TOWARDS AN EVOLUTIONARY THEORY OF STRESS RESPONSES

Barbara Taborsky[1], Sinead English[2], Tim W. Fawcett[3], Bram Kuijper[4,5], Olof Leimar[6], John M. McNamara[7], Suvi Ruuskanen[8], Carmen Sandi[9]

[1]Behavioural Ecology Division, Institute of Ecology and Evolution, University of Bern, Switzerland

[2]School of Biological Sciences, University of Bristol, UK

[3]Centre for Research in Animal Behaviour (CRAB), University of Exeter, UK

[4]Centre for Ecology and Conservation, University of Exeter, Penryn Campus, UK

[5]Institute for Data Science and Artificial Intelligence, University of Exeter, UK

[6]Department of Zoology, Stockholm University, Sweden

[7]School of Mathematics, University of Bristol, UK

[8]Department of Biology, University of Turku, Finland

[9]Brain Mind Institute, Ecole Polytechnique Federale de Lausanne (EPFL), Switzerland

Correspondence:

Barbara Taborsky, Behavioural Ecology Division, Institute of Ecology and Evolution, University of Bern, Switzerland; e-mail: *barbara.taborsky@iee.unibe.ch*

Abstract

All organisms have a stress response system to cope with environmental threats, yet its precise form varies hugely within and across individuals, populations and species. While the physiological mechanisms are increasingly understood, how stress responses have evolved remains elusive. Here, we show that important insights can be gained from models that incorporate physiological mechanisms within an evolutionary optimality analysis (the 'evo-mecho' approach). Our approach reveals environmental predictability and physiological constraints as key factors shaping stress response evolution, generating testable predictions about variation across species and contexts. We call for an integrated research programme combining theory, experimental evolution and comparative analysis to advance scientific understanding of how this core physiological system has evolved.

Keywords: stress hormones, glucocorticoids, evolutionary simulations, optimality models, temporal autocorrelation, predation risk

Stress Responses: A Highly Variable Physiological System

Stress (see Glossary) is a process enabling organisms to cope with stressors in their environment, such as extreme weather conditions [1], changes in resource availability [2] and encounters with competitors, predators or pathogens [3,4]. All organisms have stress responses, typically mediated by hormones (e.g. glucocorticoids, GCs, in vertebrates) (Box 1). The characteristic features of stress responses—a baseline level of stress molecules, a stress-induced peak level and a decay phase (Fig. 1)—vary greatly across taxa [5], among and within populations, even within individuals [6,7], depending on both internal and external factors such as sex, body condition, life-history stage [6,7] and the type and temporal pattern of stressors [8].

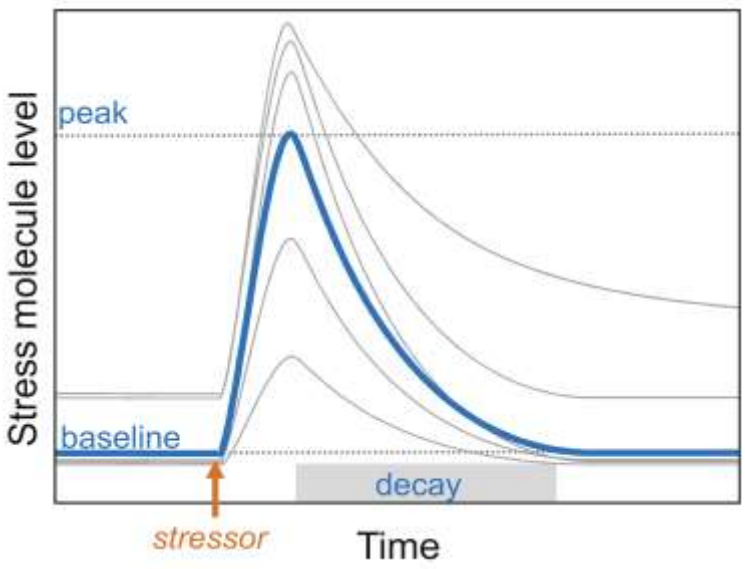

Figure 1: General shape of an organismal stress response. Stress responses involve three dynamic features: From a *baseline* level (bottom dashed line), the level of stress molecules (e.g. hormones; blue line) rises to a *peak* (upper dashed line) following a stressor (orange arrow), falling back to baseline during a *decay* phase (grey area). These three features can vary across taxa, among and within populations, and within individuals (thin grey lines).

There is a wealth of hypotheses to explain observed associations between **stress response features** and fitness [9,10], but some are contradictory and there is no clear consensus in conclusions from empirical studies [11]. Crucially, there are few mathematical models to predict optimal stress responses, and none that takes into account the physiological mechanisms involved. Here we propose an **evo-mecho** approach [12], integrating knowledge about underlying physiological mechanisms with evolutionary optimality analyses, to identify the key features of stress responses that help organisms meet the challenges they face in natural environments, where stressors come and go over time.

General Features of the Vertebrate Neuroendocrine Stress Response

All organisms, from bacteria [13] to vertebrates [5], have evolved a fast-acting stress response, although the physiological mechanisms differ greatly between taxa (Box 1; Table S1 in Online Supplementary Material, SM). Here we take the well-studied glucocorticoid stress response of vertebrates [5,14] as an example, but the general principles and insights outlined below hold for all stress responses characterized by the three stress response features (Fig 1, Box 1).

Baseline GCs are essential for supporting basic metabolic and behavioural processes, but can also stimulate reproduction [7,15]. Baseline GCs may increase with overall risk [16], perhaps reflecting a preparedness for future stressors.

The hormonal stress response functions over different timescales. First, it responds to the immediate presence of a stressor (e.g. cold weather or predators), where it benefits short-term survival by mobilizing energy [7]. Even when the stressor is no longer present, the response prepares the organism for its possible return (e.g. the reappearance of a recently encountered

predator). On a longer timescale, the response can modulate immune function and enhance memories of stressors [17].

At the same time, stress-induced GCs can entail fitness costs: they decrease time and energy allocated to feeding and reproduction [14,18,19], and, if chronically elevated, they inflict costs at cellular, tissue and organismal levels [9,14,15,20–23]. Therefore, a decay phase bringing **stress hormones** back to baseline levels is essential.

Box 1: Stress Responses Across Organisms

The general shape of the stress response is similar across organisms (Figure I), although the precise molecules involved can differ. The *vertebrate* stress response activates the **sympathetic nervous system (SNS)** and the **hypothalamic-pituitary-adrenal (HPA, or interrenal, HPI)** axis. Following stressor exposure, the SNS rapidly activates cardiovascular and endocrine responses, mediated by catecholamines. Thereafter, activation of the HPA/HPI axis leads to the release of the glucocorticoid (GC) hormone **cortisol** (most mammals, fish) or **corticosterone** (rodents, birds, reptiles and amphibians) from the adrenal or interrenal glands into the bloodstream. Glucocorticoids act through two receptor types: high-affinity mineralocorticoid receptors (MRs), largely occupied at baseline; glucocorticoid receptors (GRs) have 10-fold lower affinity and become transiently activated under increased GCs. In addition to genomic actions, GCs can exert rapid non-genomic effects through membrane actions [24]. After a stressor is perceived, blood GCs rise sharply within a few minutes, typically reaching a peak within 15-60 min, followed by a decay phase and return to baseline after several hours (Figure 1A) or days [22]. The stress physiology of invertebrates differs between taxa. Insects have a fast first wave mediated by octopamine [3] and a second, slower wave mediated by adipokinetic hormones (Table S1). In

mussels, stress responses are mediated by noradrenaline (Figure IB). *Plants* use different stress hormones, such as terpenoid hormones during periods of drought (Figure IC), whereas in *fungi* like yeast (Figure ID) stress responses involve the expression of numerous genes (see details in Table S1).

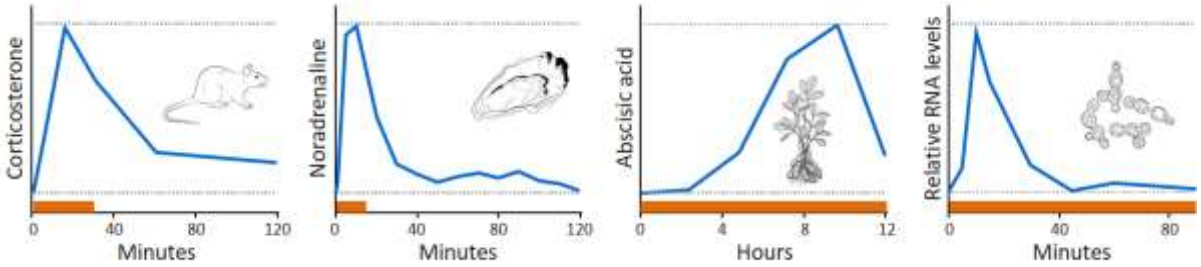

Figure I: Stress responses across the tree of life. (A) GC response after restraint in rats (after [25]). (B) Noradrenaline response of oysters to 15 min rotation (after [26]). (C) ABA response in peanut plants during simulated drought (after [27]). (D) Regulation of CYC7 gene in yeast during osmotic shock (after [28]). Orange bars indicate duration of stressor, dotted lines represent baseline and peak stress molecule levels. Mean stress response curves are shown. Drawings from shutterstock.com.

Hypotheses About Stress Response Evolution

For stress response features (baseline, peak and decay) to evolve under natural selection, they must show heritable variation that is correlated with fitness. There is evidence consistent with this criterion (Box 2), although for fitness effects the support is largely correlational [29,30]. A recent review [9] listed over 130 published hypotheses making explicit predictions about the relationship between stress physiology and fitness; some predict the direction of the relationship between baseline and/or stress-induced GC levels and survival and/or reproduction, while others focus on the role of particular stressors, such as predators or resource limitation, or on particular

life stages [9]. Very few hypotheses consider other molecular components of the stress response (Box 1), or make predictions about the speed of the decay phase [31–33].

Box 2. Are Stress-Response Mechanisms Evolvable?

In vertebrates, both baseline and stress-induced GC levels vary consistently among individuals [34–36], with repeatability generally higher for the latter [35,36]. In natural populations, GC levels are often heritable and under selection, although due to pleiotropic effects, the evolution of hormonal traits depends on how they alter phenotypic trait combinations [11]. Breeding experiments in rainbow trout (*Oncorhynchus mykiss*) [37] and pedigree analyses of free-living bird populations [38–40] show higher heritability for stress-induced GCs than baseline GCs. To our knowledge, the heritability of GC decay rates has not been estimated.

Further evidence comes from artificial **selection experiments**. In great tits (*Parus major*) selected for personality type, slow-shy explorers showed higher stress-induced GCs than fast-bold explorers, but no difference in baseline GCs [41]. Direct selection for high vs. low GC response to a stressor in several vertebrate species led to the expected divergence in peak GCs but no accompanying change in the baseline [42–44]. Thus, baseline and stress-induced GCs can respond independently to selection, implying that they may be genetically uncorrelated. While confirmed by field studies on two swallow species [39,40], this is not a universal finding, with a strong genetic correlation (r = 0.68–0.80) between baseline and stress-induced GCs reported for barn owl *(Tyto alba)* nestlings [38].

A phylogenetically controlled comparative analysis in tetrapods suggests that higher baseline GCs have evolved in species exposed to frequent challenges, whereas stress-induced GC levels are

dampened in species with fewer lifetime breeding attempts, perhaps to reduce fitness costs of elevated GCs [5]. Thus both short-term benefits (protection against threats) and long-term costs (e.g. physiological damage, suppressed reproduction) of elevated GC levels are important when considering the evolution of the stress response.

Phenotypic correlations between fitness components and stress response features have been studied widely in the field, but are typically confounded by individual variation in condition, making it difficult to infer selective pressures [15]. An alternative approach is to manipulate circulating GC levels experimentally, e.g. using implants, injections or dietary supplements. However, apparent fitness effects can be difficult to interpret because exogenous GC administration interferes with endogenous production and can have non-targeted physiological effects [7,45]. Furthermore, fitness consequences of endocrine responses may depend on ecological context [29], and experimental manipulation could decrease fitness if plastic organisms already express near-optimal phenotypes [46].

Several hypotheses propose that CORT-fitness relationships respond plastically to environmental contexts (e.g. [47–50]). For example, the **adaptive calibration model** [51] suggests that the physiological mechanisms controlling stress responses can be modified throughout life to match current environmental conditions, for which there is ample empirical support [51]. In some cases, several hypotheses combine in a more coherent theory. To explain the evolution of baseline GC levels, for example, the **CORT-adaptation hypothesis** derives from the **CORT-fitness hypothesis** by including allostatic costs of reproduction [52]. The most influential hypothesis to predict fitness effects of stress responses, the **CORT-tradeoff hypothesis,** postulates that stress-induced GC levels are positively associated with survival but negatively with reproduction [53].

To understand adaptive variation in stress responses, mathematical formulations of stress response evolution [54] are helpful because they can integrate subfields such as physiology and life-history evolution. Mathematical models are explicit about underlying assumptions and can uncover hidden constraints and feedbacks [55], while lacking unmeasured confounds that in empirical studies may underlie apparent hormone-fitness relationships [29]. Several mathematical models of endocrine stress responses exist in systems biology [56], but they typically ignore evolution and focus instead on the dynamic consequences of a given molecular mechanism. By contrast, adaptive explanations of stress response mechanisms and how they are shaped by environments have received less attention from modellers, with few exceptions, such as the optimal allocation model by McNamara & Buchanan [57]. Their model predicts that individuals should invest heavily in stress hormone expression whenever long-term damage costs are small relative to the mortality risk from predation, but investment should decrease with the likely duration of the stressful event. However, their model only considers the response to a one-off stressor that, once gone, will not reappear. It does not consider cases in which the temporary appearance of a stressor makes its return more likely, and so cannot be used to explain the observed time course of GCs after a stressful event. Given that physiological stress responses are often easier to measure than causes of mortality, new evo-mecho models that predict stress response features in different environments would be of great value to evolutionary ecologists.

Towards Formal Evolutionary Models of Stress Response Mechanisms

Evolutionary models can predict how the stress response of an individual varies plastically with age, experience and seasonal changes amongst other factors. Since predictions will depend on the environment and life history, the models can also predict across-species differences in stress

responses. We propose that one key environmental feature is **temporal autocorrelation**, which determines the predictability of stressors. While the effects of predictability on plastic stress responses within an individual have been widely studied (dating back to [58]), evolutionary responses to predictability have been overlooked. Furthermore, an adaptive theory should account for the mechanistic constraints and feedback loops inherent in physiological networks [59,60]. Within this context, life-history trade-offs are essential, but only when considered in the environmental setting that governs stress response evolution.

To illustrate how an evo-mecho modelling approach can provide new insights, Box 3 compares two evolutionary models of hormone production in response to a stressor with varying levels of autocorrelation. One is an unconstrained optimality model in which the organism can freely express any hormone level in response to current threat, with the optimal strategy found using **state-dependent dynamic programming**. The other is a mechanistically constrained **evolutionary simulation** in which a physiological stress response is generated by three interacting traits: baseline hormone influx, stress-induced hormone influx and hormone clearance. While such a three-trait model is simplistic [56], it highlights how plausible mechanistic constraints can alter stress response evolution, compared to optimality predictions free from constraints (Box 3).

Box 3: Evolution of the Stress Response in Autocorrelated Environments

Here we show how autocorrelated stressors can drive the evolution of stress response features. Consider an organism facing a survival threat, such as a predator, that comes and goes over time. While the threat is present, it kills the organism with a certain probability, which the organism can reduce by elevating its circulating levels of a hormone, but this diverts resources away from

196 reproduction. This trade-off between survival and reproduction determines the optimal hormone
197 level at any given moment, as a function of the perceived current threat.
198
199 The thick grey lines in Fig. I show theoretically optimal stress responses, computed using dynamic
200 programming. With no autocorrelation, the optimal hormone level is constant over time (panels
201 A, C). With positive temporal autocorrelation, the stress response shows three key features
202 (panels B, D): a *baseline* hormone level, expressed prior to the threat; a *peak* hormone level, i.e.
203 the maximum expressed soon after the threat is detected; and a *decay* phase in which the level
204 returns to baseline. This optimal response assumes that the hormone level expressed at any
205 given moment is unconstrained and independent of earlier levels, and is thus a direct result of
206 positively autocorrelated stressors.
207
208 We can model the stress response in a more mechanistic way by simulating the evolution of a
209 physiological mechanism involving three genetic traits: *I*, a baseline influx rate of hormone; *S*, an
210 additional influx rate when detecting a threat; and *C*, a clearance mechanism controlling the rate
211 of hormone removal. The evolved stress responses (light blue lines in Fig. I) share important
212 features with the unconstrained optimal response: more dangerous random environments select
213 for higher baseline levels (panel A vs C), and when threats are more persistent (i.e., stronger
214 autocorrelation) the stress response lasts longer (panel B vs D).
215
216 Importantly, there are differences between the unconstrained optimal and physiologically
217 constrained responses. In the simulations, hormone clearance is more gradual, due to
218 mechanistic constraints (e.g. physical limits on hormone decay rates); and baselines are lower in
219 autocorrelated environments to compensate for prolonged periods of reduced reproduction

associated with slow clearance. However, expected lifetime reproduction in the simulations is only slightly lower than that for the unconstrained optimal strategy, suggesting that selection around the optimum is weak. Results remain qualitatively similar when low hormone levels enhance reproduction (e.g., [61]) (SM, Fig. S1).

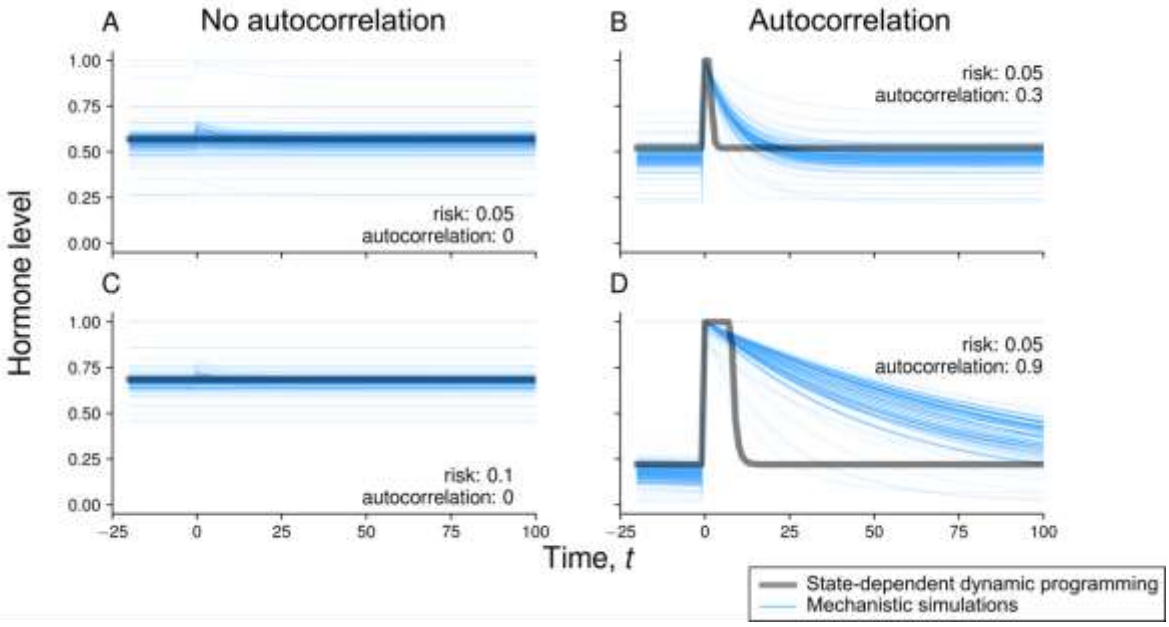

Figure I. Evo-mecho predictions for the stress response. Optimal stress responses identified by state-dependent dynamic programming (thick grey lines) compared to evolved stress responses from a mechanistic evolutionary simulation model (light blue lines, showing stress responses of different individuals), in response to a threat detected at time $t = 0$. Risk values represent the overall long-term proportion of time for which the threat is present, while autocorrelation values represent correlation coefficients in the presence/absence of the threat between time points one unit apart. Panels show predictions for (A) low risk, zero autocorrelation; (B) low risk, moderate positive autocorrelation; (C) high risk, zero autocorrelation; and (D) low risk, strong positive autocorrelation. See Part 2 of SM for full model details and other parameter values.

These models show how different degrees of stressor predictability shape evolved stress responses: when stressor occurrences are positively autocorrelated, such that they tend to be clustered in time, a clear stress response evolves with a low baseline hormone level prior to encountering a stressor, followed by a high hormone peak and a clearance phase (Box 3, Fig. IB; note that when the autocorrelation is higher, clearance is slower; cf. Box 3, Fig. ID). This pattern occurs because, when stressors are clustered in time, the probability of encountering a stressor is highest immediately after encountering a previous stressor, but as time passes this probability gradually declines, until the next stressor appears. By contrast, in environments with zero autocorrelation, an encounter with one stressor provides no information about when the next stressor will appear, and so the model predicts a uniform stress hormone level, with higher baseline levels of stress hormones in more dangerous environments (Box 3, Fig. IA vs C). Changing the autocorrelation affects the stress response more than changing the overall danger, which illustrates that temporal predictability is crucial in shaping the evolved stress response.

The optimality model predicts a stress response that fluctuates much more rapidly between high and low stress hormone levels than the more gradual decay pattern predicted by the mechanistic model (Box 3, Fig. IB,D), which more closely matches empirically observed stress responses (Box 1). This emphasises that physiological mechanisms can impose important constraints on adaptation, in this case regarding the evolution of hormone clearance, that are overlooked by simple optimality arguments.

While necessarily simplistic, a key advantage of models like these is that they provide a benchmark against which more realistic assumptions can be systematically analysed. For example, in Figure S1 we consider a model extension in which low stress hormone levels enhance

(rather than reduce) fecundity, showing that our key result that autocorrelations in stressor presence determine presence or absence of a stress response is upheld. It may well be that autocorrelations matter far less when making other assumptions about underlying mechanisms or life-histories (see the research agenda below), which is exactly the point of a formal theory of stress response evolution that yields testable predictions.

More empirical data are needed to test these predictions. Studies comparing stress responses in natural populations show mixed results, with high-risk populations showing baseline or peak hormone levels that are higher [16,62,63], similar [64] or even lower [4,65,66] compared to low-risk populations. Providing experimental predator cues tends to increase HPA/HPI activity [67]. Within populations over time, variable predation risk elicits different patterns of baseline and peak across species [68]. The role of developmental plasticity versus evolutionary adaptation in these cases is unclear. There is a need for more data on autocorrelation in natural stressors such as predation, as well as **experimental evolution** studies in which autocorrelation can be artificially manipulated [69].

Stress Response Evolution: A Research Agenda

We propose an integrated research programme combining theory, experimental evolution and comparative analysis (Figure 2).

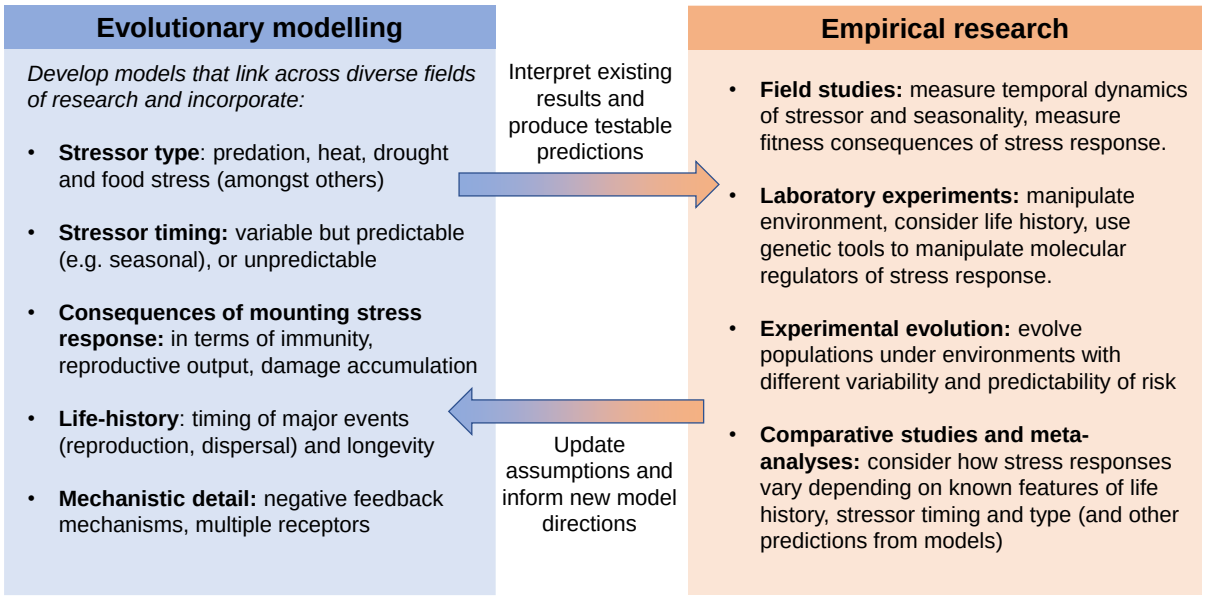

Figure 2. An integrated research programme for studying the evolution of the stress response system.

Evolutionary models of the stress response

To model the evolution of stress responses, we advocate a two-stage process (following Box 3): first, use optimality models to understand how key factors influence the optimal stress response, in the absence of constraints; then use evolutionary simulations to investigate how mechanistic constraints alter the predicted outcome. The simplified scenario modelled in Box 3 could be extended in numerous directions; here we highlight some important ones.

Level and timing of risk. A more general model could examine how the stress response depends on risk level and its likely duration [10]. Models of more complex environments, for example with slow switching between different patterns of autocorrelation (see Box 1 in [70]), could be used to predict how prior exposure to stressors (e.g. during sensitive developmental phases) modifies stress responses.

Damage. We considered the cost of mounting a stress response as an immediate drop in reproductive output, but elevated stress hormones may also cause long-term somatic damage.

295 An organism cannot afford to respond strongly to successive stressors if doing so causes
296 cumulative damage [57].

297 *Life history.* Mathematical models also need to be placed in a life-history context,
298 accounting for longevity and seasonal effects [5,7,10]. For example, we might predict a weaker
299 stress response prior to and during an annual breeding season, to reduce damage caused by high
300 GC levels that would interfere with breeding. Long-lived animals might respond more strongly to
301 stressors because they can afford to reduce their reproductive output in one season, whereas
302 short-lived animals cannot. Major events such as moult or migration, in which the balance of
303 fitness trade-offs may change, will also affect the optimal stress response [7,71].

304 *Mechanisms.* Beyond example in Box 3, other possibilities that could be modelled include:
305 (i) a decay mechanism that allows active inhibition of further hormone production through
306 negative feedback [72]; (ii) evolvable densities of different types of hormone receptors across
307 tissues; (iii) pleiotropic effects, which may underlie variation across species in the degree of
308 genetic correlation among stress response features (Box 2).

309

310 *Empirical research on evolution of the stress response*

311 Future laboratory and field studies should test predictions of evolutionary models with explicit
312 consideration of environmental predictability and life history, and manipulate salient features of
313 a species' stress response where feasible (Figure 2). *Experimental evolution* can be used to test
314 how different environmental conditions shape the stress response. Previous experimental
315 evolution studies have focused mainly on tolerance to stressors by measuring survival or
316 population growth, rather than changes in the underlying stress response, and are largely
317 restricted to microbes (e.g. [73]). As gene expression networks underlying stress responses are
318 well characterized in model systems like *Caenorhabditis elegans* [74], there is ample opportunity

to study how the stress response evolves in environments that vary in the variability and predictability of stressors. For example, one could test our model's novel prediction that organisms living in environments with no autocorrelation in stressors (unlikely in most natural systems [75,76]) should evolve to have no stress response.

Large-scale comparative studies (e.g. [5]) and meta-analyses (e.g. [46]) can help identify and compare putative selective pressures operating on stress responses. This includes molecular studies that investigate how stress responses based on different mechanisms have evolved in deep evolutionary time. Our overview of the molecular mechanisms involved in organismal stress responses (Table S1) emphasizes that different mechanisms can lead to convergent outcomes. Recent research has investigated how stress response variation across species is linked to ecological and life-history variation [5], but so far has not considered the role of environmental autocorrelation [76], which can be challenging to measure (but see [75]).

Concluding Remarks

The evo-mecho approach can integrate concepts across different subfields and yield new, testable predictions for empirical research on stress response variation. The simplified model in Box 3 suggests that (1) explicitly modelling mechanistic constraints on the decay phase of the response, a feature largely ignored in previous research, strongly influences evolutionary outcomes. (2) Environmental context is also a key factor in stress response evolution: notably, our model shows that temporal autocorrelation (affecting stressor predictability) should critically influence evolved stress responses, perhaps more strongly than the overall level of risk. To resolve debate about predicted relationships between stress response features and fitness, it is necessary to consider both evolutionary trade-offs and environmental factors such as stressor

predictability. Temporal autocorrelation has been considered empirically for climatic factors [77], but not, to our knowledge, for biotic stressors such as predation risk.

Understanding the evolution of stress responses and their constraints is important for predicting how organisms respond to environmental changes. Here we have made a first step towards a predictive mathematical theory of stress response evolution, highlighting previously neglected mechanistic and ecological details to understand how a core, highly conserved physiological system has evolved. We hope this will spark new field studies, experimental work and further theory development (see 'Outstanding Questions').

Outstanding questions

Future evolutionary models should involve close collaboration between theoreticians and stress physiologists, so that mechanistic details such as receptor densities and negative-feedback processes can be explicitly modelled. How does the incorporation of more realistic mechanisms alter evolutionary predictions?

By linking valuable new comparative databases like HormoneBase [79] and the Wildlife Endocrinology Information Network [80] to environmental and life-history data across species (e.g. [5]), can we test predictions of evolutionary models of the stress response at the macroevolutionary scale?

How do different types of damage (e.g. somatic damage, immunosuppression) caused by stress hormones affect selection on stress response features? How do evolutionary predictions depend on different damage types and the time scale over which they act?

Can formal evolutionary models help explain the widespread empirical evidence that exposure to stressors early in life affects later stress physiology; and, specifically, identify conditions when such responses are adaptive?

What is the genetic architecture of the stress response (e.g. linkage between stress response features, pleiotropic effects), how does this affect the predicted outcomes from evolutionary models, and can this account for differences between empirical systems in which stress response features are genetically correlated versus uncorrelated?

Acknowledgments

The authors are grateful to all participants of the CUSO workshop “Early-environment effects: Towards integrating theoretical and empirical approaches" in Arolla, Switzerland, and for funding by the Conference Universitaire de Suisse Occidentale (CUSO). We dedicate this work to the memory of Victoria Braithwaite, who made many valuable contributions to our discussions in Arolla. Financial support was provided by the Swiss National Science Foundation and a University of Bristol Benjamin Meaker Visiting Professorship to BT, a Royal Society Dorothy Hodgkin Fellowship to SE, the Academy of Finland to SR, the Swedish Research Council to OL.

Glossary

Adaptive calibration model: A verbal evolutionary–developmental model explaining the development of individual differences in stress responsiveness across life stages, through plastic adjustments to particular environments.

CORT-adaptation hypothesis: Extension of the CORT-fitness hypothesis including reproduction as an environmental challenge.

CORT-fitness hypothesis: Hypothesis stating that baseline GC levels reflect exposure to challenges, and therefore that individuals or populations with high baseline GCs have lower fitness than those with lower baseline GCs.

CORT-tradeoff hypothesis: Hypothesis stating that stress-induced hormone levels mediate a life-history trade-off between protective and damaging effects of GCs, such that higher stress-induced GC levels are positively correlated with survival but negatively with reproduction.

Corticosterone: A glucocorticoid hormone produced by rodents, birds, reptiles and amphibians.

Cortisol: A glucocorticoid hormone produced by most mammals (except rodents) and fish.

Evo-mecho: Theoretical approach that integrates an evolutionary optimality analysis with knowledge about the underlying psychological, physiological or molecular mechanisms.

Evolutionary simulation model: Computer program simulating a population of organisms with specified genetic traits that change across generations due to pre-defined processes of mutation and selection.

Experimental evolution: Experimental approach to explore evolutionary dynamics as experimental populations adapt to new environmental conditions by natural selection.

Glucocorticoids (GCs): Steroid hormones of vertebrates, in particular cortisol and corticosterone, secreted naturally by the adrenal gland (see HPA axis) or interrenal gland (see HPI axis). Generally important for the regulation of glucose metabolism and energy balance.

Hypothalamic-pituitary-adrenal (HPA) axis: An endocrine axis comprising the sequential involvement of hypothalamic corticotropin-releasing hormone (CRH), pituitary adrenocorticotropic hormone (ACTH) and GCs released from the adrenal gland in mammals, birds and reptiles.

Hypothalamic-pituitary-interrenal (HPI) axis: An endocrine axis in fish and amphibians that is homologous with the mammalian/avian HPA system, but in which GCs are excreted from structures within the kidneys (interrenal).

Selection experiment: Experimental approach that artificially selects for a trait, typically in order to observe changes in other, genetically correlated traits.

State-dependent dynamic programming: A numerical optimisation technique used to find the best (i.e. fitness-maximising) decision strategy through an iterative calculation that runs backwards through a sequence of decision points, evaluating the available options (e.g. possible hormone levels) in each state (e.g. each time interval since the last predatory attack) in terms of expected future reproductive success at the next decision point.

Stress: The process whereby an organism reacts to stressors, including detection of the stressor and the stress response.

Stress hormone: Hormone whose circulating levels are elevated in response to an external stressor (such as presence of a predator). Also termed 'stress-induced hormone' or 'stress-associated hormone' [78].

Stress molecule: Stress hormones or other products of genes mediating stress responses.

Stress response: The activation of coordinated neurophysiological responses in the brain and periphery to cope with environmental demands or stressors.

Stress response features: Three key features that characterise the stress response: a *baseline* circulating level of stress molecules before a stressor appears; a *peak* (maximum) level reached in the period after the stressor is detected; a *decay* phase, when the stress molecule levels return to baseline.

Stressor: A stimulus or feature in the environment that creates a demanding or threatening situation for an organism.

Sympathetic nervous system (SNS): Part of the autonomic nervous system that is responsible for fast, unconscious responses to stressors and to elicit fight-flight-or-freeze reactions.

Temporal autocorrelation: An association across time in some environmental parameter, such as the presence of a stressor. Positive temporal autocorrelation (our focus here) implies that stressful events occur in clusters (i.e. are overdispersed), rather than at randomly spaced intervals.

References

1 de Bruijn, R. and Romero, L.M. (2018) The role of glucocorticoids in the vertebrate response to weather. *Gen. Comp. Endocr.* 269, 11–32

2 Kitaysky, A.S. *et al.* (2010) Food availability and population processes: severity of nutritional stress during reproduction predicts survival of long-lived seabirds. *Funct. Ecol.* 24, 625–637

3 Adamo, S.A. *et al.* (2013) The behavioural effects of predator-induced stress responses in the cricket (*Gryllus texensis*): the upside of the stress response. *J. Exp. Biol.* 216, 4608–4614

4 Fischer, E.K. *et al.* (2014) Predator exposure alters stress physiology in guppies across timescales. *Horm. Behav.* 65, 165–172

5 Vitousek, M.N. *et al.* (2019) Macroevolutionary patterning in glucocorticoids suggests different selective pressures shape baseline and stress-induced levels. *Am. Nat.* 193, 866–880

6 Guindre-Parker, S. (2020) Individual variation in glucocorticoid plasticity: considerations & future directions. *Integr. Comp. Biol.* DOI: 10.1093/icb/icaa003

7 Hau, M. *et al.* (2016) Glucocorticoid-mediated phenotypes in vertebrates: multilevel variation and evolution. *Adv. Stud. Behav.* 48, 41–115

8 Houslay, T.M. *et al.* (2019) Habituation and individual variation in the endocrine stress response in the Trinidadian guppy (*Poecilia reticulata*). *Gen. Comp. Endocr.* 270, 113–122

9 Harris, B.N. (2020) Stress hypothesis overload: 131 hypotheses exploring the role of stress in tradeoffs, transitions, and health. *Gen. Comp. Endocr.* 288, 113355

10 Schoenle, L.A. *et al.* (2018) Understanding context dependence in glucocorticoid–fitness relationships: the role of the nature of the challenge, the intensity and frequency of stressors, and life history. *Integr. Comp. Biol.* 58, 777–789

11 Cox, R.M. *et al.* (2016) Hormones as mediators of phenotypic and genetic integration: an evolutionary genetics approach. *Integr. Comp. Biol.* 56, 126–137

12 McNamara, J.M. and Houston, A.I. (2009) Integrating function and mechanism. *Trends Ecol. Evol.* 24, 670–675

13 Fux, C.A. *et al.* (2005) Survival strategies of infectious biofilms. *Trends Microbiol.* 13, 34–40

14 Sapolsky, R.M. *et al.* (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr. Rev.* 21, 55–89

15 Wingfield, J.C. and Sapolsky, R.M. (2003) Reproduction and resistance to stress: when and how. *J. Neuroendocrinol.* 15, 711–724

16 Broin, F.D. *et al.* (2020) Predation risk and mountain goat reproduction: Evidence for stress-induced breeding suppression in a wild ungulate. *Funct. Ecol.* 34, 1003–1014

17 Cordero, M.I. and Sandi, C. (2007) Stress amplifies memory for social hierarchy. *Front. Neurosci.* 1, 175–184

18 Nesse, R.M. *et al.* (2016) Evolutionary origins and functions of the stress response system. In *Stress: Concepts, Cognition, Emotion, and Behavior* pp. 95–101, Elsevier

19 Romero, M.L. and Butler, L.K. (2007) Endocrinology of stress. *Int. J. Comp. Psychol.* 20, 89–95

20 McEwen, B.S. (2012) Brain on stress: How the social environment gets under the skin. *Proc. Natl. Acad. Sci. U. S. A.* 109, 17180–17185

21 Spencer, K.A. (2017) Developmental stress and social phenotypes: integrating neuroendocrine, behavioural and evolutionary perspectives. *Phil. Trans. Roy. Soc. B Biol. Sci.* 372, 20160242

22 Joëls, M. and Baram, T.Z. (2009) The neuro-symphony of stress. *Nat. Rev. Neurosci.* 10, 459–466

23 Sandi, C. and Haller, J. (2015) Stress and the social brain: behavioural effects and neurobiological mechanisms. *Nat. Rev. Neurosci.* 16, 290–304

24 de Kloet, E.R. (2013) Functional profile of the binary brain corticosteroid receptor system: Mediating, multitasking, coordinating, integrating. *Eur. J. Pharmacol.* 719, 53–62

25 Brabham, T. *et al.* (2000) Effects of prenatal dexamethasone on spatial learning and response to stress is influenced by maternal factors. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 279, R1899–R1909

26 Lacoste, A. *et al.* (2001) Evidence for a form of adrenergic response to stress in the mollusc *Crassostrea gigas*. *J. Exp. Biol.* 204, 1247-1255

27 Liu, S. *et al.* (2016) Negative feedback regulation of ABA biosynthesis in peanut (*Arachis hypogaea*): a transcription factor complex inhibits AhNCED1 expression during water stress. *Sci. Rep.* 6, 1–11

28 Bose, S. *et al.* (2005) Genetic factors that regulate the attenuation of the general stress response of yeast. *Genetics* 169, 1215–1226

29 Bonier, F. and Martin, P.R. (2016) How can we estimate natural selection on endocrine traits? Lessons from evolutionary biology. *Proc. R. Soc. B. Biol. Sci.* 283, 20161887

30 Breuner, C.W. *et al.* (2008) In search of relationships between the acute adrenocortical response and fitness. *Gen. Comp. Endocr.* 157, 288–295

31 de Kloet, E.R. *et al.* (2007) Therapy Insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? *Nat. Clin. Pract. Endoc.* 3, 168–179

32 Joëls, M. *et al.* (2008) The coming out of the brain mineralocorticoid receptor. *Trends Neurosci.* 31, 1–7

33 Oitzl, M.S. *et al.* (2010) Brain development under stress: Hypotheses of glucocorticoid actions revisited. *Neurosci. Biobehav. Rev.* 34, 853–866

34 Cockrem, J.F. (2013) Individual variation in glucocorticoid stress responses in animals. *Gen. Comp. Endocr.* 181, 45–58

35 Schoenemann, K.L. and Bonier, F. (2018) Repeatability of glucocorticoid hormones in vertebrates: a meta-analysis. *PeerJ* 6, e4398

36 Taff, C.C. *et al.* (2018) The repeatability of glucocorticoids: A review and meta-analysis. *Gen. Comp. Endocr.* 260, 136–145

37 Fevolden, S.-E. *et al.* (1999) Poststress levels of lysozyme and cortisol in adult rainbow trout: heritabilities and genetic correlations. *J. Fish Biol.* 54, 900–910

38 Béziers, P. *et al.* (2019) Baseline and stress-induced corticosterone levels are heritable and genetically correlated in a barn owl population. *Heredity* 123, 337–348

39 Jenkins, B.R. *et al.* (2014) An experimental analysis of the heritability of variation in glucocorticoid concentrations in a wild avian population. *Proc. R. Soc. Lond. B Biol. Sci.* 281, 20141302

40 Stedman, J.M. *et al.* (2017) Heritable variation in circulating glucocorticoids and endocrine flexibility in a free-living songbird. *J. Evol. Biol.* 30, 1724–1735

41 Baugh, A.T. *et al.* (2012) Corticosterone responses differ between lines of great tits (*Parus major*) selected for divergent personalities. *Gen. Comp. Endocr.* 175, 488–494

42 Pottinger, T.G. and Carrick, T.R. (1999) Modification of the plasma cortisol response to stress in rainbow trout by selective breeding. *Gen. Comp. Endocr.* 116, 122–132

43 Jones, R.B. *et al.* (1994) Fear of humans in Japanese quail selected for low or high adrenocortical response. *Physiol. Behav.* 52, 379–383

44 Walker, S.E. *et al.* (2017) Constitutive differences in glucocorticoid responsiveness to stress are related to variation in aggression and anxiety-related behaviors. *Psychoneuroendocrinology* 84, 1–10

45 Crossin, G.T. *et al.* (2016) Glucocorticoid manipulations in free-living animals: considerations of dose delivery, life-history context and reproductive state. *Funct. Ecol.* 30, 116–125

46 Bonier, F. and Cox, R.M. (2020) Do hormone manipulations reduce fitness? A meta-analytic test of the Optimal Endocrine Phenotype Hypothesis. *Mol. Cell. Endocrinol.* 500, 110640

47 Boyce, W.T. and Ellis, B.J. (2005) Biological sensitivity to context: I. An evolutionary–developmental theory of the origins and functions of stress reactivity. *Dev. Psychopathol.* 17, 271–301

48 Gluckman, P.D. *et al.* (2007) Early life events and their consequences for later disease: A life history and evolutionary perspective. *Am. J. Hum. Biol.* 19, 1–19

49 Lattin, C.R. *et al.* (2016) Does corticosterone regulate the onset of breeding in free-living birds?: The CORT-Flexibility Hypothesis and six potential mechanisms for priming corticosteroid function. *Horm. Behav.* 78, 107–120

50 Spencer, K.A. and MacDougall-Shackleton, S.A. (2011) Indicators of development as sexually selected traits: the developmental stress hypothesis in context. *Behav. Ecol.* 22, 1–9

51 Del Giudice, M. *et al.* (2011) The Adaptive Calibration Model of stress responsivity. *Neurosci. Biobehav. Rev.* 35, 1562–1592

52 Bonier, F. *et al.* (2009) Do baseline glucocorticoids predict fitness? *Trends Ecol. Evol.* 24, 634–642

53 Patterson, S.H. *et al.* (2014) Natural selection and glucocorticoid physiology. *J. Evol. Biol.* 27, 259–274

54 Del Giudice, M. *et al.* (2018) What is stress? A systems perspective. *Integr. Comp. Biol.* 58, 1019–1032

55 Servedio, M.R. *et al.* (2014) Not just a theory—the utility of mathematical models in evolutionary biology. *PLoS Biol.* 12, e1002017

556 56 Zavala, E. *et al.* (2019) Mathematical modelling of endocrine systems. *Trends Endocrin. Met.* 30,
557 244–257

558 57 McNamara, J.M. and Buchanan, K.L. (2005) Stress, resource allocation, and mortality. *Behav. Ecol.*
559 16, 1008–1017

560 58 Weiss, J.M. (1970) Somatic effects of predictable and unpredictable shock. *Psychosom. Med.* 32,
561 397–408

562 59 Gestel, J. van and Weissing, F.J. (2016) Regulatory mechanisms link phenotypic plasticity to
563 evolvability. *Sci. Rep.* 6, 1–15

564 60 Cohen, A.A. *et al.* (2012) Physiological regulatory networks: ecological roles and evolutionary
565 constraints. *Trends Ecol. Evol.* 27, 428–435

566 61 Crossin, G.T. *et al.* (2012) Corticosterone predicts foraging behavior and parental care in macaroni
567 penguins. *Amer. Nat.* 180, E31–E41

568 62 Berger, S. *et al.* (2007) Behavioral and physiological adjustments to new predators in an endemic
569 island species, the Galápagos marine iguana. *Horm. Behav.* 52, 653–663

570 63 Clinchy, M. *et al.* (2004) Balancing food and predator pressure induces chronic stress in songbirds.
571 *Proc. R. Soc. B. Biol. Sci.* 271, 2473–2479

572 64 Robertson, J.M. *et al.* (2011) Colonization of novel White Sands habitat is associated with changes in
573 lizard anti-predator behaviour. *Biol. J Linn. Soc.* 103, 657–667

574 65 Archard, G.A. *et al.* (2012) Correlated behaviour and stress physiology in fish exposed to different
575 levels of predation pressure. *Funct. Ecol.* 26, 637–645

576 66 Brown, C. *et al.* (2005) Differential stress responses in fish from areas of high- and low-predation
577 pressure. *J. Comp. Physiol. B* 175, 305–312

578 67 Harris, B.N. and Carr, J.A. (2016) The role of the hypothalamus-pituitary-adrenal/interrenal axis in
579 mediating predator-avoidance trade-offs. *Gen. Comp. Endocr.* 230–231, 110–142

580 68 Boonstra, R. (2013) Reality as the leading cause of stress: rethinking the impact of chronic stress in
581 nature. *Funct. Ecol.* 27, 11–23

582 69 Dey, S. *et al.* (2016) Adaptation to temporally fluctuating environments by the evolution of maternal
583 effects. *PLoS Biol.* 14, e1002388

584 70 Fawcett, T.W. *et al.* (2014) The evolution of decision rules in complex environments. *Trends Cogn.*
585 *Sci.* 18, 153–161

586 71 Holberton, R.L. *et al.* (1996) Modulation of the adrenocortical stress response in neotropical
587 migrants during autumn migration. *Auk* 113, 558–564

588 72 Herman, J.P. *et al.* (2016) Regulation of the hypothalamic-pituitary-adrenocortical stress response.
589 *Compr. Physiol.* 6, 603–621

590 73 Duncan, A.B. *et al.* (2013) Stochastic environmental fluctuations drive epidemiology in experimental
591 host–parasite metapopulations. *Proc. R. Soc. Lond. B Biol. Sci.* 280, 20131747

592 74 Rodriguez, M. *et al.* (2013) Worms under stress: *C. elegans* stress response and its relevance to
593 complex human disease and aging. *Trends Genet.* 29, 367–374

594 75 Burgess, S.C. and Marshall, D.J. (2014) Adaptive parental effects: the importance of estimating
595 environmental predictability and offspring fitness appropriately. *Oikos* 123, 769–776

596 76 Vasseur, D.A. and Yodzis, P. (2004) The color of environmental noise. *Ecology* 85, 1146–1152

77 Di Cecco, G.J. and Gouhier, T.C. (2018) Increased spatial and temporal autocorrelation of temperature under climate change. *Sci. Rep.* 8, 1–9

78 MacDougall-Shackleton, S.A. *et al.* (2019) Glucocorticoids and "stress" are not synonymous. *Integr. Org. Biol.* 1, 1–8

79 Vitousek, M.N. *et al.* (2018) HormoneBase, a population-level database of steroid hormone levels across vertebrates. *Sci. Data* 5, 1–7

80 Vitousek, M.N. *et al.* (2018) Illuminating endocrine evolution: the power and potential of large-scale comparative analyses. *Integr. Comp. Biol.* 58, 712–719