Opinion

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] and Carmen Sandi[9]

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.

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; Figure 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].

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 the supplemental information online). Here, we take the well-studied glucocorticoid stress response of vertebrates [5,14] as an example, but the general principles and insights outlined herein hold for all stress responses characterised by the three stress response features (Figure 1 and Box 1).

Highlights

Extensive experimental and comparative studies provide a solid understanding of the physiological basis of the stress response system and its variation across and within species.

However, lagging behind this is a formal theoretical framework to help unify the wealth of existing verbal hypotheses linking stress response mechanisms and fitness, and to explain how such a response system has evolved.

We propose an evo-mecho approach, combining optimality models and evolutionary simulations with empirical evidence about the underlying physiology, to show how mechanistic constraints and the predictability of environmental risks shape the stress response.

A deeper understanding of stress response evolution will require mechanistically informed evolutionary models, phylogenetically controlled comparative analyses, and experimental evolution studies.

[1]Behavioural Ecology Division, Institute of Ecology and Evolution, University of Bern, Bern, Switzerland
[2]School of Biological Sciences, University of Bristol, Bristol, UK
[3]Centre for Research in Animal Behaviour (CRAB), University of Exeter, Exeter, UK
[4]Centre for Ecology and Conservation, University of Exeter, Penryn Campus, Penryn, UK
[5]Institute for Data Science and Artificial Intelligence, University of Exeter, Exeter, UK
[6]Department of Zoology, Stockholm University, Stockholm, Sweden
[7]School of Mathematics, University of Bristol, Bristol, UK

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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 improves short-term survival prospects by mobilising 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.

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 the support is largely correlational for fitness effects [24,25]. A recent review [9] listed over 130 published hypotheses making explicit predictions about the

[8]Department of Biology, University of Turku, Turku, Finland
[9]Brain Mind Institute, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, Switzerland

*Correspondence:
barbara.taborsky@iee.unibe.ch
(B. Taborsky).

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 HPA or 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 GC hormone **cortisol** (most mammals and 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, largely occupied at baseline; and GC receptors, which have tenfold lower affinity and become transiently activated under increased GCs. In addition to genomic actions, GCs can exert rapid nongenomic effects through membrane actions [63].

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 IA) 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 (see Table S1 in the supplemental information online). 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, such as yeast (Figure ID), stress responses involve the expression of numerous genes (see details in Table S1 in the supplemental information online).
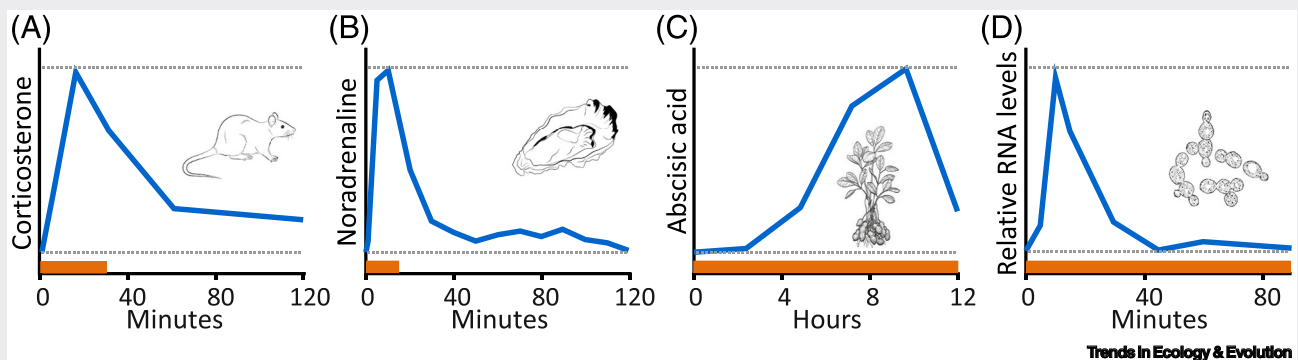

Figure I. Stress Responses across the Tree of Life. (A) Glucocorticoid (GC) response after restraint in rats. (B) Noradrenaline response of oysters to 15-min rotation. (C) Abscisic acid (ABA) response in peanut plants during simulated drought. (D) Regulation of the *CYC7* gene in yeast during osmotic shock. Orange bars indicate the duration of the stressor, and dotted lines represent baseline and peak stress molecule levels. Mean stress response curves are shown. Drawings from shutterstock.com. Reproduced from [64] (A), [65] (B), [66] (C), and [67] (D).
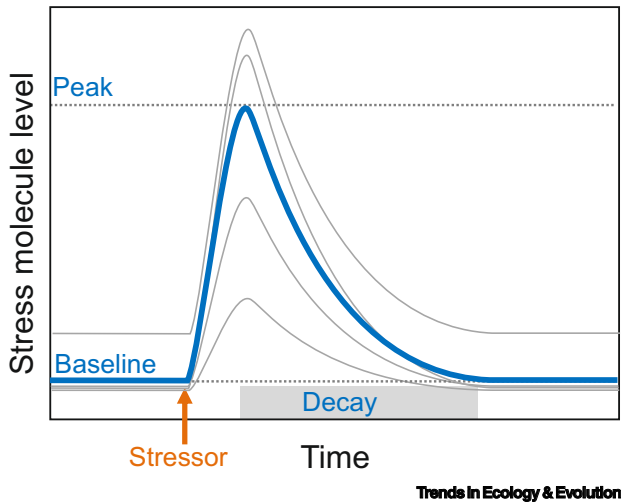
Figure 1. General Shape of an Organismal Stress Response. Stress responses involve three dynamic features: from a baseline level (bottom broken line), the level of stress molecules (e.g., hormones; blue line) rises to a peak (upper broken line) following a stressor (orange arrow), falling back to baseline during a decay phase (grey area). These three features can vary across taxa, among and within populations, and within individuals (thin grey lines).

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 tradeoff 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 GC hormone produced by rodents, birds, reptiles, and amphibians.
Cortisol: a GC 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 predefined 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.
Hypothalamus–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.

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 [26–28].

Several hypotheses propose that CORT-fitness relationships respond plastically to environmental contexts (e.g., [29–32]). For example, the **adaptive calibration model** [33] 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 [33]. 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 [34]. 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 [35].

To understand adaptive variation in stress responses, mathematical formulations of stress response evolution [36] 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 [37], while lacking unmeasured confounds that in empirical studies may underlie apparent hormone–fitness relationships [24]. Several mathematical models of endocrine stress responses exist in systems biology [38], 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 and Buchanan [39]. 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

Box 2. Are Stress-Response Mechanisms Evolvable?

In vertebrates, both baseline and stress-induced GC levels vary consistently among individuals [68–70], with repeatability generally higher for the latter [69,70]. 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*) [71] and pedigree analyses of free-living bird populations [72–74] show higher heritability for stress-induced GCs than for 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 did fast-bold explorers, but no difference in baseline GCs [75]. Direct selection for high versus 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 [76–78]. 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 [73,74], 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 [72].

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 nontargeted physiological effects [7,79]. Furthermore, fitness consequences of endocrine responses may depend on ecological context [24], and experimental manipulation could decrease fitness if plastic organisms already express near-optimal phenotypes [58].

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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 are 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 among 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 [40]), evolutionary responses to predictability have been overlooked. Furthermore, an adaptive theory should account for the mechanistic constraints and feedback loops inherent in physiological networks [41,42]. Within this context, life-history tradeoffs 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 model** in which a physiological stress response is generated by three interacting traits: baseline hormone influx, stress-induced hormone influx, and hormone

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

Stress hormone: hormone the circulating levels of which are elevated in response to an external stressor (such as presence of a predator); also termed 'stress-induced hormone' or 'stress-associated hormone' [62].

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

Stress response: 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.

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 reproduction. This tradeoff between survival and reproduction determines the optimal hormone level at any given moment, as a function of the perceived current threat.

The thick grey lines in Figure I show theoretically optimal stress responses, computed using dynamic programming. With no autocorrelation, the optimal hormone level is constant over time (Figure IA,C). With positive temporal autocorrelation, the stress response shows three key features (Figure IB,D): a baseline hormone level, expressed before the threat; a peak hormone level (i.e., the maximum expressed soon after the threat is detected); and a decay phase, in which the level returns to baseline. This optimal response assumes that the hormone level expressed at any given moment is unconstrained and independent of earlier levels, and, thus, is a direct result of positively autocorrelated stressors.

We can model the stress response in a more mechanistic way by simulating the evolution of a physiological mechanism involving three genetic traits: I, a baseline influx rate of hormone; S, an additional influx rate when detecting a threat; and C, a clearance mechanism controlling the rate of hormone removal. The evolved stress responses (light-blue lines in Figure I) share important features with the unconstrained optimal response: more dangerous random environments select for higher baseline levels (Figure IA vs. C), and when threats are more persistent (i.e., stronger autocorrelation) the stress response lasts longer (Figure IB vs. D).

Importantly, there are differences between the unconstrained optimal and physiologically constrained responses. In the simulations, hormone clearance is more gradual, due to mechanistic constraints (e.g., physical limits on hormone decay rates); and baselines are lower in 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., [80]) (see Figure S1 in the supplemental information online).
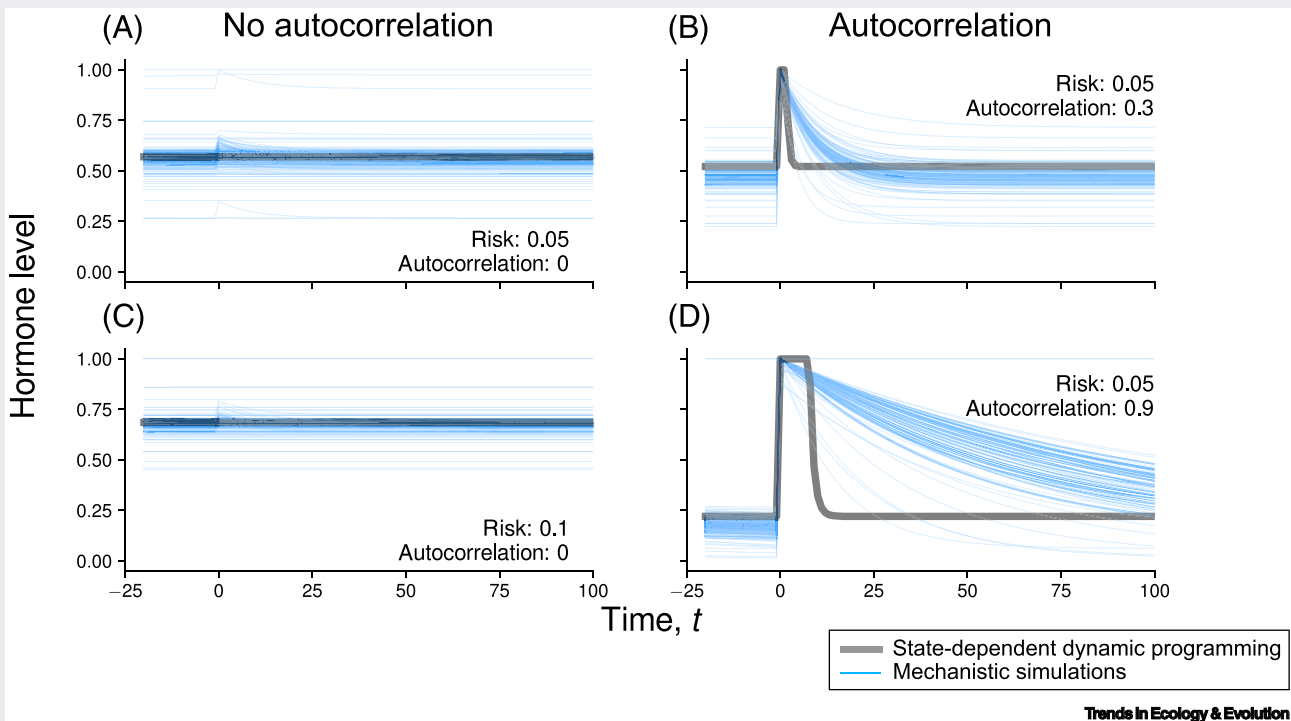

Figure I. Evo-Mecho Predictions for the Stress Response. Optimal stress responses identified by state-dependent dynamic programming (thick grey lines) compared with evolved stress responses from a mechanistic evolutionary simulation model (light-blue lines, showing stress responses of different individuals), 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 the supplemental information online for full model details and other parameter values.

clearance. While such a three-trait model is simplistic [38], it highlights how plausible mechanistic constraints can alter stress response evolution, compared with optimality predictions free from constraints (Box 3).

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 before encountering a stressor, followed by a high hormone peak and a clearance phase (see Figure IB in Box 3; note that when the autocorrelation is higher, clearance is slower, see Figure ID in Box 3). 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, thus, the model predicts a uniform stress hormone level, with higher baseline levels of stress hormones in more dangerous environments (Box 3, Figure IA vs. C). Changing the autocorrelation affects the stress response more than does 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 more rapidly between high and low stress hormone levels than does the more gradual decay pattern predicted by the mechanistic model (see Figure IB,D in Box 3), 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 in the supplemental information online, 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 less when making other assumptions about underlying mechanisms or life-histories (see the research agenda discussed later), which is exactly the point of a formal theory of stress response evolution that yields testable predictions.
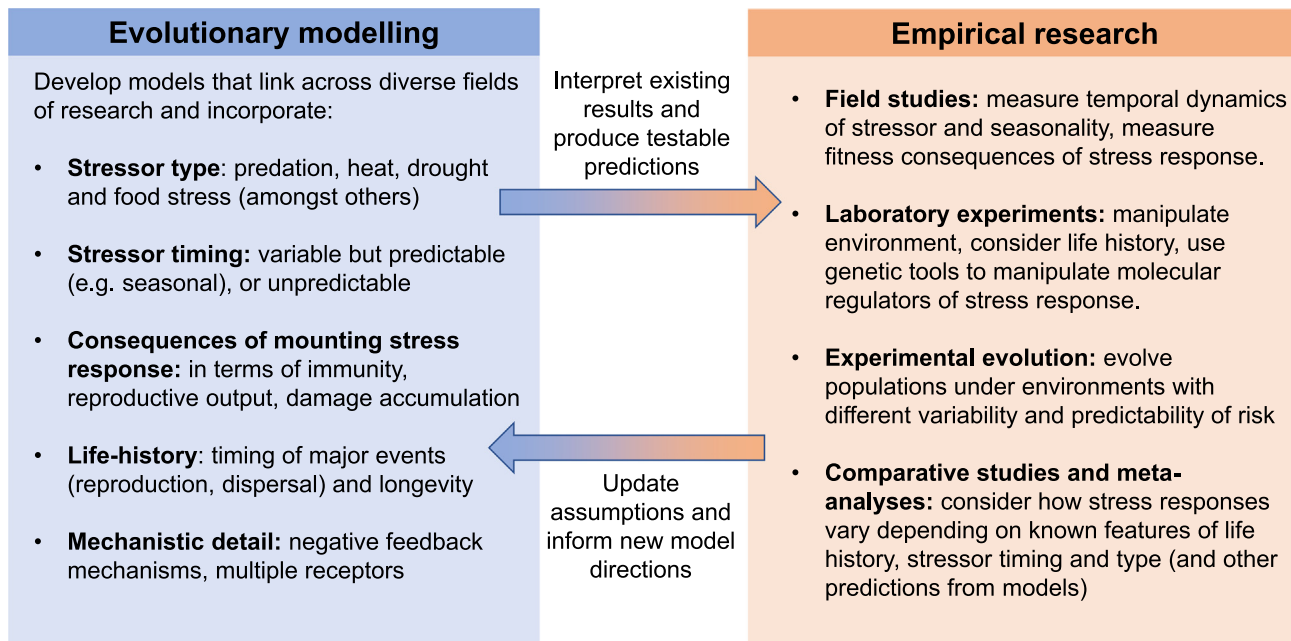
More empirical data are needed to test these predictions. Studies comparing stress responses in natural populations show mixed results, with high-risk populations showing baseline or peak hormone levels that are higher [16,43,44], similar [45], or even lower [4,46,47] compared with low-risk populations. Providing experimental predator cues tends to increase **hypothalamus–pituitary–adrenal/hypothalamus–pituitary–interrenal** (HPA/HPI) activity [48]. Within populations over time, variable predation risk elicits different patterns of baseline and peak across species [49]. 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 [50].

Stress Response Evolution: A Research Agenda

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

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

Evolutionary modelling		Empirical research
Develop models that link across diverse fields of research and incorporate: • **Stressor type**: predation, heat, drought and food stress (amongst others) • **Stressor timing:** variable but predictable (e.g. seasonal), or unpredictable • **Consequences of mounting stress response:** in terms of immunity, reproductive output, damage accumulation • **Life-history**: timing of major events (reproduction, dispersal) and longevity • **Mechanistic detail:** negative feedback mechanisms, multiple receptors	Interpret existing results and produce testable predictions Update assumptions and inform new model directions	• **Field studies:** measure temporal dynamics of stressor and seasonality, measure fitness consequences of stress response. • **Laboratory experiments:** manipulate environment, consider life history, use genetic tools to manipulate molecular regulators of stress response. • **Experimental evolution:** evolve populations under environments with different variability and predictability of risk • **Comparative studies and meta-analyses:** consider how stress responses vary depending on known features of life history, stressor timing and type (and other predictions from models)

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Figure 2. An Integrated Research Programme for Studying the Evolution of the Stress Response System.

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 [51]), 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. An organism cannot afford to respond strongly to successive stressors if doing so causes cumulative damage [39].

Life History
Mathematical models also need to be placed in a life-history context, accounting for longevity and seasonal effects [5,7,10]. For example, we might predict a weaker stress response before and during an annual breeding season, to reduce damage caused by high GC levels that would interfere with breeding. Long-lived animals might respond more strongly to stressors because they can afford to reduce their reproductive output in one season, whereas short-lived animals cannot. Major events, such as moult or migration, in which the balance of fitness tradeoffs may change, will also affect the optimal stress response [7,52].

Mechanisms
Beyond the example in Box 3, other possibilities that could be modelled include: (i) a decay mechanism that allows active inhibition of further hormone production through negative feedback

[53]; (ii) evolvable densities of different types of hormone receptor across tissues; and (iii) pleiotropic effects, which may underlie variation across species in the degree of genetic correlation among stress response features (Box 2).

Empirical Research on Evolution of the Stress Response

Future laboratory and field studies should test predictions of evolutionary models with explicit consideration of environmental predictability and life history, and manipulate salient features of the stress response of a species where feasible (Figure 2).

Experimental Evolution

Experimental evolution can be used to test how different environmental conditions shape the stress response. Previous experimental evolution studies have focussed mainly on tolerance to stressors by measuring survival or population growth, rather than on changes in the underlying stress response, and are largely restricted to microbes (e.g., [54]). Given that gene expression networks underlying stress responses are well characterised in model systems, such as *Caenorhabditis elegans* [55], 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 the novel prediction of our model that organisms living in environments with no autocorrelation in stressors (unlikely in most natural systems [56,57]) should evolve to have no stress response.

Comparative Studies and Meta-analyses

Large-scale comparative studies (e.g., [5]) and meta-analyses (e.g., [58]) 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 in the supplemental information online) emphasises 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 [57], which can be challenging to measure (but see [56]).

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: (i) explicitly modelling mechanistic constraints on the decay phase of the response, a feature largely ignored in previous research, strongly influences evolutionary outcomes; and (ii) 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 tradeoffs and environmental factors, such as stressor predictability. Temporal autocorrelation has been considered empirically for climatic factors [59], 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, such as HormoneBase [60] and the Wildlife Endocrinology Information Network [61], 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 or immunosuppression) caused by stress hormones affect selection on stress response features? How do evolutionary predictions depend on the time scale over which the damage acts?

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 or 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?

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Supplemental Information

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