The circadian rhythms of cortisol: Modelling their role in regulating homeostasis and personalized resilience and adaptation

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Abstract: The hypothalamic-pituitary-adrenal (HPA) axis orchestrates the physiological response stress. Moreover, the HPA axis exhibits prominent circadian activity and synchronizes peripheral circadian clocks to daily environmental cycles, thereby promoting homeostasis. Persistent disruption of homeostatic glucocorticoid circadian rhythmicity due to chronic stress exposure is correlated with the incidence of various pathological conditions including depression, diabetes and cancer. Allostatic habituation of the HPA axis can therefore confer fitness advantages by preventing the sustained dysregulation of glucocorticoid-responsive signaling pathways. However, such allostatic adaptation results in a physiological cost (allostatic load) that might impair the homeostatic stress-responsive and synchronizing functions of the HPA axis. We use mathematical modeling to characterize specific chronic stress-induced allostatic adaptations in the HPA network. We predict the existence of multiple personalized regulatory strategies enabling the maintenance of homeostatic glucocorticoid rhythms, while allowing for flexible HPA response characteristics. We show that this regulatory variability produces a trade-off between the stress-responsive and time-keeping properties of the HPA axis. Finally, allostatic regulatory adaptations are predicted to cause a time-of-day dependent sensitization of the acute stress response and impair the entrainability of the HPA axis

Keywords: biomedical systems, adaptation, circadian rhythms, cortisol, robustness, resilience

1. INTRODUCTION

The hypothalamic-pituitary-adrenal (HPA) axis coordinates the internal physiological environment, through an intricate network of glucocorticoid (GC)-sensitive pathways, enabling the host to anticipate predictable and unpredictable changes (Chrousos and Gold 1992). The HPA axis is a central player driving the release of glucocorticoids (GCs) which are critical for maintaining homeostasis (Dick, Molkov et al. 2012). GCs exhibit circadian rhythmicity (24hr periodic activity) which peaks right before the start of the active phase (Mavroudis, Scheff et al. 2013). Circadian glucocorticoid rhythms are critical for the host to optimize its behavior in anticipation of periodic changes, most notably the daily variability in light, temperature, food as well as diverse environmental stressors (Chrousos 2009, Riede, van der Vinne et al. 2017). Therefore, circadian GC rhythms play a critical role in synchronizing physiology to the environment (Oster, Challet et al. 2017). In response to acute stress, GCs (leading among them being cortisol) transiently deviate from homeostatic circadian levels. However, chronic deviation of glucocorticoids from their homeostatic levels through prolonged activation results in a physiological cost (known as *allostatic load*) and is associated with long-term detrimental outcomes (Karatsoreos and McEwen 2011). Adaptation of the HPA axis, such that GCs

maintain homeostatic levels under chronic stress provides the host with fitness advantages by optimizing distribution of resources and minimizing persistent downstream dysregulation (Peters and McEwen 2015). However, successful adaptation requires the engagement of allostatic regulatory mechanisms, which in turn place a high burden on homeostatic regulatory mechanisms. This burden (allostatic load) can impact the functioning of physiological systems, altering their response to subsequent acute stressors.

Given the complexity of the response, mathematical modeling has provided tremendous insight, regarding the importance of chronic stress habituation and individual variability, using biochemical models of the HPA axis (Stanojević, Marković et al. 2018). Recent results advocate that allostatic habituation to chronic stress drives alterations in the feedback regulatory mechanisms of the HPA network (Rao and Androulakis 2017). It was hypothesized that that despite the ability of the system to return to pre-stress circadian rhythmic dynamics, the resulting allostatic habituation sensitized the response of the system to a subsequent acute stressor. In turn this predicted response was indicative of the detrimental effects of the accumulation of allostatic load. The model-predicted chronic stress sensitization upon allostatic habituation has been established in physiological systems (Karatsoreos and McEwen 2011, Barboza Solís, Kelly-Irving

et al. 2015). Computational analyses enabled us to further demonstrate that individuals with high pre-stress adrenal sensitivity were more likely to exhibit chronic stress sensitization upon habituation. Such a personalized characterization of the regulatory dynamics of the HPA axis demonstrated a fascinating balance between the two fundamental activities of the HPA axis; robustness of the circadian time-keeping mechanism *versus* its flexibly to adapt to stress (Rao and Androulakis 2019). In this manuscript we will describe in some detail some of the ideas in order to demonstrate how mathematical modeling and computation can substantially improve our understanding the role HPA circadian rhythms play in regulating personalized adaptation and resilience to stress.

2. REPRESENTATION OF THE HPA AXIS

A skeletal network describing the release of *cortisol* (corticosterone in nocturnal animals, CORT) posits that the hypothalamus releases the *corticotropin release hormone* (CRH), which induces the release of *adrenocorticotropic hormone* (ACTH) from the anterio-pituitary, eventually driving the release of cortisol from the adrenal cortex (Fig. 1). In the discussion that follows, the model was calibrated to experimental CORT circadian rhythms from female Lewis rats (Atkinson and Waddell 1997). However, the model can also be calibrated to human data (Pierre, Schlesinger et al. 2017, Bae and Androulakis 2018, Pierre, Rao et al. 2018). While endogenous glucocorticoid levels also exhibit prominent pulsatile ultradian rhythms, for simplicity, we only model the lower frequency glucocorticoid circadian rhythmicity.The kinetics of the system are described by equations (1-7). Specifically, the synthesis of CRH is described by zero-order kinetics (K_{P1}), while the synthesis of ACTH and CORT is described by first-order kinetics k_{p2}, k_{p3} respectively). The degradation terms follow Michaelis-Menten kinetics while CRH, ACTH and CORT undergo enzymatic metabolism and degradation (Kalsbeek, van der Spek et al. 2012). The model builds on our earlier work (Mavroudis, Corbett et al. 2014, Rao, DuBois et al. 2016). Since CORT will exert its negative feedback, a critical component in generating sustained oscillation of CORT secretion rhythms, the glucocorticoid receptor (GR)-mediated pharmacodynamics is based on the works of (Ramakrishnan, DuBois et al. 2002).

The binding of released CORT to cytosolic GR is modeled using second-order kinetics. This binding leads to the formation of the receptor-glucocorticoid complex (DR), while DR(N) represents the nuclear activated receptor-glucocorticoid complex. It is the latter that drives the receptor-mediated effects of glucocorticoids, leading to the receptor mediated inhibition of CRH and ACTH accounting for the negative feedback loop of the HPA axis. DR(N) also negatively regulates its own transcription, GR mRNA. The inhibition constants K_{p1}, K_{p2} reflect the strength of inhibition in the negative feedback loop, with smaller values indicative of stronger negative feedback. The HPA axis is not just an autonomous oscillator, but also an entrainable oscillator. A major entrainer of the HPA axis is light, through the exertion of an inhibitory influence on CRH production in nocturnal animals (Kalsbeek, Fliers et al. 2010). Therefore, we assume that light mediates its inhibitory influence by inducing the

degradation of CRH. For the purpose of this discussion, the lumped effects of light on the HPA axis are captured by the composite term [light effect]. Detailed presentation and discussion of the model can be found at (Rao and Androulakis 2019), whereas the light entrainment was originally discussed in (Mavroudis, Corbett et al. 2014).
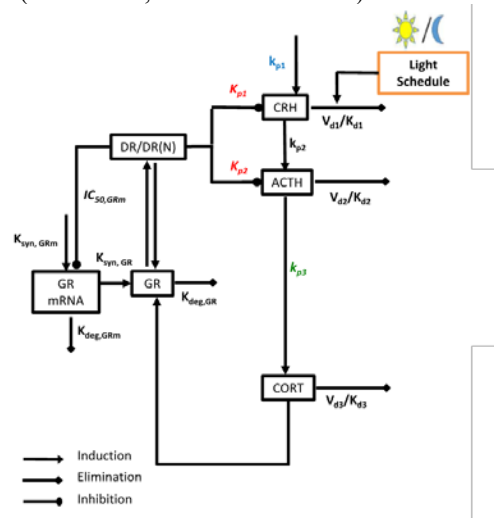

Fig. 1. *Basic structure of the HPA axis network. The feedforward adrenal sensitivity, k_{p3} the hypothalamic negative feedback (K_{p1}) and pituitary negative feedback (K_{p2}) represent the key regulators the system.*

3. HPA ADAPTATION TO CHRONIC STRESS: ALLOSTATIC LOAD

Robust oscillations of the HPA axis result in the periodic release of cortisol (corticosterone). This endocrine hormone in turn, regulates numerous physiological and biochemical processes. In response to stress, the HPA axis is transiently activated increasing the release of cortisol/corticosterone (Ranabir and Reetu 2011). These increases, and subsequent decreases, should be considered on top of the temporal variation of the hormone level during the day (McEwen 2019). Moreover, a further layer of complexity must be considered as within these homeostatic bounds, CORT rhythms exhibit substantial intra-individual and inter-individual variability. Thus, we further accounted for this homeostatic variability in the regulatory processes of the HPA axis in our mathematical model. In doing so, we assume that the critical system parameters, the feedforward adrenal sensitivity (k_{p3}) the hypothalamic negative feedback (K_{p1}) and pituitary negative feedback (K_{P2}) in the HPA network also define the regulatory variability in its homeostatic activity while also adjusting in a compensatory manner to conserve the CORT circadian phenotype within reasonable physiological bounds (represented by the nominal parametric subspace in Fig. 2).

Persistently elevated levels of cortisol upon exposure to chronic stress, often manifest not just as elevation of levels but also as diminished amplitude of oscillations, leads to adverse effects not only because the levels are increased, but rather because in the presence of stress, the HPA system adapts in order to maintain cortisol levels within the homeostatic range without resolving the underlying driver of stress thus, leading to the accumulation of allostatic load (McEwen 1998).

Therefore, the regulatory plasticity, as expressed through the parameters K_{p1}, K_{p2}, k_{p3} enables the feedback regulation to modulate itself in such a way so as to maintain physiological levels of cortisol, allowing us to model the regulatory adaptation of the system upon habituation to chronic stress.

$$\frac{dCRH}{dt} = \frac{k_{p1} \cdot K_{p1}}{k_{p1} + DR(N)} - V_{d1} \frac{CRH \cdot \left(1 + \frac{light_{effect}}{1 + light_{effect}}\right)}{K_{d1} + CRH} \quad (1)$$

$$\frac{dACTH}{dt} = \frac{k_{p2} \cdot K_{p2} \cdot CRH}{K_{p2} + DR(N)} - V_{d2} \cdot \frac{ACTH}{K_{d2} + ACTH} \quad (2)$$

$$\frac{dCORT}{dt} = k_{p3} \cdot ACTH - V_{d3} \cdot \frac{CORT}{K_{d3} + CORT} \quad (3)$$

$$\frac{dGR_{mRNA}}{dt} = k_{synGRm} \cdot \left(1 - \frac{DR(N)}{IC_{50GRm} + DR(N)}\right) - k_{deg} \cdot GR_{mRNA} \quad (4)$$

$$\frac{dGR}{dt} = k_{synGR} \cdot GR_{mRNA} + r_f \cdot k_{re} \cdot DR(N) - k_{on} \cdot CORT \cdot GR - k_{degGR} \cdot GR \quad (5)$$

$$\frac{DR}{dt} = k_{on} \cdot CORT \cdot GR - k_T \cdot DR \quad (6)$$

$$\frac{DR(N)}{dt} = k_T \cdot DR - r_f \cdot k_{re} \cdot DR(N) \quad (7)$$

To simulate chronic stress, we assumed a persistently overactive hypothalamus as suggested by Sriram et al. (Sriram, Rodriguez-Fernandez et al. 2012) thus, increasing the baseline of the parameter k_{p1} (see Fig. 1), which emulates a chronic increase in the CRH drive to the HPA axis as a result of chronic stress. Following this, we resample the three parameters, K_{p1}, K_{p2}, k_{p3}, which define the nominal parametric subspace, such that the corticosterone profiles generated by the resampled parameters in the chronically stressed state also satisfy the error criteria ($\pm$ 1 S.D. of CORT measurements) with respect to the homeostatic experimental corticosterone profiles from Atkinson & Wadell. However, for conceptual and computational simplicity, we assume that only the three parameters hypothesized to account for regulatory variability, representing important feedback and feedforward processes, are involved in allostatic adaptation. This procedure was carried out for three different values of k_{p1}, representing the "nominal", "intermediate" and "high" level of chronic stress. Model simulations indicate that homeostatic glucocorticoid rhythms (Rao and Androulakis 2017) are attained within a well-defined regions of parameter values (Fig. 2). Furthermore, the adrenal responsiveness and negative feedback processes are predicted to vary in an interdependent manner, such that changes in adrenal sensitivity (k_{p3}) are compensated for by adjustments in the strength of negative feedback (K_{p1}) in order to maintain the homeostatic circadian patterns of glucocorticoid activity. Therefore, we determine that the system exploits its parametric plasticity to develop resilience by adjusting the relative strengths of the feedforward and feedback processes of the HPA axis in a way that conserves phenotypic similarity and maintain homeostasis. It is hypothesized that such regulatory plasticity in the feedforward and feedback mechanisms of HPA axis might be biochemically mediated through the generation of alternative splice variants of the GR (Ramamoorthy and Cidlowski 2013), dynamic regulation of steroidogenic acute regulatory protein (StAR) or neuronal and sympathetic mechanisms (Spiga, Walker et al. 2015).

Upon adaptation to chronic stress the accessible parameter space (surfaces indicated in Fig. 2) allostatically adapts to increasing levels of chronic stress such that the system maintains homeostatic corticosterone rhythms. The adaptation as manifested by the redistribution of the parameter space results in a decrease in the area of the surfaces with increasing chronic levels of chronic stress, implying a decrease in the underlying regulatory flexibility of the system (surfaces become smaller as they move to the left in Fig. 2). Therefore, the "price" the system needs to pay to maintain homeostasis (i.e., its allostatic load) is the loss of regulatory plasticity.
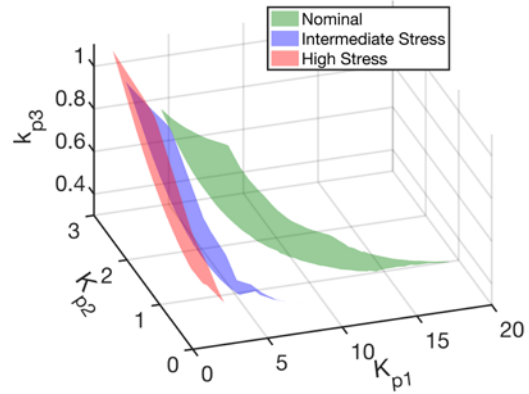

Fig. 2. *Basic structure of the HPA axis network. The feedforward adrenal sensitivity (k_{p3}), the hypothalamic negative feedback (K_{p1}) and pituitary negative feedback (K_{p2}) represent the key regulators the system.*

4. TRADE-OFFS: ADAPTATION *versus* ROBUSTNESS

Circadian oscillations have been shown to endow physiological systems with the ability to adapt and respond to expected and unexpected variations of the external environment. Having established the broad characteristics of a diversified population with the ability to produce the same circadian phenotype, we assessed whether the genetic plasticity, which results in phenotypic similarity, impacted the ability of the individuals to accommodate external perturbations in an individualized manner.

We hypothesized that the regulatory diversity will impact the tendency of the system to adapt to changes in external (environmental) characteristics. This can be especially important, given that the circadian dynamics of the HPA axis function as an important physiological cue to which numerous glucocorticoid-sensitive signaling elements are aligned in a time-of-day dependent manner. Such a property must be evolutionarily finely tuned as on the one hand, flexibility in entrainment characteristics might enable the system to adequately adapt to changes in external signals, while over-responsiveness might compromise the time-keeping properties of the oscillator by making it too sensitive to noisy environmental stimuli. Therefore, we measured the tendency of the system to adapt as its ability to be entrained by an external oscillating signals (zeitgeber). Interestingly, we predict that the higher the adrenal sensitivity the larger the domain of entrainment as expressed in the form of Arnold tongues (Fig. 3, bottom), that is the greater its flexibility in adaptation to changing environments (indicated as we trace the

three point of Fig. 3, Top, from the highest to the lowest). We, therefore, conclude that individuals with higher adrenal sensitivity are more flexibly entrained to changes in the zeitgeber frequency.
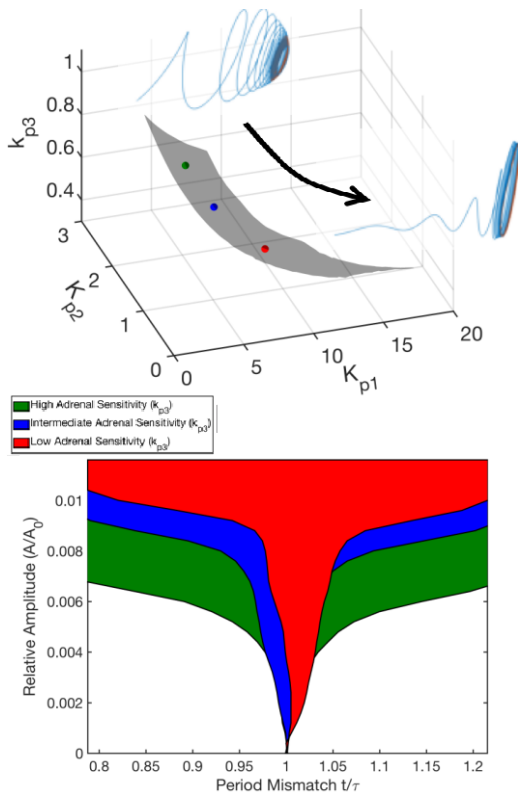

Fig. 3. *Relaxation times (top) and domain of entrainment (bottom) with decreasing adrenal sensitivity [green: high adrenal sensitivity, blue: moderate adrenal sensitivity, red: low adrenal sensitivity].*

On the other hand, the ability of the system to withstand acute perturbations increases with decreasing adrenal sensitivity as depicted qualitatively by the rapid return of the system to the stable homeostatic oscillatory solution after an acute perturbation (Fig 3., Top) – formally quantified via the calculation of the corresponding Floquet exponents, representative of the amplitude stability of the oscillatory system (Rao and Androulakis 2019). Therefore, individuals that more easily adapt to permanent changes in environment appear to take longer to recover from acute perturbations. Hence, we observe that regulatory or genotypic variability despite the fact that it endowed the population with phenotypic similarity, does so in a way that introduces a significant trade-off between the ability to adapt to chronic changes and respond to acute perturbations. Interestingly, our model predicts that chronic stress will not only reduce the regulatory plasticity (Fig. 2), but further predicts that even for similar strengths of adrenal sensitivity (k_{p3}) the ability of the system to be entrained, i.e., to adapt to a new environment, is reduced (Fig 4). Thus, the ensuing allostatic habituation makes it harder for stressed individuals to adapt to fluctuations in zeitgeber frequencies, despite having maintained homeostatic levels of HPA activity. Therefore, the allostatic load resulting from the host's preference to maintain homeostatic acute stress

responsive characteristics (adrenal sensitivity), results in the system adapting its regulatory characteristics in a way that eventually diminishes its long-term ability to adapt.
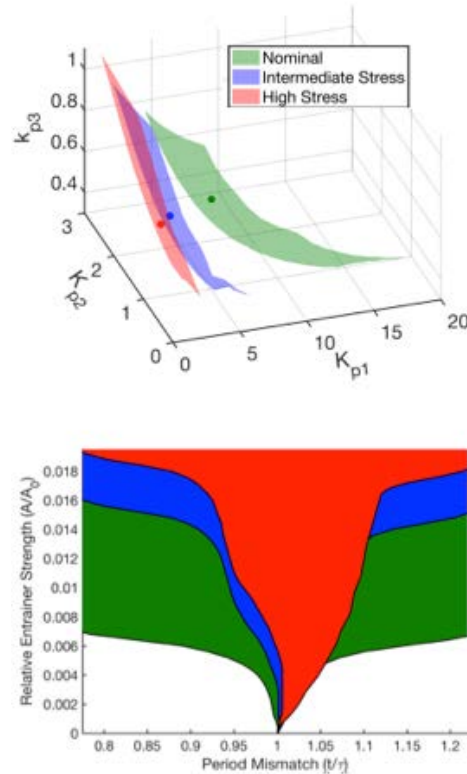

Fig. 4. *The domain of entrainment decreases with increasing levels of chronic stress when comparing parameter sets at the same level of adrenal sensitivity [green: nominal, blue: intermediate chronic stress, red: high chronic stress].*

5. PERSONALIZED ADAPTATION AND RESPONSE

In order to better characterize the implications of the regulatory adaptation and the associated accumulation of allostatic load on the functional properties of the HPA network, we studied its response to an acute stressor subsequent to simulated chronic stress induced allostatic habituation. The acute stressor was simulated by transiently increasing CRH synthesis resulting in a corresponding temporary increase in CRH levels, as is experimentally observed upon exposure to an acute HPA axis stimulant, such as bacterial lipopolysaccharide (Fonken, Weber et al. 2016). The acute stress response of the HPA axis is quantified as the change in the area under the curve (AUC) of CORT over a 4h period following exposure to the simulated acute stressor relative to the nominal CORT rhythm (Fekedulegn, Andrew et al. 2007). Interestingly, model simulations predict that the stress response to a secondary acute stressor is altered in a time-of-day dependent manner upon allostatic habituation to chronic stress. More specifically, the simulated chronic stress induced allostatic regulatory adaptation, results in an amplified acute stress response relative to the nominal homeostatic state when exposure to the stressor occurs towards the middle of the inactive phase. Furthermore, in order to characterize

individual differences in acute stress response we used a method of symbolic representation developed by Lin et al. to semi-quantitatively partition acute stress response in the nominal and chronic stress-habituated states (Lin, Keogh et al. 2003). The symbolic representation of the difference in AUC, referred to as the symbolic difference in AUC, is depicted in Fig. 5. In the absence of chronic stress exposure (nominal case), as expected, individuals with higher adrenal sensitivity tend to have a more robust acute stress response. Subsequently, we hypothesized that chronic stress habituation would alter how simulated individuals with the same level of adrenal sensitivity would respond to a secondary acute stressor administered during the inactive phase. We find that the chronic stress habituation is predicted to sensitize the acute stress response in the inactive phase, such that subjects with identical levels of adrenal sensitivity exhibit a more pronounced acute stress response upon chronic stress habituation. This sensitization of the acute stress response of the HPA axis potentially causes pathological overexposure of downstream glucocorticoid-sensitive signaling pathways to endogenous glucocorticoids. Such chronic stress-induced sensitization of the acute stress response has been repeatedly observed experimentally and is thought to be associated with the incidence of chronic stress associated physiological dysregulation (Herman, McKlveen et al. 2016).

6. CONCLUSIONS

Circadian rhythms likely express an evolutionary conserved mechanism of adaptation. In the work that was presented in this paper, we demonstrated how mathematical modeling enabled us to decipher some of the complexities of the circadian dynamics of the HPA axis. We argue that the existence of a trade-off between the ability of the HPA axis to respond to stress and its ability to be robust in a noisy environment. We emphasized the implications of allostatic regulatory adaptations while the system acclimates to conditions of chronic stress that influence the response and entrainment properties of the HPA. We hypothesize that the genotypic plasticity in response to allostatic habituation to chronic stress forces the system to compromise either its entrainment characteristics (adaptation) or its responsiveness (robustness) to external stimuli, or in many cases both. Furthermore, we established individual differences in the susceptibility to allostatic load accumulation. Interestingly, we predict that individuals with greater adrenal sensitivity, manifest a greater sensitization of the acute stress response upon allostatic habituation to a chronic stressor, and thus might be more susceptible to the incidence of chronic stress disorders. This type of insight could have profound implications in our efforts to better understand the regulatory characteristics of complex physiological systems and their likely implications in the context of health and disease. Furthermore, while we have not explicitly considered the implications for circadian control in this work; we envision that an understanding of individual variability in the regulatory dynamics of the HPA axis can motivate personalized approaches for manipulating glucocorticoid and other physiological circadian rhythms by applying approaches from optimal control. An important limitation of the current work is that we do not explicitly account for the ultradian dynamics of

glucocorticoids in our model. Moreover, we assume that circadian rhythms of the HPA axis are endogenous and do not separately account for the influence of the SCN and peripheral circadian clocks. While there has been some disagreement about whether the ultradian and circadian rhythms of the HPA axis are endogenous in nature, recent evidence shows that the peripheral adrenal clock can to some extent generate circadian glucocorticoid rhythms after disconnection from the SCN (Oster, Challet et al. 2017).
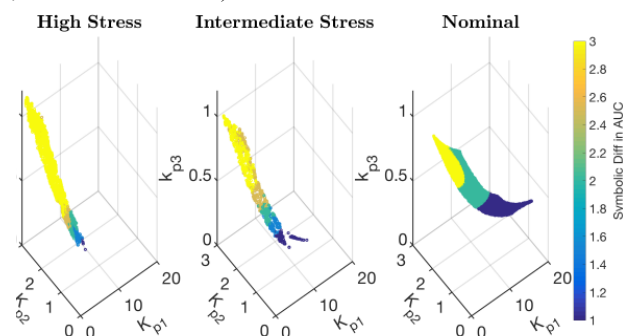

Fig. 5. *Sensitization of the stress response upon habituation to chronic stress, with individuals with higher adrenal sensitivity more likely to exhibit stress sensitization as indicated by the increase in the proportion of parameters exhibiting the most robust acute stress response.*

Moreover, glucocorticoids have been shown to have complex feedback effects on both peripheral clocks (including the adrenal peripheral clock) and central circadian clocks, thus adding further complexity to the circadian dynamics of glucocorticoids (Pezuk, Mohawk et al. 2012). In future versions of the model, we will incorporate the separate influences of the peripheral and central circadian clocks on the generation of circadian rhythms of the glucocorticoids. Nonetheless, many of the relevant properties of glucocorticoid rhythms such as the observed temporal dependence of the stress response, amplitude and entrainment dynamics can be explained using limit cycle oscillators as model systems (Sriram, Rodriguez-Fernandez et al. 2012, Stanojević, Marković et al. 2018) and many of our results are preserved even after separately accounting for these influences.

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