SYMPOSIUM

Stress Resilience and the Dynamic Regulation of Glucocorticoids

Maren N. Vitousek,[1,*,†] Conor C. Taff,[*,†] Thomas A. Ryan[*] and Cedric Zimmer[*]

*Department of Ecology and Evolutionary Biology, Cornell University, Ithaca, NY 14853, USA; †Cornell Lab of Ornithology, Ithaca, NY 14850, USA

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[1]E-mail: mnv6@cornell.edu

Synopsis Vertebrates respond to a diversity of stressors by rapidly elevating glucocorticoid (GC) levels. The changes in physiology and behavior triggered by this response can be crucial for surviving a variety of challenges. Yet the same process that is invaluable in coping with immediate threats can also impose substantial damage over time. In addition to the pathological effects of long-term exposure to stress hormones, even relatively brief elevations can impair the expression of a variety of behaviors and physiological processes central to fitness, including sexual behavior, parental behavior, and immune function. Therefore, the ability to rapidly and effectively terminate the short-term response to stress may be fundamental to surviving and reproducing in dynamic environments. Here we review the evidence that variation in the ability to terminate the stress response through negative feedback is an important component of stress coping capacity. We suggest that coping capacity may also be influenced by variation in the dynamic regulation of GCs—specifically, the ability to rapidly turn on and off the stress response. Most tests of the fitness effects of these traits to date have focused on organisms experiencing severe or prolonged stressors. Here we use data collected from a long-term study of tree swallows (*Tachycineta bicolor*) to test whether variation in negative feedback, or other measures of GC regulation, predict components of fitness in non-chronically stressed populations. We find relatively consistent, but generally weak relationships between different fitness components and the strength of negative feedback. Reproductive success was highest in individuals that both mounted a robust stress response and had strong negative feedback. We did not see consistent evidence of a relationship between negative feedback and adult or nestling survival: negative feedback was retained in the best supported models of nestling and adult survival, but in two of three survival-related analyses the intercept-only model received only slightly less support. Both negative feedback and stress-induced GC levels—but not baseline GCs—were individually repeatable. These measures of GC activity did not consistently covary across ages and life history stages, indicating that they are independently regulated. Overall, the patterns seen here are consistent with the predictions that negative feedback—and the dynamic regulation of GCs—are important components of stress coping capacity, but that the fitness benefits of having strong negative feedback during the reproductive period are likely to manifest primarily in individuals exposed to chronic or repeated stressors.

Introduction

What makes some individuals able to survive and thrive despite the presence of challenges that prove fatal to others? This question lies at the heart of both evolutionary biology and integrative organismal biology. Vertebrates respond to a wide array of challenges by activating broadly similar endocrine responses; the magnitude and duration of these endocrine responses can, however, vary substantially. Variation in the endocrine stress response is often predicted to underlie differences among individuals, and between species, in the capacity to cope with stress—yet determining when and how endocrine regulation influences fitness has proven challenging.

When vertebrates are faced with an acute challenge—the attack of a predator, a severe storm, a major injury—they mount a coordinated stress response that often dramatically alters behavior and physiology. The rapid but brief first wave of this response includes the activation of the sympathetic

nervous system and the secretion of catecholamines. At the same time, the activation of the hypothalamic–pituitary–adrenal (HPA) axis culminates in the secretion of glucocorticoid (GC) hormones, the most widespread and persistent mediators of the stress response. GCs bind to receptors throughout the body, influencing the expression of an enormous diversity of behaviors and physiological processes through both genomic and non-genomic routes (Sapolsky et al. 2000; Dallman 2005; Groeneweg et al. 2011). This powerful response is ultimately self-regulated through negative feedback (Sapolsky 1983; Dallman et al. 1992; Tasker et al. 2006).

The activation of the GC stress response is an important part of coping with challenges (Wingfield and Romero 2001). Individuals that are prevented from elevating GCs show inappropriate behavioral (Thaker et al. 2010) and physiological responses to threats, and rapidly succumb when exposed to some types of severe stressors (Darlington et al. 1990). As Selye (1946) discovered decades ago, however, the same processes that are enormously beneficial during the short-term response to a stressor can cause substantial damage over time. The pathological effects of long-term exposure to GCs are well-described, and include oxidative stress, telomere shortening, and hippocampal damage (McEwen 2001; Rich and Romero 2005; Haussmann et al. 2012; Monaghan 2014). Even relatively short-term increases in GCs can hinder the expression of a multitude of behaviors and physiological processes that are central to fitness, including sexual behavior, parental behavior, and immune function (Wingfield and Sapolsky 2003). The optimal stress response thus represents a delicate balance: it must be sufficiently robust to afford protection from likely stressors, while simultaneously minimizing the potential damage induced by the response itself.

Effectively coping with stressors is therefore likely to involve not only mounting a vigorous stress response, but efficiently and effectively terminating this response to return to normal behaviors and physiological processes. Yet while the fitness correlates of mounting a strong stress response have been studied in a number of species (e.g., Breuner et al. 2008; Satterthwaite et al. 2010; Ouyang et al. 2013; Schmid et al. 2013; Vitousek et al. 2014), much less is known about whether individual variation in the ability to terminate the response to stress predicts performance or fitness (Romero and Wikelski 2010; Zimmer et al. 2019). Furthermore, while conceptual models of the stress response suggest that successful coping may necessitate the combination of a strong stress response with effective negative feedback (e.g., Breuner et al. 2008; Schmidt et al. 2012), components of GC regulation are almost always assessed independently, or using aggregate metrics that do not enable the separation of the immediate response from the ability to terminate that response (e.g., total area under the curve of GC secretion).

Negative feedback in the HPA axis, performance, and fitness

Differences within and among populations in the effective termination of the stress response may influence the capacity to cope with stressors through at least two mechanisms. First, prolonged stress responses could increase the expression or cumulative effect of changes in behavioral or physiological processes that are not pathological, but could impair fitness when sustained over time (e.g., the interruption of parental care). Second, according to the reactive scope model of stress the ability of organisms to resist the pathological effects of elevated GCs declines throughout the stress response (Romero et al. 2009). Because of this, the duration of the acute stress response may be a major determinant of the amount of phenotypic damage provoked by each stressful event in organisms facing prolonged or repeated stressors (Romero 2012). Under normal conditions the acute stress response is brief and infrequent; it does not impose pathological damage, and the ability to resist damage recovers following the cessation of the stress response. But when organisms are exposed to repeated or chronic stressors there may be insufficient recovery time to enable the capacity to resist damage to return to normal levels. In this case, the duration of the GC stress response—and the associated decline in the resistance to pathological damage—could predict cumulative phenotypic damage and the propensity to shift into an "emergency life history stage" (Wingfield et al. 1998) in an attempt to cope with the stressor. In contrast, circulating hormones during the early stages of the response, when organisms are less susceptible to the deleterious effects of GCs, may be a relatively poor predictor of phenotypic damage (Fig. 1).

Because negative feedback reduces the likelihood of GC-induced damage, it is generally predicted that optimal GC regulation entails strong negative feedback (Sapolsky 1983; Meaney 2001; McEwen and Wingfield 2003; Romero et al. 2009; Bauer et al. 2015). But if strong negative feedback confers a fitness benefit, why do individuals vary considerably in
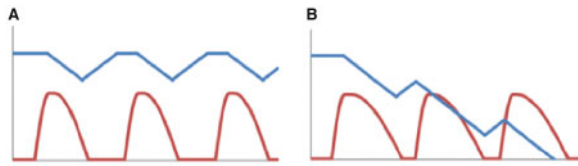
Fig. 1 Predicted relationships between the strength of negative feedback and cumulative phenotypic damage when stressors are frequent. The lower (red) line represents circulating GCs, and the upper (blue) line represents the ability to resist phenotypic damage. When an organism mounts a stress response, the ability to resist phenotypic damage declines for the duration of the stress response, but begins to recover when the response ceases. When stressors are frequent, the susceptibility to pathological damage (which occurs when circulating hormone levels are greater than the resistance to damage) depends on the efficacy of negative feedback. (a) In individuals with strong negative feedback, the stress response is shorter, and the ability to resist phenotypic damage recovers between stressors. (b) In individuals with weaker negative feedback, the prolonged stress response shortens the recovery time between stressors and increases the likelihood that the stress response will induce pathological damage. Diagrams are modeled on the predictions of the reactive scope model (Romero et al. 2009).

the strength of negative feedback (Sapolsky 1983; Romero and Wikelski 2010; Miles et al. 2018)? Weak feedback is often considered to be a pathological outcome of developing under challenging conditions (Meaney 2001) or to result from the dysregulation of the HPA axis following exposure to chronic stressors (e.g., Young et al. 1990; McEwen and Wingfield 2003; Dickens et al. 2009). It is also possible, however, that weaker GC feedback confers a fitness benefit under some conditions. For example, organisms facing severe threats that can be mitigated or avoided by GC-mediated responses (e.g., some predation scenarios) might benefit from mounting a longer GC response; in these environments, the benefit of GC-mediated phenotypic changes could outweigh the risk of GC-induced phenotypic damage. It is also conceivable that weaker negative feedback increases the sensitivity of organisms to environmental cues—perhaps providing a mechanism of adjusting the timing of breeding (Lattin et al. 2016), or foraging or movement patterns (Zimmer et al. 2013), based on likely fitness payoffs. Intriguingly, in some semelparous species a dramatic reduction in the strength of negative feedback simultaneously facilitates enormous energetic investment in reproduction, and ultimately causes death (Stein-Behrens and Sapolsky 1992; Carruth 2002). In these species, reproductive investment is not down-regulated by GCs, as is typically the case. Variation in the strength of feedback could also result from exposure to one stressor facilitating or

conditioning the response to future challenges (Dallman et al. 1992; Del Giudice et al. 2018); depending on the context this type of conditioning may or may not be adaptive (Taff and Vitousek 2016). Regardless of the mechanisms generating variation, if expressing strong negative feedback carries both costs and benefits then within-population trait variation could result from evolutionary trade-offs that manifest among individuals (if the strength of negative feedback is individually consistent), or within individuals (if negative feedback shows adaptive flexibility).

Determining the evolutionary causes of variation in negative feedback efficacy and other elements of GC regulation will entail linking trait variation with fitness. To date, research in free-living organisms has focused almost exclusively on the relationships between baseline and/or stress-induced GCs and fitness. However, compelling findings from the biomedical literature suggest that aspects of health and performance—including the behavioral response to challenges—are predicted by variation in the ability to terminate the stress response through negative feedback. Laboratory work in mammalian model systems has revealed that weaker negative feedback is associated with a heightened behavioral response to stressors (Meaney 2001) and diminished parental behavior (Liu et al. 1997). Intriguingly, in rats, variation in the efficacy of negative feedback is related to epigenetic changes in regions of the genome that influence the expression of GC receptor proteins (Weaver et al. 2004). Rats exposed to higher GC levels during development—as a result of less parental care—show more methylation of the GC receptor promoter region in the brain, resulting in a life-long decrease in the efficacy of negative feedback the expression of more anxiety and wariness, and less aggression (Vallée et al. 1996; Francis et al. 1999; Weaver et al. 2005). In humans, the reduced efficacy of negative feedback is both a potent biomarker for depression (Holsboer 2000) and a precipitant of senescence (Stein-Behrens and Sapolsky 1992).

The long-term studies of Robert Sapolsky have revealed that free-living baboons with weaker negative feedback are less socially dominant, suffer from higher levels of hypercortisolism (Sapolsky 1983; Sapolsky et al. 1997), and are more susceptible to certain diseases. Variation in the strength of negative feedback has also been linked with variation in personality (Baugh et al. 2017b; but see Baugh et al. 2017a), wound healing (DuRant et al. 2016; Love et al. 2017), immune parameters (Schmidt et al.

2012), and the timing of breeding (MacDougall-Shackleton et al. 2013) in birds.

Very few studies have assessed the relationship between negative feedback efficacy and fitness in natural populations. The most comprehensive test of the response to naturally occurring stressors to date found that the ability to terminate the acute stress response was strongly associated with mortality. Galápagos marine iguanas with weaker negative feedback—but not those with lower peak hormone levels in response to a restraint stressor—were more likely to die during acute El Niño-induced food shortages (Romero and Wikelski 2010). This is consistent with the idea that the continued secretion of high levels of GCs over an extended period may have negatively impacted survival—in this case by increasing the speed at which individuals entered the later stages of starvation (Romero and Wikelski 2010). Negative feedback was not associated with over-wintering survival in a single-year analysis in song sparrows (MacDougall-Shackleton et al. 2013), but has recently been found to predict both stress resilience (defined as the ability to continue reproducing in the presence of a stressor) and the speed of recovery of the HPA axis from perturbations in tree swallows (Taff et al. 2018; Zimmer et al. 2019; see below).

Although the strength of negative feedback is increasingly commonly measured, we currently lack a generalized framework predicting of when variation in negative feedback is likely to be adaptive. Because of the importance of negative feedback in recovering from stress (e.g., Sapolsky 1983; Dallman et al. 1992; Romero et al. 2009), we predict that the fitness effects of negative feedback will manifest predominantly in individuals and populations facing frequent or chronic stressors. In populations that encounter only infrequent acute stressors—or those that face a diverse set of challenges with different optimal responses—variation in the ability to terminate the stress response could have no detectable fitness effects. Under most frequent or chronic stress regimes, we predict that having stronger negative feedback will confer a fitness benefit. However, both life history and the nature of the stressor are likely to impact feedback–fitness relationships (Schoenle et al. 2018). Specifically, we expect strong negative feedback to be particularly beneficial in organisms engaged in valuable reproductive attempts (Astheimer et al. 1994; Wingfield and Kitaysky 2002), including in aging organisms with terminal reproductive investment (Stein-Behrens and Sapolsky 1992; Heidinger et al. 2008; Elliott et al. 2014). We also expect stronger negative feedback to

be favored in populations facing frequent disturbances that do not present a direct threat to survival (e.g., Soldatini et al. 2015). Conversely, weaker feedback may be favored in environments in which encountering one acute stressor is highly predictive of additional encounters in the near future (e.g., some predation scenarios: Boonstra et al. 1998; Boonstra 2013). In these environments, individuals with weaker feedback could be more sensitive to, and better able to avoid, threats. If weaker negative feedback increases the sensitivity to environmental cues of the likelihood of reproductive success (Lattin et al. 2016), we also predict weaker feedback in populations with more flexible reproductive strategies.

Interactions among GC regulatory elements

Because mounting an acute GC response to stress can confer both costs and benefits, the regulation of this response is likely to be shaped by fitness trade-offs. Trade-offs have long been incorporated into predictions about when it would be beneficial to mount a stronger or a weaker immediate stress response (e.g., Wingfield and Sapolsky 2003; Lendvai et al. 2007; Bókony et al. 2009; Vitousek et al. 2019), but the potential for a certain component of the GC "regulatory phenotype" to be beneficial only when coupled with other elements has largely been neglected. Breuner et al. (2008) predicted that "a combination of low baseline, fast increase, and rapid induction of negative feedback represents a 'good' response"; however, very few studies have explicitly tested whether interactions among GC regulatory traits are important predictors of performance or fitness.

Interactions among GC regulatory elements could influence the fitness outcomes of mounting an endocrine response in several ways. Organisms facing major stressors—whose effects could be mitigated through elevated GCs—might benefit from mounting a strong acute GC response. However, because mounting a strong GC response could elevate the risk of GC-induced costs (Romero et al. 2009; Vitousek et al. 2018a)—which may be particularly problematic in organisms engaged in valuable reproductive attempts (Wingfield and Sapolsky 2003)—mounting a strong stress response may only be beneficial if it is coupled with strong negative feedback (Zimmer et al. 2019). Alternatively, in demanding environments or life history stages, organisms may benefit from elevating baseline GCs to support energetic regulation (Bókony et al. 2009; Bonier et al. 2011; Crossin et al. 2012; Vitousek et al. 2019);

however, if long-term elevations in baseline GCs increase the likelihood of entering into an emergency life history stage (Romero et al. 2009), then elevating baseline GC levels might confer a fitness benefit only if coupled with mounting a relatively weak acute GC response to stress (Vitousek et al. 2018b).

Overall, we predict that explicitly incorporating the potential for interactions among components of endocrine regulation to influence performance and fitness will provide significant insight into the function and evolution of hormone systems. As described above, the optimal combination of GC regulatory components is likely to differ substantially across environments and species. Three particularly important elements of context-dependency in endocrine trade-offs, described in more detail in Schoenle et al. (2018), are the nature of the stressor, the frequency and duration of exposure, and organismal life history. These and other aspects of context-dependency can have independent impacts on the costs and benefits of specific components of GC regulation, or favor the expression of certain combinations of GC regulatory traits.

Stress resilience in a free-living model species: the tree swallow

Our research has been using free-living songbirds (tree swallows: *Tachycineta bicolor*) to test when and how GC regulation influences the ability to cope with stressors. Tree swallows are an excellent model species for studies of physiological regulation because they are highly site-faithful and resistant to disturbance, and can be sampled during specific time periods in order to minimize variation due to circadian rhythms or life history substages (Ardia 2007; Bonier et al. 2009; Wada et al. 2009; Madliger and Love 2016; Injaian et al. 2018; Bentz et al. 2019).

Both baseline and stress-induced GCs show heritable variation in our primary study population of tree swallows in New York, USA (Stedman et al. 2017). However, previous analyses have suggested that baseline levels have much higher intraindividual variation: across years, GC responses to acute stress—but not baseline hormone levels—were individually repeatable (Vitousek et al. 2018b). These patterns are consistent with recent analyses in captive populations of other songbirds, which suggest relatively high individual consistency in both stress-induced GCs and negative feedback (Baugh et al. 2017b; Jimeno et al. 2017, 2018). Intriguingly, negative feedback seems to have substantially higher among-individual variation than baseline or stress-induced GCs (or other morphological traits); a

pattern that has now been observed in two tree swallow populations (Miles et al. 2018). Greater within-population variation is often observed in traits that are not shaped by selection; however, this pattern could also indicate that selection is favoring alternative feedback phenotypes (Miles et al. 2018).

Several recent studies in tree swallows have supported the prediction that strong negative feedback is an important element of stress coping capacity. In one of these studies (Zimmer et al. 2019), free-living birds were exposed to one of two ecologically relevant stressors: an increase in the perceived risk of predation (using predator mounts) or a simulated decline in food availability (induced by securing primary feathers together to temporarily reduce flight efficiency: Taff et al. 2019). Natural predators and periods of low ambient temperature (which reduce the availability of insect prey: Winkler et al. 2013) elevate the risk of nest abandonment during incubation. We found that across treatments, pre-exposure GC phenotype predicted stress resilience (defined as the ability to continue reproducing despite the presence of a stressor; Taff et al. 2019; Zimmer et al. 2019). Birds that both mounted a strong acute GC stress response and had strong negative feedback were less likely to abandon nests during incubation (Zimmer et al. 2019). This pattern indicates that mounting a strong GC response may help individuals to cope with an immediate stressor—perhaps by mobilizing energy to support the response. However, this response appeared to only confer a fitness benefit if it was coupled with the ability to rapidly and effectively terminate the GC response through negative feedback. Thus, in addition to providing support for the role of negative feedback in influencing stress coping capacity, these results are consistent with the idea that optimal GC regulation may depend on having certain combinations of GC regulatory traits.

Negative feedback efficacy was also associated with stress coping capacity in another recent study, which tested the predictors of the ability of the HPA axis to recover from repeated perturbations (Taff et al. 2018). Free-living tree swallows were exposed to a series of brief acute increases in exogenous GCs (by applying GCs to dummy eggs installed in the nest of incubating females once daily; Vitousek et al. 2018a); and resampled for 2 weeks to measure how rapidly they returned to pre-disturbance GC regulation (normal baseline GC levels). Individuals that were better able to terminate the GC response through negative feedback prior to the disturbance

recovered from treatment more rapidly (Taff et al. 2018). As predicted, recovery was unrelated to variation in pre-disturbance baseline or stress-induced GC levels.

These findings are consistent with the idea that, in organisms facing repeated or chronic stressors, the ability to rapidly terminate the stress response through negative feedback reduces GC-induced pathological damage, and promotes faster recovery, reducing the likelihood of entering an "emergency-life history stage" in which reproductive effort is abandoned in favor of self-maintenance (Wingfield et al. 1998; Romero et al. 2009). However, what remains less clear is whether having stronger negative feedback confers a fitness benefit among individuals that are not experiencing chronic or repeated stressors. A previous multi-year analysis of the predictors of fitness in unmanipulated tree swallows found that interactions between baseline and stress-induced GCs predicted some components of fitness. Females that had lower baseline GCs coupled with a stronger stress response (or the reverse) during the nestling provisioning period fledged the most young (Vitousek et al. 2018b). This analysis did not, however, include measurements of the efficacy of negative feedback.

Here we use data from nestling and adult free-living tree swallows, collected over a 5-year time period, to test whether variation in the strength of negative feedback in the HPA axis, or other components of GC regulation, predict survival and reproductive success. Specifically, we test the predictions that individuals that: a) have stronger negative feedback, or b) have stronger negative feedback coupled with a strong stress response will successfully rear more young and will have higher short-term survival (nestlings) and inter-annual survival and return rates (adults). Alternatively, if negative feedback influences fitness primarily through altering the capacity to cope with frequent or chronic stressors, then negative feedback efficacy could be unrelated to components of fitness in unstressed populations. Over the period of study environmental conditions varied. Some individuals almost certainly experienced periods of frequent or prolonged stress (e.g., from periods of inclement weather; Winkler et al. 2013) which can trigger a reduction in reproductive effort or nest abandonment in tree swallows (Ouyang et al. 2015; Taff et al. 2019). However, average reproductive success during the years studied here was similar to the long-term averages, suggesting that most individuals were not chronically stressed during the period of study.

We also assess the extent to which negative feedback is an independent and individually consistent trait. Using a larger dataset of measures collected from our primary study population, we assess patterns of covariation among GC regulatory elements across ages and life history stages. Additionally, we estimate repeatability in the strength of negative feedback within and across years, and compare it with estimates of the repeatability of baseline and stress-induced GCs.

Materials and methods

Field data were collected from 2014 to 2018 in our long-term nest-box breeding population of tree swallows in Tompkins County, New York (42.5°N, 76.5°W, 340 m elevation). Birds were captured at nest boxes by hand or using a manually activated internal wig-wag trap. All birds were captured and sampled on specific days of life history substages, and during a set time of day, to reduce the variation in circulating hormone levels that results from circadian rhythms. Adult females were captured between 07:00 and 10:00 h, first during the incubation period (days 6–7), and again during the nestling provisioning period (days 3–7). Nestlings were sampled 12 days after hatching, between 12:00 and 15:00 h. Nests were monitored every 1–2 days throughout the breeding season, with the exception of the last week of the nestling period (when disturbance can cause premature fledging). Boxes were checked 22–24 days after hatching to determine the fate of all nestlings alive at banding.

Blood samples were collected from the alar vein, within 3 min of initial disturbance, to measure baseline levels of circulating corticosterone (the primary avian GC). A second sample was collected following 30 min of restraint in a cloth bag, to measure stress-induced GC levels. Immediately after the second sample was taken birds were injected with dexamethasone (dex), a synthetic GC, which binds to receptors in the hippocampus, hypothalamus, and pituitary, inducing negative feedback (Zimmer et al. 2019). A third and final blood sample enabled the measurement of negative feedback. In all adults, and in nestlings sampled during the first of 2 years of study, this final blood sample was collected 30 min post-injection. In nestling samples collected during the second year of measurement (2018), nestlings were returned to the nest following the injection of dexamethasone, and then removed again 60 min post-injection for the collection of the final blood sample.

Blood samples were kept on ice until centrifugation. Following the conclusion of the breeding season, plasma GC levels were assayed as previously described (Vitousek et al. 2018b). In brief, circulating levels were measured using either a miniaturized double antibody radioimmunoassay (ImmuChem Corticosterone I-RIA, MP Biomedicals: 07-120103; in 2014–2015) or an enzyme immunoassay (DetectX Corticosterone, Arbor Assays: K014-H5; in 2015–2018). Measured corticosterone concentrations show high correspondence across these methods ($r^2 = 0.93$) but absolute levels differ (Stedman et al. 2017). Concentrations measured using RIA were therefore corrected to EIA equivalents as previously described: $(CORT_{RIA} + 0.889)/1.43 = CORT_{EIA}$ (Stedman et al. 2017). Full validation information for both of these kits in tree swallows has been previously published (Palacios et al. 2007; Taff et al. 2019). Within years, all samples from the same individual were run in the same assay.

Data analyses were conducted using R v. 3.4.2 (R Development Core Team 2017). Covariation among GC regulatory traits was estimated using linear models ("lm") during the nestling period, and separately in incubating and provisioning females. In cases in which the same individual was measured in multiple years, one record was randomly excluded. Individual repeatability was estimated for all three GC measures using all available data from adult females only (nestlings were only sampled once). Prior to analysis, a single outlier was excluded from each GC category. Repeatability metrics were determined using the restricted maximum-likelihood (REML) method in linear mixed-effects models, using "rptR" (Nakagawa and Schielzeth 2010). Identity was included as a random factor. Confidence intervals were estimated using parametric bootstrapping (1000 iterations).

A model selection approach was used to identify predictors of annual reproductive success (the number of offspring that fledged from the nest) and inter-annual return likelihood in adult tree swallows sampled during the nestling provisioning period, and survival-to-fledging in nestlings. Analyses used generalized linear mixed models; reproductive success was modeled with a Poisson distribution with a log link function ("glmer" function in the "lme4" package) (Bates et al. 2015), and survival-to-fledging and inter-annual return likelihood were modeled with a binomial distribution. The best supported models were identified by comparing Corrected Akaike Information Criterion (AICc) scores. Because data were collected from birds in different years, under different environmental conditions, and from birds experiencing different minor nest-level manipulations, all adult models contained "Year-Treatment" as a random effect. In cases where the same individual was measured in multiple years, we randomly excluded one record from analysis. Candidate models contained combinations of: baseline GCs, stress-induced GCs, and post-dexamethasone GCs. To test the hypothesis that fitness is influenced by having specific combinations of GC regulatory traits, we also included candidate models that contained two-way interactions among these variables (Vitousek et al. 2018b). All candidate model sets also included an intercept-only model, which included only the random effect.

Analyses of annual reproductive success (the number of offspring that fledged from the nest) used the strictest filtering criterion, because of the potential for manipulations to influence reproductive effort or success. Before analysis, all birds that had been exposed to significant manipulations (e.g., simulated predator encounters or flight efficiency manipulations) were excluded from the data set. Because previous analyses have found no effect of treatment on survival rates, models of adult inter-annual survival included data collected from a larger group of provisioning females. In cases where the same individual was measured in multiple years, we randomly excluded one record from analysis. In adult tree swallows, the majority of birds that survive to the following year return to the breeding site (Winkler et al. 2004). Thus, among adult tree swallows, it is reasonable to assume that most non-returning birds did not survive. A previous mark–recapture analysis of endocrine repeatability in this population showed no evidence of missed detections (Vitousek et al. 2018b); however, some surviving individuals in this study may have dispersed between years. The predictors of survival-to-fledging used data from nestling tree swallows in which all three measures of GC regulation had been assessed in 12 day old birds. Because nestling fates are not independent within nests, and could also be impacted by prior treatments applied to parents, models of survival-to-fledging included social nest as a random effect, and year-treatment as a fixed effect.

Results

Covariation among components of GC regulation differed by age and life history stage. Baseline and stress-induced GCs were positively correlated among nestlings (adjusted $R^2 = 0.164$; $P < 0.001$, $n = 284$), but were unrelated in adult females during the incubation (adjusted $R^2 < 0.001$; $P = 0.30$, $n = 136$), or nestling provisioning periods (adjusted $R^2 = 0.009$;

$P = 0.64$, $n = 89$). Stress-induced and post-dexamethasone GCs were unrelated in nestlings (adjusted $R^2 = 0.006$; $P = 0.119$, $n = 256$) and provisioning females (adjusted $R^2 < 0.0001$; $P = 0.32$, $n = 88$), but were positively correlated in incubating females (adjusted $R^2 = 0.10$; $P < 0.001$, $n = 132$). Likewise, baseline and post-dexamethasone GCs were unrelated in nestlings (adjusted $R^2 = -0.003$; $P = 0.73$, $n = 257$) and provisioning females (adjusted $R^2 = 0.004$; $P = 0.42$, $n = 85$) but positively covaried in incubating females (adjusted $R^2 = 0.09$; $P < 0.001$, $n = 132$).

Individual repeatability of baseline GCs was low (0.07, 95% CI: 0.00–0.19; $n = 374$ observations from 137 females), whereas both stress-induced and post-dexamethasone GCs showed moderate repeatability (stress-induced: 0.25, 95% CI: 0.11–0.38, $n = 316$ observations from 133 females; post-dexamethasone: 0.36, 95% CI: 0.21–0.47, $n = 299$ observations from 125 females). Repeatability estimates increased slightly for negative feedback, and decreased for stress-induced corticosterone, when analyses were restricted to samples collected within the same year (baseline: 0.12, 95% CI: 0.00–0.31; $n = 176$ observations from 87 females; stress-induced: 0.17, 95% CI: 0.00–0.36; $n = 177$ observations from 87 females; post-dexamethasone: 0.45, 95% CI: 0.26–0.59; $n = 161$ observations from 79 females).

The model of annual reproductive success (number of nestlings fledged) that received the most support included stress-induced GCs, negative feedback, and their interaction (Table 1; weight: 0.40). Within this model, reproductive success was highest among individuals that mounted a robust GC stress response, and had strong negative feedback (Table 2 and Fig. 2). The second ranked model included stress-induced GCs alone (weight: 0.20), and the intercept-only model ranked third (weight: 0.18). While these findings suggest some uncertainty in model fit, a comparison of the log likelihood scores of these candidate models also suggests that the inclusion of the interaction between stress-induced GCs and negative feedback efficacy improves model fit (Table 1).

In contrast, a comparison of models of inter-annual survival and return did not clearly support a consistent relationship with GC regulation during breeding. The model of inter-annual return that received the most support contained post-dexamethasone GC levels alone (Table 1). However, within this model the effect of post-dexamethasone GCs was weak (post-dexamethasone GCs: Est[SE] = 0.46[0.32], z-value = 1.4, $P = 0.154$).

Table 1 Candidate models of annual reproductive success (the number of nestlings fledged) and the likelihood of inter-annual survival and return among female tree swallows as a function of GC regulation

	Log likelihood	K	Delta AICc	Weight
Reproductive success ($n=68$)				
Stress-induced * Post-dex (feedback)	−130.5	5	0.00	0.40
Stress-induced	−133.4	3	1.35	0.20
Intercept only	−134.7	2	1.62	0.18
Survival and return ($n=86$)				
Post-dex (feedback)	−52.21	3	0.00	0.34
Intercept only	−53.51	2	0.45	0.27

Because some of the nests in this study were a part of other experiments, which differed across years, all models contain the random effect of year+treatment group. Models with two-way interactions also contain both main effects. All models within 2 ΔAICc of the best supported model in each category are shown.

Table 2 The best supported model of annual reproductive success (number of nestlings fledged) among female tree swallows

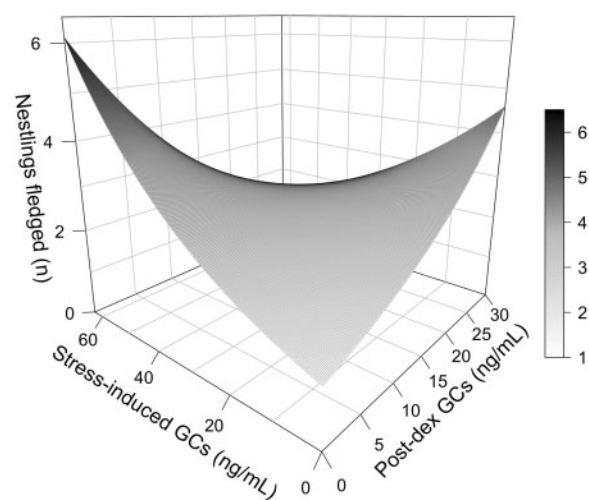|	Est (±SE)	Z	P
Intercept	0.53 (0.29)	1.8	0.070
Stress-induced	0.11 (0.07)	1.6	0.122
Post-dex (feedback)	0.08 (0.10)	0.8	0.401
Stress-induced * Post-dex (feedback)	−0.17 (0.07)	−2.3	0.021

Fig. 2 Three-dimensional surface plot illustrates the relationships between GC regulation and annual reproductive success. Among females breeding in New York, the highest reproductive success was seen in individuals that both mounted a strong stress response and had effective negative feedback (low post-dexamethasone GCs).

Table 3 Candidate models of the likelihood of nestling survival-to-fledging as a function of GC regulation (GC levels)

Model	Log likelihood	K	Delta AICc	Weight
Nestlings ($n =256$)				
Post-dex (feedback)	−90.3	4	0.00	0.46
Nestlings; outlier removed ($n =255$)				
Post-dex (feedback)	−90.1	4	0.00	0.25
Baseline	−90.3	4	0.48	0.19
Intercept only	−91.4	3	0.52	0.19

All models contain year+treatment group as a fixed effect, and rearing nest as a random effect. All models within 2 ΔAICc of the best supported model are shown.

The intercept-only model also received only slightly less support (relative weights: 0.34 vs. 0.27).

When data from all nestlings were included, the only model of survival-to-fledging that received substantial support contained post-dexamethasone GC levels alone (Table 3). Within this model, birds with lower post-dexamethasone GC levels (stronger negative feedback) were more likely to survive (post-dexamethasone GCs: Est[SE] $= -1.04[0.40]$, z-value $= 2.6$, $P = 0.010$). However, the dataset contained a single outlier with very high post-dexamethasone GC levels. When this individual was removed from the dataset, the best supported model was still the same (post-dexamethasone GCs: Est[SE] $= 0.62[0.40]$, z-value $= 1.6$, $P = 0.12$). However, two additional models received very similar support, the model with baseline GCs alone and the intercept-only model (Table 3). Thus, when the outlier was excluded we did not see convincing evidence of a consistent relationship between negative feedback efficacy and survival to fledging in nestling tree swallows.

Discussion

Our results indicate that the ability to terminate the GC stress response through negative feedback is an individually repeatable trait in free-living tree swallows that does not consistently covary with other measured components of GC regulation (baseline and stress-induced GCs). Thus, selection could independently operate on the strength of feedback—if this trait is heritable.

Variation in the capacity to down-regulate the stress response has long been predicted to be an important part of coping with challenges, Individual differences in the strength of feedback have previously been shown to predict the capacity to cope with major stressors (Romero and Wikelski 2010;

Zimmer et al. 2019) and the speed of recovery from simulated challenges (Taff et al. 2018). Here we find that reproductive success in female tree swallows is predicted by variation in the ability to both turn on and off the stress response—the same endocrine profile that predicts the capacity to cope with experimental stressors in this population (Zimmer et al. 2019). We did not find clear support for a relationship between GC regulation and survival in nestlings or adults, although the single best supported model in both cases included the strength of negative feedback. These patterns, together with those revealed by prior experimental manipulations in this population (Taff et al. 2018; Vitousek et al 2018a; Zimmer et al. 2019), support the prediction that negative feedback is an important component of stress coping capacity (e.g., Dallman et al. 1992; Breuner et al. 2008; Romero et al. 2009; Schmidt et al. 2012). They are also consistent with the prediction that the fitness benefits of having strong negative feedback are likely to be highly context-dependent, and to manifest primarily in individuals exposed to chronic or repeated stressors.

The presence and strength of the relationship between negative feedback and nestling survival-to-fledging differed depending on whether a single outlier was included in the analysis. When all birds were included the only model of survival-to-fledging that received substantial support contained negative feedback alone. Nestlings with stronger negative feedback were more likely to survive to fledging. However, when this outlier was excluded, this model received very similar support to the intercept-only model, suggesting that none of the measured traits were strong predictors of survival to fledging. Nest environments vary, but overall the pre-fledging period is a period of high mortality: 21% of the nestlings measured in this study died before fledging. Additional mortality occurred during the early nestling period, before the birds in this study were sampled. Most of the acute challenges that nestlings face are ones for which successful coping is unlikely to be aided by elevated GCs—until they are ready to fledge, nestling songbirds are unable to escape from predators and other challenges, and are dependent on their parents for food. Thus, mounting a strong acute stress response is unlikely to be favored during this period. It is however possible that individuals that are better able to terminate the stress response through negative feedback could suffer less GC-induced damage. Overall, we predict that the relationship between nestling mortality and GC regulation will differ depending on the causes of mortality. During years in which nestling mortality is

driven predominantly by starvation of some individuals within each brood we expect that nestlings with stronger negative feedback will have higher survival, because these individuals will be better able to delay the transition into the third and final stage of starvation, in which proteins are metabolized (Romero et al. 2009; Romero and Wikelski 2010). In contrast, during years in which nestling mortality results predominantly from nest abandonment or predation, we expect that negative feedback will be unrelated to survival to fledging. Future analyses that incorporate data from a larger number of years, collected across a range of conditions, could test these predictions.

Covariation among components of GC regulation varied across ages and life history stages. Consistent with previous findings from our primary study population, baseline and stress-induced GCs were positively correlated in nestling tree swallows (Stedman et al. 2017), but not in adults (Zimmer et al. 2019; but see Vitousek et al. 2018b). Neither of the other two GC trait pairs covaried in nestlings. In adults there was a weak but significant positive relationship between post-dexamethasone GC levels and both baseline and stress-induced GCs during incubation. In contrast, post-dexamethasone GCs were unrelated to baseline or stress-induced GCs during the provisioning period. These patterns are consistent with the idea that baseline hormone levels, the acute stress response, and the strength of negative feedback are independent traits that are separately modulated (Romero 2004). However, recent evidence suggests that the presence of genetic covariations among GC regulatory traits may differ across species. While baseline and stress-induced GCs are not genetically correlated in the two species of passerine birds in which this has been assessed (tree swallows: Stedman et al. 2017; barn swallows: Jenkins et al. 2014), a recent analysis in barn owls found that these traits were positively genetically correlated (Béziers et al. 2019). Determining whether the strength of negative feedback is genetically correlated with other components of HPA activity could help to illuminate the likely response to selection operating on this trait. Likewise, future research into the factors influencing within-individual flexibility in GCs could reveal why modulation results in phenotypic covariation in some ages and life history stages but not others.

Repeatability analyses yielded very similar metrics to those found previously in this population for baseline and stress-induced GCs: baseline GCs were not significantly repeatable, whereas stress-induced GCs showed moderate and significant repeatability

(Vitousek et al. 2018b). The repeatability of post-dexamethasone GCs, which has not been previously estimated in this population, was also significant and moderate. These estimates are similar to findings in the few other analyses of repeatability in negative feedback, which have used captive populations of other songbird species (Baugh et al. 2017b; Jimeno et al. 2018). If individual variation in the efficacy of negative feedback is heritable, as is the case for baseline and stress-induced GCs in this population (Stedman et al. 2017), then variation in negative feedback—when it impacts fitness—could be shaped by selection.

Conclusions and future directions

The patterns seen here, together with recent findings from several experimental studies, suggest that the capacity to dynamically regulate GCs may be an important determinant of stress coping capacity, and—under some conditions—fitness. Although the fitness benefit of rapidly and effectively terminating the GC response is likely to be particularly apparent in organisms facing repeated or chronic stressors (Romero and Wikelski 2010; Taff et al. 2018; Zimmer et al. 2019), these analyses support the potential for negative feedback to predict reproductive success in natural populations that are not experiencing widespread chronic stressors; however, the weak effects seen here suggest that this relationship may be driven primarily by individuals that are experiencing greater challenges. More broadly, we suggest that the fitness benefit of this endocrine profile is likely to vary across contexts, depending on the nature and frequency of the stressor, and the life history of organisms. Future studies that test and refine the predictions described here, and generate and test new predictions, will help to elucidate when and how selection shapes stress responsiveness, and why some individuals cope with challenges more effectively than others.

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