Hormonal dysregulation after prolonged HPA axis activation can be explained by changes of adrenal and corticotroph masses

Omer Karin, Moriya Raz, Avichai Tendler, Alon Bar, Yael Korem Kohanim, Tomer Milo, Uri Alon*

Dept. Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel 76100
*Corresponding author, email: uri.alon@weizmann.ac.il

Abstract

Stress activates a complex network of hormones known as the Hypothalamic-Pituitary-Adrenal (HPA) axis. The HPA axis regulates multiple metabolic, immune, and behavioral endpoints. Dysregulation of the HPA axis is a hallmark of several psychiatric conditions, including depression and substance-abuse disorders. However, little is known about the origin of this dysregulation, and we currently lack mathematical models that can explain its dynamics on the timescale of weeks. Specifically, accumulated experimental evidence indicates that after prolonged activation of the HPA axis, ACTH responses become blunted, and this blunting persists for weeks even after normalization of cortisol levels and responses. Here, we use mathematical modelling to show that this dysregulation can be explained by changes in the functional masses of the glands (total mass of the cells) that secrete ACTH and cortisol. These mass changes occur because the hormones CRH and ACTH regulate the growth of corticotroph and adrenal cortex cells, respectively. Furthermore, we show that impaired glucocorticoid receptor (GR) feedback exacerbates this dysregulation, providing a rationale for the role of GR in depression. We propose that this dysregulation is a side-effect of a circuit with a physiological function, in which gland-mass changes provide dynamical compensation to physiological variation. These findings suggest that gland-mass dynamics may play a role in the pathophysiology of stress-related disorders.
Introduction

Physical and psychological challenges activate a network of endocrine interactions, known as the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1A, (1–4)). The HPA axis generates an adaptive stress response, and its dysregulation is implicated in a range of diseases (5–10). Activation of the HPA axis begins in the hypothalamus, which secretes corticotropin releasing hormone (CRH) in response to stressors. CRH stimulates the secretion of adrenocorticotropic hormone (ACTH) from corticotroph cells in the anterior pituitary. ACTH is secreted into the circulation and causes cells in the adrenal cortex to secrete cortisol. Cortisol then inhibits HPA axis activity by feedback through high affinity receptors (Mineralocorticoid Receptor, MR) and low affinity receptors (Glucocorticoid Receptor, GR). This feedback affects the response to stressors, as well as circadian and ultradian rhythms of the HPA axis (6,11,12). The activity of the GR is affected by epigenetic regulation (13–15). Cortisol, the primary output of the HPA axis, affects multiple physiological endpoints, including behavioral, immune and metabolic systems.

Several psychiatric disorders and physiological situations involve dysregulation of the HPA axis which develops over months. In major depression, a condition associated with chronic stress, about 40%-60% of drug-free patients have hypercortisolemia (16). One way to test the HPA axis is the CRH test, in which CRH is administered and cortisol and ACTH dynamics are measured. Major depression is associated with a blunted (reduced) ACTH response (17–19) in the CRH test (Figure 1A). Elevated cortisol and blunted ACTH responses are also observed in other conditions that involve prolonged HPA axis activation, including anorexia nervosa (20) (Figure 1B), alcohol abuse disorder (21) (Figure 1C), and pregnancy (22) (Figure 1D). In all these conditions, the resolution of HPA over-activation (e.g. by weight normalization after anorexia, cessation of alcohol consumption, and childbirth respectively) leads to return to baseline of cortisol levels within a few weeks. In contrast, ACTH responses remain blunted for many weeks after cortisol levels normalize. This blunting may be causal for some of the clinical aspects in these conditions, since ACTH is co-regulated with other peptides that modulate pain and mood (23–28). In anorexia and postpartum, both ACTH and cortisol normalize many weeks after stress resolution (for alcohol abuse disorder this time-point was not measured in (21)) (Figure 1B,D).
Figure 1. After prolonged stress, ACTH response is blunted for weeks after cortisol response normalizes. (A) Schema of the classic HPA axis. CRH causes the secretion of ACTH and cortisol. In the CRH test, the secretion of these hormones is measured after CRH administration. Patients suffering from major depressive disorder (MDD) show a blunted response to CRH (black line), compared with control (gray line) and with MDD patients treated with a blocker of cortisol synthesis (metyrapone, purple line)- data from (29). (B) Patients suffering from anorexia and admitted to treatment show a blunted ACTH response and hypercortisolemia, which resolves within 6-24 months after weight normalization- data from (20). However, 3-4 weeks after weight normalization, cortisol dynamics are normal whereas ACTH dynamics are blunted. (C) Individuals recovering from alcohol abuse show hypercortisolism and blunted ACTH response after admission – data from (21). After 2-6 weeks, these individuals show normal cortisol dynamics, but blunted ACTH responses persist. (D) Pregnancy is associated with elevated cortisol levels due to CRH secretion by the placenta. 3-6 weeks after delivery, cortisol levels and dynamics return to normal, whereas ACTH dynamics are blunted- data from (22). After 12 weeks, ACTH dynamics normalize as well. In all panels, patient data are denoted by thin gray line, and controls by a thicker black line.

The persistent blunting of ACTH responses after the resolution of hyper-cortisolemia is surprising. The dynamics of ACTH in the classical HPA axis model is strongly associated with the dynamics of cortisol, and so once cortisol normalizes, so should ACTH. It is also unclear how a deficient ACTH response produces a normal cortisol response, given that ACTH is the main regulator of cortisol secretion. Explaining this dysregulation thus requires a process on the scale of weeks that decouples the dynamics of ACTH and cortisol. This timescale cannot be readily explained by existing models of the HPA axis, where the relevant timescale is the lifetime of hormones, which is minutes to hours (30). One important process with potentially a timescale of weeks is epigenetic regulation of GR sensitivity (31–33). This process, however,
does not break the association between ACTH and cortisol, and cannot explain, on its own, the dysregulation.

To address the dysregulation of ACTH and cortisol after prolonged HPA activation, we therefore turn to additional interactions in the HPA axis, which are experimentally characterized but have not been considered on the systems level. These are the interactions between the HPA hormones and the functional mass of the HPA glands, whereby ‘functional mass of a gland’ we mean the total capacity of the cells for the secretion of a hormone. A large body of research, starting from the pioneering research of Hans Selye in the 1930s, showed that the mass and number of adrenal cortisol-secreting cells increases under stress. Subsequent studies established the role of ACTH as the principle regulator of the functional mass of the adrenal cortex (34,35). Imaging and post-mortem studies also demonstrated that adrenal mass increases in humans suffering from major depression (36–42), and returns to its original size after remission (43).

Similarly, CRH causes the growth of pituitary corticotrophs: prolonged administration of CRH (or a CRH-secreting tumor) leads to dramatic increases in POMC content and ACTH output (44,45), as well as to growth of corticotroph cell mass (46–52). Adrenalectomy, which removes negative feedback inhibition from the HPA axis, shows similar effects in rodents (44,47,53,54), and leads to increased proliferation of corticotrophs (53) which is potentiated by CRH treatment.

Changes in functional masses can occur by hypertrophy (enlarged cells) and/or hyperplasia (more cells); the exact mechanism does not matter for the present analysis. The changes in functional mass take weeks, due to the slow turnover time of cell mass. We therefore asked whether the interplay of interactions between hormones and gland mass in the HPA axis can explain the observed dysregulation of the HPA axis on the time scale of weeks to months in the pathological and physiological situations mentioned above. We also tested other slow processes such as epigenetic regulation of GR (and more generally, GR resistance), slow changes in the input signal, or in the removal rate of cortisol.

To understand the dynamics of gland mass changes, we developed a mathematical model that incorporates both the hormonal interactions and the gland mass dynamics in the HPA axis. The model incorporates cortisol feedback through the high-affinity MR and low-affinity GR. We find that prolonged HPA activation enlarges the functional masses of the pituitary corticotrophs and adrenal cortex, and that the recovery of these functional masses takes weeks after stress is removed. The dynamics of this recovery explains the observed HPA dysregulation: ACTH responses remain blunted for weeks after cortisol has normalized. The
other slow processes we tested cannot explain this dysregulation because they do not break the
strong association between ACTH and cortisol. We further show that the GR protects the HPA
axis against this dysregulation after high levels of stress, providing a new explanation for the
association between deficient GR feedback and depression. Finally, we demonstrate the
physiological advantages conferred by the control of functional mass. Thus, functional mass
changes provide an integrated explanation of HPA dysregulation and dynamics on the scale of
weeks to months.

Results

Model for HPA axis dynamics that includes functional mass changes

We consider two timescales of HPA axis dynamics (Figure 2A). On the fast timescale, of
minutes to hours, hormones are secreted and degraded. Physical, circadian or psychological
stresses act as input signals to the HPA axis. Such inputs include low blood glucose, low blood
pressure or inflammation signals, psychological stressors, or effects of drugs such as alcohol,
cocaine, or amphetamines. We consider all inputs acting at a given time-point as a combined
input signal which we denote as $u$. This input signal causes the secretion of CRH.

We modelled the classic HPA cascade and cortisol feedback loop based on previous
modelling studies (6,55,56). The equations describe ACTH stimulation by CRH, cortisol
stimulation by ACTH, and the feedback from cortisol on upstream hormones due to the MR
and GR receptors. The equations are provided in the methods section. Hormone half-lives are
on the order of minutes-hours (30), and therefore this model cannot explain dysregulation over
the timescale of weeks presented in Figure 1. Most previous models of the HPA axis included
only this fast timescale, and could follow phenomena such as changes during the circadian
cycle (6), ultradian rhythms (57–59), and bistability (31,55,56).

To study the dysregulation of the HPA axis over the timescale of weeks and beyond, we
incorporate interactions between the hormones and the total functional mass of the cells that
secrete these hormones. We introduce two new variables, the functional mass of the
corticotrophs, C(t), and of the cortisol-secreting cells in the adrenal cortex, A(t). To focus on
the role of the mass, we separate the secretion of ACTH as follows: secretion rate of ACTH is
$b_2 C CRH$, where $C$ is the corticotroph mass, $b_2$ is the rate of ACTH secretion per unit
corticotroph mass, and CRH is the concentration of CRH. The parameter $b_2$ thus includes the
metabolic capacity of the corticotrophs, the number of CRH receptors, the effects of cytokines
and neuronal inputs, and the total blood volume which dilutes out ACTH. A similar equation
describes the production of cortisol, secretion rate of cortisol is $b_3 A ACTH$. To isolate the
effects of mass changes, we assume that the per-unit-biomass secretion rates $b_2$ and $b_3$ are constant.

In order to describe the dynamics of the functional masses, we model the known major factors that affect cell mass, namely the upstream hormones. CRH increases the growth of the functional mass of pituitary corticotrophs, and ACTH increases the growth of the functional mass of the adrenal cortex. After perturbations, the doubling time of the corticotrophs is on the order of days in rats (47), while that of the adrenal mass is on the order of weeks in rats and other animal models (34).

These hormone-driven mass changes are described by two additional equations, for the masses of the corticotrophs and the adrenal cortex (Figure 2A and Methods). The important parameters in these equations are the turnover times of the functional masses, which we estimate to be on the order of days-weeks in order to explain the observed hormone dynamics in Figure 1. Parameter values are given in Table 1. Note that the dynamics of the functional masses is thus much slower than the dynamics of the hormones which have half-lives of minutes to hours.

**Model shows HPA axis dysregulation after prolonged activation**

We simulated the response of the HPA model to a prolonged stress input. We model the effect of a prolonged stressor as a pulse of input $u$ to the HPA axis which lasts for several weeks or longer.
We then simulated a CRH test at several time-points after the end of the input stress pulse. The CRH test is modelled by adding CRH and measuring ACTH and cortisol over 4 hours of simulated time (methods). We find three phases of recovery. In the first few weeks after the end of the input pulse, cortisol is high and ACTH responses are blunted (Figure 2B). Then, for a period of several months, cortisol has returned to its original baseline but ACTH is remains blunted (Figure 2C). Finally, after several months, both cortisol and ACTH return to their original baselines (Figure 2D). Thus, the model recapitulates the observed dynamics of Figure 1.

To understand these dynamics in detail, we plot in Figure 3 the full behavior of the functional masses and hormones during and after the pulse of input. Importantly, the qualitative conclusions are independent on the precise values of the model parameters. The HPA model...
has several distinct phases of dysregulation during and after prolonged stress (Figure 3). These phases are caused by changes in the functional masses of the pituitary corticotrophs and adrenal cortex (Figure 3AB). These functional mass changes lead to changes in the level of the hormones (Figure 3C). We also simulated a CRH test at each timepoint and calculated the response as the peak hormone level after CRH administration relative to a control simulation without the prolonged stress input (Figure 3D). We plotted the CRH response as a function of time for ACTH and cortisol in Figure 3E. A blunted response corresponds a response below 1.0.

The initial phase occurs after the onset of the stressor and before adaptation to the stressor (Marked ONSET in Figure 3). It lasts several weeks. In this phase, the increase in input \( u \) causes elevated levels and responses of hypothalamic CRH, ACTH and cortisol. However, over weeks of stress input, the corticotroph and adrenal masses grow. The gland masses thus effectively adjust to the stressor, as example of the more general phenomenon of \textit{dynamical compensation} in physiological systems (61), discussed below. This functional mass growth causes a return to baseline of hypothalamic CRH and ACTH, due to negative feedback by cortisol. More precisely, a larger adrenal functional mass means that less ACTH is needed to produce a concentration of cortisol that drives ACTH down to baseline.
Such a return to baseline is called exact adaptation. Exact adaptation is a robust feature of this circuit due to a mathematical principle in the functional mass equations called integral feedback (61) (Methods). Exact adaptation does not occur in models without the effects of functional mass changes - the hormones do not adapt to the stressor (Figure S1, Supplementary Section 1).

The enlarged functional masses result in elevated cortisol levels during the stress period, but in adapted (that is, baseline) levels of CRH, ACTH, and blunted responses of CRH and ACTH to inputs (Figure 3DE). During prolonged stress there is thus a transition from an elevated to a blunted response of ACTH that occurs due to changes in functional masses, and results from cortisol negative feedback.

At the end of the prolonged stress pulse, which we term Early Withdrawal (or EW), the functional masses are abnormal, and take weeks to months to recover. This fundamental process is the reason for the hormonal dysregulation that is the subject of this study. In the first weeks after the stressor is removed, the adrenal and corticotroph functional masses shrink, accompanied by dropping cortisol levels. ACTH responses are blunted, and blunting may even worsen over time.

Then, cortisol and CRH levels and responses simultaneously normalize. This marks the beginning of the next phase which we term Intermediate Withdrawal (IW, Figure 3). In this phase, ACTH responses remain blunted, despite the fact that cortisol is back to baseline, because adrenal functional mass is enlarged, and corticotroph functional mass is deficient. Finally, over time, the entire dynamics of the HPA axis normalize (Late Withdrawal, LW in Figure 3), and the system has fully recovered.

These recovery phases are robust features of the HPA model with mass dynamics. After withdrawal of the stressor, cortisol and CRH levels and dynamics recover together, before the recovery of ACTH. This order occurs regardless of parameter values such as turnover times of the tissues (proof in Methods). The intuitive reason for this is that before CRH returns to baseline, the growth rate of the pituitary corticotrophs is negative, preventing ACTH from returning to baseline.

We conclude that the model is sufficient to explain the dynamics of recovery from chronic HPA activation in several conditions mentioned in the introduction – anorexia, alcohol addiction, and pregnancy (Figure 3). In order to explain the timescales of recovery, the only model parameters that matter are the tissue turnover times. Good agreement is found with turnover times on the scale of 1-3 weeks for the corticotrophs and adrenal cortex cells (see Figure S2 for comparison of different turnover times, Supplementary Section 2).
therefore explains how ACTH responses remain blunted despite normalization of cortisol baseline and dynamics.

A model in which functional masses remain constant does not show these phenomena, but instead shows an immediate normalization of hormone levels and CRH-test responses after stress (Figure S1, red lines). We also tested several alternative mechanisms with a slow timescale of weeks. We tested models with constant gland masses and the following processes to which we assigned time constants on the order of one month: GR resistance following HPA activation (Figure S1, purple lines), slow changes in input signal (Figure S1, blue lines), and slow changes in cortisol removal rate (Figure S1, gray lines). None of these models shows the dysregulation that we consider. The reason is that these slow processes do not cause a mismatch between ACTH and cortisol needed to capture the blunting of ACTH despite normal cortisol responses.

Deficient GR feedback exacerbates HPA dysregulation following prolonged stress

We next considered the role of glucocorticoid receptor (GR) in recovery from prolonged HPA activation. GR mediates the negative feedback of cortisol on CRH and ACTH secretion. Impaired feedback by GR is observed in many cases of depression. For example, administration of dexamethasone, which binds the GR in the pituitary, fails to suppress cortisol secretion in the majority of individuals suffering from depression (62). Reduced expression of GR and impaired GR function in people with depression was also demonstrated in post mortem brains (13,63–65) and in peripheral tissues (66). The feedback strength of the GR is regulated epigenetically, and is affected by early-life adversity (13,67).

The relation between depression and impaired GR function seems paradoxical, since GR signaling mediates many of the detrimental effects associated with high cortisol levels such as hippocampal atrophy (68). One explanation for the association between impaired GR feedback and depression is that impaired GR feedback leads to failure of the HPA axis to terminate the stress response on the timescale of hours, leading to excessive cortisol levels (7,14). GR feedback also plays a role in ultradian and circadian rhythms in the HPA axis (12,57,69).

Here we present an additional explanation for the association between GR feedback and depression, based on the functional mass dynamics model. Model simulations show that negative feedback by GR protects the HPA axis against large changes in hormone levels and responses on the timescale of weeks after the end of a period of prolonged stress input (Figure 4A). The extent of the impaired dynamics of cortisol and ACTH after prolonged stress is
reduced when GR affinity is high. In other words, dysregulation is more severe the weaker the feedback from GR.

Figure 4. GR provides resilience to the HPA axis against prolonged stressors. Here we show the dynamics of the HPA axis during and after a prolonged pulse of stress, described in Figure 3, for $K_{GR}=2$ (strong feedback), $K_{GR}=4$ (moderate feedback), and $K_{GR}=8$ (weak feedback). Stronger feedback from the GR attenuates the dysregulation of all HPA axis hormones.

The reason for this effect is as follows. After an increase in stress levels ($u_1 \rightarrow u_2$), the adrenal gland mass increases (Figure 4B). When GR feedback is weak ($K_{GR} \gg u_2$), the adrenal increases by about a factor of $u_2/u_1$. However, if GR feedback is strong ($K_{GR} \ll u_2$), the adrenal increases to a smaller extent, because less cortisol is required to inhibit ACTH to the level required for precise adaptation. The smaller adrenal mass means a smaller dysregulation of cortisol and ACTH after stress. Strong GR feedback therefore provides resilience to the HPA axis against stress on the slow timescale.

Mass changes provide robustness and dynamic compensation to the HPA axis

Finally, we discuss several potential advantages provided by the functional mass changes in the HPA axis. The first advantage is a natural way for the cell populations to maintain their steady-state mass, by balancing growth and removal. Growth and removal must be precisely balanced in order to avoid exponential growth or decay of the tissue. Thus, although cells turn over, the feedback through the hormones couples with the hormone trophic effects to set the masses at a functional level.
The second beneficial feature is the robustness of the steady-state hormone levels with respect to physiological parameters. The simple form of the equations for the masses $C(t)$ and $A(t)$ (given in Figure 2) locks the hormones CRH and ACTH into a unique steady-state determined only by the growth and removal parameters of the tissue. Thus $CRH_{st} = \frac{ac}{bc}$ and $ACTH_{st} = \frac{aa}{bb}$. This is remarkable because all other model parameters do not affect these steady-states. Similarly, the cortisol baseline level, $CORT_{st} \approx \left(\frac{bb}{a2a3}u\right)^{1/n1}$, depends on very few parameters. As appropriate for a stress-response hormone, cortisol steady state depends monotonously on the input $u$ to the hypothalamus (averaged over weeks), which corresponds to physiological and psychological stresses. It is independent on almost all other parameters, including production rate per cell $(b2, b3)$ or removal rates $(a2, a3)$ of CRH and ACTH, as well as the rates of the proliferation and removal of the adrenal cortex cells $bA$ and $aA$. This robustness is due to the ability of the functional masses to grow or shrink to buffer changes in these parameters.

This robustness also makes the steady-state level of cortisol and ACTH independent of total blood volume. This is because blood volume only enters through the production parameters $b2, b3$. These parameters describe the secretion rate per cell, and since hormone concentration is distributed throughout the circulation, these parameters go as one over the blood volume ($b1$ relates to the hypophyseal portal vein and not to total blood volume (70)). The functional masses therefore adjust to stay proportional to blood volume.

The third feature of the present model is dynamical compensation, in which masses $C$ and $A$ change to make the fast-timescale response of the system invariant to changes in the production rates $b2, b3$. A full analysis of dynamical compensation in the HPA axis is provided in the SI (Supplementary Section 3).

**Discussion**

In this study we sought to understand the physiological mechanisms that underlies HPA axis dysregulation after prolonged stress. In particular, we focused on a puzzling phenomenon which recurs in several conditions: ACTH responses remain blunted for a few weeks after cortisol dynamics return to baseline. This cannot be readily explained by existing models of HPA axis activation. We show that a model which incorporates two known interactions that govern functional masses – control of corticotroph growth by CRH and control of adrenal growth by ACTH – is sufficient to explain this dysregulation. The dysregulation is a robust property of this model, and explains clinical data with physiologically reasonable parameters.
This suggests that feedback interactions between masses and hormones may underlie the dysregulation of the HPA axis after prolonged stress.

There may be several implications of the blunted ACTH response that lasts for weeks after stress is removed. One set of psychopathological complications is due to the fact that ACTH secretion is tightly linked with the secretion of endogenous opioids such as β-endorphin. β-endorphin is secreted from the anterior pituitary, and also from POMC-neurons in the hypothalamus, in response to CRH. β-endorphin is cleaved from the same POMC polypeptide (24,71,72) that is the precursor for ACTH. Its secretion, like that of ACTH, is suppressed by cortisol (73). β-endorphin is the endogenous ligand of the mu-opioid receptor (MOR), the primary target of addictive drugs such as morphine and heroin. It mediates euphoria and analgesia in humans and animals (74–79). Dysregulation of β-endorphin occurs in depression (27), anorexia (28,80), and substance abuse disorders (26,81,82). Our results suggest that the dysregulation of β-endorphin, which we assume is similar to that of ACTH, persists for many weeks after cessation of stress. It can therefore contribute to pain and anhedonia in depression and addiction withdrawal.

The present mass model can further provide insight into a physiological hallmark of several psychiatric disorders: deficient GR feedback. Impaired GR feedback is implicated in depression (7), and several genetic and environmental factors have been associated with this impaired feedback (83,84). Deficient GR feedback has been suggested to affect ultradian (57) and circadian (69) HPA rhythms. We find that strong GR feedback (high GR affinity to cortisol) can also work via functional mass dynamics on the timescale of weeks: it protects the HPA axis from dysregulation after prolonged activation. Reduced GR feedback causes larger dysregulation after prolonged stress. This effect is directly mediated by changes in adrenal and corticotroph masses: strong feedback allows smaller changes of adrenal mass during the stress period, and hence to a smaller dysregulation after stress is removed.

Since chronic stress can by itself lead to reduced GR sensitivity (“glucocorticoid resistance”) (31), the present findings suggest that prolonged stress makes the HPA less resilient to the next prolonged stress. Perhaps this reduced resilience is relevant to the progression of depressive episodes (85).

If the present model is correct, functional masses are potential targets to address HPA dysregulation. Measuring these masses and their dynamics using imaging may test this model and provide clinically relevant information. Interventions that seek to normalize functional masses can potentially reduce the extent of dysregulation during and after prolonged stresses. One class of interventions may use control-engineering approaches, by periodically measuring
masses or hormones and administering defined HPA agonists or antagonist doses in order to reach desired functional masses and hormone levels (86).

The interactions between functional masses and hormones which underlie the present HPA axis dysregulation also provide exact adaptation to CRH and ACTH (Figure 3) during stress. Exact adaption has been extensively studied in the context of biochemical circuits (87), but less is known about the role of exact adaptation in physiological circuits, and, in particular, about its relevance to psychopathologies. One exception is mass changes in the insulin-glucose system, in which exact adaptation can provide control of glucose levels and dynamics (61) despite changes in insulin resistance, a form of dynamical compensation. It would be fascinating to study what functional roles exact adaptation has in the HPA axis, in order to understand the trade-offs that impact its dysregulation. The present modelling approach may be able to address such questions.
Methods.

HPA axis model.

We model HPA axis using the following equations, where cortisol provides negative feedback on CRH secretion through MR, and negative feedback on both CRH and ACTH secretion through GR. The functional mass of corticotrophs in the pituitary is C, and that of the cortisol-secreting cells in the adrenal cortex is A. We assume a linear dependence of secretion on the upstream hormones (55).

\[
\frac{d[CRH]}{dt} = b_1 u(t) \cdot MR([CORT]) \cdot GR([CORT]) - a_1[CRH] \quad [1]
\]

\[
\frac{d[ACTH]}{dt} = b_2 C[CRH] \cdot GR([CORT]) - a_2[ACTH] \quad [2]
\]

\[
\frac{d[CORT]}{dt} = b_3 A[ACTH] - a_3[CORT] \quad [3]
\]

\[
MR([CORT]) = \frac{1}{[CORT]^{n_1}} \quad [4]
\]

\[
GR([CORT]) = \frac{1}{1 + \left(\frac{[CORT]}{K_{GR}}\right)^{n_2}} \quad [5]
\]

We added to this classic description of the HPA axis the following equations for functional mass dynamics, C(t) and A(t). The equations describe functional mass growth due to the upstream hormones, and mass decline at turnover rates \(a_C\) and \(a_A\), which are much smaller than the hormone turnover rates:

\[
\frac{dC}{dt} = C (b_c [CRH] - a_C) \quad [6]
\]

\[
\frac{dA}{dt} = A (b_A [ACTH] - a_A) \quad [7]
\]

In the simulations of Figure 2, and 3, we use dimensionless units such that the steady state levels of the hormones and functional masses are equal to 1. Thus,

\[
\frac{d[CRH]}{dt} = \gamma_{CRH}(u(t) \cdot MR([CORT]) \cdot GR([CORT]) - [CRH]) \quad [8]
\]

\[
\frac{d[ACTH]}{dt} = \gamma_{ACTH}(C[CRH] \cdot GR([CORT]) - [ACTH]) \quad [9]
\]

\[
\frac{d[CORT]}{dt} = \gamma_{CORT}(A[ACTH] - [CORT]) \quad [10]
\]

\[
MR([CORT]) = \frac{1}{[CORT]^{n_1}} \quad [11]
\]
GR([CORT]) = \frac{1}{1 + \left(\frac{[CORT]}{K_{GR}}\right)^{n_2}} \quad [12] \\
\frac{dC}{dt} = \gamma_C C ([CRH] - 1) \quad [13] \\
\frac{dA}{dt} = \gamma_A A ([ACTH] - 1) \quad [14] \\

Where the gamma parameters are the turnover rates. All parameters are provided in Table 1.

Code to simulate the equations and generate the figures is provided in

[https://github.com/omerka-weizmann/hpa_dynamics](https://github.com/omerka-weizmann/hpa_dynamics). We note that one can solve the quasi-steady state of Eqs. [8-10] by setting time derivatives equal to zero. This yields at basal input:

\[
[ACTH] \approx C^{\frac{1}{1+n_1}} A^{\frac{n_1}{1+n_1}} \quad [15] \\
[CORTISOL] \approx (CA)^{\frac{n_1}{1+n_1}} \quad [16] \\
[CRH] \approx (CA)^{\frac{n_1}{1+n_1}} \quad [17]
\]

**Alternative models.**

The model without functional mass dynamics is provided by Eq. [8-12]. To this model, we added, instead of gland-mass dynamics, several alternative biological processes that have a slow timescale, potentially on the order of a month. The first process is glucocorticoid resistance, where chronically elevated cortisol levels cause weaker feedback from the GR (31,33). One possible mechanism involves epigenetic effects such as DNA methylation (15). To model GR resistance, we added a variable R that modifies the effective binding coefficient, into Eq. 5, yielding:

\[
GR([CORT]) = \frac{1}{1 + \left(\frac{R [CORT]}{K_{GR}}\right)^{n_2}} \quad [18]
\]

For R we use the following equation, based on a model of leptin resistance by Jacquier et al. (88). It describes the decline of R with CORT levels:

\[
\frac{dR}{dt} = \gamma_R (f([CORT]) - g([CORT]) R) \quad [19]
\]

For high cortisol levels to induce strong resistance, we use the simple forms: \(f(x)=1, g(x)=1 + \lambda x^2\).

The second alternative slow process is a slow decrease in input, \(u\). We considered an exponentially decreasing input signal (Figure S1).
The third alternative process is a putative slow decrease in cortisol clearance rate. To model this, we added a term $C_R$ to the removal term equation [3]:

$$\frac{d[CORT]}{dt} = \gamma_{CORT}(A \cdot [ACTH] - C_R^{-1}[CORT]) \quad [20]$$

Because there is no well-characterized biological process that governs removal on the scale of weeks, we use a putative description in which cortisol reduces its own removal rate by increasing $C_R$:

$$\frac{dC_R}{dt} = \gamma_{C_R}([CORT] - C_R) \quad [21]$$

All processes were provided with a month timescale, by setting $\gamma_{C_R} = \gamma_R = \frac{\log(2)}{30} \text{day}^{-1}$.

Simulation results are shown in the SI.

CRH test.

We modeled the CRH test by adding the following equation for the concentration of externally administrated CRH, denoted $[CRH_E]$:

$$\frac{d[CRH_E]}{dt} = \gamma_{CRH_E}(\delta(t) - CRH_E) \quad [22]$$

Where $\delta(t)$ describes a dose $D$ of external CRH injected at $T_{inj}$ and lasting a time $W$:

$$\delta(t) = \begin{cases} D & T_{inj} < t \leq T_{inj} + W \\ 0 & \text{otherwise} \end{cases}$$

and the removal rate is $\gamma_{CRH_E}$ as described in (89). Extrinsic administrated CRH causes the pituitary to secrete ACTH, as described by adding $CRH_E$ to the intrinsic CRH (units of $CRH_E$ are set to have equal biological effect to CRH). Thus, [Eq. 9] was modified to:

$$\frac{d[ACTH]}{dt} = \gamma_{ACTH}(C \cdot ([CRH] + [CRH_E]) \cdot GR([CORT]) - [ACTH]) \quad [23]$$

The dose $D$ and pulse width $W$ were calibrated to provide the observed mean CRH test results in non-stressed control subjects, providing $D=20$ and $W=30$ min.

Proof for dysregulation of ACTH after cortisol normalization.

We briefly show how the model Eq. 8-14 provide ACTH dysregulation even after cortisol normalizes. Consider a prolonged stressor, like the one presented in Figure 3 (that is, a pulse increase in the input $u$). Since ACTH and CRH are adapted to the stressor, within hours after withdrawal of the stressor, CRH and ACTH levels drop to below their pre-stressor baseline, whereas cortisol remains above its pre-stressor baseline. CRH and cortisol recover simultaneously over a few weeks because CRH dynamics depend only on cortisol and the input $u$. It therefore remains to be shown that ACTH does not recover before cortisol. Since ACTH recovers from below baseline ACTH=1, it recovers with a positive temporal derivative.
\[ \frac{d[ACTH]}{dt} > 0. \] If (by negation) this happens before CRH and cortisol recover, we will come to a contradiction: since CRH is below its baseline CRH=1, C has a negative derivative due to Eq. 13; the derivative of A is zero due to Eq. 7. Because ACTH levels are approximately proportional to \( C^{1+\eta_1}A^{-\eta_2} \) (Eq. 15) we find that ACTH has a negative temporal derivative when it crosses its baseline. We come to a contradiction. We conclude that CRH and cortisol return to baseline before ACTH does.

**Cortisol shows normal fast timescale response after recovery despite ACTH blunting.**

We now use the HPA model Eq. 8-14 to show that when CRH and cortisol levels return to baseline after stress (point IW in Figure 3), their entire dynamics in response to any fast-timescale input (such as a CRH test) normalize, even if ACTH responses have not yet normalized. The mass of the adrenal cortex and pituitary corticotrophs at baseline is denoted \( A_0, C_0, \) and their size at the timepoint IW where cortisol and CRH first normalize (\( [CORT] = [CRH] = 1 \)) is \( \lambda_A A_0, \lambda_C C_0. \) Because cortisol and CRH are at baseline, and both are proportional to the product of gland masses \( AC \) (Eq. 15-16), as noted above, one obtains \( \lambda_A \lambda_C = 1. \) Replacing \( [ACTH] = \lambda_C [ACTH] \) in Eq. 8-10 yields revised equations for the fast timescale dynamics:

\[
\frac{d[CRH]}{dt} = \gamma_{CRH} (u(t) \cdot MR([CORT]) \cdot GR([CORT]) - [CRH]) \quad [24]
\]

\[
\frac{d[ACTH]}{dt} = \frac{d[ACTH]}{dt} \cdot \frac{1}{\lambda_C} = \frac{1}{\lambda_C} \gamma_{ACTH} (\lambda_C C_0 \cdot [CRH] \cdot GR([CORT]) - \lambda_C [ACTH]) \quad [25]
\]

\[
\frac{d[CORT]}{dt} = \gamma_{CORT} (\lambda_A A_0 \cdot [ACTH] - [CORT]) = \gamma_{CORT} (A_0 \cdot [ACTH] - [CORT]) \quad [26]
\]

Note that Eq. [24-26] are the same as Eq. [8-10] when \( A = A_0 \) and \( C = C_0, \) that is, they are independent of \( \lambda_A, \lambda_C. \) In addition, the initial conditions for the hormones are also independent of \( \lambda_A, \lambda_C, \) because \( [CORT] = [CRH] = 1 \) are at baseline, while ACTH, which is proportional to \( C^{1+\eta_1}A^{-\eta_2} \) scales with \( \lambda_C, \) so that \( [ACTH] \) is also independent of \( \lambda_A, \lambda_C. \) We conclude that after cortisol and CRH return to baseline, the fast timescale dynamics of cortisol and CRH to any input (such as a CRH test) becomes normalized and equal to the dynamics before the stressor. In the simulations, after CRH and cortisol have normalized for the first time, they only deviate from baseline slightly (at most 9%), and so this consideration holds approximately for further times in the scenario of Figure 3.
### Table 1. Parameter values.

| Parameter  | Value                        |
|------------|------------------------------|
| $\gamma_{CRH}$ | 0.17/min (55)               |
| $\gamma_{ACTH}$ | 0.035/min (55)              |
| $\gamma_{CORT}$ | 0.0091/min (55)             |
| $\gamma_{P}$      | 0.099/day                    |
| $\gamma_{A}$      | 0.049/day                    |
| $K_{GR}$        | 4                            |
| $\gamma_{CRH_E}$ | 0.016/min (89)              |
| $W$            | 30 min                       |
| $D$            | 20                           |
| $\gamma_{CE}$  | 0.023/day                    |
| $\lambda$      | 1                            |
| $\gamma_{R}$    | 0.023/day                    |
| $n_1$          | 1                            |
| $n_2$          | 3 (55)                       |
1. Tsigos C, Chrousos GP. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002;53(4):865–871.

2. Zavala E, Wedgwood KC, Voliotis M, Tabak J, Spiga F, Lightman SL, et al. Mathematical modelling of endocrine systems. Trends Endocrinol Metab. 2019;

3. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams textbook of endocrinology. Elsevier Health Sciences; 2015.

4. Hosseinichimeh N, Rahmandad H, Wittenborn AK. Modeling the hypothalamus–pituitary–adrenal axis: A review and extension. Math Biosci. 2015;268:52–65.

5. Chen A, editor. Stress resilience. Cambridge: Elsevier; 2019.

6. Sriram K, Rodriguez-Fernandez M, Doyle FJ. Modeling Cortisol Dynamics in the Neuro-endocrine Axis Distinguishes Normal, Depression, and Post-traumatic Stress Disorder (PTSD) in Humans. Sporns O, editor. PLoS Comput Biol. 2012 Feb 16;8(2):e1002379.

7. De Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005;6(6):463.

8. McEwen BS, Stellar E. Stress and the individual: mechanisms leading to disease. Arch Intern Med. 1993;153(18):2093–2101.

9. Sapolsky RM. Why stress is bad for your brain. Science. 1996;273(5276):749–750.

10. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10(6):434.

11. Gudmand-Hoeyer J, Timmermann S, Ottesen JT. Patient-specific modeling of the neuroendocrine HPA-axis and its relation to depression: Ultradian and circadian oscillations. Math Biosci. 2014 Nov;257:23–32.

12. Stavreva DA, Wiench M, John S, Conway-Campbell BL, McKenna MA, Pooley JR, et al. Ultradian hormone stimulation induces glucocorticoid receptor-mediated pulses of gene transcription. Nat Cell Biol. 2009 Sep;11(9):1093–102.

13. McGowan PO, Sasaki A, D’Alessio AC, Dymov S, Labonté B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009 Mar;12(3):342–8.

14. Anacker C, Zunszain PA, Carvalho LA, Pariante CM. The glucocorticoid receptor: pivot of depression and of antidepressant treatment? Psychoneuroendocrinology. 2011 Apr;36(3):415–25.

15. Watkeys OJ, Kremerskothen K, Quidé Y, Fullerton JM, Green MJ. Glucocorticoid receptor gene (NR3C1) DNA methylation in association with trauma, psychopathology,
transcript expression, or genotypic variation: A systematic review. Neurosci Biobehav Rev. 2018;95:85–122.

16. Murphy BE. Steroids and depression. J Steroid Biochem Mol Biol. 1991 May;38(5):537–59.

17. Gold PW, Loriaux DL, Roy A, Kling MA, Calabrese JR, Kellner CH, et al. Responses to Corticotropin-Releasing Hormone in the Hypercortisolism of Depression and Cushing’s Disease. N Engl J Med. 1986 May 22;314(21):1329–35.

18. Bardeleben U von, Holsboer F. Cortisol Response to a Combined Dexamethasone-Human Corticotrophin-Releasing Hormone Challenge in Patients with Depression. J Neuroendocrinol. 1989;1(6):485–8.

19. Holsboer F, Von Bardeleben U, Gerken A, Stalla GK, Müller OA. Blunted corticotropin and normal cortisol response to human corticotropin-releasing factor in depression. N Engl J Med. 1984 Oct 25;311(17):1127.

20. Gold PW, Gwirtsman H, Avgerinos PC, Nieman LK, Gallucci WT, Kaye W, et al. Abnormal hypothalamic–pituitary–adrenal function in anorexia nervosa. N Engl J Med. 1986;314(21):1335–1342.

21. von Bardeleben U, Heuser I, Holsboer F. Human CRH stimulation response during acute withdrawal and after medium-term abstinence from alcohol abuse. Psychoneuroendocrinology. 1989;14(6):441–449.

22. Magiakou MA, Mastorakos G, Rabin D, Dubbert B, Gold PW, Chrousos GP. Hypothalamic corticotropin-releasing hormone suppression during the postpartum period: implications for the increase in psychiatric manifestations at this time. J Clin Endocrinol Metab. 1996;81(5):1912–1917.

23. Adinoff B, Junghanns K, Kiefer F, Krishnan-Sarin S. Suppression of the HPA axis stress-response: implications for relapse. Alcohol Clin Exp Res. 2005 Jul;29(7):1351–5.

24. Guillemin R, Vargo T, Rossier J, Minick S, Ling N, Rivier C, et al. Beta-Endorphin and adrenocorticotropic peptide are selected concomitantly by the pituitary gland. Science. 1977 Sep 30;197(4311):1367–9.

25. Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science. 1981 Sep 18;213(4514):1394–7.

26. Racz I, Schürmann B, Karpushova A, Reuter M, Cichon S, Montag C, et al. The opioid peptides enkephalin and β-endorphin in alcohol dependence. Biol Psychiatry. 2008 Dec 1;64(11):989–97.

27. Peciña M, Karp JF, Mathew S, Todtenkopf MS, Ehrich EW, Zubieta J-K. Endogenous opioid system dysregulation in depression: implications for new therapeutic approaches. Mol Psychiatry. 2019;24(4):576–587.
28. Marrazzi MA, Luby ED. An auto-addiction opioid model of chronic anorexia nervosa. Int J Eat Disord. 1986;5(2):191–208.

29. von Bardeleben U, Stalla GK, Müller OA, Holsboer F. Blunting of ACTH response to human CRH in depressed patients is avoided by metyrapone pretreatment. Biol Psychiatry. 1988 Nov;24(7):782–6.

30. Bingzheng L, Zhenye Z, Liansong C. A mathematical model of the regulation system of the secretion of glucocorticoids. J Biol Phys. 1990;17(4):221–233.

31. Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc Natl Acad Sci. 2012 Apr 17;109(16):5995–9.

32. Turner JD, Alt SR, Cao L, Vernocchi S, Trifonova S, Battello N, et al. Transcriptional control of the glucocorticoid receptor: CpG islands, epigenetics and more. Biochem Pharmacol. 2010;80(12):1860–1868.

33. Schaaf MJM, Cidlowski JA. Molecular mechanisms of glucocorticoid action and resistance. J Steroid Biochem Mol Biol. 2002 Dec;83(1–5):37–48.

34. Swann HG. THE PITUITARY-ADRENOCORTICAL RELATIONSHIP. Physiol Rev. 1940 Oct;20(4):493–521.

35. Lotfi CFP, de Mendonca PO. Comparative effect of ACTH and related peptides on proliferation and growth of rat adrenal gland. Front Endocrinol. 2016;7:39.

36. Nemeroff CB, Krishnan KRR, Reed D, Leder R, Beam C, Dunnick NR. Adrenal gland enlargement in major depression: a computed tomographic study. Arch Gen Psychiatry. 1992;49(5):384–387.

37. Amsterdam JD, Marinelli DL, Arger P, Winokur A. Assessment of adrenal gland volume by computed tomography in depressed patients and healthy volunteers: a pilot study. Psychiatry Res. 1987 Jul;21(3):189–97.

38. Dorovini-Zis K, Zis AP. Increased adrenal weight in victims of violent suicide. Am J Psychiatry. 1987;

39. Dumser T, Barocka A, Schubert E. Weight of adrenal glands may be increased in persons who commit suicide. Am J Forensic Med Pathol. 1998 Mar;19(1):72–6.

40. Szigethy E, Conwell Y, Forbes NT, Cox C, Caine ED. Adrenal weight and morphology in victims of completed suicide. Biol Psychiatry. 1994 Sep 15;36(6):374–80.

41. Rubin RT, Phillips JJ, McCracken JT, Sadow TF. Adrenal gland volume in major depression: relationship to basal and stimulated pituitary-adrenal cortical axis function. Biol Psychiatry. 1996 Jul 15;40(2):89–97.
42. Ludescher B, Najib A, Baar S, MacHann J, Schick F, Buchkremer G, et al. Increase of Visceral Fat and Adrenal Gland Volume in Women with Depression: Preliminary Results of a Morphometric MRI Study. Int J Psychiatry Med. 2008 Sep;38(3):229–40.

43. Rubin RT, Phillips JJ, Sadow TF, McCracken JT. Adrenal gland volume in major depression. Increase during the depressive episode and decrease with successful treatment. Arch Gen Psychiatry. 1995 Mar;52(3):213–8.

44. Bruhn TO, Sutton RE, Rivier CL, Vale WW. Corticotropin-Releasing Factor Regulates Proopiomelanocortin Messenger Ribonucleic Acid Levels in vivo. Neuroendocrinology. 1984;39(2):170–5.

45. Young E, Akil H. Changes in releasability of ACTH and beta-endorphin with chronic stress. Neuropeptides. 1985;5(4–6):545–548.

46. Gertz BJ, Contreras LN, McComb DJ, Kovacs K, Tyrrell JB, Dallman MF. Chronic administration of corticotropin-releasing factor increases pituitary corticotroph number. Endocrinology. 1987 Jan;120(1):381–8.

47. Westlund KN, Aguilera G, Childs GV. Quantification of Morphological Changes in Pituitary Corticotropes Produced by in Vivo Corticotropin-Releasing Factor Stimulation and Adrenalectomy. Endocrinology. 1985 Jan 1;116(1):439–45.

48. Carey RM, Varma SK, Drake Jr CR, Thorner MO, Kovacs K, Rivier J, et al. Ectopic secretion of corticotropin-releasing factor as a cause of Cushing’s syndrome: a clinical, morphologic, and biochemical study. N Engl J Med. 1984;311(1):13–20.

49. Horvath E. Pituitary hyperplasia. Pathol - Res Pract. 1988 Sep 1;183(5):623–5.

50. Schteingart DE, Lloyd RV, Akil H, Chandler WF, Ibarra-Perez G, Rosen SG, et al. Cushing’s Syndrome Secondary to Ectopic Corticotropin-Releasing Hormone-Adrenocorticotropic Secretion*. J Clin Endocrinol Metab. 1986 Sep;63(3):770–5.

51. O’Brien T, Young Jr WF, Davilla DG, Schelthauer BW, Kovacs K, Horvath E, et al. Cushing’s syndrome associated with ectopic production of corticotrophin-releasing hormone, corticotrophin and vasopressin by a phaeochromocytoma. Clin Endocrinol (Oxf). 1992;37(5):460–467.

52. Asa SL, Kovacs K, Hammer GD, Liu B, Roos BA, Low MJ. Pituitary corticotroph hyperplasia in rats implanted with a medullary thyroid carcinoma cell line transfected with a corticotropin-releasing hormone complementary deoxyribonucleic acid expression vector. Endocrinology. 1992 Aug;131(2):715–20.

53. Gulyas M, Pusztai L, Rappay G, Makara GB. Pituitary corticotrophs proliferate temporarily after adrenalectomy. Histochemistry. 1991;96(2):185–189.

54. McNicol AM, Kubba MAG, McTeague E. The mitogenic effects of corticotrophin-releasing factor on the anterior pituitary gland of the rat. J Endocrinol. 1988 Aug;118(2):237-NP.
55. Andersen M, Vinther F, Ottesen JT. Mathematical modeling of the hypothalamic-pituitary-adrenal gland (HPA) axis, including hippocampal mechanisms. Math Biosci. 2013 Nov;246(1):122–38.

56. Gupta S, Aslakson E, Gurbaxani BM, Vernon SD. Inclusion of the glucocorticoid receptor in a hypothalamic pituitary adrenal axis model reveals bistability. Theor Biol Med Model. 2007 Feb 14;4:8.

57. Walker JJ, Terry JR, Lightman SL. Origin of ultradian pulsatility in the hypothalamic–pituitary–adrenal axis. Proc R Soc B Biol Sci. 2010 Jun 7;277(1688):1627–33.

58. Marković VM, Čupić Ž, Vukojević V, Kolar-Anić L. Predictive modeling of the hypothalamic-pituitary-adrenal (HPA) axis response to acute and chronic stress. Endocrinology. 2011;58(10):889–904.

59. Scheff JD, Calvano SE, Lowry SF, Androulakis IP. Transcriptional implications of ultradian glucocorticoid secretion in homeostasis and in the acute stress response. Physiol Genomics. 2012 Feb 1;44(2):121–9.

60. Selye H. The story of the adaptation syndrome. (Told in the form of informal, illustrated lectures.). Story Adapt Syndr Form Informal Illus Lect. 1952;

61. Karin O, Swisa A, Glaser B, Dor Y, Alon U. Dynamical compensation in physiological circuits. Mol Syst Biol. 2016;12(11).

62. Coppen A, Abou-Saleh M, Milln P, Metcalfe M, Harwood J, Bailey J. Dexamethasone Suppression Test in Depression and other Psychiatric Illness. Br J Psychiatry. 1983 May;142(5):498–504.

63. López JF, Chalmers DT, Little KY, Watson SJ. Regulation of Serotonin1A, Glucocorticoid, and Mineralocorticoid Receptor in Rat and Human Hippocampus: Implications for the Neurobiology of Depression. Biol Psychiatry. 1998 Apr 15;43(8):547–73.

64. Pandey GN, Rizavi HS, Ren X, Dwivedi Y, Palkovits M. Region-specific alterations in glucocorticoid receptor expression in the postmortem brain of teenage suicide victims. Psychoneuroendocrinology. 2013;38(11):2628–2639.

65. Webster MJ, Knable MB, O’grady J, Orthmann J, Weickert CS. Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. Mol Psychiatry. 2002;7(9):985.

66. Pariante CM. Glucocorticoid Receptor Function In Vitro in Patients with Major Depression. Stress. 2004 Dec 1;7(4):209–19.

67. Weaver ICG, Cervoni N, Champagne FA, D’Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. Nat Neurosci. 2004 Aug;7(8):847–54.

68. Sapolsky RM, Krey LC, McEwen BS. Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. J Neurosci. 1985 May 1;5(5):1222–7.
69. Sriram K, Rodriguez-Fernandez M, Iii FJD. Modeling Cortisol Dynamics in the Neuro-endocrine Axis Distinguishes Normal, Depression, and Post-traumatic Stress Disorder (PTSD) in Humans. PLOS Comput Biol. 2012 Feb 16;8(2):e1002379.

70. Owens MJ, Nemeroff CB. Physiology and pharmacology of corticotropin-releasing factor. Pharmacol Rev. 1991 Dec;43(4):425–73.

71. Rivier C, Brownstein M, Spiess J, Rivier J, Vale W. In vivo corticotropin-releasing factor-induced secretion of adrenocorticotropin, beta-endorphin, and corticosterone. Endocrinology. 1982 Jan;110(1):272–8.

72. Hargreaves KM, Schmidt EA, Mueller GP, Dionne RA. Dexamethasone alters plasma levels of beta-endorphin and postoperative pain. Clin Pharmacol Ther. 1987;42(6):601–7.

73. Lim AT, Khalib B a. K, Clements J, Funder JW. Glucocorticoid and Mineralocorticoid Effects on Adrenocorticotropin and β-Endorphin in the Adrenalectomized Rat. J Clin Invest. 1982 May 1;69(5):1191–8.

74. Hawkes CH. Endorphins: the basis of pleasure? J Neurol Neurosurg Psychiatry. 1992 Apr;55(4):247–50.

75. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl). 2008 Aug 1;199(3):457–80.

76. Peciña S, Smith KS, Berridge KC. Hedonic hot spots in the brain. Neurosci Rev J Bringing Neurobiol Neurol Psychiatry. 2006 Dec;12(6):500–11.

77. Drewnowski A, Krahn DD, Demitrack MA, Nairn K, Gosnell BA. Taste responses and preferences for sweet high-fat foods: evidence for opioid involvement. Physiol Behav. 1992 Feb;51(2):371–9.

78. Chelnokova O, Laeng B, Eikemo M, Riegels J, Løseth G, Maurud H, et al. Rewards of beauty: the opioid system mediates social motivation in humans. Mol Psychiatry. 2014 Jul;19(7):746–7.

79. Buchel C, Miedl S, Sprenger C. Hedonic processing in humans is mediated by an opioidergic mechanism in a mesocorticolimbic system. eLife. 2018 Nov 16;7:e39648.

80. Marrazzi MA, Mullings-Britton J, Stack L, Powers RJ, Lawhorn J, Graham V, et al. Atypical endogenous opioid systems in mice in relation to an auto-addiction opioid model of anorexia nervosa. Life Sci. 1990;47(16):1427–1435.

81. Roth-DerI I, Green-Sadan T, Yadid G. β-Endorphin and drug-induced reward and reinforcement. Prog Neurobiol. 2008;86(1):1–21.

82. Kiefer F, Horntrich M, Jahn H, Wiedemann K. Is withdrawal-induced anxiety in alcoholism based on β-endorphin deficiency? Psychopharmacology (Berl). 2002;162(4):433–437.
83. Spijker AT, Van Rossum EF. Glucocorticoid receptor polymorphisms in major depression. Focus on glucocorticoid sensitivity and neurocognitive functioning. Ann NY Acad Sci. 2009;1179:199–215.

84. Bet PM, Penninx BWJH, Bochdanovits Z, Uitterlinden AG, Beekman ATF, Schoor NM, et al. Glucocorticoid receptor gene polymorphisms and childhood adversity are associated with depression: New evidence for a gene–environment interaction. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(5):660–9.

85. Kendler KS, Thornton LM, Gardner CO. Genetic Risk, Number of Previous Depressive Episodes, and Stressful Life Events in Predicting Onset of Major Depression. Am J Psychiatry. 2001 Apr 1;158(4):582–6.

86. Ben-Zvi A, Vernon SD, Broderick G. Model-Based Therapeutic Correction of Hypothalamic-Pituitary-Adrenal Axis Dysfunction. PLOS Comput Biol. 2009 Jan 23;5(1):e1000273.

87. Ferrell Jr JE. Perfect and near-perfect adaptation in cell signaling. Cell Syst. 2016;2(2):62–67.

88. Jacquier M, Soula HA, Crauste F. A mathematical model of leptin resistance. Math Biosci. 2015 Sep 1;267:10–23.

89. Saphier PW, Faria M, Grossman A, Coy DH, Besser GM, Hodson B, et al. A comparison of the clearance of ovine and human corticotrophin-releasing hormone (CRH) in man and sheep: a possible role for CRH-binding protein. J Endocrinol. 1992 Jun;133(3):487–95.