Timing and bistability in the hypothalamic-pituitary-adrenal axis: a model for onset and exposure therapy of stress disorders

Lae Un Kim [*], **Maria D'Orsogna** [†], **Tom Chou** [‡]

[*]Department of Biomathematics, UCLA, Los Angeles, CA 90095-1766,[†]Department of Mathematics, CalState-Northridge, Los Angeles, CA 91330, and [‡]Departments of Biomathematics and Mathematics, UCLA, Los Angeles, CA 90095-1766

Submitted to Proceedings of the National Academy of Sciences of the United States of America

The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine system that regulates numerous physiological processes. This regulation is mediated by the inhibition of peptide hormones such as corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) by circulating glucocorticoids such as cortisol (CORT). Disruptions in the activity of the HPA axis are correlated with many stress-related diseases such as post-traumatic stress disorder (PTSD) and major depressive disorder. In this paper, we hypothesize that normal and diseased states can be characterized in terms of different basins of attraction of a dynamical system. Our model distinguishes two components of negative feedback by cortisol on circulating CRH levels: a slow direct suppression of CRH synthesis and a fast indirect effect on CRH release. Key physiological features such as ultradian oscillations, CRH self-upregulation of CRH release, and external stressors are also incorporated. We show how these key ingredients in our model can yield two stable limit cycles which we associate with normal and diseased states. Transitions between the two can be induced by applying acute external stressors of appropriate intensity and duration. The occurrence of a transition is highly dependent upon the initiation time of external stress relative to the phase of the intrinsic ultradian oscillation. Our results suggest that the timing of traumatic events may be an important factor in determining if and how patients will exhibit hallmarks of PTSD.

HPA-axis | PTSD | Stress Disorders | Dynamical system

Stress is an essential component of an organism's attempt to adjust its internal state in response to environmental change. The experience, or even the perception of physical and/or environmental change, induces stress responses such as the secretion of glucocorticoids hormones (CORT) – cortisol in humans and corticosterone in rodents – by the adrenal gland. The adrenal gland is one component of the hypothalamic-pituitary-adrenal (HPA) "axis," a group of interacting endocrine glands that play a central role in stress response.

The basic interactions involving the HPA axis are shown in Fig. 1. The paraventricular nucleus (PVN) of the hypothalamus receives synaptic inputs from various neural pathways via the central nervous system that are activated by both cognitive and physical stressors. Once stimulated, CRH neurons in the PVN secrete corticotropin-releasing hormone (CRH), which then stimulates the anterior pituitary gland to release adrenocorticotropin hormone (ACTH) into the bloodstream. ACTH then activates a complex signaling cascade in the adrenal cortex, which ultimately releases glucocorticoids (Fig. 1B). In return, glucocorticoids exert a negative feedback on the hypothalamus and pituitary, suppressing CRH and ACTH release and synthesis in an effort to return them to baseline levels. Classic stress responses include transient increases in levels of CRH, ACTH, and cortisol. The basic components and organization of the vertebrate neuroendocrine stress axis arose early in evolution and the HPA axis, in particular, has been conserved across mammals [1].

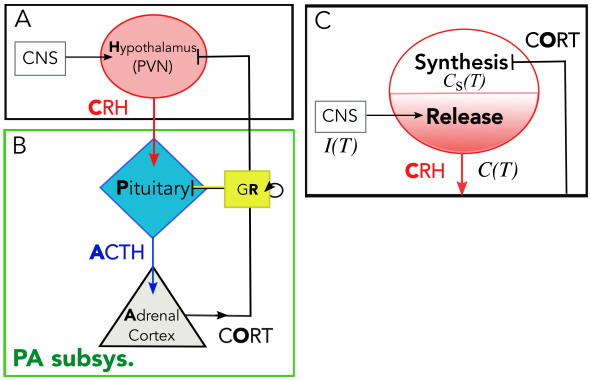

Fig. 1. Schematic of HPA axis. (A) Stress is processed in the central nervous system (CNS) and a signal is relayed to the PVN in the hypothalamus to activate CRH secretion into the hypophyseal portal system. (B) CRH diffuses to the pituitary gland and activate ACTH secretion. ACTH travels down to the adrenal cortex to activate cortisol (CORT) release. Cortisol inhibits both CRH and ACTH secretion to down-regulate its own production, forming a closed loop. In the pituitary gland, cortisol binds to glucocorticoid receptors (GR) (yellow box) to inhibit ACTH and self-upregulate GR production. This part of the axis comprises the PA subsystem. (C) Negative feedback of cortisol affects the synthesis process in the hypothalamus, which indirectly suppresses the release of CRH. External inputs such as stressors and circadian inputs directly affect the release rate of the CRH.

Significance

While correlations between HPA-axis dysregulation and psychological stress disorders such as PTSD are known, to date, there is little mechanistic understanding of how stress response can cause altered activity of the HPA axis. By separating the synthesis and release processes in CRH neurons in the hypothalamus and by incorporating a delayed response in the adrenal cortex, we model the HPA axis as an excitable system with alternate stable oscillating "normal" and "diseased" states. Transitions between the two oscillating states can be induced by external stress of sufficiently long duration. Our mechanistic hypotheses provide insight into how stress response can alter HPA axis dynamics and how re-exposure to stress can restore normal HPA activity.

Reserved for Publication Footnotes

Mathematical models of the HPA axis have been previously formulated in terms of dynamical systems of ordinary differential equations (ODEs) [2, 3, 4, 5] or delay differential equations (DDEs) [6, 7, 8] that describe the time-evolution of the key regulating hormones of the HPA axis: CRH, ACTH, and cortisol. These mathematical models [6, 7, 9] include the description of positive self-regulation of glucocorticoid receptor expression in the pituitary, which may generate bistability in the dynamical structure of the model [10]. Of the two stable equilibrium states, one is characterized by higher levels of cortisol and is identified as the "normal" state. The other is characterized by lower levels of cortisol and can be interpreted as one of the "diseased" states associated with hypocortisolism, as mentioned above. Stresses that affect the activity of neurons in the PVN are described as perturbations to endogenous CRH secretion activity. Depending on the length and magnitude of the stress input, the system may or may not shift from the basin of attraction of the normal steady state towards that of the diseased one. If such a transition does occur, it may be interpreted as the onset of disease. A later model [9] describes the effect of stress on the HPA axis as a gradual change in the parameter values representing the maximum rate of CRH production and the strength of the negative feedback activity of cortisol. Here, changes in cortisol levels are assumed to arise from anatomical changes in the HPA axis.

Both classes of models imply qualitatively different time courses of disease progression [10, 9]. The former suggests that the abnormal state is a pre-existing basin of attraction of a dynamical model that stays dormant until a sudden transition is triggered by exposure to trauma [10]. In contrast, the latter assumes that the abnormal state is reached by the slow development of structural changes in physiology due to the traumatic experience [9]. Although both models [10, 9] describe changes in hormonal levels experienced by PTSD patients, they both fail to exhibit stable ultradian oscillations in cortisol, which, as we shall see, play an essential role in coupling HPA axis dynamics to external stress inputs.

In this study, we will demonstrate the functional importance of a number of distinctive physiological features of the HPA axis that have not been previously considered in mathematical models. These include, for example, the effects of intrinsic ultradian oscillations on HPA dysregulation, distinct fast and slow feedback mechanisms, and the correlation between HPA imbalance and disorders induced by external stress. First, as with the majority of hormones released by the body, cortisol levels undergo a circadian rhythm, starting low during night sleep, rapidly rising in the early morning, then gradually falling before rising again in the late afternoon. Superposed on this slow diurnal cycle is an ultradian rhythm consisting of approximately hourly pulses. CRH, ACTH, and cortisol are all secreted episodically, with the pulses of ACTH slightly preceding those of cortisol [11]. As for many other hormones such as gonadotropin-releasing hormone (GnRH), insulin, and growth hormone (GH), the ultradian release pattern of glucocorticoids is important in sustaining normal physiological functions, such as regulating gene expression in the hippocampus [12]. It is unclear what role oscillations play in homeostasis, but the time of onset of a stressor in relation to the phase of the ultradian oscillation has been shown to influence the physiological response elicited by the stressor [13]. A second property is the separation between the synthesis and release process of CRH. CRH must first be synthesized before released by CRH neurons in the PVN (Fig. 1C). CRH release is mediated by synaptic signals while synthesis requires the up-regulation of transcription and translation. Therefore, the two fundamentally different processes of release and synthesis operate over very different timescales [14]. Finally, dysregulation in the HPA axis is known to correlate with a number of stress-related disorders. Increased cortisol (hypercortisolism) is associated with major depressive disorder (MDD) [15, 16], while decreased cortisol (hypocortisolism) is a feature of post-traumatic stress disorder (PTSD), post infectious fatigue, and chronic fatigue syndrome (CFS) [17, 18, 19, 20]. Since PTSD develops in the aftermath of extreme levels of stress experienced during traumatic incidents like combat, sexual abuse, or life-threatening accidents, its progression may be strongly correlated with disruption of the HPA axis caused by stress response. For example, lower peak and nadir cortisol levels were found in patients with combat-related PTSD [21].

The mathematical model we derive incorporates the above physiological features and reflects the basic physiology of the HPA axis associated with delays in signaling, fast and slow negative feedback mechanisms, and CRH self-upregulation. Depending on the parameters, our model may exhibit two distinct stable *oscillating* states. When two oscillating states arise, one will have a larger oscillation amplitude and a higher base cortisol level than the other. These two states will be interpreted as normal and diseased states. A similar two-state dynamical structure arises in the classic Fitzhugh-Nagumo model of a single neuron, in which the resting and spiking states can be represented as bistable modes of the model [22], and in models of neuronal networks where an "epileptic brain" is described in terms of the distance between a normal attractor and a seizure attractor in phase-space [23]. All of these systems, including the HPA axis, can be driven to switch from one mode of activity to another by changes in system parameters or external stress inputs (Fig. 1).

Dynamical Model

Previous models of HPA dynamics [10, 6, 9, 7, 24] are typically expressed in terms of ordinary differential equations (ODEs):

$$\frac{\mathrm{d}C}{\mathrm{d}T} = p_C I(T) f_C(O) - d_C(C), \qquad [1]$$

$$\frac{\mathrm{d}A}{\mathrm{d}T} = p_A C f_A(OR, O) - d_A(A), \qquad [2]$$

$$\frac{\mathrm{d}O}{\mathrm{d}T} = p_O A(T) - d_O(O), \qquad [3]$$

$$\frac{\mathrm{d}R}{\mathrm{d}T} = p_R g_R(OR) - d_R(R), \qquad [4]$$

where $C(T), A(T)$, and $O(T)$ denote the plasma concentrations of CRH, ACTH, and cortisol, respectively. $R(T)$ represents the availability of glucocorticoid receptor (GR) in the anterior pituitary. Cortisol and cortisol-GR complex are typically near equilibrium so its concentration is approximately proportional to the product $O(T)R(T)$ [10]. The parameters p_α ($\alpha \in \{C, A, O, R\}$) relate the production rate of each species to specific factors that regulate the rate of release/synthesis of the corresponding species α. External stresses that drive CRH release by the PVN in the hypothalamus are represented by the input signal $I(T)$. The function $f_C(O)$ describes the negative feedback of cortisol on CRH levels in the PVN while $f_A(OR, O)$ describes the negative feedback of cortisol or cortisol-GR complex (at concentration $O(T)R(T)$) in the pituitary. They are mathematically characterized as being positive, decreasing functions so that $f_{A,C}(\cdot) \geq 0$ and $f'_{A,C}(\cdot) < 0$. On the other hand, the function $g_R(OR)$ describes the self-upregulation effect of the cortisol-GR complex on GR production in the anterior pituitary [25]. In contrast to $f_{A,C}(\cdot)$, $g_R(\cdot)$ is a positive but increasing function of OR so that $g_R(\cdot) \geq 0$ and $g'_R(\cdot) > 0$. Finally, the

degradation functions $d_\alpha(\cdot)$ describe how each hormone and receptor is cleared and may be linear or nonlinear.

Without including the effects of the glucocorticoid receptor (neglecting Eq. 4 and assuming $f_A(OR, O) = f_A(O)$ in Eq. 2), Eqs. 1-3 form a rudimentary "minimal" model of the HPA axis [2, 26]. If $f_{A,C}(\cdot)$ are Hill-type feedback functions dependent only on $O(T)$ and $d_\alpha(\cdot)$ are linear, a unique global stable point exists. This equilibrium point transitions to a limit cycle through a Hopf bifurcation but only within nonphysiological parameter regimes [2]. The inclusion of GR and its self-upregulation in the anterior pituitary [10] creates two stable equilibrium states of the system, but still does not generate oscillatory behavior. More recent studies extend the model to include nonlinear degradation [9] or constant delay to account for delivery of ACTH and synthesis of glucocorticoid in the adrenal gland [6]. These two extended models exhibit intrinsic circadian [9] or ultradian [6] oscillations. However, both models permit only one oscillating cycle for any given set of parameter values [9, 6] precluding the mathematical distinction between normal and diseased states.

Here, we develop a new model of the HPA axis by first introducing a physiologically-motivated delay directly into Eq. 3. This delay ultimately gives rise to the observed ultradian oscillations [6]. We then distinguish the roles of slow direct CRH synthesis and fast CRH release in the negative feedback of cortisol on CRH neurons. This allows us to separate the model into slow and fast components. Finally, self-upregulation of cortisol release is introduced which allows for bistability in our model. These ingredients can be realistically combined in a way that leads to novel, clinically identifiable features and are systematically developed below.

Ultradian rhythm and time delay - In order to capture the observed ultradian oscillations in ACTH and cortisol levels, we adapt a previous DDE model that incorporates a delayed feedforward and negative feedback interaction between the adrenal and pituitary glands, downstream of the hypothalamus. Indeed, experiments on rats show a 3-6 minute inherent delay in the response of the adrenal gland to ACTH [27]. Moreover, in experiments performed on sheep [28], persistent ultradian oscillations were observed even after surgically removing the hypothalamus, implying that oscillations are inherent to the PA subsystem. Since oscillations can be induced by delays, we assume, as in Walker *et al.* [6], a time delay T_d in the ACTH-mediated activation of cortisol production downstream of the hypothalamus. Eq. 3 is thus modified to

$$\frac{\mathrm{d}O}{\mathrm{d}T} = p_O A(T - T_\mathrm{d}) - d_O O. \qquad [5]$$

Walker *et al.* [6] show that for fixed physiological levels of CRH, the solution to Eqs. 2, 4 and 5 leads to oscillatory $A(T), O(T)$, and $R(T)$.

Synthesis vs. Release of CRH - CRH synthesis involves various pathways, including CRH gene transcription and transport of packaged CRH from the cell body (soma) to their axonal terminals where they are stored prior to release. Changes in these pathways and their effects on the overall rate of synthesis typically occur on a timescale of minutes to hours. On the other hand, the secretory release process depends on changes in membrane potential at the axonal terminal of CRH neurons, which occur over millisecond to second timescales.

To model the synthesis and release process separately, we distinguish two compartments of CRH: the concentration of stored CRH within CRH neurons will be denoted $C_\mathrm{s}(T)$, while levels of released CRH in the portal vein outside the neurons will be labeled $C(T)$ (Fig. 1C). Newly synthesized CRH will first be stored, thus contributing to C_s. We assume that the stored CRH level C_s relaxes toward a target value set by the function $C_\infty(O)$:

$$\frac{\mathrm{d}C_\mathrm{s}}{\mathrm{d}T} = \frac{C_\infty(O) - C_\mathrm{s}}{T_C}. \qquad [6]$$

Here, T_C is a characteristic time constant and $C_\infty(O)$ is the *cortisol-dependent* target level of stored CRH ($C_\infty(O)/T_C$ can also be interpreted as the cortisol-dependent production rate). Eq. 6 also assumes that the relatively small amounts of CRH released into the bloodstream do not significantly deplete the C_s pool. Previous studies have shown that variations in CRH gene expression due to changes in cortisol levels take at least twelve hours to detect [29, 30]. Therefore, we estimate $T_C \gtrsim 12\mathrm{hrs} = 720\mathrm{min}$. The negative feedback of cortisol on CRH levels thus acts through the production function $C_\infty(O)$ on the relatively slow timescale T_C. To motivate the functional form of $C_\infty(O)$, we rely experiments on rats with adrenal glands surgically removed [31, 14]. Glucocorticoid levels in these rats were then kept fixed (by injecting exogenous glucocorticoid) for 5-7 days before intracellular CRH mRNA levels were measured. The measured CRH mRNA levels in the PVN were found to decrease exponentially with the level of administered glucocorticoid [31, 14]. Thus, assuming the amount of releasable CRH is proportional to the amount of measured intracellular CRH mRNA, we will approximate $C_\infty(O)$ as a decreasing exponential function of cortisol level O.

In contrast to the inhibitory effect of glucocorticoids on the synthesis process, the secretory response of CRH neurons has been shown not to be directly sensitive to glucocorticoids under many types of stressors, including restraint and circulatory shock (hypovolemia) [32]. We limit our attention to these types of stressors and assume that the release of CRH from the intracellular pool is not directly dependent on cortisol levels.

Self-upregulation of CRH release - Finally, it has been hypothesized that CRH enhances its own release [33], especially when external stressors are present. The enhancement of CRH release by CRH is mediated by activation of the membrane-bound G-protein-coupled receptor CRHR-1 whose downstream signaling pathways operate on timescales from milliseconds to seconds [34, 35]. Thus, self-upregulation of CRH release will be modeled by including a positive and increasing function $g_C(C)$ in the source term in Eq. 1.

The secretion of CRH through synaptic transmission-like mechanisms will also depend upon the amount of stored *releasable* CRH, $C_\mathrm{s}(T)$, within the neuron and inside the synaptic vesicles. Therefore, C_s will also be factored into Eq. 1 through a source term proportional to $h(C_\mathrm{s})$ which is a function describing the amount of CRH released per unit of action potential activity of CRH neurons (for example, $I(t)$ describes the overall firing rate of CRH neurons). Combining the two proposed self-upregulation processes, we can rewrite Eq. 1 by replacing $f_C(O)$ with $h(C_\mathrm{s})g_C(C)$:

$$\frac{\mathrm{d}C}{\mathrm{d}T} = p_C I(T) h(C_\mathrm{s}) g_C(C) - d_C C. \qquad [7]$$

In this model, cortisol no longer *directly* suppresses CRH levels, rather, it decreases CRH synthesis through Eq. 6, in turn suppressing C_s. The combination $h(C_\mathrm{s})g_C(C)$ in Eq. 7 indicates the release rate of stored CRH decreases when either C_s or C decreases. We assume that inputs into the CRH neurons modulate the overall release process with weight p_C.

Complete delay-differential equation model -We are now ready to incorporate the mechanisms described above into a new, more comprehensive mathematical model of the HPA axis. In summary, our model includes

(i) A delayed response of the adrenal cortex to cortisol (Eq. 5).
(ii) A slow time-scale negative feedback by cortisol on CRH synthesis (through the $C_\infty(O)$ production term in Eq. 6).
(iii) A fast-acting positive feedback of stored and circulating CRH on CRH release (through the $h(C_s)g_C(C)$ term in Eq. 7);

The complete mathematical model thus consists of Eqs. 2, 4, 5, 6, and 7. We henceforth assume $f_A(OR, O) = f_A(OR)$ depends on only the cortisol-GR complex and use specific, previously used Hill-type functions for $f_A(OR)$ and $g_R(OR)$ [6, 7, 10, 9]. Our full theory is characterized by the following system of delay differential equations:

$$\frac{\mathrm{d}C_\mathrm{s}}{\mathrm{d}T} = \frac{C_\infty(O) - C_\mathrm{s}}{T_C}, \quad [8]$$

$$\frac{\mathrm{d}C}{\mathrm{d}T} = p_C I(T) h(C_\mathrm{s}) g_C(C) - d_C C, \quad [9]$$

$$\frac{\mathrm{d}A}{\mathrm{d}T} = p_A C \left(\frac{K_A}{K_A + OR}\right) - d_A A, \quad [10]$$

$$\frac{\mathrm{d}O}{\mathrm{d}T} = p_O A(T - T_d) - d_O O, \quad [11]$$

$$\frac{\mathrm{d}R}{\mathrm{d}T} = p_R \left(1 - \frac{\mu_R K_R^2}{K_R^2 + (OR)^2}\right) - d_R R. \quad [12]$$

The parameters $K_{A,R}$ represent the level of A and R at which the negative or positive effect are at their half maximum and $1 - \mu_R$ represents the basal production rate for GR when $OR = 0$. For a more detailed derivation and justification of Eqs. 10-12 and the choice of the functional forms, we refer the reader to [10, 6].

Nondimensionalization - To simplify the further development and analysis of our model, we nondimensionalize our equations by rescaling all variables and parameters in a manner similar to that of Walker *et al.* [6], as explicitly shown in the Supporting Information (SI). The dimensionless forms of Eqs. 8-11 become

$$\frac{\mathrm{d}c_\mathrm{s}}{\mathrm{d}t} = \frac{c_\infty(o) - c_\mathrm{s}}{t_c}, \quad [13]$$

$$\frac{\mathrm{d}c}{\mathrm{d}t} = q_0 I(t) h(c_\mathrm{s}) g_c(c) - q_2 c, \quad [14]$$

$$\frac{\mathrm{d}a}{\mathrm{d}t} = \frac{c}{1 + p_2(or)} - p_3 a, \quad [15]$$

$$\frac{\mathrm{d}o}{\mathrm{d}t} = a(t - t_\mathrm{d}) - o, \quad [16]$$

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \frac{(or)^2}{p_4 + (or)^2} + p_5 - p_6 a, \quad [17]$$

where c_s, c, a, r, o are the dimensionless versions of the original concentrations C_s, C, A, R, O, respectively. The dimensionless delay in activation of cortisol production by ACTH is now denoted t_d. All dimensionless parameters q_i, p_i, t_d, and t_c are combinations of the physical parameters and are explicitly given in the SI. The functions $c_\infty(o)$, $h(c_\mathrm{s})$, and $g_c(c)$ are dimensionless versions of $C_\infty(O)$, $h(C_\mathrm{s})$, and $g_C(C)$, respectively, and will be chosen phenomenologically to be

$$\begin{aligned} c_\infty(o) &= \bar{c}_\infty + e^{-bo}, \\ h(c_\mathrm{s}) &= 1 - e^{-kc_\mathrm{s}}, \\ g_c(c) &= 1 - \frac{\mu_\mathrm{c}}{1 + (q_1 c)^n}. \end{aligned} \quad [18]$$

The form of $c_\infty(o)$ is based on the above-mentioned exponential relation observed in the experiments on adrenalectomized rats [31, 14]. The parameters $\bar{c}_\infty$ and b represent the minimum dimensionless level of stored CRH and the decay rate of the function, respectively. How the rate of CRH release increases with c_s is given by the function $h(c_\mathrm{s})$. Since the amount of CRH packaged in release vesicles is likely regulated, we assume $h(c_\mathrm{s})$ saturates at high c_s. The choice of a decreasing form for $c_\infty(o)$ implies that increasing cortisol levels will decrease the target level (or production rate) of c_s in Eq. 13. The reduced production of c_s will then lead to a smaller $h(c_\mathrm{s})$ and ultimately a reduced release source for c (Eq. 14). As expected, the overall effect of increasing cortisol is a decrease in the release rate of CRH. Finally, since the upregulation of CRH release by circulating CRH is mediated by binding to CRH receptor, $g_c(c)$ will be chosen to be a Hill-type function, with Hill-exponent n, similar in form to the function $g_R(OR)$ used in Eqs. 12 and 17. The parameter $1 - \mu_\mathrm{c}$ represents the basal release rate of CRH relative to the maximum release rate and q_1^{-1} represents the normalized CRH level at which the positive effect is at half-maximum.

Fast-slow variable separation and bistability -Since we assume the negative feedback effect of cortisol on synthesis of CRH operates over the longest characteristic timescale t_c in the problem, the full model must be studied across two separate timescales, a *fast timescale* t, and a *slow timescale* $\tau = t/t_\mathrm{c} \equiv \varepsilon t$. The full model (Eqs. 13-17) can be succinctly written in the form

$$\frac{\mathrm{d}c_\mathrm{s}}{\mathrm{d}t} = \varepsilon(c_\infty(o) - c_\mathrm{s}), \quad [19]$$

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \mathbf{F}(c_\mathrm{s}, \mathbf{x}), \quad [20]$$

where $\mathbf{x} = (c, a, o, r)$ is the vector of fast dynamical variables, and $\mathbf{F}(c_\mathrm{s}, \mathbf{x})$ denotes the right-hand-sides of Eqs. 14-17. We refer to the fast dynamics described by $\mathrm{d}\mathbf{x}/\mathrm{d}t = \mathbf{F}(c_\mathrm{s}, \mathbf{x})$ as a *fast flow*. In the $\varepsilon \to 0$ limit, it is also easy to see that to lowest order c_s is a constant across the fast timescale and is a function of only the slow variable τ.

Under this timescale separation, the first component of Eq. 20 (Eq. 14) can be written as

$$\frac{\mathrm{d}c}{\mathrm{d}t} = q(c_\mathrm{s}(\tau), I) g_c(c) - q_2 c, \quad [21]$$

where $q(c_\mathrm{s}(\tau), I) \equiv q_0 I h(c_\mathrm{s}(\tau)) = q_0 I(1 - e^{-kc_\mathrm{s}(\tau)})$ is a function of $c_\mathrm{s}(\tau)$ and I. Since c_s is a function only of the slow timescale τ, q can be viewed as a bifurcation parameter controlling, over short timescales, the fast flow described by Eq. 21. Once $c(t)$ quickly reaches its non-oscillating quasi-equilibrium value defined by $\mathrm{d}c/\mathrm{d}t = q g_c(c) - q_2 c = 0$, it can be viewed as a parametric term in Eq. 15 of the pituitary-adrenal (PA) subsystem.

Due to the nonlinearity of $g_c(c)$, the equilibrium value $c(q)$ satisfying $q g_c(c) = q_2 c$ may be multi-valued depending on q, as shown in Fig. 2A. For certain values of the free parameters, such as $n, 1 - \mu_\mathrm{c}$, and q_1, bistability can emerge through

a saddle-node bifurcation with respect to the bifurcation parameter q. Fig. 2B shows the bifurcation diagram, *i.e.*, the nullcline of c defined by $qg_c(c) = q_2 c$.

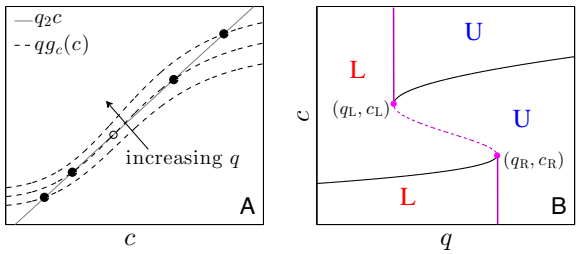

Fig. 2. Nonlinear $g_c(c)$ and bistability of fast variables. (A) The stable states of the decoupled system in Eq. 21 can be visualized as the intersection of the two functions $qg_c(c)$ (dashed curve) and $q_2 c$ (gray line). For a given Hill-type function $g_c(c)$, Eq. 21 can admit one or two stable states (solid circles), depending on function parameters. The unstable steady state is indicated by the open circle. (B) Bifurcation diagram of the decoupled system (Eq. 21) with q as the bifurcation parameter. Solid and dashed segments represent stable and unstable steady states of the fast variables, respectively. L and U label basins of attraction associated with the lower and upper stable branches of the c-nullcline. Left and right bifurcation points (q_L, c_L) and (q_R, c_R) are indicated. Fixed points of c appear and disappear through saddle node bifurcations as q is varied through q_L and q_R.

While the circulating CRH level c reaches an equilibrium value defined by the c-nullcline, the PA-subsystem can exhibit a limit cycle in (a, o, r) when c lies within a certain range [6]. Values of (a, o, r) on the limit cycle can be expressed as $(a^*(\theta; c), o^*(\theta; c), r^*(\theta; c))$, where $\theta = 2\pi t/t_p(c)$ is the phase along the limit cycle.

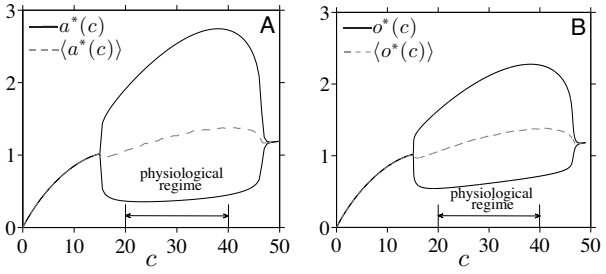

Fig. 3. Dynamics of the oscillating PA-subsystem as a function of fixed c. (A) Maximum/minimum and period-averaged values of ACTH, $a(t)$, as a function of circulating CRH. (B) Maximum/minimum and period-averaged values of cortisol $o(t)$. Within physiological CRH levels, ACTH, GR, and cortisol oscillate. The minima, maxima, and period-averaged cortisol levels typically increase with increasing c. The plot was generated using dimensionless variables c, a, and o with parameter values specified in [36] and $t_d = 1.44$, corresponding to a delay of $T_d = 15$min.

The dynamics of the PA-subsystem depicted in Fig. 3 indicate the range of c values that admit limit cycle behavior for (a, o, r), while the fast c-nullcline depicted in Fig. 2B restricts the range of bistable c values. Thus, bistable states that also support oscillating (a, o, r) are possible only for values of c that satisfy both criteria.

Since in the $\varepsilon \to 0$ limit, circulating CRH only feeds forward into a, o, and r, a complete description of all the fast variables can be constructed from just c (Eq. 14 or 21). Therefore, to visualize and approximate the dynamics of the full five-dimensional model, we only need to consider the 2D projection onto the fast c and slow c_s variable. A summary of the time-separated dynamics of the variables in our model is given in Fig. 4.

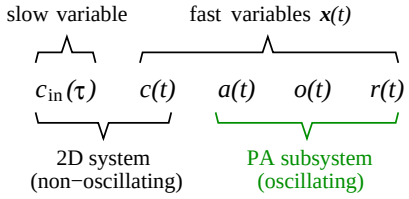

Fig. 4. Classification of variables. Variables of the full five-dimensional model are grouped according to their dynamical behavior. $c_s(\tau)$ is a slow variable, while $\mathbf{x}(t) = (c, a, o, r)$ are fast variables. Of these, (a, o, r) form the typically oscillatory PA-subsystem that is recapitulated by c. In the $\varepsilon = 1/t_c \ll 1$ limit, the variable $c_s(\tau)$ slowly relaxes towards a period-averaged value $\langle c_\infty(o(c))\rangle$. Therefore, the full model can be accurately described by its projection onto the 2D (c_s, c) phase space.

To analyze the evolution of the slow variable $c_s(\tau)$, we write our equations in terms of $\tau = \varepsilon t$:

$$\frac{dc_s}{d\tau} = (c_\infty(o) - c_s), \qquad [22]$$

$$\varepsilon\frac{d\mathbf{x}}{d\tau} = \mathbf{F}(c_s, \mathbf{x}). \qquad [23]$$

In the $\varepsilon \to 0$ limit, the "outer solution" $\mathbf{F}(c_s, \mathbf{x}) \approx 0$ simply constrains the system to be on the fast c-nullcline. The slow evolution of $c_s(\tau)$ along the fast c-nullcline depends on the value of the fast variable $o(t)$ through $c_\infty(o)$. To close the slow flow subsystem for $c_s(\tau)$, we fix c to its equilibrium value as defined by the fast subsystem and approximate $c_\infty(o(c))$ in Eq. 22 by its period-averaged value

$$\langle c_\infty(c)\rangle \equiv \int_0^{2\pi} c_\infty(o^*(\theta; c))\frac{d\theta}{2\pi} = \bar{c}_\infty + \int_0^{2\pi} e^{-bo^*(\theta;c)}\frac{d\theta}{2\pi}. \qquad [24]$$

Since o^* increases with c, $\langle c_\infty(c)\rangle$ is a decreasing function of c under physiological parameter regimes. This period-averaging approximation allows us to relate the evolution of $c_s(\tau)$ in the slow subsystem directly to c. The evolution of the slow subsystem can be estimated by the closed 2D (c_s, c) system

$$\frac{dc_s}{d\tau} = \langle c_\infty(c)\rangle - c_s, \qquad [25]$$

$$0 = q_0 h(c_s) I(t) g_c(c) - q_2 c. \qquad [26]$$

By self-consistently solving Eqs. 25 and 26, we can estimate trajectories of the full model when they are near the c-nullcline in the 2D (c_s, c)-subsystem. We will verify this in the following section.

Nullcline structure and projected dynamics - The separation of timescales results in a natural description of the fast c-nullcline in terms of the parameter q (Fig. 2) and the slow c_s-nullcline in terms of c. However, the c-nullcline is plotted in the (q, c)-plane while the c_s-nullcline is defined in the (c, c_s)-plane. In order to plot the nullclines together, we relate the equilibrium value of c_s, $\langle c_\infty(c)\rangle$, to the q coordinate through the monotonic relationship $q(c_s) = q_0 I h(\langle c_\infty(c)\rangle) = q_0 I(1 - e^{-k\langle c_\infty(c)\rangle})$ and transform the c_s variable into the q direction.

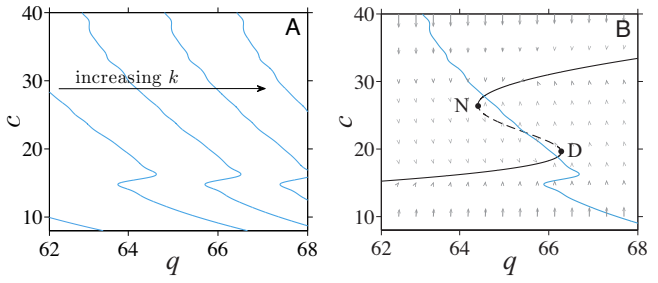

Fig. 5. Slow and fast nullclines and overall flow field. (A) The nullcline of c_s in the $\varepsilon \to 0$ limit is defined by $c_s = \langle c_\infty(c) \rangle$. These can be transformed into nullclines of q through the relation $q = q_0 h(\langle c_\infty(c) \rangle)$. For each fixed value of c, $o(t; c)$ is computed by employing a built-in DDE solver dde23 in MATLAB. The numerical solution is then used to approximate $\langle c_\infty(c) \rangle$ in Eq. 24 by Euler's method. The q-nullcline shifts to the right and gets steeper as k increases. (B) The fast c-nullcline defined by $q g_c(c) = q_2 c$ (black curve) is plotted together with the slow q-nullcline (blue curve). Here, two intersections arise corresponding to a high-cortisol normal (N) stable state and a low-cortisol diseased (D) stable state. The flow vector field is predominantly aligned with the fast directions toward the c-nullcline.

Upon assuming a fixed basal stress input $I = 1$, these transformed nullclines – the "q-nullclines" – are plotted in Fig. 5A for increasing values of k, the parameter governing the sensitivity of CRH release to stored CRH. From the form $h(\langle c_\infty(c) \rangle) = (1 - e^{-k\langle c_\infty(c) \rangle})$, both the position and the steepness of the q-nullcline in (q, c)-space depend strongly on k. Fig. 5B shows the two nullclines intersecting at both stable branches of the c-nullcline. The projected 2D flows fields indicate that the trajectory is governed by fast flow over most of the (q, c)-space.

Clearly, how the fast and slow nullclines cross controls the long-term behavior of our model in the small ε limit. In general, the number of allowable nullcline intersections will depend on input level I and our parameters $(q_0, ..., p_6, b, k, n, \mu_c, t_d)$. Note that k, which relates the amount of CRH inside the PVN neurons to its release rate in Eq. 14, mostly controls the location and steepness of the slow q-nullcline. Other parameters such as q_0, q_1, and μ_c appear directly in the fast equation for c and thus most strongly control the fast c-nullcline. Fig. 6A shows that for a basal stress input of $I = 1$ and an intermediate value of k, the nullclines cross at both stable branches of the fast subsystem. As expected, numerical simulations of our full model show the fast variables (a, o, r) quickly reaching their oscillating states defined by the c-nullcline while the slow variable $q = q_0 I h(c_s)$ remains fairly constant. Independent of initial configurations that are nogt near the c-nullcline in (q, c)-space, trajectories quickly jump to one of the stable branches of the c-nullcline with little motion towards the q-nullcline, as indicated by ξ_f.

Once near the c-nullcline, say when $|\mathbf{F}(c_s, \mathbf{x})| \ll \varepsilon$, the trajectories vary slowly according to Eqs. 22. Here, the slow variable c_s relaxes to its steady state value while satisfying the constraint $\mathbf{F}(c_s, \mathbf{x}) \approx 0$. In $(q, c)-$space, the system slowly slides along the c-nullcline towards the q-nullcline (the ξ_s paths in Fig. 6A). This latter phase of the evolution continues until the system reaches an intersection of the two nullclines, at which the reduced subsystem in c_s and c reach equilibrium.

If the fast variable c is bistable, the two nullclines may intersect at each of the two stable branches of the c-nullcline and yield the two distinct stable solutions shown in Fig. 6A. Depending on the parameters, such as large k, the two nullclines may only intersect on one stable branch of the c-nullcline as shown in Fig. 6B. Trajectories that start within the basin of attraction of the lower stable branch of the c-nullcline ("initial state 2" in Fig. 6B) will stay on this branch for a long time before eventually sliding off near the bifurcation point and jumping to the upper stable branch. Thus, the long-term behavior of our full model can be described in terms of the locations of the intersections of nullclines of the reduced system.

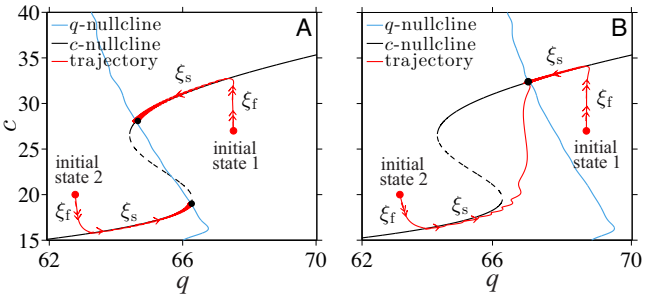

Fig. 6. Equilibria at the intersections of nullclines. (A) For intermediate values of k, there are three intersections, two of them representing stable equilibria. Solid red lines are projections of two trajectories of the full model, with initial states indicated by red dots and final stable states shown by black dots. The full trajectories approach the intersections of the q-nullcline (blue) and c-nullcline (black). (B) For large k there is only one intersection at the upper branch of the c-nullcline. Two trajectories with initial states near different branches of the c-nullcline both approach the unique intersection (•) on the upper branch. The scenario shown here corresponds to a Type I nullcline structure as described in the SI.

Results and Discussion

Changes in parameters that accompany trauma can lead to shifts in the position of the nullclines. For example, if the stored CRH release process is sufficiently compromised by trauma, the q-nullcline moves to the left, driving a bistable or fully resistant organism into a permanent diseased state. Interventions that increase k would need to overcome hysteresis in order to restore normal HPA function. More permanent physiological changes such as those resulting from traumatic brain injury (TBI) may decrease the sensitivity of the pituitary to cortisol-GR complex. This change would be described by decreasing p_2 in our model, leading to a leftward shift of the q-nullcline and an increased likelihood of hypocortisolism.

In this study, we shall focus on how external stress inputs can by themselves induce permanent but reversible transitions in HPA dynamics *without* changes in physiologic parameters. Specifically, we consider only temporary changes in $I(t)$ and consider the time-autonomous problem. Since the majority of neural circuits that project to the PVN are excitatory [37], we assume external stress stimulates CRH neurons to release CRH above its unit basal rate and that $I(t) = 1 + I_{ext}(t)$ with $I_{ext} \geq 0$.

To be concrete, we will estimate or construct many of the parameters from values used in previous studies, as listed in Table S1 in the SI. Of the four remaining parameters, μ_c, q_0, q_1, and k, we will study how our model depends on k while fixing μ_c, q_0, and q_1. Three possible nullcline configurations arise according to the values of μ_c, q_0, and q_1 and are delineated in the SI. We have also implicitly considered only parameter regimes that yield oscillations in the PA subsystem at the stable states defined by the nullcline intersections.

Given these considerations, we chose $\mu_c = 0.6$, $q_1 = 0.04$, and $q_0 = 77.8$ for the rest of our analysis. This choice of parameters is motivated in the SI and corresponds to a so-

called "Type I" nullcline structure. In this case, three possibilities arise: one intersection on the lower stable branch of the c-nullcline if $k < k_{\rm L}$, two intersections if $k_{\rm L} < k < k_{\rm R}$ (Fig. 6A), and one intersection on the upper stable branch of the c-nullcline if $k > k_{\rm R}$ (Fig. 6B). For our chosen set of parameters and a basal stress input $I = 1$, the critical values $k_{\rm L} = 2.5 < k_{\rm R} = 2.54$ are given by Eq. S3 in the SI.

Normal stress response - Activation of the HPA axis by acute stress culminates in an increased secretion of all three main hormones of the HPA axis. Persistent hypersecretion may lead to numerous metabolic, affective, and psychotic dysfunctions [38, 39]. Therefore, recovery after stress-induced perturbation is essential to normal HPA function. We explore the stability of the HPA axis by initiating the system in the upper of the two stable points shown in Fig. 7A and then imposing a 120min external stress input $I_{\rm ext} = 0.1$. The HPA axis responds with an increase in the peak level of cortisol before relaxing back to its original state after the stress is terminated (Fig. 7B). This transient process is depicted in the projected (q, c)-space in Fig. 7A.

Upon turning on the stress, the lumped parameter q and its nullcline shift to the right by 10% since $q = q_0(1 + I_{\rm ext})h(\langle c_\infty(c)\rangle)$. The trajectory will then move rapidly upward towards the new value of c on the c-nullcline; afterwards, it moves very slowly along the c-nullcline towards the shifted q-nullcline. After 120min, the system arrives at the "×" on the c-nullcline. When the stress is shut off, $I = 1.1 \to I = 1$, and the q-nullcline returns to its original position defined by $I = 1$. The trajectory also jumps back to near $(q, c) = (64.4, 36)$ and subsequently quickly returns to the original upper-branch stable point.

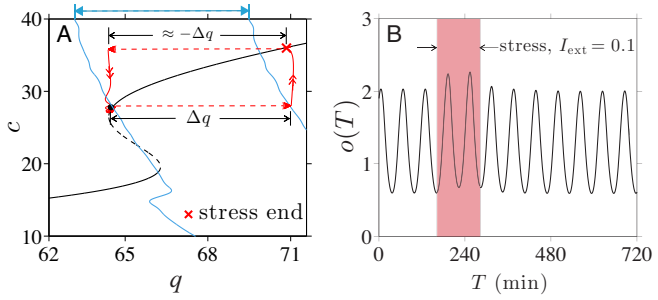

Fig. 7. Normal stress response. Numerical solution for the response to a 120min external stress $I_{\rm ext} = 0.1$. (A) At the moment the external stress is turned on, the value of q increases from 64.4 to 71 and the circulating CRH level c, quickly reaches its nullcline before slowly evolving along it towards the slow q-nullcline. After short durations of stress, the system returns to the normal state basin. (B) The peaks of the cortisol level are increased during stress (red) but return to their original oscillating values after the stress is turned off.

External stress induces transition from normal to diseased state - Next, we discuss how transitions from a normal state to a diseased state can be induced by stress of sufficient duration. Such transitions can be induced by a *positive* (excitatory) external stressor $I_{\rm ext}$ of sufficient duration. Upon stimulation of the CRH neurons, both CRH and average glucocorticoid levels are increased while the average value of $c_\infty(o(t))$ is decreased since $c_\infty(o)$ is a decreasing function of o. As $c_{\rm s}(\tau)$ slowly decays towards the decreased target value of $\langle c_\infty(o(c))\rangle$, $h(c_{\rm s}(\tau))$, and hence $q(c_{\rm s})$, also decrease. Much of this decrease occurs along the stable branch of the c-nullcline. After the external stress is switched off, q will jump back down by a factor of $1/(1 + I_{\rm ext})$. If the net decrease in q is sufficient to bring it below the bifurcation value q_L, the system crosses the separatrix and approaches the alternate, diseased state. Thus, the normal-to-diseased transition is more likely to occur if the external stress is maintained long enough to cause a large net decrease in q. The decrease in q incurred during the slow relaxation phase, plus the drop in q associated with the cessation of stress, represents the maximum possible reduction in q and most likely crossing of the upper separatrix.

A numerical solution of our model with a 30hr $I_{\rm ext} = 0.2$ was performed, and the trajectory in (q, c)-space is shown in Fig. 8A. The corresponding cortisol level along this trajectory is plotted in Fig. 8B, showing that indeed a permanent transition to the lower cortisol state occurred shortly after the cessation of stress.

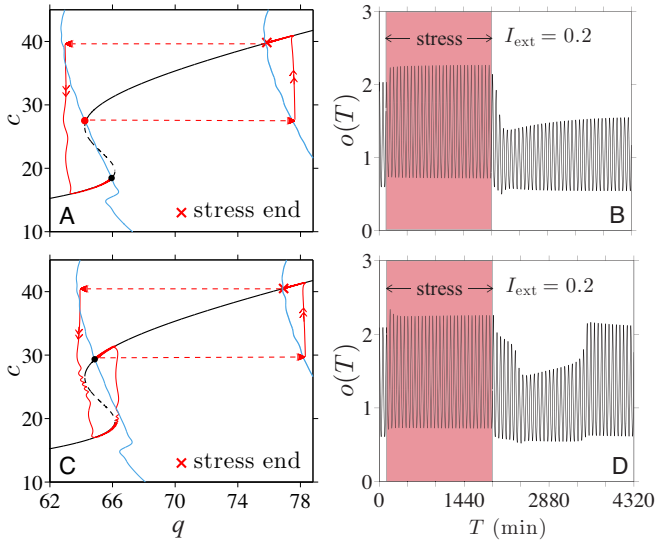

Fig. 8. Stress-induced transitions into an oscillating low-cortisol diseased state. An excitatory external stress $I_{\rm ext} = 0.2$ is applied for 30hrs. Here, the system reaches the new stable point set by $I = 1.2$ before stress is terminated and the q-nullcline reverts to its original position set by $I = 1$. (A) At intermediate values of $2.5 < k < 2.54$, when two stable state arise, a transition from the normal high-cortisol state into the diseased low-cortisol state can be induced by chronic external stress. (B) Numerical solutions of cortisol level $o(T)$ plotted against the original time variable T shows the transition to the low-cortisol diseased state shortly after cessation of stress. (C) and (D) If $k > k_{\rm R} = 2.54$, only the normal stable state exists. The system will recover and return to its original healthy state after a transient period of low cortisol.

In addition to a long-term external stress, the permanent transition to a diseased state requires $2.5 < k < 2.54$ and the existence of two stable points. On the other hand, when $k > k_{\rm R} = 2.54$, the enhanced CRH release stimulates enough cortisol production to drive the sole long term solution to the stable upper normal branch of the c-nullcline, rendering the HPA system *resistant* to stress-induced transitions.

The response to chronic stress initially follows the same pattern as described above for the two-stable-state case, as shown in Fig. 8C. However, the system will continue to evolve along the lower branch towards the q-nullcline, eventually sliding off the lower branch near the right bifurcation point $(q_{\rm R}, c_{\rm R})$ and returning to the single normal equilibrium state. Thus, when k is sufficiently high, the system may experience a transient period of lowered cortisol level after chronic stress but will

eventually recover and return to the normal cortisol state. The corresponding cortisol level shown in Fig. 8D shows this recovery at $T \approx 3400$min, which occurs approximately 1500min after the cessation of stress.

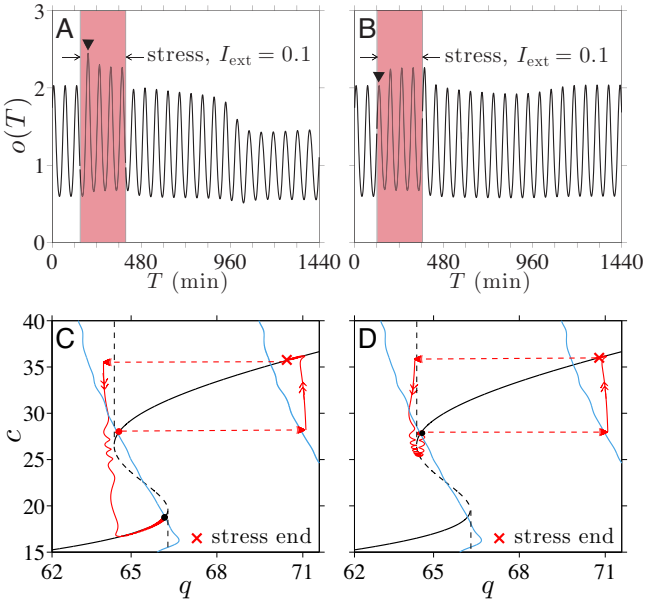

Fig. 9. Stress timing and transition to low-cortisol oscillating state. Cortisol levels in response to $I_{\text{ext}} = 0.1$ applied over 250min. (A) If stress is initiated at $T = 150$min, a transition to the low-cortisol diseased state is triggered. (B) If stress is initiated at $T = 120$min, the system returns to its normal high-cortisol state. Note that the first peak (marked by "▼") during the stress in (A) is higher than the first peak in (B). (C) If stress is initiated at $T = 150$min 150min, stress cessation and the slow relaxation along the c-nullcline during stress are sufficient to bring q just left of the separatrix, inducing the transition. (D) For initiation time $T = 120$min, q remains to the right of the separatrix, precluding the transition.

Transition to diseased state depends on stress timing - We have shown how transitions between the oscillating normal and diseased states depend on the duration of the external stress I_{ext}. However, whether a transition occurs also depends on the *time*, relative to the phase of the intrinsic ultradian oscillations, at which a fixed-duration external stress is initiated. To illustrate this dependence on phase, we plot in Figs. 9A and B two solutions for $o(T)$ obtained with a 250min $I_{\text{ext}} = 0.1$ initiated at different phases of the underlying cortisol oscillation. If stress is initiated during the rising phase of the oscillations, a transition to the low-cortisol diseased state occurs and is completed at approximately $T = 1000$min (Fig. 9A,C). If, however, stress is initiated during the falling phase, the transition does not occur and the system returns to the normal stable state (Fig. 9B,D). In this case, a longer stress duration would be required to push the trajectory past the low-q separatrix into the diseased state.

As discussed earlier, an increase in period-averaged cortisol level during stress drives a normal-to-diseased transition. We see that the period-averaged level of cortisol during stress is different for stress started at 120min from stress started at 150min. As detailed in the SI, the amplitude of the first cortisol peak after the start of stress is significantly lower when the stress starts during the falling phase of the intrinsic cortisol oscillations. The difference between initial responses in $o(t)$ affects the period-averaging in $\langle c_\infty(o)\rangle$ during external stress, ultimately influencing c_s and consequently determining whether or not a transition occurs. Note that this phase dependence is appreciable only when the stress duration is near the threshold value that brings the system close to the separatrix between normal and diseased basins of attraction. Trajectories near the separatrix are sensitive to small changes in the negative feedback of cortisol on CRH synthesis, such as those changes caused by varying the timing of the stress signal.

Stress of intermediate duration can induce "reverse" transitions - Our theory also allows the possibility for *positive* stressors I_{ext} to induce "reverse" transitions from the diseased to the normal state. Understanding these reverse transitions is useful in the context of exposure therapy (ET), where PTSD patients are subjected to stressors in a controlled and safe manner, using for example, computer-simulated "virtual reality exposure." Within our model, upon applying stress and starting from the low-c diseased equilibrium point, the horizontal shift in q resulting from ET ($I_{\text{ext}} > 0$) causes the system to move rightward across the separatrix and suggests a transition to the high-c normal state can occur.

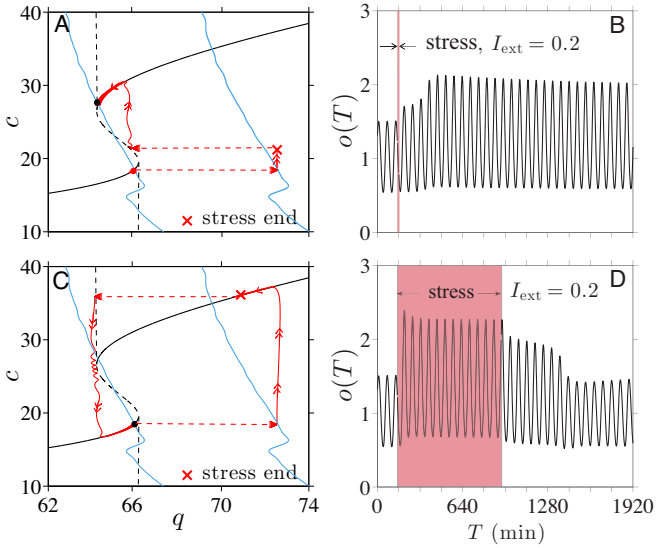

Fig. 10. Stress-induced transitions to high-cortisol oscillating state. (A) Projected 2D system dynamics when a stressor of amplitude $I_{\text{ext}} = 0.1$ is applied for 9min starting at $T = 120$min. c is increased just above the unstable branch ($c \approx 20$) to allow the unstressed system to cross the separatrix and transition to the normal high-c stable state. (B) The plot of $o(T)$ shows the transition to the high-cortisol, high-oscillation amplitude state shortly after the 9min stress. (C) A stressor turned off after 780min (13hrs) leaves the system in the basin of attraction of the diseased state. (D) Cortisol levels are pushed up but after about 1400min relax back to levels of the original diseased state.

As shown in Fig. 10A, if the stressor is applied long enough, the trajectory reaches a point above the unstable branch of the c-nullcline upon termination and the system will reach the normal, high-cortisol state (Fig. 10B). Since the initial motion is governed by fast flow, the minimum stress duration needed to incite the diseased-to-normal transition is short (on the timescale of minutes). However, if the stressor is applied for too long, a large reduction in q is experienced along the upper stable branch. Cessation of stress might then lower q back into the basin of attraction of the low-cortisol diseased

state (Fig. 10C). Fig. 10D shows the cortisol level transiently increasing to a normal level before reverting back to low levels after approximately 1400min.

Within our dynamical model, stresses need to be of *intermediate* duration in order to induce a permanent transition from the diseased to the normal state. Its occurrence may also depend on the phase (relative to the intrinsic oscillations of the fast PA subsystem) over which stress was applied, especially when the stress duration is near its transition thresholds. For a reverse diseased-to-normal transition to occur, the decrease in c_s cannot be so large that it brings the trajectory past the left separatrix, as shown in Fig. 10C. Therefore, near the maximum duration, stress initiated over the falling phase of cortisol oscillation will be more effective at triggering the transition to a normal high-cortisol state. Overall, these results imply that exposure therapy should be carefully tuned in order to optimally drive the dynamics of the HPA axis to a normal state in patients with hypocortisolism-associated stress disorders.

Summary and Conclusions

We developed a theory of HPA dynamics that includes stored CRH, circulating CRH, ACTH, cortisol and glucocorticoid receptor. Our model incorporates a fast self-upregulation of CRH release, a slow negative feedback effect of cortisol on CRH synthesis, and a delay in ACTH-activated cortisol synthesis. These ingredients allow our model to be separated into slow and fast components and projected on a 2D subspace for analysis.

Depending on physiological parameters, there may exist zero, one, or two stable simultaneous solutions of both fast and slow variables. We chose to fix the other parameters and analyze our model as a function of k, the parameter characterizing the dependence of CRH secretion on stored CRH levels. For small k, CRH release is weakened and only the low-CRH equilibrium point arises; such an organism is trapped in the low-cortisol "diseased" state. For large k, only the high-CRH normal state arises, rendering the organism resistant to acquiring the long-term, low-cortisol side-effect of certain stress disorders. When only one stable solution arises, HPA dysregulation must depend on changes in parameters resulting from permanent physiological modifications due to *e.g.,* aging, physical trauma, or stress itself [39, 40]. For example, it has been observed that older rats exhibit increased CRH secretion while maintaining normal levels of CRH mRNA in the PVN [41]. Such a change could be interpreted as an age-dependent increase in k, which, in our model, implies that aging makes the organism more resistant to stress-induced hypocortisolism. Indeed, it has been suggested that prevalence of PTSD declines with age [42, 43].

Within certain parameter regimes and for intermediate k, our theory can also exhibit bistability. When two stable solutions arise, we identify the states with low oscillating levels of cortisol as the diseased state associated with hypocortisolism. Transitions between different stable states can be induced by temporary external stress inputs, implying that HPA dysregulation may develop without permanent "structural" or physiological changes. Stresses that affect secretion of CRH by the PVN are shown to be capable of inducing transitions from normal to diseased states provided they are of sufficient duration (Fig. 8).

Our model offers a mechanistic explanation to the seemingly counter-intuitive phenomenon of lower cortisol levels after stress-induced *activation* of cortisol production. Solutions to our model demonstrate that the negative-feedback effect of a temporary increase in cortisol on the synthesis process of CRH can slowly accumulate during the stress response and eventually shift the system into a different basin of attraction. Such a mechanism provides an alternative to the hypothesis that hypocortisolism in PTSD patients results from permanent changes in physiological parameters associated with a negative-feedback mechanism [44, 45].

We also find that external stress can induce the "reverse" transition from a diseased low-cortisol state to the normal high-cortisol state. Our results imply that re-exposure to stresses of *intermediate* duration can drive the system back to normal HPA function, possibly "decoupling" stress disorders from hypocortisolism.

Interestingly, we show that the minimum durations required for either transition depends on the time at which the stress is initiated relative to the phase of the intrinsic oscillations in (a, o, r). Due to subtle differences in cortisol levels immediately following stress initiation at different phases of the intrinsic cortisol oscillation, the different cumulative negative-feedback effect on CRH can determine whether or not a trajectory crosses a separatrix (Fig. 9). When the duration of external stress is near its threshold, normal-to-diseased state transitions are easier to induce when stress is initiated during the rising phase of cortisol oscillations. Reverse diseased-to-normal transitions are more easily induced when stress is initiated during the falling phase.

In total, our theory provides a mechanistic picture that connects cortisol dysregulation with stress disorders and a mathematical framework one can use to study the downstream effects of therapies such as brief eclectic psychotherapy (BEP) and exposure therapy (ET). Both therapies involve re-experiencing stressful situations directly or through imagination, and have been consistently proven effective as first-line treatments for PTSD symptoms [46, 47, 48]. HPA activity under more complex therapy protocols can be tested via simulation of our model by using the appropriate external input function $I_{\text{ext}}(t)$.

It is important to emphasize that we modeled neuroendocrine dynamics downstream of the stress input I_{ext}. How the form of the stress function I_{ext} depends on the type of stress experienced requires a more detailed study of more upstream processes, including how hormones might feedback to these upstream processes. Since *higher* cortisol levels are found among female PTSD patients with a history of childhood abuse [49] and among PTSD patients who have experienced a nuclear accident [50], future studies of such divergent, experience-dependent dysregulation will rely on more complex input functions $I_{\text{ext}}(t)$, parameter changes, and memory effects. Many other novel features of our model remain to be explored. For example, under periodic driving, complex resonant behavior should arise depending on the amplitude and frequency of the external stress $I_{\text{ext}}(t)$ and the nullcline structure of the specific system.

Acknowledgments

This work was supported by the Army Research Office via grant W911NF-14-1-0472 and the NSF through grant BCS-1348123. The authors also thank professors T. Minor and M. Wechselberger for insightful discussions.

1. Denver, R. (2009) Structural and functional evolution of vertebrate neuroendocrine stress systems. Annals of the New York Academy of Sciences 1163, 1–16.
2. Vinther, F, Andersen, M, & Ottesen, J. T. (2011) The minimal model of the hypothalamic-pituitary-adrenal axis. Journal of Mathematical Biology 63, 663–690.
3. Jelic, S, Cupic, Z, & Kolar-Anic, L. (2005) Mathematical modeling of the hypothalmic-pituitary-adrenal system activity. Mathematical Biosciences 197, 173–187.
4. Kyrylov, V, Severyanova, L, & Vieira, A. (2005) Modeling robust oscillatory behavior of the hypothalamic-pituitary-adrenal axis. IEEE Transactions on Biomedical Engineering 52, 1977–1983.
5. Savić, D, Knežević, G, & Opačić, G. (2000) A mathematical model of stress reaction: Individual differences in threshold and duration. Psychobiology 28, 581–592.
6. Walker, J. J, Terry, J. R, & Lightman, S. L. (2010) Origin of ultradian pulsatility in the hypothalamic–pituitary–adrenal axis. Proceedings of the Royal Society of London B: Biological Sciences 277, 1627–1633.
7. Rankin, J, Walker, J, Windle, R, Lightman, S, & Terry, J. (2012) Characterizing dynamic interactions between ultradian glucocorticoid rhythmicity and acute stress using the phase response curve. PloS One 7, e30978.
8. Bairagi, N, Chatterjee, S, & Chattopadhyay, J. (2008) Variability in the secretion of corticotropin-releasing hormone, adrenocorticotropic hormone and cortisol and understandability of the hypothalamic-pituitary-adrenal axis dynamics — a mathematical study based on clinical evidence. Mathematical Medicine and Biology.
9. Sriram, K, Rodriguez-Fernandez, M, & III, F. J. D. (2012) Modeling cortisol dynamics in the neuro-endocrine axis distinguishes normal, depression, and post-traumatic stress disorder (PTSD) in humans. PLoS Computational Biology 8, e1002379.
10. Gupta, S, Aslakson, E, Gurbaxani, B. M, & Vernon, S. D. (2007) Inclusion of the glucocorticoid receptor in a hypothalamic pituitary adrenal axis model reveals bistability. Theoretical Biology and Medical Modelling 4, 8.
11. Chrousos, G. (1998) Editorial: ultradian, circadian, and stress-related hypothalamic-pituitary-adrenal axis activity — a dynamic digital-to-analog modulation. Endocrinology 139, 437–440.
12. Conway-Campbell, B, Sarabdjitsingh, R, McKenna, M, Pooley, J, Kershaw, Y, Meijer, O, Kloet, E. D, & Lightman, S. (2010) Glucocorticoid ultradian rhythmicity directs cyclical gene pulsing of the clock gene period 1 in rat hippocampus. Journal of Neuroendocrinology 22, 1093–1100.
13. Windle, R, Wood, S, Shanks, N, Lightman, S, & Ingram, C. (1998) Ultradian rhythm of basal corticosterone release in the female rat: Dynamic interaction with the response to acute stress. Endocrinology 139, 443–450.
14. Watts, A. (2005) Glucocorticoid regulation of peptide genes in neuroendocrine CRH neurons: a complexity beyond negative feedback. Frontiers in Neuroendocrinology 26, 109–130.
15. Gold, P & Chrousos, G. (2002) Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Molecular Psychiatry 7, 254–275.
16. Juruena, M, Cleare, A, & Pariante, C. (2004) The hypothalamic pituitary adrenal axis, glucocorticoid receptor function and relevance to depression. Revista Brasileira de Psiquiatria 26, 189–201.
17. Rohleder, N, Joksimovic, L, Wolf, J, & Kirschbaum, C. (2004) Hypocortisolism and increased glucocorticoid sensitivity of pro-inflammatory cytokine production in bosnian war refugees with posttraumatic stress disorder. Biological Psychiatry 55, 745–751.
18. Giorgio, A. D, Hudson, M, Jerjes, W, & Cleare, A. (2005) 24-hour pituitary and adrenal hormone profiles in chronic fatigue syndrome. Psychosomatic Medicine 67, 433–440.
19. Jerjesnd, W, Peters, T, Taylor, N, Wood, P, Wessely, S, & Cleare, A. (2006) Diurnal excretion of urinary cortisol, cortisone, and cortisol metabolites in chronic fatigue syndrome. Journal of Psychosomatic Research 60, 145–153.
20. Crofford, L, Young, E, Cary, N. E. K, Korszun, A, Brucksch, C, McClure, L, Brown, M, & Demitrack, M. (2004) Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. Brain, Behavior, and Immunity 18, 314–325.
21. Yehuda, R, Teicher, M, Levengood, R, Trestman, R, & Siever, L. (1994) Circadian regulation of basal cortisol levels in posttraumatic stress disorder. Annals of the New York Academy of Sciences 746, 378–380.
22. FitzHugh, R. (1955) Mathematical models of threshold phenomena in the nerve membrane. The Bulletin of Mathematical Biophysics 17, 257–278.
23. Silva, F. L. D, Blanes, W, Kalitzin, S, Parra, J, Suffczynski, P, & Velis, D. (2003) Epilepsies as dynamical diseases of brain systems: basic models of the transition between normal and epileptic activity. Epilepsia 44, 72–83.
24. Ben-Zvi, A, Vernon, S. D, & Broderick, G. (2009) Model-based therapeutic correction of hypothalamic-pituitary-adrenal axis dysfunction. PLoS Computational Biology 5, e1000273.
25. Tsai, S. Y, Carlstedt-Duke, J, Weigel, N. L, Dahlman, K, Gustafsson, J, M.Tsai, & O'Malley, B. W. (1988) Molecular interactions of steroid hormone receptor with its enhancer element: evidence for receptor dimer formation. Cell 55, 361–369.
26. Andersen, M, Vinther, F, & Ottesen, J. (2013) Mathematical modeling of the hypothalamic–pituitary–adrenal gland (HPA) axis, including hippocampal mechanisms. Mathematical Biosciences 246, 122–138.
27. Papaikonomou, E. (1977) Rat adrenocortical dynamics. The Journal of Physiology 265, 119–131.
28. Engler, D, Pham, T, Liu, J, Fullerton, M, Clarke, I, & Funder, J. (1990) Studies of the regulation of the hypothalamic-pituitary-adrenal axis in sheep with hypothalamic-pituitary disconnection. II. evidence for in vivo ultradian hypersecretion of proopiomelanocortin peptides by the isolated anterior and intermediate pituitary. Endocrinology 127, 1956–1966.
29. Ma, X & Aguilera, G. (1999) Differential regulation of corticotropin-releasing hormone and vasopressin transcription by glucocorticoids. Endocrinology 140, 5642–5650.
30. Swanson, L. (1991) Biochemical switching in hypothalamic circuits mediating responses to stress. Progress in Brain Research 87, 181–200.
31. Watts, A & Sanchez-Watts, G. (1995) Region-specific regulation of neuropeptide mRNAs in rat limbic forebrain neurones by aldosterone and corticosterone. The Journal of Physiology 484, 721–736.
32. Ginsberg, A, Campeau, S, Day, H, & Spencer, R. (2003) Acute glucocorticoid pretreatment suppresses stress-induced hypothalamic-pituitary-adrenal axis hormone secretion and expression of corticotropin-releasing hormone hnRNA but does not affect c-fos mRNA or fos protein expression in the paraventricular nucleus of the hypothalamus. Journal of Neuroendocrinology 15, 1075–1083.
33. Ono, N, Castro, J. D, & McCann, S. (1985) Ultrashort-loop positive feedback of corticotropin (ACTH)-releasing factor to enhance ACTH release in stress. Proceedings of the National Academy of Sciences 82, 3528–3531.
34. Papadimitriou, A & Priftis, K. (2009) Regulation of the hypothalamic-pituitary-adrenal axis. Neuroimmunomodulation 16, 265.
35. Makino, S, Hashimoto, K, & Gold, P. (2002) Multiple feedback mechanisms activating corticotropin-releasing hormone system in the brain during stress. Pharmacology Biochemistry and Behavior 73, 147–158.
36. Lightman, S, Wiles, C, Atkinson, H, Henley, D, Russell, G, Leendertz, J, McKenna, M, Spiga, F, Wood, S, & Conway-Campbell, B. (2008) The significance of glucocorticoid pulsatility. European Journal of Pharmacology 583, 255–262.
37. Herman, J. P, Figueiredo, H, Mueller, N. K, Ulrich-Lai, Y, Ostrander, M, Choi, D, & Cullinan, W. (2003) Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamopituitaryadrenocortical responsiveness. Frontiers in Neuroendocrinology 24, 151 – 180.
38. McEwen, B. S & Stellar, E. (1993) Stress and the individual: mechanisms leading to disease. Arch. Intern. Med. 153, 2093–2101.
39. McEwen, B. S. (1998) Stress, adaptation, and disease: Allostasis and allostatic load. Annals of the New York Academy of Sciences 840, 33–44.
40. Dince, S. M, Rome, R. D, McEwen, B. S, & Tang, A. C. (2014) Enhancing offspring hypothalamic-pituitary-adrenal (hpa) regulation via systematic novelty exposure: the influence of maternal HPA function. Frontiers in Behavioral Neuroscience 8.
41. Hauger, R. L, Thrivikraman, K. V, & Plotsky, P. M. (1994) Age-related alterations of hypothalamic-pituitary-adrenal axis function in male Fischer 344 rats. Endocrinology 134, 1528–1536.
42. Averill, P & Beck, J. (2000) Posttraumatic stress disorder in older adults: a conceptual review. Journal of Anxiety Disorders 14, 133–156.
43. Regier, D, Boyd, J, Burke, J, Rae, D, Myers, J, Kramer, M, Robins, L, George, L, Karno, M, & Locke, B. (1988) One-month prevalence of mental disorders in the united states: based on five epidemiologic catchment area sites. Archives of General Psychiatry 45, 977–986.
44. Yehuda, R, Teicher, M, Levengood, R, Trestman, R, Levengood, R, & Siever, L. (1996) Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. Biological Psychiatry 40, 79–88.
45. Yehuda, R & LeDoux, J. (2007) Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron 56, 19–32.
46. Olff, M, de Vries, G, Güzelcan, Y, Assies, J, & Gersons, B. (2007) Changes in cortisol and DHEA plasma levels after psychotherapy for PTSD. Psychoneuroendocrinology 32, 619–626.
47. Foa, E, Keane, T, Friedman, M, & Cohen, J. (2008) Effective treatments for PTSD: practice guidelines from the International Society for Traumatic Stress Studies. (Guilford Press).
48. Rauch, S, Eftekhari, A, & Ruzek, J. (2012) Review of exposure therapy: a gold standard for PTSD treatment. The Journal of Rehabilitation Research and Development pp. 679–88.
49. Lemieux, A & Coe, C. (1995) Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. Psychosomatic Medicine 57, 105–115.
50. Baum, A. (1993) Implications of psychological research on stress and technological accidents. American Psychologist 48, 665.