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An evolutionary perspective on stress responses, damage and repair

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ABSTRACT

Variation in stress responses has been investigated in relation to environmental factors, species ecology, life history and fitness. Moreover, mechanistic studies have unravelled molecular mechanisms of how acute and chronic stress responses cause physiological impacts ('damage'), and how this damage can be repaired. However, it is not yet understood how the fitness effects of damage and repair influence stress response evolution. Here we study the evolution of hormone levels as a function of stressor occurrence, damage and the efficiency of repair. We hypothesise that the evolution of stress responses depends on the fitness consequences of damage and the ability to repair that damage. To obtain some general insights, we model a simplified scenario in which an organism repeatedly encounters a stressor with a certain frequency and predictability (temporal autocorrelation). The organism can defend itself by mounting a stress response (elevated hormone level), but this causes damage that takes time to repair. We identify optimal strategies in this scenario and then investigate how those strategies respond to acute and chronic exposures to the stressor. We find that for higher repair rates, baseline and peak hormone levels are higher. This typically means that the organism experiences higher levels of damage, which it can afford because that damage is repaired more quickly, but for very high repair rates the damage does not build up. With increasing predictability of the stressor, stress responses are sustained for longer, because the animal expects the stressor to persist, and thus damage builds up. This can result in very high (and potentially fatal) levels of damage when organisms are exposed to chronic stressors to which they are not evolutionarily adapted. Overall, our results highlight that at least three factors need to be considered jointly to advance our understanding of how stress physiology has evolved: (i) temporal dynamics of stressor occurrence; (ii) relative mortality risk imposed by the stressor itself versus damage caused by the stress response; and (iii) the efficiency of repair mechanisms.

1. Introduction

1.1. Stress responses and stressors

Stress responses are universal in organisms, occurring from microbes to vertebrates (Taborsky et al., 2021), and have evolved to allow organisms to cope with a broad range of physical and biotic threats. Stress responses occur at the cellular (e.g., heat shock proteins), tissue (e.g., inflammatory responses) and organismal (e.g., catecholamine and adrenocortical responses) level (Schwartz and Bronikowski, 2013; Wada, 2019). Mechanistically, stress responses often involve the rapid increase of certain molecules after perception of a stressor, such as the appearance of a predator or onset of a cold spell; the best-studied examples are glucocorticoid (GC) hormones in vertebrates, which increase within minutes after encountering a stressor and gradually decrease back to a baseline level over the following hours (Chrousos and Gold, 1992; Sapolsky et al., 2000; Selye, 1956). Stress responses have beneficial effects, particularly in the short term to cope with a stressor

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(Koolhaas et al., 2011; Sapolsky et al., 2000). The hypothalamic pituitary adrenal/interrenal (HPA/HPI) axis and the sympathetic adrenomedullary (SAM) system, two key players in the vertebrate stress response (Chrousos and Gold, 1992), mobilize energy to fight immediate danger, aid the redistribution of oxygen and nutrients to active organs and tissues and change behavior adaptively (e.g., decreased foraging, increased escape behavior) (Koolhaas et al., 2011; Sapolsky et al., 2000). The GC response also helps individuals in future stressor encounters by memorizing the stressful circumstances and responses (Sandi et al., 1995; Sandi and Rose, 1994; Schwabe et al., 2012).

In terms of ecology, stressors are highly diverse and differ in type, duration and strength. Still, they can be broadly categorised depending on both the level of risk they pose to survival and reproduction, and their temporal dynamics, i.e., the predictability of the stressor (De Boer et al., 1990; Weiss, 1970) and whether it returns after a short or long period (Taborsky et al., 2021). Such variation can give rise to acute exposure or to sustained, chronic exposure to stressors, which has implications both for the shape of the stress response itself (Taborsky et al., 2021) and the positive and negative fitness consequences for the organism (e.g., Blas et al., 2007; Breuner et al., 2008; Cordero and Sandi, 2007; Hau et al., 2016; Joëls and Baram, 2009; Romero and Wikelski, 2001; Sandi and Haller, 2015).

1.2. Damage and fitness

Mild stressors can improve fitness outcomes. For instance, moderate exercise, moderate caloric restriction, or hypothermia can have positive and stimulatory effects on physiology and fitness due to reduction of oxidative damage or enhanced constitutive innate immunity, and improved longevity (Vágási et al., 2018; Zhang and Hood, 2016). Strong, acute stressors, however, such as intense exercise (Gallego-Selles et al., 2020), or repeated or enduring exposure to stressors leading to a chronic stress response (e.g., Orzechowski et al., 2002; Sapolsky et al., 1985) can result in harmful physiological effects (Table S1), referred to as damage (Wada, 2019). Damage may result as a direct consequence of the stress response (e.g., oxidative damage, Costantini et al., 2011), but it might also occur indirectly, for example through energy reallocation.

Damage occurs at the level of molecules (e.g., proteins, lipids, DNA, Orzechowski et al., 2002), cells and immune system (e.g., Engler et al., 2004; Schwartz and Bronikowski, 2013), tissues and organs (e.g., McKittrick et al., 2000; Orzechowski et al., 2002). For example, a chronic GC response can lead to a weakened cardiovascular system due to hypertension, bone tissue breakdown due to prolonged calcium mobilization, muscle atrophy due to protein breakdown for glucose, impairment of memory formation and impaired immune function (McEwen, 2008; examples in Table S1). These effects can scale up to influence individual fitness (Bize et al., 2008; Gormally et al., 2019; Isaksson et al., 2011). The same stress response mechanism that protects an organism at a low dose during short exposure to a stressor can lead to physiological damage at a high dose or prolonged exposure to a stressor (e.g., immunoenhancement vs. immunosuppression after acute or chronic stress, respectively; Dhabhar, 2008). These findings suggest the existence of non-linear relationships between stressor exposure and fitness, as predicted by the concept of hormesis, where a low stressor exposure is generally favourable over no stressor or higher stressor exposure (reviewed in Calabrese et al., 2007; Mattson, 2008).

According to a recent conceptual model, the Damage-Fitness model (Wada, 2019), the accumulation of damage in cells and tissues reduces fitness when repair mechanisms are insufficient to cope with the stressors faced. This model builds on previous verbal models of the stress response, such as allostasis (McEwen and Wingfield, 2003), the Reactive Scope model (Romero et al., 2009), Physiological Regulatory Networks (Cohen et al., 2012), and Control Theory models (e.g., Stear, 1975; Zhang and Andersen, 2007), with the distinction that it focuses on fitness consequences of damage rather than physiological aspects of the stress response alone. The model predicts that damage accumulates when stress response mechanisms are not efficient or become dysregulated (see also Wada and Heidinger, 2019), resulting in allostatic load (e.g., McEwen, 2007). There is considerable empirical support for the negative association between damage and fitness, in terms of both survival and reproduction (Wada and Heidinger, 2019). For example, shortened telomeres resulting from chronic stressors (e.g., Kotrschal et al., 2007) are associated with reduced lifespan in both epidemiological and experimental studies (Arbeev et al., 2020; Heidinger et al., 2012; Muñoz-Lorente et al., 2019; Wilbourn et al., 2018). Damage may also lead to reduced reproduction: for example, higher oxidative damage prior to reproduction is negatively correlated with future reproduction in several species (Costantini and Dell'Omo, 2015; Stier et al., 2012).

1.3. Repair and fitness

Organisms have evolved mechanisms to either limit the amount of damage, such as antioxidants or the negative feedback of the HPA-axis (Romero et al., 2009), or repair mechanisms to alleviate or fully reverse negative effects of damage. These include DNA repair (such as the telomerase enzyme), neurogenesis and other tissue remodelling (Table S1). Although it seems straightforward to assume beneficial effects of repair processes on reproduction and survival, fitness consequences of repair mechanisms have rarely been directly investigated. A notable exception is work on sirtuins, which are a repair mechanism for oxidative damage that have been shown to have beneficial effects on lifespan and senescence (Ristow and Schmeisser, 2014). While suppression of the sirtuin 'SIRT6' resulted in genetic instability and premature aging (Mostoslavsky et al., 2006), its overexpression promoted lifespan extension in male mice (Kanfi et al., 2012). However, repair mechanisms may also negatively affect fitness if produced at high doses; for example, telomerase, which reduces telomere attrition and is directly linked with lifespan (e.g., in zebrafish, Henriques et al., 2013), is associated with increased cancer risk (Shay and Wright, 2011).

1.4. Outstanding questions

Many empirical studies have focused on explaining variation in stress responses in relation to ecology, life history and reproduction (e.g., Bókony et al., 2009; Vitousek et al., 2019), individual state (e.g., Kitaysky et al., 2003) and previous experiences (e.g., Antunes et al., 2021; Spencer et al., 2009), and have studied their associations with fitness (reviewed in Harris, 2020). In turn, mechanistic studies have investigated mechanisms of damage and repair to molecules, cells, tissues, and organs (see Table S1), but these consist almost entirely of biomedical studies in laboratory models (Gormally et al., 2019), where fitness consequences or evolutionary responses have not been considered. In the presence of efficient repair mechanisms, damage may be an important component of optimal behavioral strategies: it may sometimes serve an individual's fitness interests to accumulate damage. Even without repair, damage may be optimised differently depending on the organism's life-history strategy; for instance, higher levels of damage accumulation might be tolerated in short-lived or semelparous organisms than in long-lived or iteroparous organisms. This is analogous to insights from host-parasite ecology, where under certain life-history conditions it may be better to tolerate rather than resist a parasite (e.g., Sears et al., 2015). Evolutionary studies are needed to understand how such damage and repair processes contribute to adaptive variation in the stress response.

Damage generally increases with the intensity, duration, or frequency of stressors and also with chronological age, and it may harm fitness if repair mechanisms are not effective in preventing or removing damage (Wada, 2019). Yet several aspects of the relationship between stressors, damage and repair are complex and little understood. First, the role of damage accumulation as an evolved strategy in challenging environments, and thus as a component of an optimal strategy, has not yet been explored. Second, and related to the first point, it is not known how

damage accumulation is affected by how quickly it can be repaired, if indeed repair is possible. Third, it is currently unclear how the temporal predictability and persistence (e.g., acute or chronic) of stressors influences associations between stress responses, damage and repair. One reason is that short-term (acute) and long-term (chronic) stressors are often conflated in empirical studies when biomarkers of stress response, damage and repair are not appropriately selected to reflect the correct timescales (Gormally and Romero, 2020). Fourth, more work is needed to understand how optimal stress responses vary with organisms' life history (e.g., lifespan) or differences in ecological conditions (e.g., resource availability).

1.5. Modelling the evolution of stress responses

The evolution of stress responses can be analysed using the "evo-mecho" approach (McNamara and Houston, 2009; see e.g., Taborsky et al., 2021), where knowledge about underlying physiological mechanisms is integrated with evolutionary optimality analyses to identify key features of stress responses that help organisms meet the challenges they face in natural environments. We believe that such an approach should be integrated into the modern evolutionary endocrinology research toolkit, to help generate robust predictions for the evolution of endocrine responses and to support hypothesis testing. In this approach, the physiological mechanism captures the relevant life-history trade-off; for example, it can capture the trade-off between avoiding death from the stressor and avoiding the deleterious effects of mounting a prolonged stress response. McNamara and Buchanan (2005) incorporated this trade-off in a model that predicts the optimal stress response when there is a single stressor, such as a spell of cold weather, that persists for some time. They showed that there can be circumstances where most mortality occurs from the stress response rather than the actual stressor. In contrast, our previous modelling approach considered the possibility of multiple short stressful events, where the likelihood of a stressor appearing depended on the time since the last stressor occurred (Taborsky et al., 2021). We found that the temporal pattern of stressors (i.e. their frequency of occurrence and predictability) should affect the magnitude and duration of stress responses: when autocorrelation (and hence predictability) is high, individuals mount a stronger stress response and hormone levels stay high for longer, whereas when autocorrelation is low (or zero), individuals show a weaker (or no) stress response but increase baseline hormone levels in more dangerous environments (MacDougall-Shackleton et al., 2019; Taborsky et al., 2021).

We propose that formal modelling approaches can be especially useful to study how damage and repair affect the evolution of the stress response, as experimental studies in an ecologically relevant environment and time scale are often limited (e.g., because frequent sampling in wild organisms is not feasible), and as our current knowledge is largely limited to biomedical investigations of the underlying mechanisms. A key recent modelling study by Luttbeg et al. (2021) on optimal hormone level regulation focused on the limitations to the speed of hormonal responses but also included indices of damage (termed 'allostatic overload costs'). Luttbeg et al. (2021) concluded that in the presence of allostatic overload costs, glucocorticoid levels should be lower and more dependent on the frequency of past acute stressors. However, Luttbeg et al. modelled damage as occurring at a fixed rate, not as a consequence of evolving traits, and they did not include the possibility of repair. Relaxing these assumptions is likely to alter evolutionarily adaptive stress responses.

1.6. Our hypotheses

Building on Taborsky et al. (2021), here we study negative physiological impacts of acute and chronic stress responses ('damage') and investigate how the existence of repair mechanisms, which reduce damage, changes the evolution of stress responses and damage accumulation. We hypothesise that evolution of the stress response depends on (1) its direct and indirect physiological impacts and their fitness consequences (damage) and (2) the ability of the organism to reverse those physiological impacts (repair).

We model a scenario in which we vary the overall level of risk (long-term average probability that a stressor occurs at a given time step) and its predictability (temporal autocorrelation). We expect that the presence of repair mechanisms should allow organisms both to maintain a higher baseline hormone level (in the absence of the stressor) and to produce higher peak hormone levels (when the stressor appears), because the damage incurred can then be removed. Furthermore, more efficient mechanisms of repair could allow longer durations of higher peak and baseline levels, especially under chronic stress. Based on our previous model (Taborsky et al., 2021), we also expect that predictability of a stressor (i.e., whether stressor occurrences are autocorrelated) will influence stress responses more than the overall risk level (i.e., the overall probability that a stressor is present).

2. The model

We use an evolutionary optimality model to assess how stress responses evolve (and what form they take) when elevated expression of a hormone associated with an external stressor (further referred to as 'stress hormones', see MacDougall-Shackleton et al., 2019) can result in the accumulation of damage. Our aim is not to build a comprehensive model of the stress response. Instead, we seek to illustrate some general points about how damage and repair mechanisms influence the evolution of the stress response, by focusing on one specific model of a scenario that, while necessarily simplified, captures some of the key features of interest. Many other models are possible and may elucidate other important features not covered here, some of which we consider in the 'Discussion' section. The model extends a previous dynamic programming model by Taborsky et al. (2021), which considers an organism faced with an intermittent survival threat (such as a predator or a bout of harsh weather) that comes and goes over a relatively short timescale (minutes, hours or days; note that we are not considering seasonal changes here). Here we provide an overview of the model; for a detailed model description see the 'Supplementary Model Description'.

A threat (e.g., a predator or a weather depression) appears with probability λ_A in any given time step, whereas it leaves with probability λ_L. In this paper, we focus on two key summary variables that reflect different ecological contexts that organisms may experience. First, we consider the long-term proportion of time that the threat is present, $\gamma = \lambda_A/(\lambda_A + \lambda_L)$, hereafter called 'risk'. Second, we consider whether the presence of the threat predicts its continued presence in the near future, which occurs when the threat has a non-zero autocorrelation $\rho = 1 - \lambda_A - \lambda_L$.

2.1. Stressors and hormones

Each time step t that the threat is present, the organism directly encounters it with probability p_{att}; depending on the type of threat, this could represent, for example, an attack by the predator, or the occurrence of a snowstorm. We assume that $p_{att} < 1$ and that the organism only detects that the threat is present when it directly encounters it, otherwise it is uncertain whether the threat is present or absent (in the Discussion we suggest modifications to relax this assumption). Note that when there is a positive autocorrelation, the longer it has been since the last encounter with the stressor, the less likely it is that the threat is still present (see Eq. (S4), which provides the probability that the threat is still present τ time steps after it was last encountered, as a function of p_{att}, $\lambda_A$and λ_L). During an encounter with the stressor, the organism is killed with probability p_{kill} (see Eq. (S1)), which decreases with increasing levels of the stress hormone h, because increased h allows the organism to respond more quickly to challenges. We also include an additional source of mortality, with probability $\mu(d_t)$ per time step (see Eq. (S2)), that is not directly caused by the stressor, but that is dependent

on the level of damage an individual has accrued at time step t (see section "Damage and repair" below). If the organism survives both sources of mortality, it expresses a level of hormone h (see section "Strategies" below) in the next time step, and the cycle continues.

2.2. Damage and repair

While the elevated expression of stress hormone h may help the organism survive in the face of a direct threat, it can also result in longer-term negative physiological impacts ('damage'). To accommodate this in the current model, we assume that at time t the organism is characterized by a level of damage d_t, where $0 \leq d_t \leq 1000$. The level of damage is assumed to increase as an accelerating function of the current stress hormone level, relative to a reference level h_θ at which damage is minimised. When stress hormone levels are either above or below this optimum, damage levels increase, leading to a U-shaped pattern. However, the organism is also able to repair a certain amount of damage r during each time step, where r is assumed to be a constant parameter. Specifically, the level of damage d_{t+1} in the next time step is given by

$$d_{t+1} = d_t + a(h_t - h_\theta)^2 - r \quad (1)$$

where a reflects the strength with which hormone levels above or below h_θ increase damage. The current amount of damage d_t affects the probability of background mortality $\mu(d_t)$ (see Eq. (S2)), which increases with d_t in a linear fashion.

2.3. Strategies

We assume that the hormone expression level $h(\tau, d)$ (where $0 \leq h(\tau, d) \leq 1$) during each time step is allowed to depend on two state variables: the time since the individual last encountered the stressor $\tau = 1, 2, 3, \ldots$ and the individual's current level of damage d. We then use dynamic programming (see online supplement for details) to identify the optimal values of the hormone $h^*(\tau, d)$ for all values of τ and d that maximise long-term survival (see Figs. S3 and S4 for values of $h^*(\tau, d)$ across τ and d). The model assumes that there are no constraints in the speed with which hormone levels can change between time steps, similar to the 'unconstrained' model that we previously developed (see Box 3 in Taborsky et al., 2021). In Taborsky et al. (2021), we also compared results to a more mechanistic version that included constraints on hormone speed (see also Luttbeg et al., 2021), finding that stressor risk and autocorrelation have qualitatively similar effects regardless of the action of constraints.

2.4. Environmental scenarios

We investigate the consequences of optimal hormone expression strategies in different environmental scenarios: (1) whether an occurrence by the stressor provides information about any future occurrences of the stressor, which we model by varying the autocorrelation, ρ, in stressor appearance (see above); (2) whether stressors are common or rare overall, which we model by varying the risk level γ (see above). After the optimal hormone expression strategy is obtained for any particular configuration of autocorrelation and risk in stressor occurrence, we then simulate the resulting hormone profiles over 100 time steps for this evolved stress hormone system in response to: (3) a single encounter with the stressor at $t = 10$ (Figs. 1–3), which we refer to as the 'acute stressor scenario'; and (4) repeated encounters with the stressor at $t = 10$ and every subsequent time step (Fig. 4), which we refer to as the 'chronic stressor scenario'. Note that chronic stress modelled here is much more frequent and persistent than the pattern of stressors to which the organism is evolutionarily adapted. Individuals accumulate damage and experience damage-related mortality as in the evolutionary model.

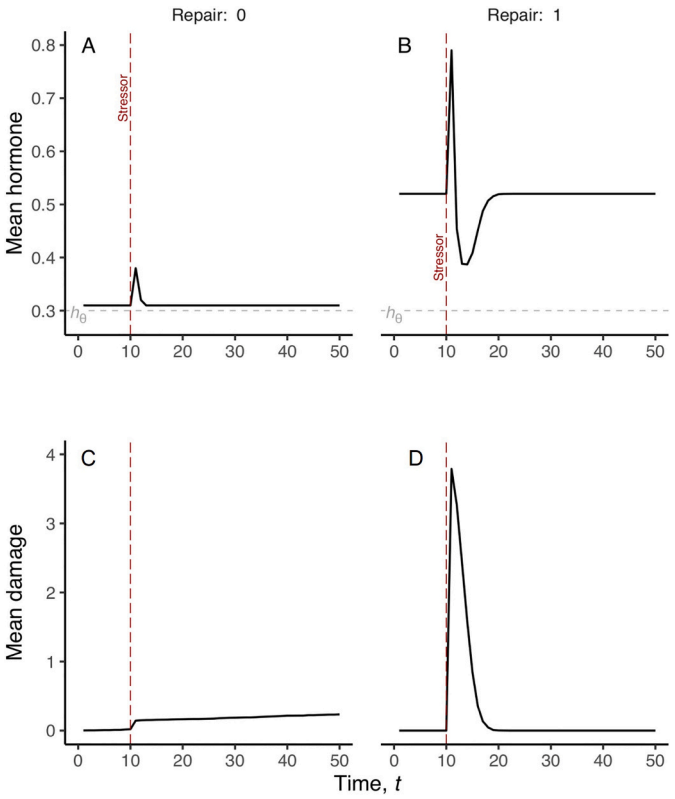

Fig. 1. Changes in hormone and damage levels before and after exposure to a stressor encountered during a single time step, at $t = 10$ (dark red vertical dashed lines). Panels A, C: no repair ($r = 0$), hence baseline and peak hormone levels are low to prevent a rapid accumulation of damage. Damage is not constant but increases slowly (C), because the baseline hormone level in A is slightly above the hormone level at which no damage accumulates $h_\theta = 0.3$ (grey horizontal dashed lines). Baseline hormone levels are favored to be higher than h_θ to enhance survival in the face of risk, at the expense of the gradual accumulation of damage. Panels B, D: repair $r = 1$: baseline and peak hormone levels are substantially higher. Parameters: $\lambda_A = 0.035$, $\lambda_L = 0.665$ (hence risk $\gamma = 0.05$, autocorrelation $\rho = 0.3$), $\mu_0 = 0.002$, $k = 1$, $\alpha = 1$, $p_{att} = 0.5$, $h_\theta = 0.3$, $a = 0.2$.

3. Results

Hormone profiles of an organism encountering an acute stressor show that, as expected, baseline and peak hormone levels are higher when organisms have the ability to repair damage (e.g., $r = 1$) compared to scenarios in which repair is absent ($r = 0$, compare Fig. 1A vs B). When repair is possible, individuals can express higher hormone levels (and thereby be more resistant to potential occurrences of a stressor) because concomitant damage will be gradually removed through repair, whereas such damage inexorably accumulates in the absence of repair (compare Fig. 1C vs D).

In general, there is a positive relationship between rate of repair and both baseline and peak hormone levels (Fig. 2A-C), for different levels of stressor risk (i.e., probability that a stressor occurs at a given timestep) and autocorrelation. In the absence of autocorrelation (Fig. 2A), individuals do not express any increase in hormone levels (i.e., no 'peak') after encountering a stressor, as this stressor is not predictive about future encounters with the stressor and so there is no benefit in temporarily increasing stress hormone levels.

With increasing predictability of stressor occurrence (i.e., increasing autocorrelation), encounters with the stressor induce a peak in hormone expression that becomes higher with increasing rates of repair (Fig. 2 from panel B to C). However, at higher rates of repair, baseline hormone levels approach the levels of peak values. Thus, our model predicts that

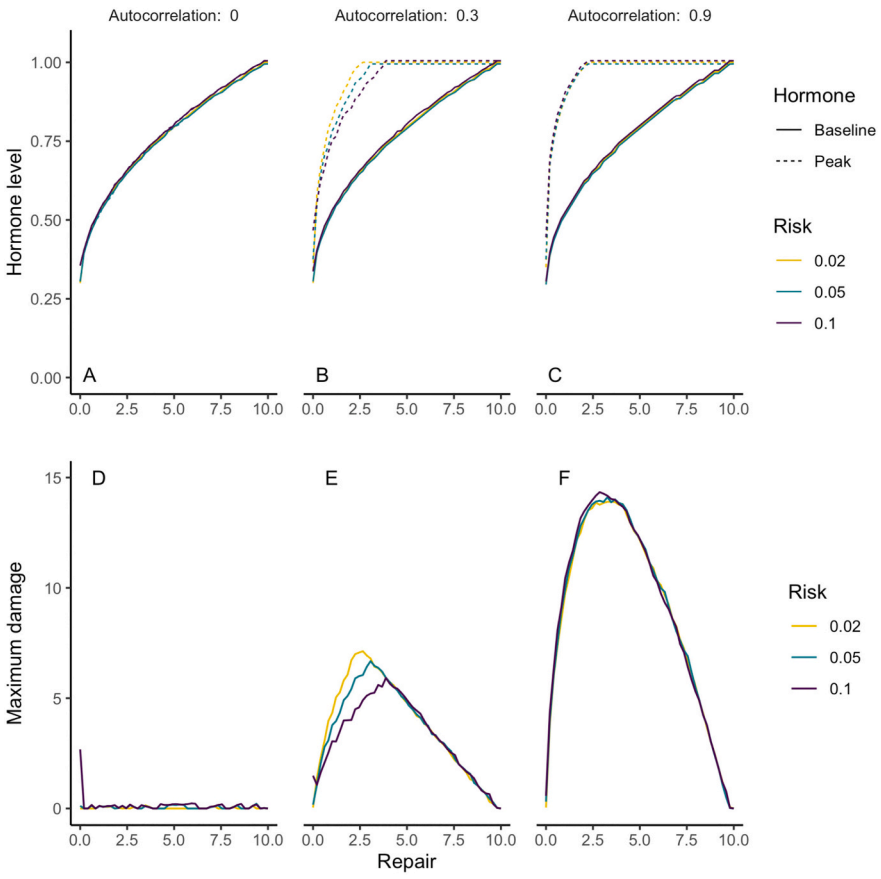

Fig. 2. Effects of repair on baseline and peak hormone levels (panels A–C) and on the maximum level of damage within 40 time steps after a single encounter with the stressor (panels D–F). Panels A–C show that increasing the rate of repair increases both baseline and peak hormone levels, as repair allows for the removal of damage resulting from high hormone levels. Panels D–F show that increasing the autocorrelation increases maximum damage levels that are attained, as peak levels of hormones last longer, because the animal can expect subsequent encounters with the stressor (see also Fig. IB vs D in Taborsky et al., 2021). Parameters: $\mu_0 = 0.002$, $k = 1$, $\alpha = 1$, $h_\theta = 0.3$, $p_{\text{att}} = 0.5$, $a = 0.2$. Values of λ_A and λ_L can be calculated from the values of risk γ and the autocorrelation ρ where $\lambda_A = \gamma(1-\rho)$ and $\lambda_L = (1-\rho)(1-\gamma)$.

the biggest difference between baseline and peak hormone levels is seen at modest rates of repair. While these peaks result in higher maximum levels of costly damage (compare Fig. 2D with Fig. 2E,F), the existence of a repair mechanism allows such damage to be gradually removed. In the extreme case where repair rates are very high ($r = 10$), damage does not build up at all, so peak hormone levels are replaced by constant high baseline levels of stress hormone.

For strongly autocorrelated and hence highly predictable stressors, the stress response is expected to last longer (i.e., take longer to get back to baseline after a stressor) (see Fig. S1), because after an initial encounter with the stressor, the organism expects to encounter it again in the near future (see also Taborsky et al., 2021). Consequently, due to the longer-lasting response, maximum damage levels are also higher (Fig. 2F). As predicted above, following Taborsky et al. (2021), average long-term risk did not affect the baseline, and it also had only a relatively minor effect on hormone peak levels. Risk did not increase baseline hormone levels in the presence of damage accumulation, as a higher baseline would lead to further deviation away from the optimal hormone level of h_θ and hence result in a more rapid accumulation of damage.

The probability of death due to the stressor is highest for stressors that cannot be anticipated (characterized by an autocorrelation of zero, left hand sides of Fig. 3A and B) and for those that occur more often (i.e., higher values of risk). When repair is absent, the probability of death due to damage is also higher in environments with zero autocorrelation (Fig. 3C). This is because individuals do not mount a stress response and can only use their baseline hormone level to mitigate the effect of the stressor (see Fig. S1), which invariably results in the accumulation of long-term damage. By contrast, when repair is present, the probability of death due to damage is higher for environments that are strongly autocorrelated, as this is where stress responses last relatively long (see Fig. S1), thereby resulting in higher levels of maximum damage. Notably, with the current model parameters, on average the probability to die from damage is minute relative to the probability to die from the stressor itself.

Fig. 4 shows the resulting hormone expression levels when we place an organism, whose stress response has been adapted to its original environment (characterized by a certain autocorrelation and risk level), suddenly in a context of chronic stress in which a stressor occurs every time step. When the organism's original environment is characterized by high autocorrelation and risk, we find that small rates of repair in the face of chronic stress result in high stress hormone and damage levels (left hand sides of Fig. 4B, C and F, G). This occurs because these original environments of high autocorrelation and risk favor the expression of stress responses with high peaks (see Fig. S1A, S3G—I) that result in the rapid accumulation of damage. In the original environment, such rapid accumulation of damage can later be repaired when the stressor eventually goes away (Fig. S1B). In the chronic stressor scenario where stressors occur repeatedly, however, the hormone peaks will be expressed repeatedly, resulting in a far more prolonged stress response (see Fig. S2). As stressors do not go away, damage resulting from such high peaks cannot be slowly removed and hence accumulates, resulting in a large long-term mortality due to damage. By contrast, those organisms adapted to an original environment with low autocorrelation express stress responses with reduced peaks (see Fig. S1) that accrue only a limited amount of damage. Once exposed to a chronic stressor, the repeated expression of such reduced stress responses results in the accumulation of a lower amount of damage.

Finally, Fig. 4C shows that there is not necessarily a strictly positive relationship between increasing levels of repair and hormone levels expressed in the face of a chronic stressor. Rather, for high levels of risk ($\gamma \geq 0.05$), we find that there is a U-shaped relationship between repair and chronic hormone levels. To understand this U-shaped pattern, note that when repair is low, damage accumulation due to repeated

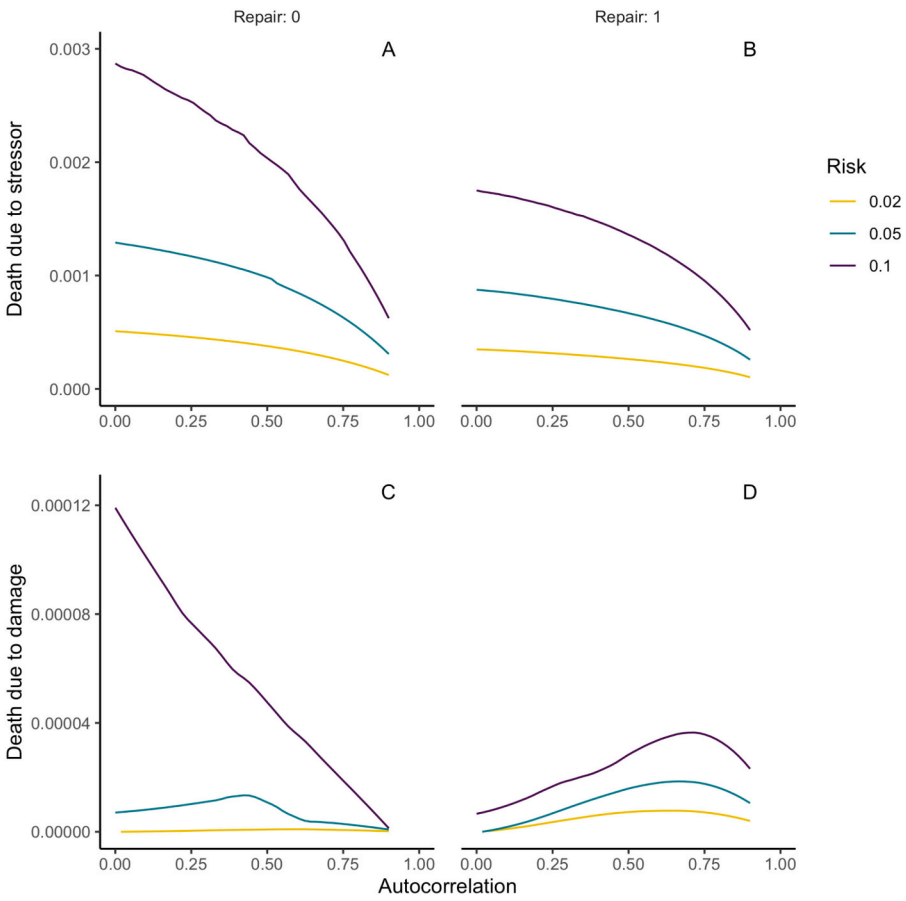

Fig. 3. Effects of autocorrelation in stressor occurrence on the probability of death directly due to the stressor (panels A, B) and on the probability of death due to accumulated damage (panels C,D) when repair is absent (left column) vs present (right column). The probability of death due to the stressor is highest for stressors that cannot be anticipated (characterized by an autocorrelation of zero, left hand sides of panels A and B) and for stressors that occur more often (i.e., higher values of risk). When repair is absent, the probability of death due to damage is also higher in environments that are uncorrelated (panel C). This is because individuals can only use their baseline hormone level to mitigate the effect of the stressor, which invariably results in the accumulation of long-term damage. By contrast, when repair is present, the probability of death due to damage is higher for environments that are strongly autocorrelated, as this is where stress responses are characterized by peak hormone levels that last relatively long, thereby resulting in the accumulation of more damage. Parameters as in Fig. 2.

expression of high stress hormone peaks is very large (see Fig. S2). What should an organism do, when faced with such high levels of damage and no opportunity to repair it? Our model predicts that in this situation, organisms should increase rather than decrease their hormone levels, at the expense of even larger levels of damage. When already faced with a large degree of mortality due to damage (and little scope to repair it), the only thing left for an organism to do would be to reduce the other source of mortality, which are the encounters with the stressor itself. The latter can be done by increasing rather than decreasing hormone levels. By contrast, for moderate rates of repair, there is a reasonable expectation that current damage can be reduced in the foreseeable future, disfavouring the expression of excessively high hormone levels. Even larger rates of repair, however, favor increased hormone levels, as any concomitant damage is now removed so quickly that there are little costs of high hormone expression.

4. Discussion

Our model provides some novel insights about evolved responses to stressors under constraints of damage and repair, but we do not claim that it provides a comprehensive account of the stress response. Rather, it is one of many possible models—each with their own assumptions about the biology of the animals and the environments to which they are adapted—which taken together can deepen our understanding of how selection acts on the stress response. Alternative models are needed to consider a range of other important factors, including, for example, the dependence of stress responses on longevity and seasonal breeding schedules, which we leave to future work. Our discussion below is focused on the insights gleaned from the specific model developed here, and its assumptions and predictions in relation to the existing empirical evidence.

4.1. Model predictions and empirical evidence

The presence of damage repair mechanisms is likely to have profound effects on the evolution of stress responses and the form they take. Indeed, our model predicts that repair mechanisms result in increased peak and baseline stress hormone levels. In the case of peak hormone levels, very high levels of stress hormones are expressed during short periods of time (and for longer when stressor occurrence is strongly autocorrelated), thereby resulting in the rapid accumulation of very high levels of damage. The higher the rate of repair, however, the easier it is for organisms to remove this damage, allowing organisms to express higher peak hormone levels at a reduced long-term mortality cost. For the same reasons, repair also facilitates the expression of higher baseline levels of stress hormones, which perform a supportive or preparative function to promote survival against future attacks, particularly in a scenario where stressors are frequent (Sapolsky et al., 2000). In an ideal scenario in which damage does not exist, such baseline levels are favored to be as high as possible, as a high baseline hormone level allows an individual to cope with unexpected occurrences of a stressor.

The so-called ‘supportive’ effects of baseline GCs help organisms respond to and recover from challenges by supporting energetically demanding activities (permissive, stimulatory, preparative and suppressive GC actions, following Sapolsky et al., 2000). There is evidence from a large-scale phylogenetic comparative analysis that in challenging environments, high baseline GCs are often found (Vitousek et al., 2019) and they are expected to function in a supportive role. However, results from large-scale studies on the peak levels are not as clear (during breeding, lower peak levels are generally found, Vitousek et al., 2019). In reality, however, a high baseline level results in damage that accrues every time step (as opposed to peak hormone levels, which only result in costs upon encountering a stressor). Hence, only when repair rates are

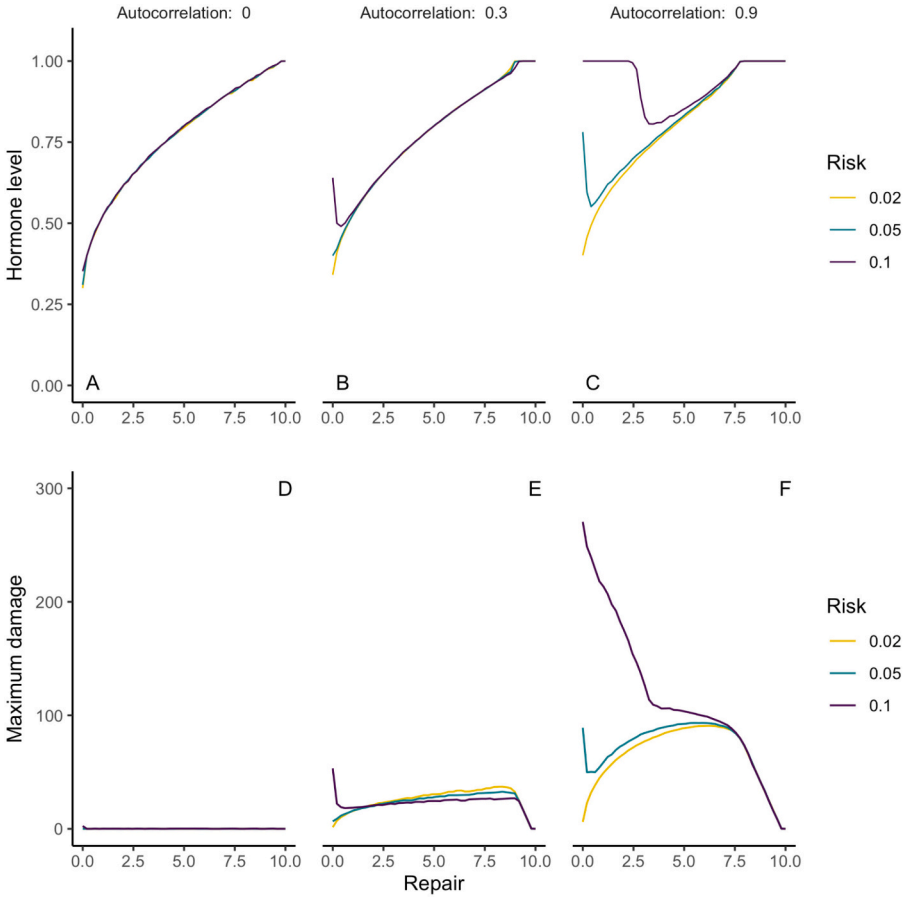

Fig. 4. Stress hormone (panels A–C) and damage levels (panels D–F) when stress responses—originally evolved in environments where acute stressors are characterized by particular values of autocorrelation and risk—suddenly have to cope with a chronic stressor that occurs every time step. When repair is relatively slow, an ancestral environment characterized by high risk and strong autocorrelation can result in high levels of damage and high hormone levels in the face of a novel, chronic stressor (left-hand sides of panels B,C,E,F). To understand this, consider the ancestral environment of high-risk, autocorrelated stressors, which selectively favors strongly peaked stress responses (see Fig. 1A,C). In the face of chronic stress, however, the repeated materialization of such peaks leads to the rapid build up of damage, which cannot be easily reduced unless the repair rate is high. Faced with high mortality due to damage, the best strategy for the organism is then to maintain high hormone levels, which at least allow it to reduce mortality due to the stressor. Only when repair levels are higher do we find that hormone levels go down, as individuals are better able to control the accumulation of damage in the face of chronic stress. Once repair levels are very high, hormone levels are again high, as any resulting damage is quickly cleared. Parameters as in Fig. 2. Hormone levels in panels A–C are those expressed after 40 time steps of continued exposure to the stressor (measured at time $t = 50$, after the stressor is first encountered at time $t = 10$ and then re-occurs every time step). See Supplementary Fig. S2 for a time profile of hormone expression levels and damage.

high can individuals afford to express high baseline levels of stress hormones. By contrast, when potential accumulation of damage is large due to low rates of repair, baseline and peak levels are predicted to be low, which aligns with the prediction by Luttbeg et al. (2021) that glucocorticoid levels should be low in those taxa with a rapid accumulation of damage.

Our model also predicts that the maximum level of observable damage following a stress response is highest in those organisms that have intermediate levels of repair (e.g., Fig. 2E,F). In organisms which have low levels of repair, both peak and baseline stress hormone levels are predicted to be low and thus accumulate little damage, as the lack of repair means there is little scope to deal with long-term costs ensuing from high hormone levels. In organisms which have very high levels of repair, by contrast, the large quantities of damage that would potentially result from the very high baseline and peak hormone levels are immediately removed. When repair levels are intermediate, for example because there are some constraints on the rate of repair, we find that accumulating damage cannot be removed immediately, resulting in a pattern where damage is maximal for intermediate levels of repair. To our knowledge, such patterns have not been reported in empirical literature. Directly testing the effect of repair mechanisms on GC levels would require empirical manipulations of the capability or rate of repair, or studies using model organisms (e.g., transgenic) with different levels of repair. To our knowledge such experimental studies are not available, while there is an abundance of research manipulating GCs that measures the effects on repair (e.g., Flint et al., 2007; Forsberg et al., 2015; Jorgensen et al., 2013; see also examples in Table S1). However, there is some evidence from a unique study system in terrestrial garter snakes (*Thamnophis elegans*): this species expresses two distinct, genetically diverged life-history ecotypes, fast (short-lived) and slow (long-lived). The long-lived, slow phenotype expresses higher oxidative damage but also a higher rate of repair (Robert and Bronikowski, 2010), partially supporting our model outcomes.

Our model suggests that organisms that are adapted to strongly autocorrelated stressors are most likely to incur large amounts of damage from prolonged, chronic stressors (see Figs. 4 and S2), while organisms evolved in environments with weakly autocorrelated stressors should incur lower damage. This happens because those organisms in strongly autocorrelated environments have evolved to mount strong stress responses when faced with a stressor. Consequently, when—in a novel environment—those stressors occur repeatedly, damage rapidly accumulates beyond the point of repair. Once faced with large amounts of irreparable damage, organisms switch to a different strategy of high hormone level expression to at least limit stressor-induced mortality. Such predictions are relevant to populations of wild animals which are currently experiencing repeated or sustained chronic stressors from anthropogenic sources (e.g., disturbance by recreational activities, Arlettaz et al., 2007; anthropogenic noise, Wright et al., 2007). Stress responses have been extensively studied in urban and rural environments, yet empirical literature shows inconsistent patterns: baseline and stress-induced GCs can be higher, lower or show no differences among urban and rural populations (reviewed in Bonier, 2012, see Bókony et al., 2021; Iglesias-Carrasco et al., 2020; Kolonin et al., 2022; Lane et al., 2021, for recent studies). To our knowledge, autocorrelation of stressors in different rural environments, and their effects on the response to urban stressors, have not been studied, which limits our ability to discuss empirical results in this context. Yet, we may speculate that the varying responses across organisms in GCs to novel stressors in empirical data might be partly explained by the variation in autocorrelations in their original environment.

Our model also showed some unexpected patterns, one of which is the post-stressor drop in hormone levels below the pre-stressor baseline,

which then gradually increases back to 'normal' baseline levels. This post-stressor drop allows the organism to avoid accumulating further damage while the incurred damage is repaired. To our knowledge there are no empirical data supporting such a pattern, yet the limited sampling intervals (10–30 min) and short duration (max. 120 min) typically used after an acute stressor do not preclude the existence of such short-term effects. A potential explanation for the appearance of this pattern is that in our model, baseline levels per se are not directly linked to fitness, but only via their effects on damage accumulation. Empirical literature, however, reports direct effects of baseline GCs on fitness, though the direction of the association varies (reviewed in e.g., Bonier et al., 2009; Harris, 2020; Schoenle et al., 2021, 2018; Sorenson et al., 2017).

4.2. Model assumptions in the context of empirical evidence

Like any model, our approach makes several assumptions, all of which may influence the predictions and, in some cases, may lead to mismatches with empirical evidence. First, we assumed that survival costs from damage materialize on a longer time scale than survival costs of the stressor, due to the gradual accumulation of damage over time. There is empirical evidence that some forms of accumulated damage, for example to telomeres or the immune system, are associated with increased mortality and shorter lifespan, which provides some empirical support for this assumption (e.g., Razzoli et al., 2018). We acknowledge that damage can occur very rapidly (see Table S1 for examples), and for example neural damage could have short-term effects on cognition and physiological performance traits (He et al., 2008), yet the fitness consequences of these rapid changes are not understood in natural systems. For the sake of simplicity, we have focused here on survival and have not considered direct effects of mounting a stress response, damage and repair on reproduction. There is empirical evidence that stressors and GCs may impair reproduction (e.g., reviewed in Hau et al., 2016; Son et al., 2022; Wingfield and Sapolsky, 2003). How stress, damage and repair affect different fitness components should therefore be considered in future models.

Second, we assumed that repair occurs by the removal of a constant amount of damage each time step, similar to how repair is implemented in models of cellular aging (Ackermann et al., 2007). While valuable for initial insights about the interplay between damage and stress hormone levels, there is much broader variation in repair mechanisms. Rates of repair can vary across circumstances: for example, re-joining of DNA strand breaks occurs continuously but rates differ, with a half-life ranging from a few minutes to 4 h (Flint et al., 2007), depending, among other factors, on the availability of antioxidants (Torbergsen and Collins, 2000). Furthermore, our model does not consider costs of the repair mechanism, yet there can be energetic costs or micronutrient-related needs for the repair mechanisms to act (e.g., antioxidants, Fletcher et al., 2013; Ruuskanen et al., 2017). Therefore, the extent of repair may depend on the environmental context such as availability of resources, and this may in turn influence the stress response mounted, something our current model does not address, but can be investigated in further studies.

Third, our model considers both damage and repair to occur within a short time in an organism's lifespan, and reversal of damage can be complete. Empirical evidence suggests that full repair of some forms of damage can happen within hours, days or weeks (Table S1, e.g., Consiglio et al., 2010; Gormally et al., 2019; McEwen, 2008), supporting this assumption. Other types of damage are rather non-reversible (e.g., permanent effects on neural cells), which our model does not address (Conrad et al., 2007; Sousa et al., 1998).

Fourth, we assumed that stressor occurrence is likely to be temporally autocorrelated (see also assumptions in Taborsky et al., 2021). Most natural environments vary stochastically and, at some scale, are almost always spatiotemporally autocorrelated. For instance, time series on climatic variables are typically autocorrelated, in particular because of thermic inertia (Cotto and Chevin, 2020), and so also climatic stressors can be autocorrelated (Di Cecco and Gouhier, 2018). Empirical data are limited, however, on the pattern of autocorrelation in biotic stressors like predator exposure. Such data will be important for testing the model predictions, and for comparing different types of stressors (e.g., predators, considered here, versus social stressors as discussed in Box 1). Furthermore, in our model we assume that individuals only experience risk when directly 'attacked', yet many organisms can experience risk from indirect cues (for example predator odour, e.g., Dulude-de Broin et al., 2020) without directly being attacked. Such scenarios should be further modelled.

Fifth, the GC-damage association was modelled as a non-linear, U-shaped function (Eq. (1)), according to which damage increases when hormone levels fall below or rise above a certain damage-minimising value at h_θ.The association between GCs and survival in our model is more complex still and is highly non-linear, emerging from the state-dependent decisions that maximise expected future fitness through a combination of short-term and long-term effects. Conceptual models, such as the 'Reactive Scope model' (Romero et al., 2009), assume such non-linear patterns.

Finally, for the occurrence of chronic stress, we examined a scenario in which organisms adapted to sporadic, acute stressors suddenly encounter a prolonged, chronic stressor to which they are not adapted. In this scenario, organisms cannot anticipate the persistence of the chronic stressor and react to it in a suboptimal way specified by their evolved physiology (see Boonstra, 2013). Future theoretical studies should also consider evolutionary scenarios in which organisms are exposed to chronic stressors, in which case they should evolve chronic stress responses to cope with these stressors (Boonstra, 2013).

4.3. Model assumptions and results in the context of conceptual models

As mentioned briefly in the introduction, two key conceptual models to explain the relationships between stress responses, damage and fitness include the 'Reactive Scope model' by Romero et al. (2009, an extension of the allostasis model by McEwen and Wingfield, 2003) and the 'Damage-Fitness model' by Wada (2019). There are both similarities and differences in the assumptions and predictions of these models compared to our own computational evolutionary model. The Reactive Scope model posits that individuals normally express (1) 'predictive homeostasis', i.e., baseline variation in GCs (or similar mediators) within a season or day, and (2) 'reactive homeostasis', in which when confronted by a stressor the mediators are required to either maintain or return the body to homeostasis. The adaptive 'baseline' and 'peak' hormone levels predicted by our model in response to sporadic encounters with brief, acute stressors could be viewed as corresponding loosely to these concepts of predictive and reactive homeostasis, respectively, but with a firm theoretical foundation of evolutionary optimisation. Romero et al. (2009) emphasised that elevated levels of the mediators during reactive homeostasis result in costly 'wear and tear', which corresponds to the damage variable in our model. The Reactive Scope model also posits two other states: (3) homeostatic failure, which happens when mediators fall below predictive homeostasis; and (4) homeostatic overload, which happens when the concentration or level of the mediator extends beyond the normal reactive scope, or remains in the reactive homeostasis range for an extended period. Our model did not predict any situations in which organisms would fall into homeostatic failure, whereas the accumulation of excessive damage under the 'chronic stressor' scenario fits well with the concept of homeostasis overload. Our model made several simplifying assumptions, and there are several features of the Reactive Scope model that it does not address: for example, circannual/circadian variation in the baseline hormone level was not included, and there was no explicit mechanism through which excessive damage could lead to collapse of the hormone level and homeostatic failure (except at the point of death).

There are some key differences also in the assumptions and predictions of the Damage-Fitness model (Wada, 2019) compared to our

Box 1
The function of stress responses and damage from allostatic load: the case of social stress.

Social interactions and social life in hierarchies involve stress responses in various ways. When comparing different experimental test conditions in rats, social defeat and victory gave rise to stronger glucocorticoid responses than many other stressors (Koolhaas et al., 2011), indicating that social interactions can be a major stressor. For instance, in standardized exposures to a range of acute social and non-social stressors, social stressors elicited about twofold responses of GC production compared to the tested physical stressors with highest responses; however, also among different physical stressors, GC responses varied by a factor of six (Koolhaas et al., 1997a, 1997b).

The stability of a hierarchy is likely to influence stress responses (Creel et al., 2013), with the most intense competition for social positions occurring when dominance relations are first established, or when they change. At the same time, relative social rank may be a feature of the environment that has higher autocorrelation, and is hence a more predictable potential stressor, than abiotic factors such as rainfall (Frankenhuis et al., 2019). Whether the excretion of GCs correlates with a dominant or subordinate rank varies within and across species and depends, among other things, on sex (Cavigelli and Caruso, 2015). A widespread assumption is that there is a positive relation between GC concentrations and the allostatic load from conflict and competition (Goymann and Wingfield, 2004). If this is the case, data on GC concentrations could indicate damage both from allostatic load, for instance from overt aggression in social interactions, and from the physiological effects of GCs per se.

The social environment might be one of the most important influences on health and lifespan in animals, including in humans (Snyder-Mackler et al., 2020). There are a number of studies on the effects of social stress on lifespan. For instance, stress in the form of aggression was found to shorten lifespan in subordinate male mice (Razzoli et al., 2018). In female baboons, there was a negative relation between GC concentration and lifespan, and top-ranking females tended to have lower concentrations (Campos et al., 2021). There can also be sex differences in the social-rank related effects of stress on lifespan. An accelerated epigenetic aging was found in male baboons of high social status, which could at least partly be explained by GC concentrations (Anderson et al., 2021). Similar sex differences might be present in chimpanzees, where GC concentrations were positively associated with male rank (Muller et al., 2021), whereas a negative or no association was found in females (Emery Thompson et al., 2020, 2010). Muller et al. (2021) also found that hierarchy instability contributed to social stress.

Such studies, some of which analyze long-term data from wild populations, indicate that social stress is qualitatively similar to other kinds of stress in giving rise to damage with consequences for health and longevity. Nevertheless, one should keep in mind that stress hormones play an important role in the dynamics of social dominance, both in how differently ranked individuals respond to stress from social defeat (Larrieu et al., 2017) and in how rank is attained (Papilloud et al., 2020). Thus, social stress provides one of the most thoroughly studied examples of the long-term consequences of stress, but at the same time social stress has special properties that could be of interest for the understanding of social hierarchies.

model. Wada's (2019) Damage-Fitness model assumes that dysregulation of physiological systems results from the accumulation of persistent damage, which directly impacts fitness-related measures. This can happen when (1) anti-damage regulators are not sufficient to avoid damage, (2) there are excessive levels of anti-damage regulators, which themselves cause damage, (3) damage cannot be repaired or removed, or (4) damage results from normal molecular and cellular activities with age. Processes (1) and (3) fit well with our theoretical assumptions, as insufficient repair in our model leads to damage and this has fitness consequences when it is not repaired. By contrast, processes (2) and (4) were not represented in our model, as we did not include the possibility of damage from repair or from normal aging-related cellular activities. Also, in Wada's model, adrenocortical responses are all considered to be a part of the anti-damage regulators, whereas in our model we considered GCs as key modulators, and repair mechanisms separate to them. Wada's conceptual model also considered how the developmental environment influences anti-damage regulators, while our model concentrated on adult, reproducing individuals. Another key difference of our theoretical model from both the Reactive Scope and Damage-Fitness models is that we explicitly modelled patterns of autocorrelation and the level of risk, as well as acute and chronic stressors. In the Reactive Scope model, the influence of medium and strong stressors on the outcome of homeostatic overload is qualitatively discussed (Romero et al., 2009), but not quantitatively tested.

4.4. Ecological modulators of damage and repair

4.4.1. Type of stressor

The magnitude of stress responses changes with the type of stressor, its intensity, frequency and duration (see Fig. 1 in Koolhaas et al., 2011), which should influence the amount of ensuing damage in the respective targets of stress (different cells, tissues and organs) and may result in different rates of repair in these targets. In our models (this study and Taborsky et al., 2021), we have varied the persistence of stressors (acute vs. chronic), but further systematic theoretical explorations of the importance of stressor type, strength and temporal dynamics are warranted. An important example is social stress (Box 1), for which there are both similarities with and differences from the kinds of stressors dealt with in our model. For example, in terms of autocorrelation of the stressor, social features of the environment (such as group size, or relative rank) may be more predictable across the life course than abiotic factors such as rainfall (Frankenhuis et al., 2019). It would be of interest to develop evolutionary models of how social stress depends on social parameters such as the rank position in a social hierarchy, but for this to succeed more information on the role played by, e.g., GC responses in the dynamics of social hierarchies (Box 1) is needed.

4.4.2. Life-history and environmental conditions

There are only a few empirical examples that study whether damage and repair vary with organisms' lifehistory and environmental quality, providing ample demand for future evolutionary models considering varying reproductive season length and longevity or levels of environmental harshness. For instance, it could be modelled how GC levels depend on lifetime opportunities to reproduce, as two recent comparative studies revealed that GC baseline was higher and stressor-induced levels lower in organisms with fewer opportunities to reproduce and higher brood value (Bókony et al., 2009; Vitousek et al., 2019). In general, we expect there to be strong impacts of life history on adaptive stress responses. In seasonal breeders, we might expect the stress response to change as the reproductive season approaches. Similarly, we might expect the lifespan of an organism to affect the stress response. For example, long-lived species should be very sensitive to damage that increases mortality, but less sensitive to missing a single reproductive bout.

Genetic mechanisms of evolutionary adaptations to stressful environmental conditions could be considered in future models. Such

mechanisms could involve direct genetic changes: selective sweep analysis revealed a number of adaptive mutations related to stress responses, oxidative stress and DNA damage repair in East African fat-tail sheep (a type of domestic sheep, *Ovis aries*) adapted to arid environments, compared to sheep subspecies living in more temperate environments (Mwacharo et al., 2017). Another mechanism is through changes in gene regulation. Such changes helped wild populations of yellow-bellied marmots, *Marmota flaviventer*, to cope with chronic exposure to predator presence, which led to an upregulation of genes regulating heat shock proteins, metabolism and DNA damage repair (Armenta et al., 2019).

4.5. Concluding remarks

Here we have presented the results of an evolutionary model, predicting higher optimal baseline and stress-induced hormone levels in response to acute and chronic stressors when stressor occurrence is temporally autocorrelated, resulting in higher levels of damage caused by hormones. When comparing different efficiencies of repairing this damage, our model further predicts that increasing the rate of repair should lead to higher hormone levels, as repair allows for the removal of damage resulting from high hormone levels. While many studies have compared variation in baseline and stress-induced hormone levels in wild populations in relation to their ecology, life history and fitness, there is an unfortunate lack of empirical research on the ecology of damage induced by stressors and by stress responses, and the repair of this damage. Nevertheless, several biomedical studies highlight that damage and repair do affect health and survival (Table S1). Therefore, beyond measuring the stress response itself, it is important to measure the extent and timescales of stress-induced damage, its fitness consequences, and its repair possibilities, both in the short and long term in the wild. This is obviously challenging, particularly in long-lived systems and under field conditions, and depends on the possibility to obtain time-series measurements of individuals or populations. We hope that the predictions derived from our model stimulate this kind of empirical research. Equally important, our simplistic model showcases the challenges faced by such evolutionary modelling, when attempting to incorporate precise, mechanistic details of stress physiology. Therefore, our study will hopefully spawn further modelling work that accounts for more realistic details of the environment and the mechanisms of stress responses, damage and repair.

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Appendix A. Supplementary data

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