004; Sapolsky et al., 2000; Wingfield et al., 1998). Such stimuli often are labeled "stressors," but note that appetitive and rewarding stimuli can increase GC concentrations equally as noxious ones (Koolhaas et al., 2011). These elevated (or "stress-induced") concentrations typically are 2—10-folds higher than baseline concentrations, and reach their maximum within 15—60 min after the onset of the stressor. Stress-induced GC concentrations exert their actions mostly by binding to GR (Landys et al., 2006; Romero, 2004; Sapolsky et al., 2000). They are considered to support the "emergency life history stage" (Wingfield et al., 1998) by rapidly promoting a suite of processes that increase the ability to cope with the challenging situation through gluconeogenesis to increase blood glucose levels; catabolism of energy reserves (protein, fat, glycogens); and inhibition of energy storage to mobilize lipids, amino acids, and glucose; promotion of cardiovascular functions, an increase in locomotor and foraging activity (Sapolsky et al., 2000). At the same time, they serve to reallocate available energy reserves by inhibiting or redirecting processes that are not immediately relevant for survival, including immune function, reproduction, digestion, and growth (Sapolsky et al., 2000). The functions of GCs can vary with time; over longer timescales (hours) stress-induced concentrations of GCs are thought to help the individual recover from and prepare for future challenging experiences (Sapolsky et al., 2000), eg, by increasing foraging behavior, decreasing metabolic rate, and promoting night-time restfulness (Wingfield et al., 1998). Elevated GC concentrations also initiate negative feedback to restore baseline concentrations (Romero, 2004). This negative feedback can help minimize adverse effects of longer term elevated GC levels, such as the inhibition of reproduction and immune function, an impairment of cognitive effects, and decreases in brain cell numbers (summaries in: McEwen, 2000; Sapolsky, Krey, & McEwen, 1986; Wingfield et al., 1998).

In light of the divergent functions of GCs at baseline and stress-induced concentrations, which are likely mediated by different receptors, we will discuss them as separate traits throughout this review (Jenkins, Vitousek, Hubbard, & Safran, 2014; Landys et al., 2006; Romero, 2004; Sapolsky et al., 2000). However, where relevant, we also emphasize emerging knowledge of interactions among the different levels of the HPA axis (Crespi et al., 2013).

1.2 External, Internal, and Developmental Factors Affecting GC Regulation

A number of excellent reviews exist that discuss the exogenous and endogenous factors that can modify GC concentrations and their effects (eg, Boonstra, 2004; Busch & Hayward, 2009; Koolhaas et al., 2011; Moore & Jessop, 2003; Romero, Reed, & Wingfield, 2000; Wingfield & Ramenofsky, 2011). Hence here we refrain from a detailed review on this topic. However, in the interest of a holistic understanding of GCs we provide a condensed discussion of some relevant factors below.

1.2.1 Variation in External Factors
1.2.1.1 Inclement Weather

Since the early days of environmental endocrinology inclement weather such as storms has been known to elevate GC concentrations of wild avian populations (Wingfield, Moore, & Farner, 1983), and subsequently observed in both adults (Astheimer, Buttemer, & Wingfield, 1995; Smith, Wingfield, & Veit, 1994; Wingfield, 1985b; see review in: Wingfield & Ramenofsky, 2011) and nestlings (Bize, Stocker, Jenni-Eiermann, Gasparini, & Roulin, 2010). Rainfall is also effective in increasing GC levels in captive birds (de Bruijn & Romero, 2013). In avian species, the elevation of baseline and stress-induced GC concentrations by inclement weather can depend on an individual's life history state, such as breeding condition (Wingfield et al., 1983) or molt status (Romero et al., 2000), and on sex (Wingfield, 1985a). Other types of inclement weather such as new snowfall can also raise baseline and stress-induced GC concentrations in wild birds (Astheimer et al., 1995; Rogers, Ramenofsky, Ketterson, Nolan, & Wingfield, 1993).

In north temperate climates, inclement weather often is accompanied by decreases in ambient temperatures. Birds tend to increase baseline and stress-induced GC concentrations with lower ambient temperatures (eg, Jenni-Eiermann, Glaus, Gruebler, Schwabl, & Jenni, 2008), although patterns again can depend on life history stage (summary in: Romero et al.,

2000). In captive European starlings (*Sturnus vulgaris*), even short-term decreases in ambient temperature by 3°C were sufficient to increase baseline GCs (de Bruijn & Romero, 2011). Likewise, in mammals (where GC metabolites in feces are often measured instead of plasma concentrations) weather extremes increase concentrations of GC metabolites (Corlatti, Palme, & Lovari, 2014; Gesquiere et al., 2008; Sheriff et al., 2012). Conversely, increases in GCs with high temperatures have been observed in reptiles (Dunlap, 1995; Tyrrell & Cree, 1998).

1.2.1.2 Food Availability

Elegant studies in Arctic seabirds demonstrated that especially baseline GCs, and to some extent stress–induced levels, increase during periods of low food abundance in adults (Buck, O'Reilly, & Kildaw, 2007; Kitaysky, Piatt, & Wingfield, 2008; Kitaysky, Wingfield, & Piatt, 1999), and chicks (Kitaysky, Kitaiskaia, Wingfield, & Piatt, 2001; although in some species chicks show opposite responses, Kitaysky, Romano, Piatt, Wingfield, & Kikuchi, 2005). Similar effects were observed in wild (Clinchy, Zanette, Boonstra, Wingfield, & Smith, 2004; Kaiser, Sillett, & Webster, 2014; Schoech, Bowman, Bridge, & Boughton, 2007; Schoech, Bowman, & Reynolds, 2004) and captive songbirds (Cornelius, Breuner, & Hahn, 2010; Lendvai et al., 2014; Lynn, Breuner, & Wingfield, 2003). Galàpagos marine iguanas (*Amblyrhynchus cristatus*) showed higher stress–induced GCs (but not baseline concentrations) when faced with extremely poor foraging conditions during an El Niño event (Romero & Wikelski, 2010). Further, unpredictable food availability, even if it does not alter body condition, can increase GC levels (Fokidis et al., 2012; Marasco, Boner, Heidinger, Griffiths, & Monaghan, 2015; but see Bauer, Glassman, Cyr, & Romero, 2011; Cote, Clobert, Poloni, Haussy, & Meylan, 2010). Interestingly, social information about food availability, like whether or not a neighboring individual was food deprived, can be an effective modulator of GC levels in birds (Cornelius et al., 2010).

1.2.1.3 Predation

The physiological, behavioral, reproductive, and psychological effects of predation pressure in vertebrates are comprehensively reviewed elsewhere (Clinchy, Sheriff, & Zanette, 2013). For example, male African stonechats (*Taxicola torquata axillaris*) that held territories overlapping with that of predatory shrikes (*Lanius collarius*) had elevated baseline GC concentrations during the parental phase (females showed the opposite response; Scheuerlein,

Van't Hof, & Gwinner, 2001). Similarly, song sparrows (*Melospiza melodia*) had higher baseline and stress-induced GC concentrations in habitats with high compared to low adult predation (Clinchy et al., 2004) or nest predation (Travers, Clinchy, Zanette, Boonstra, & Williams, 2010). Experimental exposure of wild male pied flycatchers (*Ficedula hypoleuca*) to a weasel decoy at their nest box increased baseline GC levels as well (Silverin, 1998). Effects of predation pressure on GC can be context-dependent, as great tits (*Parus major*) lacked a GC response to a stuffed predator in the wild, but responded dramatically in captivity (Cockrem & Silverin, 2002a). Predation can also increase fecal GC levels in wild snowshoe hares (*Lepus americanus*, Boonstra, Hik, Singleton, & Tinnikov, 1998; Sheriff, Krebs, & Boonstra, 2009, 2011), an effect confirmed in captivity (Sheriff et al., 2009). Conversely, habitat characteristics that reduce predation pressure such as presence of high quality cover, can reduce baseline GC levels in prey species (Bauer et al., 2013). The capture-restraint protocol used as a standardized method to increase GC concentrations (Astheimer, Buttemer, & Wingfield, 1994; Wingfield et al., 1994; Wingfield, Smith, & Farner, 1982) is often assumed to constitute a mild simulation of a predation event, and exposure to a predator typically elicits a stronger GC response (Canoine, Hayden, Rowe, & Goymann, 2002).

1.2.1.4 Social Interactions

Natural or experimental increases in population density have been linked to increased GC concentrations in mammal, bird, reptile, amphibian, and fish species, although several studies on diverse taxa failed to identify such a relationship (reviewed in: Creel, Dantzer, Goymann, & Rubenstein, 2013). In North American red squirrels (*Tamiasciurus hudsonicus*), fecal GC metabolites increased linearly with population density, and were also elevated in individuals exposed to a perceived increase in population density via playback of conspecific vocalizations (Dantzer et al., 2013). Likewise, experimental crowding of captive animals typically leads to increased GC concentrations (Wingfield et al., 1982). The effect of population density may depend on an individual's phenotype, like in female side-blotched lizards (*Uta stansburiana*) where one morph increased, while the other morph decreased baseline GC concentrations with population density (number of neighbors; Comendant, Sinervo, Svensson, & Wingfield, 2003). In birds, direct competitive interactions like those elicited during "simulated territorial intrusions" can elevate GC levels (Canoine & Gwinner, 2005; Gill, Costa, & Hau, 2008; Landys, Goymann, Raess, & Slagsvold, 2007; Silverin,

1993; Van Duyse, Pinxten, Darras, Arckens, & Eens, 2004), providing a possible link between GC concentrations and population density (Creel et al., 2013).

1.2.1.5 Social Status

An individual's status in a social group such as its rank can have dramatic influences on its HPA axis (reviewed in: Creel et al., 2013). However, whether dominant or subordinate individuals have elevated GC concentrations differs greatly among taxa. Several hypotheses have been proposed to explain this divergence. Possible factors include the degree of challenges (allostatic load, see section 1.3) associated with a specific rank (Goymann & Wingfield, 2004; Rubenstein & Shen, 2009), the degree of social support an individual receives (Abbott et al., 2003), rank stability, dominance style, and the exposure to stressors associated with a particular rank (Sapolsky, 2005).

1.2.2 Variation in Internal Variables

1.2.2.1 Sex Differences

GC responses to external and internal factors can vary between the sexes. Sex steroids such as androgens and estrogens are often involved in sex differences, although evidence is accumulating that additional factors related to an individual's genetic sex also contribute to divergence in HPA function and that they are established early in life (Deak et al., 2015; Panagiotakopoulos & Neigh, 2014). In laboratory rodents, females typically release CRH at higher concentrations and consequently reach higher GC concentrations when responding to stressors than males (Toufexis, Rivarola, Lara, & Viau, 2014). In rats, sex differences are also apparent in other aspects of the HPA axis including negative feedback mechanisms and CBG concentrations (Handa & Weiser, 2014; Panagiotakopoulos & Neigh, 2014). By contrast, sex difference in GC responses to stressors in humans may either be male biased or absent (Toufexis et al., 2014).

The reproductive (hypothalamo-pituitary-gonadal, HPG) axis and the HPA axis are known to interact reciprocally. At baseline levels, GCs often enhance reproductive processes, while their activation to stress-induced concentrations usually suppresses HPG function, thereby decreasing reproductive behavior and physiology (Wingfield & Sapolsky, 2003). In turn, the actions of sex steroids on the HPA axis vary by sex, and patterns differ across taxa. For example, natural or experimental increases in estradiol levels in female rats can increase both adrenocorticotropin and GC concentrations during a stressful event, while in males elevated testosterone levels have a

suppressive effect on HPA responses to stressors (Handa & Weiser, 2014; Panagiotakopoulos & Neigh, 2014; Toufexis et al., 2014).

Sex differences can also arise from divergences in reproductive investment, parental strategies, social status, and other aspects of life style (Bókony et al., 2009; Cavigelli & Caruso, 2015; Wingfield, O'Reilly, & Astheimer, 1995). In avian species, the sex that provides the most (or the essential) parental care typically has lower GC concentrations during the parental phase (Bókony et al., 2009; Wingfield et al., 1995). Some sex differences can be attributed to divergences in cumulative challenges ("allostatic load," see Section 1.3), with the sex carrying a greater cumulative load having higher GC concentrations (Goymann & Wingfield, 2004). For example, in social vertebrates, the sex that incurs more challenges from obtaining and maintaining its dominance status has higher GC concentrations, independent of whether it is dominant or subordinate (Goymann & Wingfield, 2004; Rubenstein & Shen, 2009).

1.2.2.2 Body Condition

As a regulator of metabolism and behavior, GC secretion is responsive to the body condition of an individual. Body condition, typically expressed as a measure of body mass relative to body size, is often used as a proxy for the amount of energy reserves that an individual carries and allocates to processes should the need arise. In avian species, individuals with lower body condition often have increased baseline GC concentrations (Angelier, Moe, Blanc, & Chastel, 2009; Jaatinen et al., 2013; Jenni-Eiermann et al., 2008; Kitaysky et al., 1999; Lindstrom, Hawley, Davis, & Wikelski, 2005; Love, Chin, Wynne-Edwards, & Williams, 2005). Stress-induced GC concentrations in birds vary with body condition in more complex ways, as positive (Fokidis, Hurley, Rogowski, Sweazea, & Deviche, 2011; Jenni, Jenni-Eiermann, Spina, & Schwabl, 2000; Schoech et al., 2007; Smith et al., 1994), negative (Angelier, Moe, et al., 2009; Kitaysky et al., 1999; Smith et al., 1994), and no relationship have been observed (Lindstrom et al., 2005; Lormee, Jouventin, Trouve, & Chastel, 2003). A likely explanation for this diversity of relationships is that body condition can indeed influence HPA activity, but that the direction of this activation will change with the context under which it occurs.

1.2.2.3 Life History State

The activity of the HPA axis also varies rather dramatically with the life history state an individual is in, a topic excellently summarized elsewhere

(Romero, 2002). Both baseline and stress–induced GC concentrations are higher during the reproductive phase in reptiles, amphibians, and avian species, but not in mammals. This pattern likely results from a combination of the need to mobilize energy for costly reproductive processes, to express specific reproductive behaviors, and to be prepared for a number of stressors that commonly occur during the breeding season (Romero, 2002). However, certain species or individuals can show reduced stress–induced GC concentrations during the breeding season, for example, semelparous species that breed only once in a life time or the sex (or both sexes) that provide essential parental care in species with short breeding seasons (Crossin, Love, Cooke, & Williams, 2016; Holberton & Wingfield, 2003; O'Reilly & Wingfield, 2001; Wingfield & Sapolsky, 2003). In other seasonal states (pre- or postbreeding), GCs are often much lower than during breeding, and in birds GC concentrations are especially low during molt (Astheimer et al., 1995; Romero, 2002; Romero & Remage-Healey, 2000; Romero, Soma, & Wingfield, 1998b).

1.2.2.4 Age

Stress–induced concentrations have been shown to decrease with age in female rats (Stein–Behrens & Sapolsky, 1992), in bird species (Lendvai, Giraudeau, Bókony, Angelier, & Chastel, 2015; Wilcoxen, Boughton, Bridge, Rensel, & Schoech, 2011), and in older age-classes of green turtles (*Chelonia mydas*; Jessop & Hamann, 2005), although patterns can also be complex or opposite. In free-living common terns (*Sterna hirundo*), a decrease in stress–induced GC concentrations with age was accompanied by a reduced GC response to adrenocorticotropin (ACTH) injections, suggesting a decline in adrenal capacity to release maximal concentrations of GC (Heidinger, Nisbet, & Ketterson, 2006, 2008). However, other mechanisms may contribute to this phenomenon, including age-dependent changes in hippocampal GRs (Stein–Behrens & Sapolsky, 1992).

1.2.2.5 Oxidative Stress

Oxidative stress (OxS) occurs when the metabolic production of reactive molecule species (pro-oxidants) outweighs the antioxidant protection of the organism (Halliwell & Gutteridge, 2007). OxS can impair DNA function, degrade proteins and lipids, impact cognitive and noncognitive brain performance (Sorce & Krause, 2009), and can decrease fitness-relevant traits including reproduction and longevity (Costantini, 2008; Haussmann & Mauck, 2008; Metcalfe & Alonso-Alvarez, 2010; Monaghan, Metcalfe, &

Torres, 2009), including effects on biomarkers of senescence such as telomeres (Haussmann & Marchetto, 2010). There is a clear bidirectional link between GCs and oxidative stress (Cohen, Martin, Wingfield, McWilliams, & Dunne, 2012; Costantini, Marasco, & Moller, 2011). For example, elevated GC concentrations can increase the metabolic production of reactive molecule species, decrease the organismal antioxidant protection, and disrupt the repair mechanisms of oxidative damage (Haussmann & Marchetto, 2010). Thus, an endocrine stress response is often associated with a condition of OxS both in the short and long term (Haussmann, Longenecker, Marchetto, Juliano, & Bowden, 2012). In turn, cell state can also influence GC dynamics. For example, pro-oxidant molecules can affect the functioning of the HPA axis, like when only moderate levels of OxS inhibit the expression of the genes encoding for GRs (Allen & Tresini, 2000). Reactive molecule species may not only affect receptor gene expression but also alter the function of already expressed ones (Morel & Barouki, 1999). Common reactive oxygen species can oxidize the amino acid methionine, which is a component of ACTH, thus disrupting its function (Brot & Weissbach, 1983). Furthermore, the free radical nitric oxide is a regulator of steroidogenesis in several tissues and can stimulate the production of GCs by mimicking the effect of ACTH (Mohn et al., 2005).

1.2.2.6 Immune Function

Finally, interactions of GCs with the immune system are also well-known. In general, GCs are considered to suppress immune function, although specific patterns often vary depending on type and time course of the stressor and the specifics of the immune response (Demas, Adamo, & French, 2011; Martin, 2009). While chronic stress usually is immunosuppressive (Sapolsky et al., 2000), acute stressful experiences can lead to improved immune function, for example, in skin (Dhabhar, 2000). However, the interactions between the HPA axis and immune function clearly are bidirectional (Deak et al., 2015; Demas et al., 2011; Turnbull & Rivier, 1999). Immune activation typically stimulates GC release through immune signals like cytokines and growth factors (Turnbull & Rivier, 1999), often stimulating CRH and ACTH secretion centrally, but also acting within the adrenal gland (Bornstein, Rutkowski, & Vrezas, 2004). The resulting increases in GCs are thought to suppress immune processes in order to contain the immune response and prevent it from overshooting. Indeed, wild house finches (*Carpodacus mexicanus*) showing symptoms of a *Mycoplasma* infection had elevated stress–induced concentrations of GCs (Lindstrom et al., 2005).

Likewise, captive song sparrows injected with lipopolysaccharide (LPS) increased baseline GCs within 6 h (Adelman, Bentley, Wingfield, Martin, & Hau, 2010), while free-living house wrens (*Troglodytes aedon*) laid eggs with higher GC content following LPS injection (Bowers, Bowden, Sakaluk, & Thompson, 2015). Some infections can also lead to a decrease in HPA activity, as when rainbow trout (*Oncorhynchus mykiss*) were infected with a hemoflagellate (Madison, Woo, & Bernier, 2013). Immune processes can also interact with GCs locally at the site of the inflammation (or within immune organs like lymphocytes, Taves et al., 2011). For example, in mammalian skin there is evidence for local GC production (Taves et al., 2011), which can be induced by cytokines and wounding (Vukelic et al., 2011). Furthermore, GRs in skin can be influenced by wounding; in captive house sparrows (*Passer domesticus*) wounding decreased the density of MR in skin within 24 h (Lattin, Durant, & Romero, 2015).

1.2.3 Effects During Development

Developmental effects are an important topic in stress physiology because of their defining and often long-lasting impact on organismal physiology. However, given space constraints we only provide a condensed overview below and refer interested readers to excellent reviews (Brown & Spencer, 2013; Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006; Love, McGowan, & Sheriff, 2013; Monaghan, 2008; Monaghan & Haussmann, 2015). Conditions during early development (both pre- and postnatal) including food availability, sibling competition, the quality of parental care, exposure to environmental stressors, and immune stimulation can have direct canalizing effects on the GC phenotype of offspring that can last into adulthood, thereby altering fitness across the life span (Breuner, 2008; Love et al., 2013; Love & Williams, 2008b; Monaghan & Haussmann, 2015; Sheriff & Love, 2013; Spencer, Evans, & Monaghan, 2009; Wada, 2008). Additionally, stressors experienced by the mothers can also induce indirect effects on offspring phenotype across vertebrate taxa, resulting in *trans*-generational hormonal plasticity that typically involve the actions of GCs (Giesing, Suski, Warner, & Bell, 2011; McGowan et al., 2009; Monaghan & Haussmann, 2015; Spencer et al., 2009; Weaver et al., 2004). In general, stressed mothers produce offspring with an altered HPA axis function, as represented by a reduced density of GRs, higher GC concentrations during an endocrine stress response, decreased capacity to recover from an acute stressor, overall higher GC and glucose levels, and reduced sensitivity to insulin (Love & Williams, 2008b; Sheriff & Love, 2013). Often, these

physiological patterns are associated with specific behavioral alterations such as decreased locomotor activity, impairment in special learning, and a general state of fearfulness. The classical interpretation of these effects is as being negative for the fitness of the individual. However, developmental phenotypic plasticity can be highly adaptive, for example, when individuals are better able to cope with an environment that matches their early-life experience (different names have been put forward for this phenomenon, including "environmental matching," Monaghan, 2008; "maternal match hypothesis," Breuner, 2008; Love & Williams, 2008b; "predictive adaptive responses," Monaghan & Haussmann, 2015). For example, female sticklebacks (*Gasterosteus aculeatus*) living in environments with a high predation risk can convey information on their current environment by transferring more GCs into their eggs, producing offspring that are able to rapidly mount a stress response, and to exhibit enhanced anti-predator behavior such as reduced locomotor activity and greater fearfulness or anxiety (Giesing et al., 2011). Likewise, the functioning of the HPA axis of mice that were raised under matched adverse conditions was similar to individuals that were raised in a matched benign environment, while mismatched conditions caused a downregulation of baseline GCs (Santarelli et al., 2014). Overall, these studies demonstrate that GC phenotypes are difficult to interpret without knowing the past and present conditions experienced by an individual.

The mechanisms underpinning developmental plasticity of the HPA axis are not entirely known, but it is becoming increasingly clear that epigenetic processes, for example, DNA methylation that silences the transcription of genes encoding for the GR play a major role (Love et al., 2013). DNA methylation can occur even during postnatal phases of development. Rats receiving high quality parental care by their mothers (eg, with a high frequency of licking and grooming), for example, show lower levels of methylation of GR genes and consequently a higher expression of GR in the brain (Liu et al., 1997; Weaver et al., 2007). This in turn was associated with a decreased GC stress response and enhanced negative feedback. Epigenetic effects do not only involve GR expression. Daily separation of mice pups from their mother induces a hypomethylation of genes encoding for proopiomelanocortin, one of the precursors of ACTH (Patchev, Rodrigues, Sousa, Spengler, & Almeida, 2014). The resulting overexpression of this gene leads to high levels of ACTH and an ensuing modification of HPA axis function (Patchev et al., 2014). Taken together these studies indicate that early life experiences can cause major changes in the HPA axis that

last into adulthood. Early experience can shape the capacity for resilience of an individual to a particular environment. Since epigenetic processes are complex and multifaceted, further studies are needed to understand how they generate individual variation and fitness consequences in relation to life–history traits and environmental conditions.

1.3 Concepts for GC Regulation: Homeostasis, Allostasis, and Reactive Scope

The main function of GCs is to maintain organismal metabolic balance while at the same time coordinating responses to environmental and internal stimuli. "Homeostasis" is the term that has been traditionally used for describing processes that serve to maintain stability in internal variables (Cannon, 1932; Fig. 2: regulation within each level). However, it has become apparent that the concept of homeostasis is too restrictive in light of the multitude of regulated changes in GCs that occur in individuals over the course of a day, across seasons, and during acute challenging events.
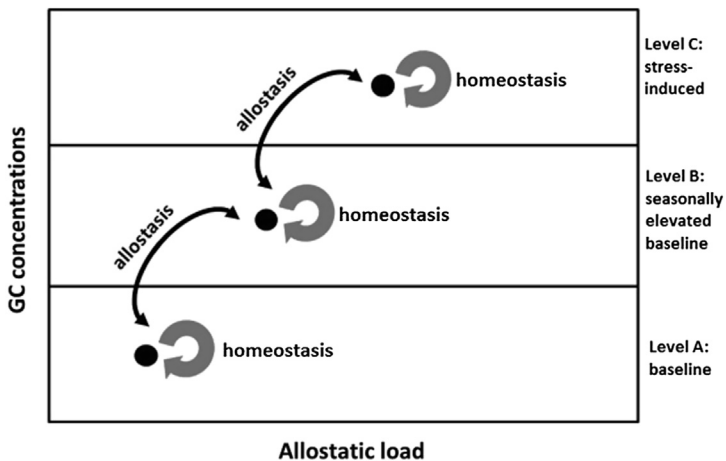
Figure 2 Graphic depiction of homeostatic (keeping set points stable, *gray circular arrows*) and allostatic (leading to changing set points, *black arrows*) mechanisms that circulating glucocorticoids (GCs) contribute to. The right-side axis indicates different allostatic states. Low GC concentrations (level A) could be maintained during the nonbreeding season, GCs might be elevated (level B) during the breeding season and level C concentrations may occur when an individuals enters an "emergency life history state." *Adapted from 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.* General and Comparative Endocrinology, 148*(2), 132–149.*

The concept of "allostasis" (McEwen & Wingfield, 2003; Sterling & Eyer, 1988) and its refinement "reactive scope" (Romero et al., 2009) have instead become highly useful models to integrate and describe the regulation of GCs and their organismal consequences. Allostasis is defined as "maintaining stability through change" (McEwen & Wingfield, 2003), and refers to a regulation in internal set points according to an individual's requirements via changes in GC levels (Landys et al., 2006; Fig. 2). For example, during the nonbreeding season in a temperate zone habitat in fall, a sedentary bird may have relatively low energy requirements because its maintenance costs during this time of year are small (Fig. 2, level A). By contrast, during cold spells in winter when thermoregulatory costs are high, or when an individual transits into a breeding state and reproductive investment increases metabolic costs, internal set points may be upregulated to support a state of higher metabolic turnover (Fig. 2, level B).

The reactive scope model is built on the same premise that set points are being regulated by GCs, but encompasses a wider set of external and internal conditions, and applies the allostasis model more strongly to natural situations (Romero et al., 2009). Both models recognize that the range of challenges an organism is exposed to at one point in time, including the costs of allostasis, add up to its "allostatic load" (McEwen & Wingfield, 2003). They also agree on the view that as long as the individual has sufficient internal and external resources available, the mechanisms of allostasis or "reactive homeostasis" (Romero et al., 2009) enable it to regulate set points accordingly and successfully cope with its allostatic load. However, if allostatic load increased such that the individual entered an energy debt (McEwen & Wingfield, 2003), or otherwise exceeded its ability to cope (its "reactive scope"; Romero et al., 2009), then a state of "allostatic overload" or "homeostatic overload" would be reached (McEwen & Wingfield, 2003; Romero et al., 2009). Such a state is characterized by a high and potentially prolonged GC secretion, which eventually may compromise health and Darwinian fitness by increasing cellular wear-and-tear, tissue pathologies, and disease risk (summaries in: McEwen & Wingfield, 2003; Romero et al., 2009; see also Section 4.4).

The allostasis and reactive scope models have proven useful for explaining the regulation in baseline GC levels on a diel or seasonal basis, differences between the sexes during the reproductive season or among individuals in social hierarchies (Goymann & Wingfield, 2004). The models also illustrate the conditions under which individuals are expected to elevate GC concentrations into stress–induced ranges, and when a dysregulation of GC

secretion with health consequences may occur. The allostasis and reactive scope frameworks have become heuristically valuable for improving our understanding of individual differences in GC responses to internal and external conditions. Their formulation provides a basis to begin to address evolutionary topics like whether we can identify components of GC traits that are repeatable (and potentially heritable). Approaching such questions requires the careful use of statistical and experimental tools to analyze within–individual variation in hormonal traits in relation to the variation observed among conspecifics.

2. PARSING TWO NOTORIOUSLY VARIABLE TRAITS, BEHAVIOR AND HORMONE CONCENTRATIONS, WITHIN AND AMONG INDIVIDUALS

Adjustments in hormonal and behavioral traits to changing environmental, social, and internal fluctuations are made possible through the process of phenotypic *flexibility*—the variable expression of traits within an animal's lifetime (Piersma & Drent, 2003). We distinguish reversible phenotypic *flexibility* from phenotypic *plasticity*, the latter often referring to developmentally induced, irreversible phenotypic changes occurring within the lifetime of an individual (Pigliucci, 2005; West–Eberhard, 2003; Whitman & Agrawal, 2009). In light of our focus on processes during adulthood (see Section 1), we consider how GCs are related to phenotypic *flexibility*.

We know that behavioral and hormonal traits are notoriously flexible; at the same time, it is also known that not all traits within an individual, nor all individuals within a population are equally capable of flexible changes in behavior (Bell, Hankison, & Laskowski, 2009) or hormones (Williams, 2008). In order to approach questions about phenotypic variation, it is essential to understand the hierarchical nature of trait variation (Fig. 3), because the biological implications depend on which levels variation is observed at (reviewed in: Martin, Nussey, Wilson, & Réale, 2011; Westneat, Wright, & Dingemanse, 2015). Statistical methods for decomposing variation in traits, including mixed effects models, are now widely accessible (Dingemanse & Dochtermann, 2013; Westneat et al., 2015). As a consequence, a renewed focus on understanding the proximate basis for trait variation has led to a quickly growing body of empirical and theoretical work.

The first step in understanding the mechanistic basis or the evolution of trait flexibility is to partition the levels at which single traits, or their
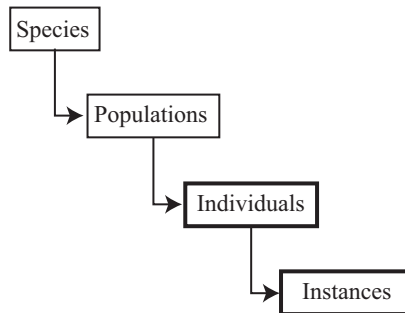
Figure 3 A single trait can vary at multiple levels, which can be nested within each other. For example, baseline (glucocorticoid concentrations GCs) can vary across different species, across different populations of a single species, across individuals within a single population (ie, *among-individual variation*) and within an individual over time (across instances; ie, *within-individual variation*). In this review we focus on variation at these two lower levels because they provide the raw material for selection to act on and a window into phenotypic flexibility, respectively.

combinations, vary. Because these topics have been discussed in detail elsewhere (Biro, 2012; Dall & Griffith, 2014; Dingemanse & Dochtermann, 2013; Lema & Kitano, 2013; Réale, Dingemanse, Kazem, & Wright, 2010), here we briefly introduce these themes and then focus on GC–behavior relationships in the context of external (cf. environmental) and internal (cf. condition and state) variation.

2.1 Multilevel Approaches

Heritable variation in traits or in trait flexibility is a prerequisite for evolution. Estimating either of these in free-living animals is often challenging because of the lack of pedigree information or multigenerational sampling; for trait flexibility the need for a repeated sampling of individuals creates additional challenges. As a start, it is therefore useful to estimate the repeatability of traits, which can set an upper bound on heritability (Lessells & Boag, 1987; but see Dohm, 2002). Note that *repeatability* is a measure of the variability of a trait at the population level, not at the individual level. For estimates of variation over time within an individual animal, *consistency* can be estimated using a number of methods (eg, Cummings & Mollaghan, 2006). Estimates of consistency can be high regardless of whether there is any variation among individuals, whereas repeatability estimates can only be high when there is relatively high variation among individuals relative to the variation within individuals. Traits that exhibit repeatable variation have, in principle, the potential to evolve in response to selection. For

this reason, our review focuses on repeatability. Repeatability (*r*) is the fraction of total phenotypic variance that is explained by the variance *among* individuals, and typically takes values from zero to one (Dingemanse & Dochtermann, 2013; Lessells & Boag, 1987).

$$r = \sigma_a^2 / \left(\sigma_a^2 + \sigma_w^2\right)$$

Traits with high among- (σ_a^2) and low within-individual variance (σ_w^2) have high repeatability and vice versa (see Fig. 4, panels a, b, f, g). However, it is important to consider the values of both among- and within individual variance to fully understand their relative contribution to repeatability. For dynamic traits such as behavior and hormone levels, *r* values of 0.3–0.5 are considered moderate to high (Baugh, Oers, Dingemanse, & Hau, 2014; Bell et al., 2009). Within-individual variance reflects the amount of variation across multiple observations of the same individual over time and therefore represents the flexibility of an individual's phenotype in response to external (eg, ambient temperature) and internal variables (eg, age, health status). Variation in the measured traits within an individual over time also reflects inherent measurement error as well as the potential influence of sensitization or habituation as a consequence of repeated sampling (Bell & Peeke, 2012). Therefore, the within-individual variance component is not strictly an estimate of flexibility. The among-individual variance component describes how much individuals in a population or sample differ from each other in their *average* phenotype. It is this component that evolutionary biologists are typically interested in because it represents those aspects of the phenotype that are stable over the course of the measurement period (eg, social hierarchy), arising in part from nongenetic factors such as maternal effects and environmental variables, as well as from heritable genetic differences. If heritable genetic variation is present, an evolutionary response to selection is possible. Therefore, among- and within-individual variation represents two levels that jointly contribute to phenotypic variance (see Fig. 4; Dingemanse & Dochtermann, 2013; Westneat et al., 2015).

2.2 How Repeatable Are Behavioral and Hormonal Traits?

Considerable effort in the field of animal personality in the past decades has documented the repeatability of behavioral traits in an assortment of species (Bell et al., 2009; Dall, Houston, & McNamara, 2004; Sih, Bell, Johnson, & Ziemba, 2004). Briefly, there is widespread support for the idea that some individuals in a population are, on average, more aggressive, risk-taking, or bold, for example, than other individuals. In cases where heritabilities have
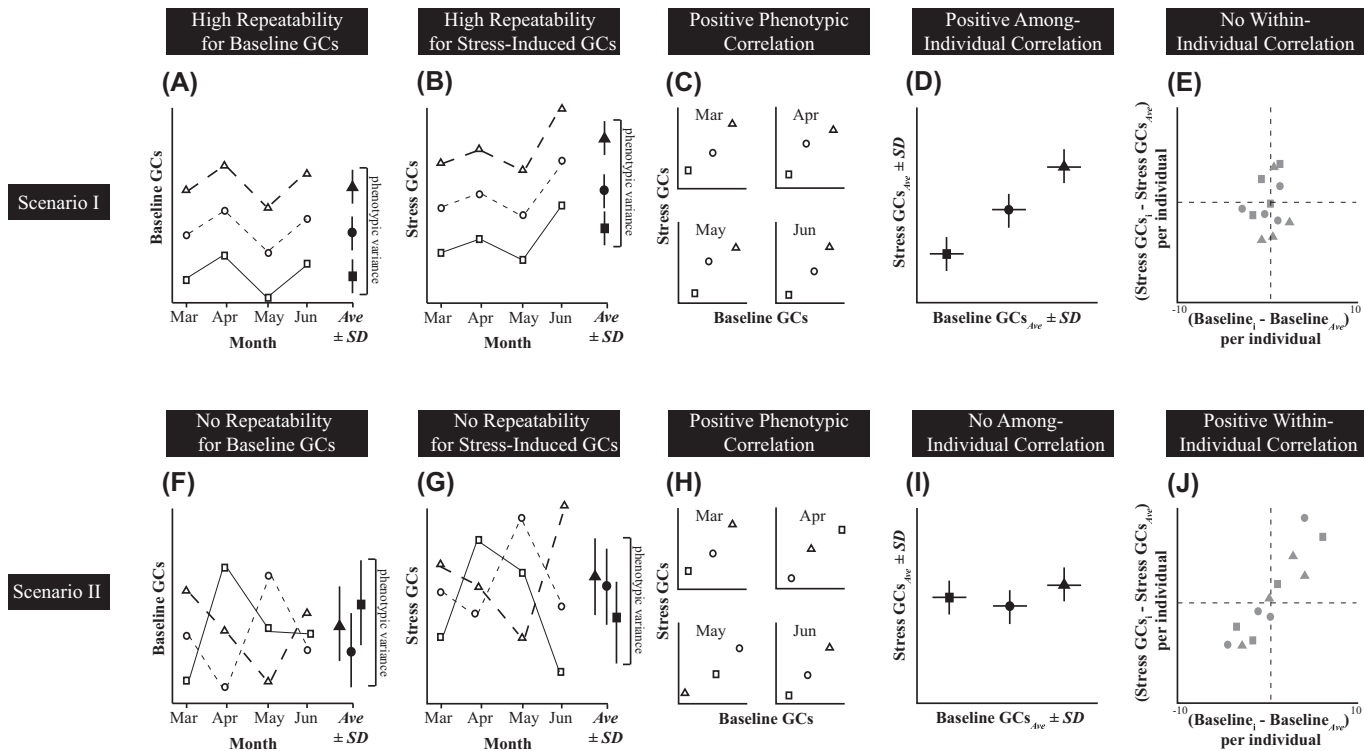
Figure 4 Illustrations of two hypothetical scenarios in which concentrations of baseline and stress-induced glucocorticoid concentrations (GCs) are measured at four time points in each of three individuals (*square*, *circle*, and *triangle*) and contain the same amount of phenotypic variance (ie, total variance). In scenario I, individuals differ consistently from each other in both baseline (A) and stress-induced (B) GCs, as indicated by the consistent rank order of each subject (eg, *triangles* are always above *circles* at any given month). Therefore, averages for both baseline and stress-induced GCs in these three individuals are distinct (solid symbols in (A) and (B)) and correspondingly, repeatability (ie, significant among individual variance) is high. In any given month, the rank order of individuals for baseline is the same as that for stress-induced GCs, leading to a positive phenotypic correlation between these two hormonal traits (C). This positive phenotypic correlation is driven by a positive among-individual correlation, and can be illustrated by the individual averages for baseline versus stress-induced concentrations (D), which is due to the fact that the rank order of individuals is stable across months (eg, *triangles* are always highest for both baseline and stress-induced). Note that error bars in (D) illustrate that there is also some within-individual variance in both baseline and stress-induced measurements. Within-individual correlations can be depicted by plotting the deviation from the average per individual for each measure (*i*) of baseline (*x*-axis) versus the deviation from the average per individual for each measure (*i*) of stress-induced GC concentrations (*y*-axis). The lack of a within-individual correlation is depicted in (E), indicating that the phenotypic correlations in (C) are driven principally by the among-individual correlation (D). Scenario II depicts an alternative situation in which each individual varies considerably from one month to the next leading to a lack of repeatability (ie, no significant among-individual variance) for both baseline (F) and stress-induced GCs (G). Nevertheless, in any given month, the ranking of individuals for baseline is the same as that for stress-induced GCs, leading to a phenotypic correlation (H) similar to scenario I. Because of the lack of repeatability, this phenotypic correlation cannot be driven by an among-individual correlation, which is illustrated by the lack of relationship between the average baseline and stress-induced phenotypes (I). Instead, it must be driven by a within-individual correlation (J), indicating the role of environmental factors in comodulating baseline and stress-induced GC concentrations simultaneously within the individual.

also been measured, these consistent behavioral differences are explained in part by heritable genetic variation among individuals (Boake, 1994; van Oers, de Jong, van Noordwijk, Kempenaers, & Drent, 2005; Stirling, Réale, & Roff, 2002). Furthermore, these individual behavioral differences can be the target of natural and sexual selection (Dingemanse & Réale, 2005; Smith & Blumstein, 2008; Thomson, Watts, Pottinger, & Sneddon, 2011).

Many of the common behavioral traits measured in studies of animal personality (eg, exploration, risk-taking, aggression) may be mediated by steroid hormones (eg, GCs, testosterone; Martins, Roberts, Giblin, Huxham, & Evans, 2007; While et al., 2010). This observation has served as the motivation to explore the potential endocrine mechanisms that subserve these consistent behavioral differences (Baugh, van Oers, Naguib, & Hau, 2013; Baugh et al., 2012; Cockrem, 2007; Koolhaas, de Boer, Buwalda, & van Reenen, 2007; Koolhaas et al., 1999; van Oers, Buchanan, Thomas, & Drent, 2011). A recent set of studies estimating the repeatability of GC profiles in vertebrates have provided some answers as well as new challenges for this field.

Studies in wild populations have reported negligible to moderate repeatabilities for circulating baseline and stress-induced GC concentrations (0–0.5; Baugh et al., 2014; Cockrem, Barrett, Candy, & Potter, 2009; Cook, O'Connor, Gilmour, & Cooke, 2011; Grace & Anderson, 2014; Jaatinen et al., 2013; Lendvai et al., 2015; Ouyang, Hau, & Bonier, 2011; Patterson, Hahn, Cornelius, & Breuner, 2014; Rensel & Schoech, 2011; Small & Schoech, 2015; Sparkman et al., 2014; Vitousek, Jenkins, & Safran, 2014). Recent reports suggest that stress-induced GC concentrations might exhibit higher repeatabilities compared to baseline concentrations (Ouyang, Hau, et al., 2011; Small & Schoech, 2015). Also, in captive populations repeatability estimates are typically higher (Cockrem & Silverin, 2002b; Pottinger, Pickering, & Hurley, 1992; Romero & Reed, 2008; Schjolden, Stoskhus, & Winberg, 2005; Sparkman et al., 2014; Wada et al., 2008). On the one hand, the fact that GC repeatability is higher in captive populations may not seem surprising given that many external factors—which are known to modulate GCs—are controlled for (eg, temperature; sampling time of day; Breuner et al., 1999; Romero et al., 2000), thereby minimizing the factors that can inflate the within-individual variance component and establishing a level playing field for the detection and estimation of average individual differences. On the other hand, this pattern of hormonal repeatability is in contrast to what has been reported for behavioral repeatability, which a meta-analysis found to be higher under natural field conditions

(Bell et al., 2009). It is interesting to speculate about the basis for this pattern. Are hormones more responsive to variation in external conditions, which is minimized in captivity, whereas behavior is more constrained by an individual's social circumstances, which are removed in a captive setting? Alternatively, does the stress of captivity destabilize normal stimulus—response behaviors—perhaps due to the induction of stereotypic behaviors (Mason, 1991)—or induce consistency, albeit potentially abnormal, in the HPA axis by virtue of a reduction in the dynamic operating range of this endocrine axis (Calisi & Bentley, 2009; Dickens, Romero, Cyr, Dunn, & Meddle, 2009; Dickens & Romero, 2009; but see Biro, 2012)?

Besides interspecific differences, part of the explanation behind the divergence in repeatability estimates across these studies lies in the nature of the HPA axis, which is inherently dynamic. Estimating an individual's *average* GC profile is complicated by ultradian (Sarabdjitsingh et al., 2010), circadian (Breuner et al., 1999), and seasonal (Romero, 2002) rhythms of GC secretion. Perhaps for this reason, studies employing briefer sampling intervals typically report higher repeatabilities (Grace & Anderson, 2014; Ouyang, Hau, et al., 2011; Rensel & Schoech, 2011; Small & Schoech, 2015). That said, one critical analytic detail deserves mention. Several published repeatability studies have performed their statistical analyses on derived GC parameters (eg, "change in corticosterone concentrations from baseline to stress–induced"; or "area under the corticosterone curve"), as opposed to the actual measurements themselves (eg, GC concentrations at capture or after 30 min of restraint). We advise against estimating repeatability for derived parameters because (1) repeatability in any one GC measurement could generate apparent repeatability in the derived variable—for example, if baseline GCs are repeatable and stress–induced levels are not, it is quite possible to detect a significant but spurious repeatability in "change in corticosterone"; and (2) performing "statistics on statistics" can inflate type 1 error rates because the uncertainty around the estimate of an individual's flexibility is discarded (Budaev, 2010; Dingemanse & Dochtermann, 2013; Nakagawa & Schielzeth, 2010). For these reasons, and others (see Romero, 2004), we encourage investigators to first estimate repeatability by decomposing the variance in each of the measured variables separately (see Fig. 4)—preferably using a mixed modeling approach (Baugh et al., 2014). If significant repeatability in those measured variables is detected, then it is possible to proceed, if desirable, with other appropriate multivariate or latent variable analyses (Budaev, 2010; Dingemanse & Dochtermann, 2013; Nakagawa & Schielzeth, 2010).

Moreover, the two distinct functions of GCs, regulation of basal metabolic process and the emergency life history stress response, further complicate characterizing this endocrine system at the individual level. Especially at low baseline concentrations, technical issues such as detection limits and reduced assay precision may inflate measurement error, potentially inflating the within-individual variance and explaining at least in part why baseline samples often have substantially higher coefficients of variation than stress-induced concentrations (Baugh et al., 2013, 2014; Cockrem & Silverin, 2002b; Cook et al., 2011). Here we are assuming that measurement error, including detection limits, are relatively uniformly problematic among individuals in a sample. If that assumption is not met, then artificially *inflated* estimates of repeatability may be found. This would be the case, for example, if some individuals consistently have hormone concentrations below the detection limit and those samples are assigned the detection limit. Additionally, "baseline" concentrations can quickly become contaminated by acute stressors, which can include unknown events preceding sample collection as well as the process of capture and handling by the investigator. This can introduce unwanted measurement error; for example, estimating the circulating concentration of baseline GCs requires rapid capture and sampling (<3 min; Romero & Reed, 2008). To further complicate this problem of temporal dynamics, in a study population of Dutch great tits we have observed personality-dependent variation in the onset latency of the stress response, with individuals exhibiting slow–shy personalities expressing a more rapid induction of stress-induced GC concentrations (Baugh et al., 2013). In part, this variation may also help explain why repeatability estimates for stress-induced concentrations tend to be higher than baseline (Baugh et al., 2014; Hau & Goymann, 2015; Rensel & Schoech, 2011). An additional complication with a temporally dynamic and multi-component endocrine system like the HPA axis is that any one component of the HPA axis might be correlated with others. For this reason, correlations among hormone traits also need to be decomposed.

2.3 Decomposing Trait Variance Is Not Sufficient: Trait Correlations Must Also Be Partitioned

Estimating the heritability (or repeatability) of a trait is not sufficient to explain phenotypic evolution because a given trait of interest may be correlated with other traits due to pleiotropy or linkage disequilibrium (Lande & Arnold, 1983). Trait correlations, regardless of their cause, can impose their own dynamics on evolution (constraining or facilitating) and these effects

can be large for both endocrine (Ketterson et al., 2009) and behavioral traits (Dingemanse & Dochtermann, 2014). In order to predict trait evolution, it is therefore critical that we estimate correlations between traits. Raw phenotypic correlations between two traits, which are simply bivariate correlations from a pool of individuals sampled once, have been used to infer their genetic correlation. This assumption may be suitable for highly stable traits such as morphological characters, but violations of this assumption are common for flexible traits like behavior and physiology (Dochtermann, 2011). As with repeatability, phenotypic correlations are the joint outcome of two components: (1) "within-individual correlations," which integrate the flexibility in both traits (which experience coordinated changes within the individual due to environmental inputs); and (2) "among-individual correlations," which are caused by genetic correlations between traits (pleiotropy or linkage disequilibrium; Roff, 1997), maternal effects (eg, hormone deposition in yolk) or "permanent" environmental influences (eg, canalization of early life experiences, see Section 1).

Because phenotypic correlations can exist in the presence or absence of within- and among-individual variation (see Fig. 4), and because these two levels of covariation can influence the evolution of trait suites, this covariance decomposition is an essential analytical step in addressing the evolution of complex regulatory systems (Martin & Cohen, 2014). If these two correlation components are the same, then the phenotypic correlation is an accurate approximation of the among-individual correlation (Dingemanse & Dochtermann, 2013). If on the other hand, they are different in sign or magnitude, which is not uncommon because these two correlation components are the product of different biological processes, then the raw phenotypic correlation can be uninformative or even misleading (Baugh et al., 2014; Dingemanse & Dochtermann, 2013).

2.4 Hormonal Syndromes

It is now clear that evolutionary inferences based on studies of single behavioral traits are limited because of the network of covariances that characterize many trait combinations and the uncertainty about which trait or trait constellations selection is targeting. For this reason, there has been considerable recent research in behavioral ecology describing behavioral syndromes, ie, the stability and covariation of multiple behavioral traits in a population (Dall et al., 2004; Sih et al., 2004). There are now many examples of behavioral trait correlations that vary among populations and species. Is there an analog for endocrine traits? Multilevel approaches are being applied to other

flexible traits, including circulating GC concentrations (Baugh et al., 2014). Although this area of study is still in its nascency, the findings so far underscore the value of this analytical approach. In our work on free-living great tits in the Netherlands, circulating levels of baseline and stress-induced GCs were not repeatable (ie, among-individual variance was not significant) and within-individual variance was large. However, there was a strong positive phenotypic correlation between these two GC components, ie, during one sampling period individuals with high baseline GC concentrations also had high stress-induced GC levels (Fig. 5; Baugh et al., 2014).

Phenotypic correlations between baseline and stress-induced GC concentrations have been observed before (Grace & Anderson, 2014; Heidinger et al., 2008; Ouyang, Sharp, Quetting, & Hau, 2013; but see Jenkins et al., 2014; Martin & Liebl, 2014), and it is tempting to consider this phenotypic correlation as indicating individual differences in the slopes of the line that characterizes stress responses. This inference, however, is only valid if the phenotypic correlation has a significant among-individual component (see Fig. 4). In the case of our population of free-living great tits, the lack of significant among-individual variance in both GC traits predicts a lack of among-individual covariance (cf. covariance requires variance). Indeed, the phenotypic correlation of baseline and stress-induced GCs resulted strictly from a within-individual correlation, indicating that an individual's state during a particular sampling period influenced its baseline and stress-induced GCs simultaneously (Fig. 4A and B; Baugh et al., 2014). However, across repeated sampling events internal (eg, nutritional state) or external factors (eg, temperature) or both varied, and consequently average baseline and stress-induced GC levels of individuals were not correlated (Fig. 5B).

The strong within-individual correlation between these two GC traits provides a statistical indication that they may not be functionally independent, but interacting at diverse levels. Such interdependence could arise from shared mechanisms responsible for their coregulation (eg, coactivation of mineralocorticoid and glucocorticoid receptors) or a sensitivity of these mechanisms to the same external or internal factors, or both. For example, it is possible that ambient temperature and photoperiod might simultaneously modulate baseline and stress-induced concentrations GCs (Breuner et al., 1999; Romero et al., 2000), though such comodulatory effects at the within- and among-individual level have not been reported (Baugh et al., 2014). More research on the topic of hormonal syndromes is clearly needed, and a focus on which internal and external factors comodulate multiple hormonal components will be particularly useful.

(A) Positive Phenotypic Correlation

first capture

second capture

third capture

Baseline GCs (ng mL^{-1})

Stress GCs (ng mL^{-1})

(B) No Among-Individual Correlation

Stress GCs$_{Ave}$

Baseline GCs$_{Ave}$

(C) Positive Within-Individual Correlation

(Stress GCs$_i$ – Stress GCs$_{Ave}$) per individual (ng mL^{-1})

(Baseline GCs$_i$ – Baseline GCs$_{Ave}$) per individual (ng mL^{-1})
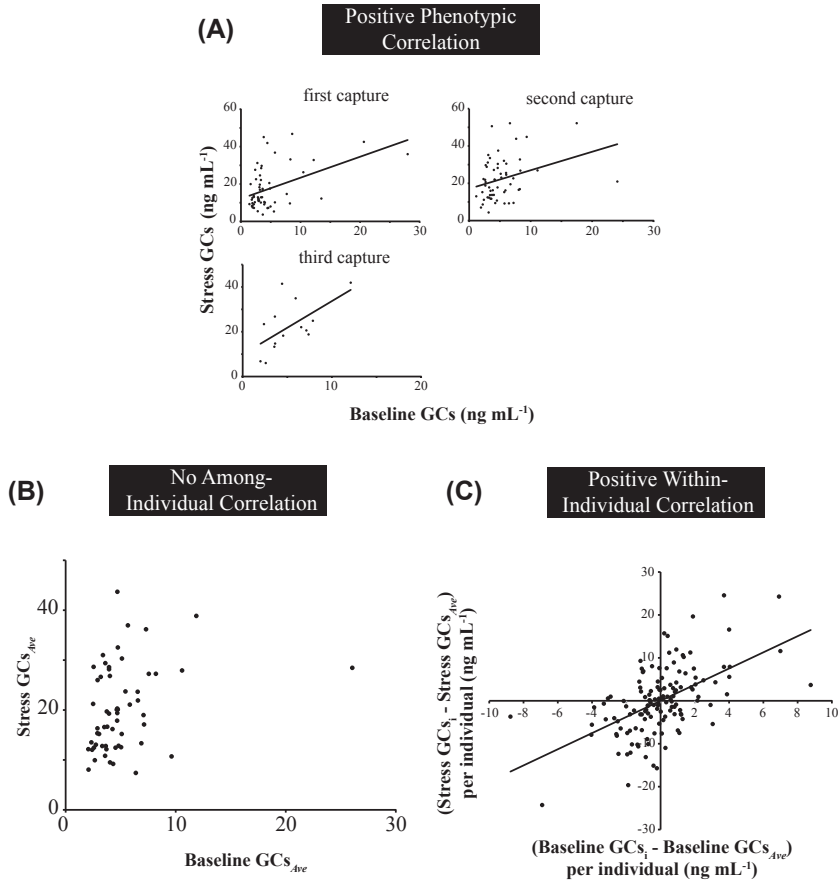
Figure 5 Baseline and stress-induced glucocorticoid (GC) concentrations during three repeated captures of great tits from our study population in the Netherlands (Baugh et al., 2014). A positive phenotypic correlation was observed at each of the three captures (A). When these repeats were averaged, there was no correlation between baseline and stress-induced GCs (B), which graphically indicates the lack of among-individual correlation. This was predicted because there was no among-individual variance (ie, repeatability was not significantly different from zero). When the deviation from the average is calculated for each of the three repeats per bird, there was a positive correlation (C), indicating that the positive phenotypic correlation in (A) was driven by a positive within-individual correlation (Baugh et al., 2014). These results thus resemble scenario II in Fig. 4.

2.5 Implications of Low Repeatabilities of Glucocorticoid Traits

Low repeatabilities in circulating GC levels, especially in baseline levels under field conditions, underscore a cautionary point: Studies that only sample

individuals at a single point in time may be principally describing variation due to differences in environmentally determined states (ie, within–individual variation; Baugh et al., 2014; Dingemanse, Edelaar, & Kempenaers, 2010; Lendvai et al., 2014). This is an important caveat in terms of our thinking about the evolution of these traits and the phenotypes they mediate. If much of the variation in hormone levels is environmentally induced and not a reliable aspect of the individual—and thus is consistent with the concept of endocrine systems as dynamic mediators of internal and external environments—we might expect this GC component to experience slower evolution. That said, we think this line of inquiry deserves more study because there are many unanswered questions. For instance, it is possible that among-individual variance (and covariance) in circulating GC levels is present, but highly context dependent. An ideal sampling design for future repeatability studies would therefore be the repeated assessment of individuals in a similar life history stage, especially under circumstances when high among-individual variation might have considerable fitness con-sequences (eg, breeding season, thermally challenging conditions). Perform-ing such studies under seminatural conditions, wherein certain key environmental variables can be controlled (eg, social context, food availabil-ity, sampling time of day), would provide an opportunity to reduce the role of external drivers and thus better estimate individual variation. Major life history events or environmental sources of stress could act to reorganize the hormone-behavior phenotype and do so differently across individuals due to variation in stress sensitivity (Careau, Buttemer, & Buchanan, 2014; Killen, Marras, Metcalfe, McKenzie, & Domenici, 2013; Lancaster, Hazard, Clobert, & Sinervo, 2008). Moreover, the standard baseline and restraint-induced circulating GC concentrations, which have been heavily studied, may not be the only relevant endocrine traits to examine (Crespi et al., 2013; Hau & Goymann, 2015; Romero & Wikelski, 2010; Williams, 2008). For example, pharmacological challenges used to induce physiological maximum secretion in GCs might better unmask hormonal repeatability (and for testosterone, these maximum levels can correlate strongly with fitness; McGlothlin et al., 2010). However, it has remained unclear whether physiological maxima in hormone secretion will ever be reached under nat-ural conditions and hence, how relevant this measure is in the wild.

Beyond circulating levels, more work is needed that explores how ligand—receptor relationships vary and covary within- and among individ-uals, and how this trait level is subjected to environmental influences (Lattin, Keniston, Reed, & Romero, 2015; Lattin & Romero, 2015; Liebl, Shimizu,

& Martin, 2013; Senft, Meddle, & Baugh, 2016). Taken together, these studies shift our attention from single to more complex traits, such as the relationships among traits (multiple behaviors; hormones and receptors), trait categories (hormone−behavior relationships), and trait−environment interactions (reactions norms; see Section 4) that may serve as the performance traits targeted by selection. Clearly, there remains considerable work ahead as we identify methods and tools for better estimating hormone traits at the individual level, but this work is critically important as we seek to understand how evolution continues to shape these essential integrators of the phenotype.

3. HERITABILITY, ARTIFICIAL SELECTION, AND FITNESS RELATIONSHIPS OF GLUCOCORTICOID TRAITS

Despite the mixed evidence for repeatability of GC traits (see Section 2), GC components can show consistent links with performance traits, such as behavior and investment in life history stages, within populations and across species (Bókony et al., 2009; Gesquiere et al., 2011; Hau, Ricklefs, Wikelski, Lee, & Brawn, 2010; Lendvai & Chastel, 2010; Love, Madliger, Bourgeon, Semeniuk, & Williams, 2014; Moore & Jessop, 2003; Ouyang, Sharp, et al., 2013). It is also likely that various parts of endocrine cascades have a genetic basis (see also below). Thus, to understand how natural selection might be acting on endocrine traits and the phenotypes they mediate, we need to not only parse individual variation (see Section 2) but also employ tools to quantify phenotypic variation in the wild together with measuring fitness and heritabilities of hormonal components and their relationships with phenotypic traits. Diverse approaches, such as using selection lines, natural variation, and phenotypic engineering have begun to elucidate hormone, behavior, and fitness relationships in free-living animals (reviewed in: Zera et al., 2007). These studies have indeed provided evidence that corticosterone traits have a genetic basis and thus would be amenable to selection and evolution.

3.1 Heritability Estimates for Hormonal Traits and Responses to Artificial Selection

One powerful approach for demonstrating that hormonal traits have a genetic basis is using directional selection tools, ie, to create lines of individuals that show either high or low GC concentrations following exposure to a

standardized stressor. One of the earliest such experiments was conducted in Japanese quail (*Coturnix japonica*), in which a significant difference in GC responses to immobilization stress between lines was obtained after four to five generations of selection (Satterlee & Johnson, 1988). In these studies, heritability estimates of stress–induced GC concentrations ranged between $h^2 = 0.15-0.33$, depending on the data set analyzed and statistics used (Odeh, Cadd, & Satterlee, 2003; Satterlee & Johnson, 1988). Similar findings were obtained by more recent experiments on zebra finches (*Taeniopygia guttata*), where replicate lines subject to directional selection on high versus low GC reactivity to restraint stress demonstrated a realized heritability of about 20% after four generations (Evans, Roberts, Buchanan, & Goldsmith, 2006). In rainbow trout, directional selection on cortisol responses to refinement stress was also successful, with heritability estimates being relatively high ($h^2 = 0.41$; Pottinger & Carrick, 1999).

Studies employing directional selection are useful approaches to elucidate the genetic mechanisms underlying traits, but known caveats are the artificiality of environmental conditions in captivity and the strength of the directional selection pressure applied (Huey & Rosenzweig, 2009). More relevant to natural situations are studies that relate variation in traits between parents and their offspring (and/or other relatives). In captive zebra finches, female stress–induced corticosterone concentrations were related to that of its offspring (Wada et al., 2008). Perhaps the first evidence in the wild for a heritability of GC traits was reported for barn owls (*Tyto alba*), where darker plumage coloration was associated with lower stress–induced corticosterone concentrations, and both plumage and GC traits were shown to be inherited from the mother to the offspring (Almasi, Jenni, Jenni-Eiermann, & Roulin, 2010). The most comprehensive experiment conducted to date in the wild used a cross-fostering design in wild barn swallow nestlings (*Hirundo rustica*) in combination with pedigree information. This study reported significant heritabilities in both baseline and stress–induced corticosterone concentrations, of 0.152 and 0.343, respectively (Jenkins et al., 2014). However, the effect of the common rearing environment was large (0.55 for baseline and 0.49 for stress–induced corticosterone), and for baseline corticosterone concentrations the rearing environment explained more of the variation than additive genetic effects (Jenkins et al., 2014).

How animals cope behaviorally with stressors has been a major field of such study, especially in commercially important species, such as poultry (Faure, Val–Laillet, Guy, Bernadet, & Guemene, 2003; Fraisse & Cockrem, 2006; Mignon-Grasteau & Minvielle, 2003) and aquacultural stocks

(Brownscombe et al., 2013; Overli et al., 2007; Øverli, Winberg, & Pottinger, 2005). Likewise, humans have been artificially selecting animals based on coping phenotypes to challenging conditions (eg, captivity stress in livestock) for centuries, so it is no surprise that experimental studies have demonstrated that a response to such selection can be rapid and sometimes profound (Harri, Mononen, Ahola, Plyusnina, & Rekilä, 2003; Swallow, Carter, & Garland, 1998). Our knowledge of how coping behavior evolves in animals is limited, but there are now a handful of studies demonstrating heritability of single coping behaviors and behavioral complexes. Captive studies are useful in this regard by demonstrating first principles. For example, in great tits, the combination of object and spatial neophobia is strongly heritable ($h^2 = 0.54$), and thus only a few generations of bidirectional artificial selection are needed to see a divergent response (Drent, van Oers, & van Noordwijk, 2003). Moreover, exposure to novelty can itself induce a moderate GC stress response (Beerling et al., 2011). For this reason, an interest in identifying any connection between these behavioral syndromes and their underlying physiological basis has been underway for several years. In rodents, the evidence points to multiple physiological systems involved in mediating coping phenotypes, including serotonin, vasopressin, and oxytocin signaling (reviewed in: Koolhaas, de Boer, Coppens, & Buwalda, 2010; Korte et al., 1992). And although correlations between coping behavior and HPA physiology have been reported as well, GC variation appears to be a consequence, not a cause, of the behavioral differentiation (Koolhaas et al., 2010). In great tits, artificial selection on neophobia results in correlated selection on the GC stress response: slow-shy birds have higher circulating corticosterone levels following physical and social stressors (Fig. 6; Baugh et al., 2012; Carere, Groothuis, Mostl, Daan, & Koolhaas, 2003; Stöwe, Rosivall, Drent, & Möstl, 2010). As with the rodent work, these correlations in great tits are not strong evidence that HPA variation causes the behavioral differences, and indeed these two aspects of the phenotype may be expected to exhibit bidirectionality.

Hence, selection on behavioral traits can lead to correlated changes in GC components, suggesting a functional or genetic linkage between the two. The converse pattern is also found, ie, that selection on endocrine stress responses leads to changes in the behavioral phenotype. For example, in Japanese quail artificial selection for high stress-induced corticosterone concentrations results in individuals that show greater avoidance and more fear-related behavior (Jones, Satterlee, & Ryder, 1994). Likewise, zebra finches selected for high stress-induced corticosterone levels to
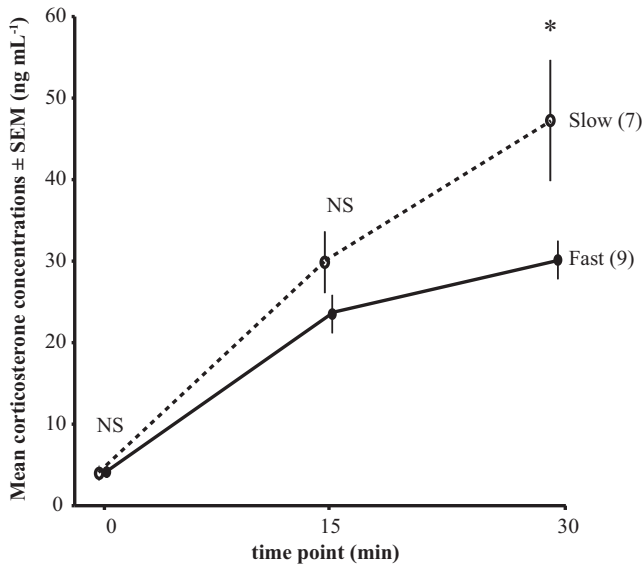
Figure 6 Baseline and stress-induced glucocorticoid (GC) concentrations for fast-bold (*solid*) and slow-shy (*dashed*) selection line great tits. GC concentrations differed between selection lines after 30 min of restraint stress. *From Baugh, A.T., Schaper, S.V., Hau, M., Cockrem, J.F., de Goede, P., & van Oers, K. (2012). Corticosterone responses differ between lines of great tits (*Parus major) selected for divergent personalities.* General and Comparative Endocrinology, 175(3), 488–494.

handling stress showed reduced spatial abilities (Hodgson et al., 2007). Again, such correlational responses do not necessarily imply that the behavioral responses are mediated by variation in GCs (Koolhaas et al., 2010). We encourage future studies to look in more detail at correlated selection between behavioral and hormonal traits, for example, by manipulating GC concentrations or their effectiveness at receptors, and assessing effects on behavior in individuals from directional selection lines on GC responses to handling stress. Or, conversely, exposing selection line individuals to behavioral challenges such as social interactions and measuring ensuing hormonal responses. Ideally, such experiments and any additional experiments conducted on wild populations should incorporate information from genetic relatedness to more directly test the possibility of genetic pleiotropy. Finally, future studies should aim at unraveling the effects that early developmental conditions (Spencer & MacDougall–Shackleton, 2011) and environmental stressors (Killen et al., 2013) have in causing functional correlations between hormonal and behavioral traits.

3.2 Natural Variation in Glucocorticoid Concentrations and Fitness

Given the evidence for a genetic basis of GC phenotypes reviewed above (Section 3.1), exploring natural variation in GC concentrations and linking it to behavioral and fitness traits is one important step for understanding evolutionary dynamics of endocrine systems (McGlothlin, Jawor, & Ketterson, 2007; Pradhan, Solomon-Lane, & Grober, 2015; Zera et al., 2007). A few studies were able to identify GC−fitness relationships in wild populations (Blas, Bortolotti, Tella, Baos, & Marchant, 2007; Cabezas, Blas, Marchant, & Moreno, 2007; Comendant et al., 2003; MacDougall-Shackleton et al., 2013; MacDougall-Shackleton et al., 2009; Pride, 2005), some indicating that GC traits are related linearly to reproductive success or survival (Angelier, Holberton, & Marra, 2009; Angelier, Wingfield, Weimerskirch, & Chastel, 2011; Bonier, Moore, Martin, & Robertson, 2009; Ouyang, Sharp, Dawson, Quetting, & Hau, 2011; Patterson et al., 2014). However, other studies were not able to find such relationships and several recent larger analyses have concluded that the evidence for relationships of GCs with fitness across studies and taxa is mixed (Bonier, Martin, et al., 2009; Breuner, Patterson, & Hahn, 2008; Crespi et al., 2013). One important limitation is that the majority of the above studies obtained only a single data point, although per year in some cases, for each individual.

To circumvent this issue, in a recent study on great tits from a population in southern Germany, we therefore attempted to repeatedly sample as many individuals as possible and assess GC−fitness relationships in a multiyear study (Ouyang, Sharp, et al., 2013). Given that baseline GCs support workload and reproductive investment requires high energy expenses, we predicted that baseline corticosterone concentrations of adults would be positively correlated with reproductive success. During our focal study period, the prebreeding season in March and the parental season in May, baseline concentrations of corticosterone were repeatable in both sexes ($r = 0.26$; Ouyang, Hau, et al., 2011). Furthermore, we detected a linear relationship between baseline corticosterone and reproductive success in both sexes and across two study years, but the direction of the relationship changed within the breeding season. Before egg-laying in March, individuals with high baseline corticosterone concentrations were more successful but during offspring provisioning in May, those with low baseline corticosterone concentrations produced more young. Indeed, seasonally plastic individuals appeared to fare best: individuals that had the highest baseline GC

concentrations in March, but the lowest levels in May produced the most offspring (Ouyang, Sharp, et al., 2013; Fig. 7). Wild house sparrows and tree swallows (*Tachicyneta bicolor*) also exhibit a seasonal change in the relationship between baseline corticosterone concentrations and reproductive success, though partly opposite to the patterns observed in great tits (Bonier, Moore, et al., 2009; Ouyang, Sharp, et al., 2011). Hence, seasonal variation
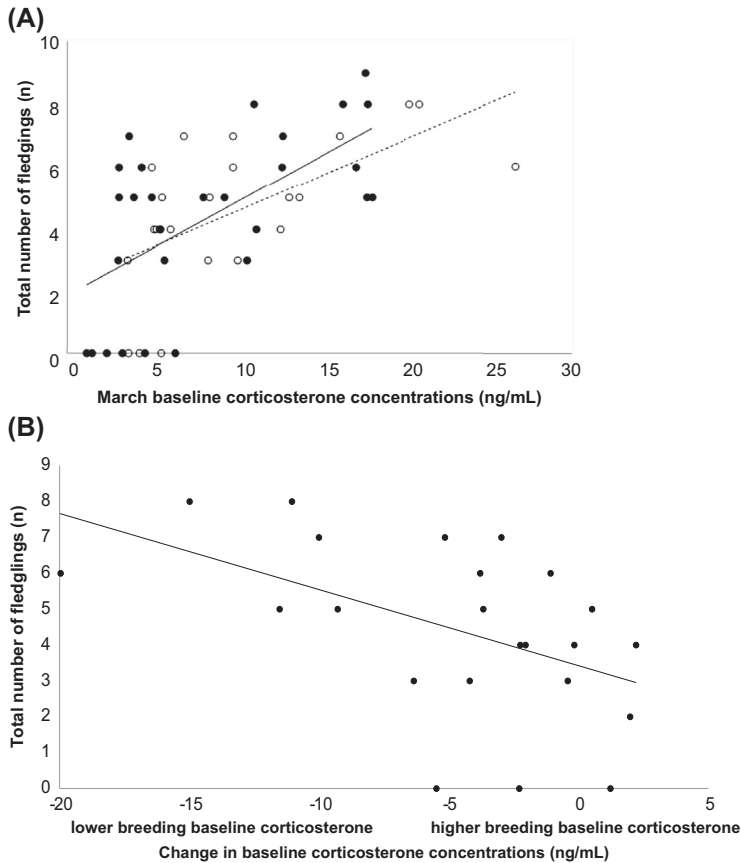
Figure 7 The number of fledglings that great tits produced during a breeding season was related to (A) baseline corticosterone concentrations (ng/mL) during the prebreeding season in March (females: *closed circles* and *solid line*; males: *open circles* and *dashed line*; (Ouyang, Sharp, et al., 2013), and (B) to the change in corticosterone concentrations from March to May (parental phase). Adults with the highest March but lowest May concentrations raised the most offspring. *Data from Ouyang, J.Q., Sharp, P., Quetting, M., & Hau, M. (2013). Endocrine phenotype, reproductive success and survival in the great tit,* Parus major. Journal of Evolutionary Biology, 26(9), 1988–1998. http://dx.doi.org/10.1111/jeb.12202.

in optimal hormonal phenotypes exist and the direction of this seasonal flexibility can be fitness relevant (Ouyang, Sharp, et al., 2013).

We had predicted stress-induced GC concentrations to vary negatively with reproductive success and positively with survival rates in wild great tits, given that they are thought to promote processes that boost survival during challenging conditions while inhibiting nonessential functions including reproduction (see Section 1). In our great tit studies, there was no evidence of stress-induced corticosterone concentrations being related to survival proxies like return rates (Ouyang, Sharp, et al., 2013). Survival rates are notoriously difficult to quantify in free-living species, and the available studies reveal opposing trends for the relationship between stress-induced corticosterone levels and return rates (Angelier, Holberton, et al., 2009; Blas et al., 2007; Cabezas et al., 2007; MacDougall-Shackleton et al., 2013; Patterson et al., 2014).

The studies discussed above provide some tentative evidence that GC phenotypes, perhaps through their effects on behavioral phenotypes, such as parental behavior, are subject to natural selection. Could sexual selection also play a role? In our study on great tits, individuals with more similar corticosterone levels during the breeding season were more likely to stay together from one year to the next, and similarity in hormone levels between a pair further increased with the time the pair stayed together (Ouyang, van Oers, Quetting, & Hau, 2014). These findings complement those of a study in graylag geese, *Anser anser*, showing that pairs with more similar testosterone levels have larger clutches and heavier eggs (Hirschenhauser, Mostl, & Kotrschal, 1999). To our knowledge, neither study has shown that individuals mate associatively, ie, choosing a partner with a greater hormonal similarity to maximize reproductive success. Thus, this avenue of research can be expanded in the future, especially to look at how sexual selection may play a role in shaping GC concentrations, perhaps again through behavioral traits (Ouyang et al., 2014; see also Rubenstein & Hauber, 2008).

Long-term studies of individual variation in hormone, performance traits, and fitness in free-living populations are important tools to begin to understand the nature and the direction of selection on hormonally mediated traits (Arnold, 1983; Husak, Irschick, McCormick, & Moore, 2009; Pradhan et al., 2015). However, given the evidence for high within-individual variation and low repeatabilities, especially of baseline GCs, such studies need to include the repeated sampling of individuals instead of relying on single point samples. Had we assessed GC concentrations of great tits only at one point in

time, we would have obtained opposing results depending on whether we sampled the birds in March or in May and would have missed the seasonal flexibility (Ouyang, Sharp, et al., 2013). Also, if we aim at moving beyond demonstrating the actions of selection and begin to infer evolutionary processes, it is imperative that the heritability of GC traits will be quantified as well as how GC concentrations and their flexible responses are shaped by past and current conditions. Transport mechanisms (CBG) and receptor density and sensitivity may all modify the strength of selection on GC systems. As a final note of caution, studies that relate natural variation to fitness are merely correlative and cannot be used to infer causal relationships (see Section 3.3).

3.3 Experimental Manipulation of Glucocorticoids to Test for Mediation of Behavior and Fitness Effects

A major experimental approach to test for adaptive functions of organismal traits is to manipulate them and compare relative fitness among phenotypes ("phenotypic engineering," Ketterson & Nolan, 1992; Sinervo & Huey, 1990; but see Zera et al., 2007). Such experiments are also useful for identifying the mechanisms that underlie hormone−fitness correlations. For endocrine traits such manipulations typically include administering exogenous hormones or pharmacologically blocking their actions (Fusani, 2008; Wingfield & Farner, 1993).

Exogenous GCs have been administered in several studies to vertebrates to test fitness implications. The "cort-fitness" hypothesis posits that if an individual is living in a stressful environment, it would have higher levels of GCs and consequently lower fitness (Bonier, Martin, et al., 2009). Therefore, exogenous GC administration would result in a decrease of fitness. However, thus far results of such manipulative studies are not conclusive (Bonier, Martin, et al., 2009; Breuner et al., 2008). While some studies in birds reported a decrease in reproductive success or survival following exogenous GC administration (Angelier, Clément-Chastel, Welcker, Gabrielsen, & Chastel, 2009; Criscuolo et al., 2005; Goutte et al., 2010; Love & Williams, 2008a; McConnachie et al., 2012; Schultner, Kitaysky, Gabrielsen, Hatch, & Bech, 2013; Silverin, 1998), others did not observe a significant effect of GC addition (Almasi, Roulin, Jenni-Eiermann, & Jenni, 2008; Love et al., 2005; Ouyang, Muturi, Quetting, & Hau, 2013; Patterson, Winkler, & Breuner, 2011). Furthermore, in species with alternative phenotypes, the effect of the hormone manipulation can vary in a morph-specific way (Lancaster et al., 2008; Svensson, Sinervo, & Comendant, 2002). On the one hand, such divergence in effects of exogenous GCs is perhaps not surprising since

we know that the functions of GCs can vary with life-history stage, ecological context, age, sex, and other factors (Beletsky, Orians, & Wingfield, 1992; Bonier, Moore, et al., 2009; Crespi et al., 2013; Crossin et al., 2016; Romero, 2002; Spencer & MacDougall-Shackleton, 2011). For example, differences in brood survival as a result of an exogenous increase of GCs in adult female tree swallows were only evident during good weather conditions and disappeared during bad weather conditions (Ouyang et al., 2015). On the other hand, at least some of these findings could be artificial because many of these manipulative studies might have resulted in circulating levels that were within the range of stress-induced concentrations, while predictions going into the study might have referred to the actions of baseline GCs (see also Crossin et al., 2016).

In our population of free-living great tits from southern Germany, we were successful in raising corticosterone concentrations within the baseline range after carefully validating the effectiveness of different types of implants filled with exogenous corticosterone (Ouyang, Muturi, et al., 2013). We aimed at testing the causality of the positive relationship between baseline corticosterone concentrations and reproductive success that we had observed during the early breeding phase in March (Fig. 7A), which likely had been mediated by greater parental care provided by individuals with higher corticosterone concentrations (Ouyang, Sharp, et al., 2013; or an ability to increase GCs more strongly with demand, Bonier, Moore, & Robertson, 2011). Indeed, our experimental treatment was effective in increasing behaviors such as incubation and mate-feeding in the early breeding phase, but once the implants had ceased releasing corticosterone, behaviors returned to normal (Ouyang, Muturi, et al., 2013). Our short-term ($\sim$40 days) manipulation did not affect reproductive success, perhaps because corticosterone concentrations had returned to normal levels during the phase of offspring provisioning or because differences in individual quality masked treatment effects. A similar, small-dose increase in corticosterone levels was effective in increasing parental behaviors in Macaroni penguins, *Eudyptes chrysolophus* (Crossin et al., 2012).

The low-level increases in corticosterone concentrations obtained in the latter two studies are different from work in which implants raised hormone concentrations to stress-induced levels, resulting in decreases in parental effort and increases in brood desertion (Silverin, 1986). It is increasingly becoming clear that the methodology, in particular the dosage of administered GCs plays a major role. Previous experiments have also found that implants, particularly those using high doses, can downregulate endogenous

GC release that circulating levels even fall below natural baseline levels (Goutte et al., 2011; Schultner et al., 2013). In light of the divergent effects of GCs at baseline versus stress–induced concentrations, it is important to (1) to verify the effects of the manipulation on circulating concentrations (if possible, during the entire duration of the study period) and carefully titrate the method to yield the desired dose (Ouyang, Muturi, et al., 2013), (2) clearly differentiate between the two different roles of GCs at the outset, (3) take life history strategies and states into account, and (4) if possible, determine individual variation in GCs or sensitivities to GCs prior to manipulation to administer individualistic dosages (see also Crossin et al., 2016).

An additional issue with hormone manipulations is that the pleiotropic nature of hormone-mediated behavioral suites may cause varying effects at different organismal levels, such that no net difference in fitness is observed. Such effects may be particularly strong for traits involved in life-history trade-offs or for linked traits (Miles, Sinervo, Hazard, Svensson, & Costa, 2007; Sinervo & Svensson, 1998) including those mediated by GCs (Crespi et al., 2013; Crossin et al., 2016). We should therefore carefully quantify the effects on multiple traits when increasing GC levels to correctly identify any trade-offs that might have been induced. These multilevel effects also illustrate why we should not only focus on experimental increases in GC concentrations but also apply pharmacological blockers or otherwise decrease the effects of endogenous GC concentrations (Breuner, Jennings, Moore, & Orchinik, 2000; Crossin et al., 2016; McConnachie et al., 2012). Studies using such techniques are severely lacking due to methodological problems relating to the availability and the efficacy of suitable substance. For example, even mitotane, a drug rather specific and effective in blocking endogenous GC secretion, causes an inability to mobilize glucose (Breuner et al., 2000). The pharmacological blockage of hormonal effects is also important for verifying the specificity of GC manipulations, as any artificial increase in hormone concentrations may have non–specific effects on a variety of traits including an individual's health (Fusani, 2008). Finally, it is important to note that while hormone implants are valuable tools, they are also rather artificial in providing hormone concentrations that do not vary over the day or according to internal and external conditions. Implants likely disrupt CRH signaling and CBG dynamics as well (Crespi et al., 2013), which is important to keep in mind.

We are just beginning to explore the causal nature and the selection pressures acting on GC-behavior-fitness relationships in free-living individuals. In general, the results from the available studies are promising in that GCs

tend to have a heritable component, they correlate with behavior and fitness traits in some systems, and manipulations often result in predicted changes in behavior, although studies with negative results also exist. Selection may be acting on hormone-behavior relationships, but the nature, level, timing, specificity, and strength of selection are still unclear, especially in free-living vertebrates. Furthermore, in future studies on GC-fitness relationships multilevel thinking is necessary rather than focusing on one behavioral or hormonal axis of an organism (Careau, Gifford, & Biro, 2014; Miles et al., 2007). Finally, few studies so far have attempted to repeatedly sample individuals and to analyze within-individual variation in hormone concentrations in relation to fitness (Bonier, Moore, et al., 2009; Bonier et al., 2011; Ouyang, Sharp, et al., 2013; Ouyang, Sharp, et al., 2011). As emphasized above, hormonal traits and especially GCs are highly responsive to environmental and internal information (see Sections 1 and 2); therefore studying hormonal flexibility in individuals is fundamental to improve our understanding of the evolutionary pressures acting on these traits and how they can evolve.

4. PHENOTYPIC FLEXIBILITY IN GC TRAITS: REACTION NORMS, COSTS AND BENEFITS OF FLEXIBILITY AND EVOLUTIONARY IMPLICATIONS

Phenotypic flexibility is a way for an organism to escape the limits imposed by the rigid programming of the genome by reversibly adjusting to current environmental conditions (see Section 2). In other words, phenotypic flexibility provides the benefit of optimizing the phenotype to the environment, but it also introduces environmental variance into a trait which renders it more difficult for us to identify the evolutionary forces that may be acting. To embrace the inherent variability of flexible traits and incorporate this flexibility into an evolutionary framework, evolutionary and physiological ecologists have studied phenotypic flexibility of individuals using reaction norm approaches (Basson & Clusella-Trullas, 2015; Careau, Gifford, et al., 2014; Dingemanse, Kazem, Reale, & Wright, 2010; Kingsolver & Huey, 1998; Nussey, Wilson, & Brommer, 2007; Via et al., 1995). Reaction norms are the graphical and statistical representation of phenotypic changes across a gradient of environment or internal conditions (Nussey et al., 2007; for hormones, "performance curves" may more adequately describe non-linear relationships across multiple repeated measures, Kingsolver, Diamond, & Gomulkiewicz, 2014). Reaction norm approaches are just beginning to be

incorporated in the field of evolutionary endocrinology (Cockrem, 2013; Fürtbauer, Pond, Heistermann, & King, 2015; Lema & Kitano, 2013; Lendvai et al., 2014; Martin & Liebl, 2014; see also Sinervo & Svensson, 1998).

In this section, we highlight that reaction norm approaches can be very useful to characterize GC variability within and among individuals in an evolutionary context. We next consider how GC flexibility within and among individuals may mechanistically arise. Finally, we discuss potential costs and benefits of among- and within-individual GC flexibility, as well as potential implications for GC evolution.

4.1 Studying GC Flexibility Using Reaction Norm Approaches

Reaction norms are ideal for analyzing changes in individual phenotypes along environmental or internal gradients, for example graphically, by plotting the values of the phenotypic trait along a gradient of interest (Fig. 8; Nussey, Postma, Gienapp, & Visser, 2005; Schlichting & Pigliucci, 1998; Via et al., 1995; Williams, 2008). Appropriate statistical analyses, such as random regression mixed–effect models, make it possible to test for individual differences in flexibility by determining the elevation, represented by the intercept, and the steepness, represented by the slope, of the regression line that describes the changes in trait value along the gradient (Dingemanse &
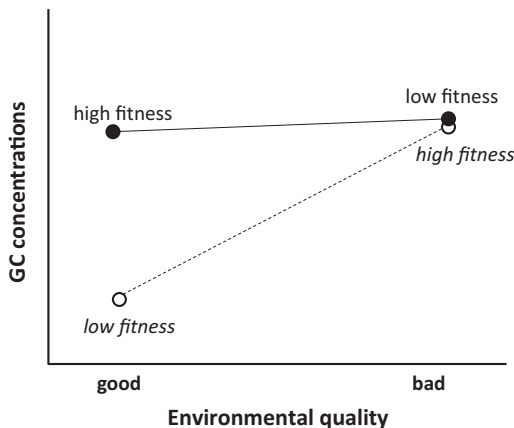

Figure 8 Graphic depiction of the usefulness of a reaction norm approach. Individual A: *filled circles*, *solid line*, and *normal font*. Individual B: *open circles*, *broken line*, and *italics*. For further explanation see text.

Dochtermann, 2013; Dingemanse, Kazem, et al., 2010; Nussey et al., 2007; van de Pol, 2012).

Here, we concentrate on reaction norms that are obtained by measuring individuals repeatedly during exposure to environmental or internal gradients. We are aware that reaction norms can be more strictly defined as phenotypic responses of a *single* genotype. However, since we are interested in evolutionary questions and working on non-model organisms, we cannot control for the genetic background of our study organisms. Instead, whenever specifically interested in genetic components underlying the flexibility of traits, we can incorporate pedigree information into our models (Araya-Ajoy, Mathot, & Dingemanse, 2015; Kruuk & Hadfield, 2007; Martin et al., 2011; Pigliucci, 2001; van de Pol, 2012; Westneat et al., 2015).

A reaction norm approach enables us to decompose the levels at which individuals may differ, carefully parsing elevation and slope that characterize hormonal flexibility. It is a highly valuable tool for studying flexible traits such as GCs because it permits an analysis of the interaction between the hormone and the environment and the way in which this interaction is related to fitness (Dingemanse, Edelaar, et al., 2010; Lendvai et al., 2014; Williams, 2008). For example, two individuals A and B, may show the same GC concentrations after moving from a good environment to a bad one, but they may dramatically differ in the extent of GC changes experienced during that transition depending on their GC levels in the good environment (Fig. 8). It is possible that individual A kept its GC concentrations almost constant while individual B significantly up-regulated its secretion of GCs. Suppose also that in the bad environment individual A, which did not change hormone levels had a lower fitness than the more flexible individual B. If the two individuals had only been studied at one point in time, in the bad environment, the erroneous conclusion would have been drawn that GC concentrations were not related to fitness. This has at least partly been an issue in attempts to identify general patterns in GC–fitness relationships (Dingemanse, Edelaar, et al., 2010; Williams, 2008).

Several recent studies have applied reaction norm approaches to analyze individual differences in specific hormonal traits to environmental conditions (Fürtbauer et al., 2015; Lema & Kitano, 2013; Lendvai et al., 2014; Martin & Liebl, 2014). In one of them, captive house sparrows were exposed in alternate weeks to either food restriction (60% of daily food intake) or *ab libitum* access to food; each individual experienced both conditions twice. This repeated-measures design enabled the authors to show that while food restriction caused an increase in baseline GC concentrations

across individuals, individuals differed in both elevation and slope of changes in baseline GC to food restriction (Lendvai et al., 2014). Such significant among-individual differences in coping with environmental challenges can have important consequences for the evolution of the mechanisms for phenotypic adjustments to fluctuations in resource abundance (Lendvai et al., 2014).

The second study used a reaction norm approach to investigate how baseline and stress-induced GC concentrations, respectively, varied with the challenge of being in captivity in two house sparrow populations from Kenya with different colonization histories (Martin & Liebl, 2014). House sparrows have been introduced to Africa around 1950 and have since been expanding their range. The study populations represented the oldest and one younger colonizing population, and in their natural environment, younger populations show larger stress-induced GC concentrations during a capture-restraint protocol than older, more established populations (Liebl & Martin, 2012). However, after one week of captivity, stress-induced levels of GCs of both populations had converged (Martin & Liebl, 2014), suggesting that the differences between populations observed in the earlier study had been a consequence of phenotypic flexibility. However, further analyses provided some tentative evidence for an individual component in the flexibility of stress-induced GC concentrations, hinting at the existence of among-individual differences in reaction norms and thus the ability to cope with the stressful conditions of captivity (Martin & Liebl, 2014). Such studies are valuable tools for assessing individual differences in resistance to stressors and consequences for colonization of new environments.

A third study did not find individual differences in GC (nor behavioral) reaction norms in captive three-spined sticklebacks (Fürtbauer et al., 2015). Individuals of different personalities were tested for behavioral and GC responses to changes in perceived predation risk. All individuals up-regulated GC concentrations during periods of increased predation risk, and significant individual differences in this response could not be identified.

These examples highlight how the reaction norm framework can help us parse the contributions of individual (genetic, maternal, developmental) versus environmental and internal factors to GC flexibility. Note that we advocate the application of reaction norm approaches to studying the flexibility of single GC components, such as baseline or stress-induced concentrations. The use of derived measures such as the "GC response", ie, the difference between baseline and stress-induced concentrations, can be difficult to interpret for statistical reasons (see also Section 2). Obviously, there is

an urgent need for more studies that quantify GC flexibility in a reaction norm framework, using an array of relevant external and internal gradients that are are known to affect GCs (see Section 1.2), to be conducted under standardized conditions in captivity as well as in natural environments. Reaction norm approaches can also be used to assess fitness consequences of among- and within-individual variation in GC profiles, for example by including a fitness proxy into the random regression model and evaluating its covariance with intercept and slope, respectively (Dingemanse, Kazem, et al., 2010) or using the slope as a variable in separate models. Finally, reaction norms also provide an instrument for analyzing covariation between the absolute levels of GCs and their degree of flexibility to determine potential constraints in flexibility of specific GC phenotypes. While such analyses are increasingly being carried out for behavioral traits (Dingemanse, Kazem, et al., 2010), only few examples exist to date for endocrine traits. The food restriction study on house sparrows (Lendvai et al., 2014), for example, found no support for a covariation between slope and intercept in corticosterone concentrations, indicating that the GC responsiveness to food unpredictability in individual house sparrows is not related to absolute levels.

Despite the paucity of studies on individual differences in GC reaction norms, two reports suggest their existence (Lendvai et al., 2014; Martin & Liebl, 2014), in line with emerging evidence for individual differences in behavioral reaction norms (Araya-Ajoy et al., 2015; Dingemanse, Kazem, et al., 2010; Mathot & Dingemanse, 2014). What may be the mechanisms that underlie such hormonal variation within and among individuals?

4.2 Possible Factors Underlying GC Variation Within and Among Individuals

The functioning of the HPA-axis is influenced by each of its components, including the neural integration of external and internal stimuli, the release of GCs and the expression of receptors. Variation can exist both among and within individuals at each of these levels (see also Pradhan et al., 2015; Senft et al., 2016; Wingfield, 2013a) and below we outline some potentially relevant pathways.

1. Processing of environmental factors and activation of the hypothalamus. HPA activation depends largely on the nature of the challenge, as different kinds of stimuli operate via different, but interconnected, neural pathways and brain processes (Boonstra, 2013b). Stimuli that signal direct physiological challenges to the individual, causing immediate "reactive" increases in GC concentrations into the stress-induced range may not

require higher-order cognitive processing. Typically, they are directly transmitted to the hypothalamus via peripheral sensory fibers and the spinal cord and hindbrain regions or through blood-borne signals (Boonstra, 2013a). Such reactive responses are caused by, eg, pain, thermal challenges, severe blood loss, respiratory obstruction as well as major metabolic disturbances (Boonstra, 2013a). Other cues may cause anticipatory (or "preparatory") increases in GC concentrations, even in the absence of a direct physiological challenge (Boonstra, 2013a; Sapolsky et al., 2000). The latter type of cues requires a cognitive evaluation of the information associated with the challenge, which is performed mainly by limbic brain structures (Boonstra, 2013a). Stimuli that trigger anticipatory increases in GC concentrations can be based on innate factors such as instinctive responses to a shape resembling a predator, or on past experiences like a rival's behavior during aggressive interactions, failure of foraging attempts or encounters with dangerous situations (Boonstra, 2013a; Sapolsky et al., 2000).

It is tempting to speculate that individuals will vary within and among each other especially in anticipatory GC responses as these require a considerable degree of central integration, the outcome of which is likely affected by an array of factors including body condition, life history stage, age, sex and past experiences. However, it is also conceivable that an individual's characteristics or its current state will affect the more involuntary reactive GC responses.

2. GC production. Individuals may also differ within and among each other in their capacity to produce GCs. GCs are synthesized from cholesterol through multi-step pathways involving five different cytochrome P450 enzymes fuelled by a NADPH-dependent redox system that includes an electron transfer chain (Lisurek & Bernhardt, 2004). Thus, the biosynthesis of GCs requires the availability of a sufficient amount of enzymes and electrons in a relatively short time. Since steroid hormones are not stored in the secreting gland (Adkins-Regan, 2005), their concentration in the circulation is therefore determined by the capacity of synthesis (Breuner et al., 2013), which needs to occur at high speed. It is thought that the conversion of cholesterol to pregnenolone by the enzyme cholesterol side-chain cleavage is the rate-limiting step in GC production (Adkins-Regan, 2005). Hence, the quantity of GCs released by the adrenal cortices in a given individual can depend on several factors, such as the availability and the activity of the various components involved in their synthesis.

GC–production is stimulated by releasing peptides such as corticotropin-releasing factor (CRH) and adrenocorticotropin (ACTH; among other molecules; Wingfield, 2013b; Fig. 1). CRH or ACTH variation within and among individuals has hardly been studied since their measurement usually requires invasive methods (for CRH) that are not compatible with most evolutionary studies, or validated protocols are still lacking (for ACTH). However, it is likely that individual differences exist in the amount of releasing hormone secreted upon maximal stimulation as well as the responsiveness of cells to a given amounts of releasing hormones. Indeed, experimental administration of CRH and ACTH can be conducted in natural populations, and within- and among individual variation in resulting GC responses can be quantified using such techniques (Astheimer et al., 1994; Boonstra et al., 2008; Dickens, Earle, & Romero, 2009; Ensminger, Somo, Houser, & Crocker, 2014; Heidinger et al., 2008; Meddle, Owen-Ashley, Richardson, & Wingfield, 2003; Romero, Soma, & Wingfield, 1998a; Thiel, Jenni-Eiermann, & Palme, 2005).

3. Effectiveness of GCs. Once released, circulating GCs can elicit physiological and behavioral responses to varying extents. This variability may at least partly be due to receptor distributions and properties. For example, the expression of mineralocorticoid (MR) and glucocorticoid receptors (GR) can vary seasonally, though specific patterns may depend on the type of tissue examined and the conditions that individuals are exposed to (Lattin & Romero, 2014, 2015; Liebl et al., 2013). The distribution of MR and GR can also vary between two populations of the same species, for example between two Kenyan populations of house sparrow (see also Section 4.1; Martin & Liebl, 2014). Individuals from a population at the front of the expansion range expressed proportionally more GR than MR, a condition that may promote the effectiveness of negative feedback, ie, the shut-down of stress-induced corticosterone secretion, than birds from more established, older sites (Martin & Liebl, 2014).

Studies on receptor processes in wild populations are relatively rare among evolutionary endocrinologists (but for GRs see, eg, Breuner et al., 2003; Dickens, Meddle, & Romero, 2011; Lattin & Romero, 2015; Liebl et al., 2013; Senft et al., 2016) because thus far birds must be killed to quantify distributions and densities. However, advances in imaging techniques like positron emission tomography (PET) and single-photon emission computed tomography (SPECT), that are already applied in clinical contexts to visualize receptor processes in vivo (Khayum, Doorduin, Glaudemans, Dierckx, & de Vries, 2014) may in the near future also be usable for small

animals from natural populations. Some information on receptor function can already be obtained from blood samples, allowing the molecular determination of genetic variants of receptor types. Genes encoding for GR and, in some cases, for MR have been sequenced and studied especially in humans (Arriza et al., 1987), rats (Alnemri, Maksymowych, Robertson, & Litwack, 1991), chicken (Proszkowiec-Weglarz & Porter, 2010) and fish (Greenwood et al., 2003).

Molecular analyses have shown that GC receptors are quite conserved among vertebrates (with exception of teleost fishes, which have two GR types instead of one, reviewed in: Stolte, van Kemenade, Savelkoul, & Flik, 2006). The existence of polymorphisms in GR genes has been demonstrated in humans (Bray & Cotton, 2003). GR polymorphism can be associated with GC physiology, for example, with the magnitude of the GC response to social stimuli and the capacity for rapid negative feedback in adult men (Wust et al., 2004). GR polymorphism in the N363S gene in humans also determines the degree of sensitivity to corticosteroid therapy and the alteration of glucose metabolism by GCs (Huizenga et al., 1998). Genotype-dependent sensitivity to GC actions have also been observed in dogs (Costa, Sellon, Court, Burke, & Mealey, 2015). These molecular studies lead us to think that polymorphisms in GC receptor genes may be related pleiotropic effects on GC traits as well as their phenotypic flexibility. We are not aware of any ecological study that has considered GC receptor polymorphisms. However, since the number of species for which the genome has been sequenced is continuously growing, linking receptor genotypes to HPA-axis flexibility will soon be possible and shed new light on our understanding of among-individual variation in GR traits.

One obvious factor that may affect the biological actions of GCs is the availability of carrier in the blood such as CBG (see Section 1). The CBG-GC complex cannot pass through the walls of the blood vessels, which prompted the hypothesis that the "free" GC concentrations determined with the usual assay methods are not biologically relevant because parts of it may be "sequestered" by their carriers and be biologically ineffective (reviewed in: Breuner et al., 2013). However, this hypothesis is lively debated since it is also possible that globulins facilitate the passage of steroids into cells (Romero, 2002; Schoech et al., 2013). More work is needed to clarify the role of CBG, but independent of its exact role it likely is a modulator of GC effectiveness.

One final aspect that will be mentioned here are dynamics of deactivating enzymes. The enzyme 11b-hydroxysteroid dehydrogenase (11b-HSD),

an enzyme important for the final step in GC synthesis has two forms: one that leads to active GC forms while the other is thought to produce inactive metabolites (Wingfield, 2013b). Any regulation of such enzymes, variation in their relative amounts or changes in their activities could result in variation of GC actions within and among individuals.

Both external and internal factors can contribute substantially to variation in GC concentrations and HPA functioning (Section 1.2). Hence, there is a wealth of ways in which within- and among-individual variation in GC patterns can arise. Clearly more work, clever experimental design and perhaps some technological advances are needed to determine whether similar processes are at the base of both within- and among-individual variation, or even of variation between populations and species. Such work will be of great importance to understand the evolutionary pathways by which such variation has been and still is being generated.

4.3 Evaluating Benefits and Costs of GC Flexibility

After having discussed the potential pathways through which individuals may differ over time and from each other, the next set of questions that are relevant to unraveling the evolution of the GC system relates to the costs and benefits of GC-mediated phenotypic flexibility.

Phenotypic flexibility is generally thought to be beneficial when it allows an individual to alter its phenotype to adaptively match a changing environment, thus to produce a phenotype with a higher fitness in a certain or across multiple environments (DeWitt, Sih, & Wilson, 1998). It is plausible to predict that in fluctuating environments flexible individuals will be more competitive and have higher reproductive success and survival than inflexible (canalized) individuals. Conversely, although more canalized individuals may have a lower potential to adapt to fluctuating environments, they may be more successful under stable conditions, especially if plasticity is costly (DeWitt et al., 1998). The existence of costs is suggested by the observation that there seem to be limits to the flexibility of an individual.

For phenotypic *plasticity*, at least nine ideas exist regarding the nature of costs, although these have rarely been discussed together and generally are not as well understood as potential benefits. Many of these ideas can be applied to GC phenotypic *flexibility*, although only few will be discussed below (for a more detailed discussion see: Lema & Kitano, 2013; Lessells, 2008). The most commonly discussed cost of phenotypic *plasticity* is that of maintaining the relevant sensory and regulatory machinery, requiring energy and materials to operate. Another frequently considered limit to

flexibility is the unreliability of environmental cues, leading to maladapted phenotypes. Costs of responses to unreliable cues have recently been included in theoretical models and, perhaps more importantly, relevant empirical studies of non-adaptive plasticity now have emerged (Ghalambor, Martin, & Arthur Woods, 2014, Ghalambor, Mckay, Carroll, & Reznick, 2007).

For signaling molecules such as GCs, production costs could indeed play a role (Adkins-Regan, 2005). However, it has been argued that costs for steroid hormones may not be high because they are synthesized from an abundant precursor (cholesterol) and do not require the inclusion of rare elements. Instead, the production of enzymes and releasing hormones, both of which are protein-based, might be more relevant (Lessells, 2008). For some endocrine glands that undergo large seasonal variation in size like the gonads, weight and space issues might come to bear (Lessells, 2008). However, even though adrenal size can vary seasonally, it is generally a rather small organ. Perhaps the biggest potential cost of increases in GC concentrations is of metabolic nature, for example through effects on the expressed phenotype like increases in locomotor activity (Crespi et al., 2013). However, how large such costs might be is still unclear for most species (Buttemer, Astheimer, & Wingfield, 1991), as well as whether the suppressive effects of increased GC concentrations on processes like reproduction, digestion or immune function can compensate for these costs. GC-specific cost may be manifest during allostatic (or homeostatic) overload, when high amounts of GCs are released for a prolonged time (Lessells, 2008; McEwen & Wingfield, 2003; Romero et al., 2009). The biomedical literature is full of examples for how a prolonged over-activation of the HPA axis ('chronic stress') can lead to a multitude of degenerative diseases including atherosclerosis, ulcers, immunosuppression, neuropathology and reproductive disorders (McEwen, 2000). However, ecologists are still debating whether chronic stress occurs in free-living vertebrates (Boonstra, 2013b; Clinchy et al., 2013; Clinchy et al., 2004; Dickens & Romero, 2013; McEwen & Wingfield, 2003; Romero, 2004). Costs may also occur from an excessive downregulation of the HPA axis for extended periods of time. The reactive scope model (see Section 1.3) illustrates that extreme conditions of low GC responsiveness (ie, homeostatic failure) are hardly compatible with life (Romero et al., 2009); however, we are not aware of any study addressing this issue in natural populations.

Despite the interest in costs and limits of phenotypic flexibility, they might be difficult to demonstrate (DeWitt et al., 1998; Lessells, 2008),

especially for endocrine systems in light of the multifaceted, pleiotropic actions of hormones. Nevertheless, for understanding under which circumstances highly flexible hormonal phenotypes will fare better than less flexible phenotypes, it will be important to design appropriate experiments to quantify the costs and benefits of hormonal flexibility.

4.4 GC-Mediated Flexibility and Evolution

The adaptive nature and potential evolvability of phenotypic *plasticity* has been discussed quite extensively (de Jong & Gavrilets, 2000; Pigliucci, 2005; Scheiner & Lyman, 1989; Via et al., 1995). In general, reaction norms in a diversity of plastic traits tend to be heritable and to respond to both artificial and natural selection (Knies, Izem, Supler, Kingsolver, & Burch, 2006; Nussey et al., 2005; Pigliucci & Murren, 2003; Pigliucci, Murren, & Schlichting, 2006; West-Eberhard, 1989; Westneat, Hatch, Wetzel, & Ensminger, 2011; Whitman & Agrawal, 2009). These findings suggest that phenotypic plasticity generally has the capacity to evolve. Individuals exhibiting adaptive plasticity in novel conditions will be favored by directional selection, leading to greater population stability and to evolutionary changes largely depending on the environment (Mathot & Dingemanse, 2014). What can we expect for phenotypic flexibility in GC traits? We know that some GC traits like circulating concentrations have a heritable component (see Section 3.1). However, it has been shown that phenotypic plasticity can be extensive despite minor genetic variation (West-Eberhard, 2005). Given the current paucity of studies that have quantified endocrine reaction norms in individuals, it cannot yet be determined whether hormonal reaction norms are repeatable or even heritable. This presents a major gap in our knowledge because the way in which individuals flexibly alter their phenotypes to cope with the environment they are experiencing can differ even if they have similar genotypes and similar maternal and epigenetic histories (Araya-Ajoy et al., 2015).

One important aspect to consider in the context of evolution is the pleiotropic actions of hormones like GCs, through which they can affect suites of traits simultaneously (Hau, 2007; Ketterson et al., 2009; McGlothlin & Ketterson, 2008; Sinervo & Svensson, 1998). At present it is unclear whether such pleiotropic effects facilitate the evolution of phenotypes or whether these impede rapid evolutionary change (Hau, 2007; Ketterson et al., 2009; McGlothlin & Ketterson, 2008). It will be fundamental to determine the endocrine control of multiple traits because a flexible trait is more likely to evolve when there are weak genetic or ecological correlations with other

traits that are under opposing selection pressures (Garland & Kelly, 2006; Ghalambor et al., 2007). Thus, GC flexibility would be favored by selective forces when it produces large benefits, and when there is a positive correlation with other favorable traits. When there is strong covariation between hormonal flexibility and another trait, like behavioral performance, among-individual differences in hormonal flexibility may not necessarily imply that genetic variation underlies the hormonal flexibility (Pigliucci, 2005). For example, it is possible for a study to find apparent evidence for selection on, and evolution of GC flexibility despite a complete lack of genetic variance for this flexibility. This can happen if there was in fact selection on, and evolution of a (eg, behavioral) trait that in turn showed genetic variation and was strongly coupled to hormonal flexibility. In such a case the endocrine reaction norm per se would not evolve, but the phenotype still may. As stated in the outset (Section 1), evolutionary endocrinology is still in its infancy and there are ample opportunities for advancing our knowledge of the external and internal gradients that induce GC flexibility (or reaction norms), the mechanisms at the base of GC flexibility, associated costs and benefits and, finally microevolutionary patterns.

5. CONCLUSIONS

Endocrine systems – and steroid hormones like GCs in particular – afford a critical window into trait evolution because they often exhibit remarkable variation, influence and integrate a variety of other phenotypic traits such as behavior, and constitute complex physiological regulatory systems that may themselves be the target of evolutionary forces, including selection via their mediation of behavior and other performance traits (Arnold, 1983; Husak et al., 2009; Ketterson et al., 2009; McGlothlin & Ketterson, 2008). It is increasingly being recognized that a considerable fraction of the remarkable variation in GC signals is *intra*-individual. We think this is in line with our conception of GCs as filters and coordinators of an organism's internal and external environments and ecological priorities, thus acting as mediators of phenotypic flexibility. One major challenge will be to determine the external and internal factors that contribute to intra-individual variation, ie, to describe GC flexibility (and other HPA components, including CBG) in a reaction norm context across a variety of possible environmental and internal gradients. At present, it is also unclear whether an individual has a given GC flexibility (or reaction norm) to

various gradients, for example, displaying either a flat or a steep slope of responses across contexts, or whether GC responses divergent responses to gradients within one individual. It is conceivable that GC flexibility and the underlying process, eg, an increase in metabolic rate that induced it, are linked. In this scenario, an individual would show similar GC flexibility to any stimulus that affect its metabolic rate, such as ambient temperature, work load, immune responses etc. Alternatively, because of the complex mechanisms by which stimuli are integrated in the brain to regulate endocrine output, it is conceivable that an individual's GC reaction norms to temperature gradients, immune challenges or behavioral stimuli may be divergent.

The next major challenge is to better understand flexibility in GC traits to determine whether such complex traits represent consistent aspects of the individual, ie, repeatability of GC reaction norms (Araya-Ajoy et al., 2015). We are not aware of any study to date that has evaluated the consistency of any endocrine reaction norm. Future studies will also need to study GC flexibility as multi-dimensional interactions along two or more environmental gradients varied at the same time, to decompose the factors that most strongly contribute to the variation among and within individuals (see also Araya-Ajoy et al., 2015; Westneat, Stewart, & Hatch, 2009).

More long-term studies on wild and semi-natural populations are also urgently needed for a deeper understanding of the evolution of HPA axis function. Such investigations should combine repeated measurements of the same individual with a careful and simultaneous recording of environmental, social and internal conditions. Quantitative genetic approaches will increasingly become important and the inclusion of information from social and genetic pedigrees will allow us to approach questions of GC heritability (Jenkins et al., 2014). The future of evolutionary endocrinology also will require a focus on understanding the links between endocrine systems and those phenotypic attributes on which selection acts directly (behavior, performance) and indirectly (other physiological systems; McGlothlin & Ketterson, 2008). Since there is now ample evidence that many components of endocrine axes and the physiological and behavioral phenotypes they mediate interact to form systems, future studies would benefit by including network approaches (Martin & Cohen, 2014; Romero et al., 2015). We now have access to highly developed analytic tools for characterizing complex networks, and we can easily imagine that questions about the evolution of GC regulatory networks could be adapted for existing theoretical frameworks (Arnold, 1983; Cohen et al., 2012; Martin & Cohen, 2014). We think that the way forward will require true conceptual and technical

integration with other emerging fields like evo-devo, network theory, and other disciplines not typically connected to endocrinology. Together, these areas will help us resolve how GCs constrain as well facilitate animal ecology and evolution.

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