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Opinion

Information theory in vertebrate stress physiology

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Information theory has been applied productively across biology, but it has been used minimally in endocrinology. Here, we advocate for the integration of information theory into stress endocrinology. Presently, the majority of models of stress center on the regulation of hormone concentrations, even though what interests most endocrinologists and matters in terms of individual health and evolutionary fitness is the information content of hormones. In neuroscience, the free energy principle, a concept offered to explain how the brain infers current and future states of the environment, could be a guide for resolving how information is instantiated in hormones such as the glucocorticoids. Here, we offer several ideas and promising options for research addressing how hormones encode and cells respond to information in glucocorticoids.

Highlights

Information theory has been applied productively in many biological subdisciplines but it has only just begun to be applied to stress endocrinology.

Information theory has been critical to the development of neuroscience as a key subdiscipline and we expect the same for endocrinology.

Integrating information theory to stress biology will allow developing fully cohesive, quantitative models of stress focused on relationships among traits, trait categories, and trait–environment interactions.

Information theory and endocrinology

Most endocrine models of stress focus on variation in hormone concentrations [1–4]. This approach is partly justified because theories are only useful when they are based on measurable things. Moreover, steroid hormones such as the glucocorticoids (GCs) clearly help organisms endure, avoid, or recover from stressors [5–7], so understanding their regulation is important. However, what inferential shortcomings do we risk when we assume that hormones alone instantiate the phenomena we want to understand? We want to know what hormone differences make a difference (i.e., result in phenotypic change), but how well do concentrations capture the difference-making propensity of GCs [8,9]?

Many readers will recognize Gregory Bateson's famous phrase 'differences that make a difference', which he offered as a simple definition of **information** (see Glossary). The concept of information and the approaches of information theory have been applied productively across biology [10,11], but they have only just begun to be applied to stress biology [12,13]. Their promise becomes obvious, though, when we confront a critical aspect of all extant endocrine models of stress: what we mean when we claim that hormones mediate other traits. Mediate implies a sort of cause–effect relationship, at least that more hormone leads to more phenotypic change. At the level of individual cells, such cause–effect relationships are plausible, but at organismal levels, hormonal effects are complex [14,15] with some manifesting and resolving over hours to days [16], others enduring very long periods [17,18], and some even spanning generations [19–21]. Across biological levels, causal relationships are also quite often **hormetic** [16,22], and vary temporally, too, with acute and chronic elevations having distinct outcomes [5,23].

In this opinion paper, we discuss how information theory could lead to a deeper understanding of how GCs mediate adaptive responses to stress [24–28]. We expect that application of an information-based concept developed in neuroscience, the **free-energy principle (FEP)**, will lead to a fully cohesive and quantitative model of stress focused on 'relationships among traits, trait categories, trait–environment interactions' and GCs [8].

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A short primer on information theory in biology

Information theory was introduced by Claude Shannon in the late 1940s in the context of improving communication systems [29]. His goal was to develop a theory for how data sources should send information, or signals, to receivers given that transmissions were likely to be altered *en route* by noise (Box 1). Many researchers were and are skeptical of the utility of information theory in biology [30]. They argue that because biological information is semantic (i.e., it has meaningful content [31]), Shannon's metrics would usually be insufficient (but see later). In fact, information theory has been incredibly useful to biology, especially neuroscience [11]. Some of the original

Box 1. Noise and structural errors in endocrine systems

In his development of information theory, Claude Shannon [29] used the idea of a communication channel: a sender that transmits information and a receiver that detects it, with a noisy channel intervening the two. In endocrine systems, communication channels consist of many parts, each of which are potential entryways for noise. The typical steps in a stress response include release of glucocorticoids (GCs) from the adrenal glands (in response to upstream perception by sensory system, processing by the hypothalamus, and stimulation of the pituitary; the HPA axis), transport of the steroids in the blood, diffusion of free hormone to cells, binding of hormone to membrane-bound or intracellular receptors, and downstream effects on second-messenger cascades and subsequent gene transcription [5,8]. Additional complications can arise from local production of high levels of GCs in some tissues [88], an information channel that lies outside the HPA axis [89]. Here we describe two kinds of noise: (i) statistical, molecular noise; and (ii) distortion by competition for binding among different ligands, and additional errors that arise when systems fail to update Bayesian priors appropriately.

Noise: noise corrupts information such that a receiver is less certain of what the sender sent. In digital communication, examples include processes that randomly change 0s to 1s or vice versa (a kind of white noise). Shannon's theory identified general principles underlying when and how information could be sent reliably, despite noise. In endocrine systems, a potential analog of Shannon noise arises from the digital nature of receptor–ligand binding: for any given receptor, the ligand is either bound or not, a kind of biological 1 or 0. Because many random events affect ligand binding (i.e., a random walk causing a hormone to arrive at a binding site) or unbinding (i.e., thermal agitation), interactions are inherently noisy. Such noise often is hidden because the physiological reactions we observe reflect the outcome of many ligands interacting with many receptors, such that noise disappears into the law of mass action. Nevertheless, many decisions made by cells depend on so few underlying molecules that they appear to operate close to the limit at which this kind of noise becomes consequential [90]. For example, based on published values of GR capacity [91,92] together with estimates of number of proteins per cell for various taxa and cell types [93], we estimate that individual brain and liver cells in small birds contain on average 10–100 GRs per cytosol. At supra-cellular levels of organization (tissues and above), small-number errors may be minimized by averaging across cells within a tissue (i.e., 'antenna diversity' used in many human wireless communication systems). However, as yet we are unsure how GC effects on cells scale up to tissue-level effects.

Distortion: distortion arises from shifts in factors such as temperature, pH, oxygen levels, and ionic contents but also injury, infection, or even developmental or genetic forces. These factors can have fundamental effects on chemical reactions and interactions that comprise communication channels [10]. In humans, for example, rising body temperature drives a steep decline in the binding affinity of corticosteroid binding globulin (CBG) for cortisol [94]; as a consequence, more hormone becomes available to diffuse into cells and interact with receptors. For individuals with hypo- or hyperthermia, these effects may systematically distort GC-signaling. Likewise, steroid receptors typically bind different ligands with different affinities, leading to the possibility of interfering crosstalk among signaling systems [95]. For distortions like the aforementioned, it often is unclear whether they represent undesirable noise (corrupting the focal signal) or a semiotic signal in their own right. Cameron *et al*. [94], for example, argue that the effect of temperature on CBG binding affinity may be adaptive during a fever.

Inappropriate updates to the Bayesian brain–body system: as argued in the main text, an animal can be viewed as a Bayesian brain that communicates with the Bayesian body, such that both the brain and body have expectations: priors. For the brain, priors are expectations about how the world works and major deviations from those priors can lead to GC surges in circulation [12]. For the body, priors describe encoded expectations about the information content of signals from the brain. Priors for both brain and body are constantly being updated by new experiences. In this context, distortions to the organismal system (i.e., chronic stress) might occur when priors (of the brain or the body) are updated in unhealthy (i.e., evolutionary atypical [96]) ways. In humans, for example, early life stress (ELS) can arise from neglectful or abusive parenting. ELS often has negative lifelong consequences, including emotional reactivity, attention deficits, and a broad range of other emotional and affective disorders. These changes can be traced to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and downstream tissues [97]. Even if children with ELS later find themselves in more stable, supportive relationships and environments, the Bayesian brain–body complex often seems unable to further update its priors to reflect these benign realities [55].

Glossary

Band-pass filters: in electronics, band-pass filters remove sound frequencies outside particular size windows. Here, we portray molecules such as FKBP5 as band-pass filters that set bounds on the semiotic (or meaningful) information fraction of glucocorticoid concentrations.
Bayesian priors: probability distribution reflecting *a priori* knowledge about a model and its parameters before a Bayesian analysis.
Emergency life history state: facultative changes in animal behavior and/or physiology induced to maintain or restore homeostasis in response to unpredictable challenges.
Entropy: a measure of disorder, the average amount of information needed to represent an event drawn from a probability distribution or density. Entropy is therefore also a measure of surprise or uncertainty.
Free-energy: an information theory quantity that places an upper limit on the entropy (surprise) of the outcome sampled from a probability distribution.
Free-energy principle (FEP): a formal statement recognizing that biological systems minimize free energy to reach equilibrium with their environments. The principle conceives living systems as nested sets of Markov blankets that try to minimize the difference between models of the world and the perceived state of the world (i.e., approximate Bayesian inference), enabling them to withstand a tendency to disorder.
Hormesis: a biphasic dose response phenomenon characterized by a low-dose response that has opposite effects at high doses.
HPA flexibility: rapid (over the course of minutes to days), reversible changes in glucocorticoids that occur within individuals in response to unpredictable challenges.
Information: the reduction in uncertainty of a system on the basis of the difference between two states of the system. Information reduces surprise and thus increases predictability.
Markov blanket: a mathematical construct that defines the boundaries of complex systems (e.g., a cell or a multicellular organism) in a statistical sense.
Reaction norms: graphical and statistical representation describing the pattern of phenotypic expression of a

models involving information in the nervous system conceived of information in either simple [32] or somewhat more complex but largely linear (i.e., frequency modulation of trains of impulses) ways [33]. These models eventually fell out of favor, but they laid a foundation for a powerful systems-based concept: the FEP [34].

The FEP was originally proposed by Karl Friston to explain brain function and organization [34,35]. However, as FEP is based on thermodynamic concepts, it is applicable to any system with distinct, independent internal and external states that persist over time (i.e., any nonequilibrium steady-state system). Any such system will, by necessity, possess a **Markov blanket**, a mathematical construct comprised of active and sensory states that enables an internal state (i.e., a system or model) to make inference about external states but also to persist in the face of **entropy** [35] (Figure 1A). In the case of the brain as a Markov blanket, how neurons fire to affect behavior at any given time comprises its active states; how neurons fire to detect photons, odors, or other conditions of the world comprise its sensory states.

Critically, the internal state of the brain (or any system with a Markov blanket) ultimately obtains a model of the external world; without one, it cannot persist. As an example, consider a drop of ink in water. Usually, such a drop would disperse rapidly, with the system (ink and water) reaching maximum entropy once the ink is fully dispersed. By contrast, a system possessing a Markov blanket would resist entropy by being self-evidencing. That is, it would maximize model evidence for its existence by comparing stimuli from active and sensory states to its internal model, then update its internal model or take action on the world to enable system persistence.

It is from comparisons of the internal model to evidence from sensory and active states that the term '**free energy**' is derived. Free energy is the difference (in terms of uncertainty) between the model of the internal state and the information gleaned from active and sensory states. The key insight of FEP is that any nonequilibrium steady-state system, generally, must work to minimize free energy, or **surprise** (i.e., the time-average of entropy or uncertainty), by comparing an existing probability distribution about stimuli the system could experience against stimuli it does experience, then act on the world or update the **Bayesian priors** of the internal model to better match evidence [36]. According to the FEP, animal brains (and any constituent parts of living things with Markov blankets) are therefore collections of information about the world, amassed over different time scales and encoded in different ways. Encodings obviously include genes, but they also include molecular epigenetic configurations [37], alternative, stable states of homeostatic feedback loops [38], electrical patterns [39], and neural memories [40]. Any factor that can provide priors against which surprise is determined can be a consequential form of information [36].

How Bayesian brains might encode information in hormones

The FEP should be valuable to endocrinology [12] because information can be encoded by any entity that reduces uncertainty in some other system [41], including a steroid molecule, but also any other factor (i.e., a hormone receptor, a steroid degrading enzyme, etc.) with a propensity to reduce uncertainty in another system. Critically, the measure of uncertainty resolved by a signal is its information content or meaning [42]. What needs to be resolved is how the brain encodes meaning about stressors into GCs. In the light of FEP, then, circulating GC concentrations can probably be understood as the outputs of active state of the brain's Markov blanket, reflecting directly whether the world is unfolding according to the brain's expectations [12] (Figure 1A). In this sense, GCs must convey to the body information about stressors, but just what form this information takes is, as yet, unclear (Box 2). In the nervous system, information is based on the timing of action potentials and/or the firing rate of neurons [43]; information as adduced by synapses that

single genotype along an environmental gradient.
Semiotic information: the meaningful fraction of information in a signal. The difference that makes a difference.
Surprise: the negative log-probability of an outcome. In a Bayesian context, a highly improbable outcome is very surprising.
Syntactic information: measure of statistical correlation between two systems, regardless of the meaning of such correlations. From the perspective of Shannon information theory, how much knowledge of the state of one system decreases statistical uncertainty about the state of another system.

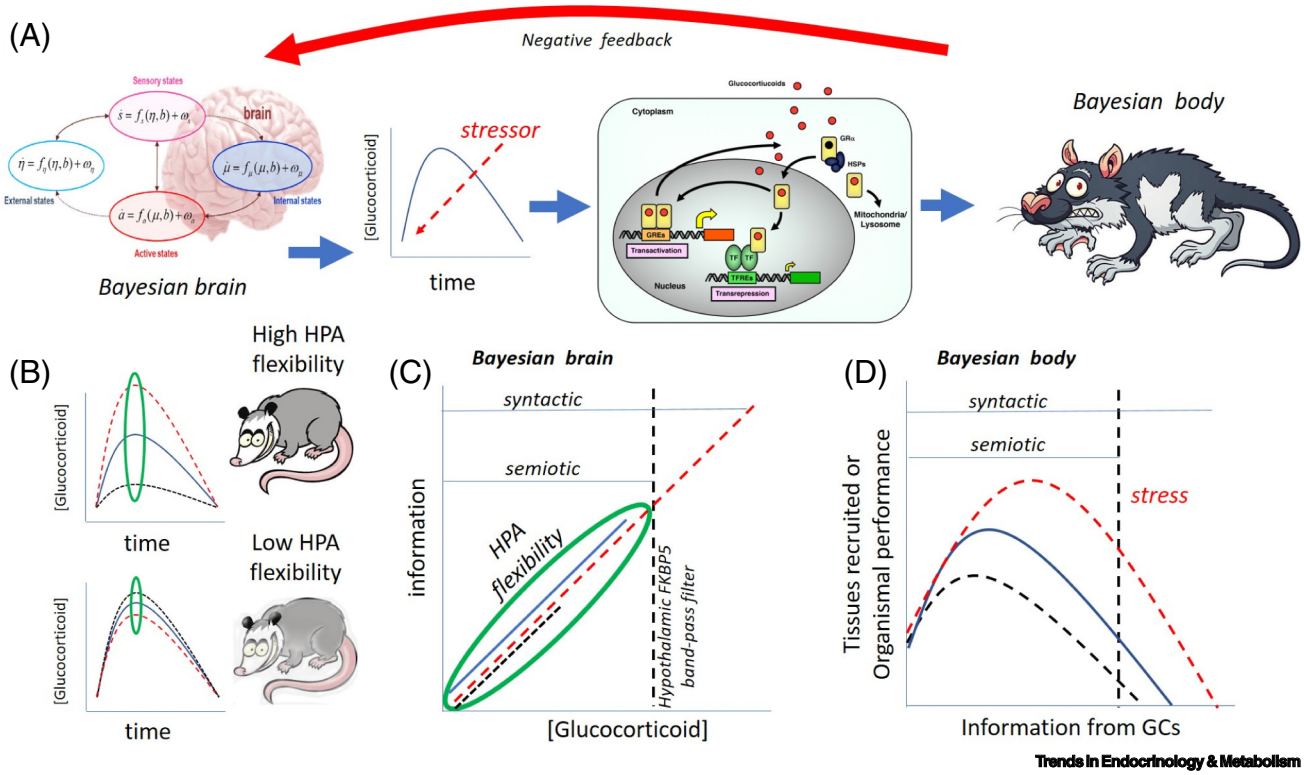

Figure 1. An information-based framework for stress endocrinology. In a broad sense, endocrinology has always been focused on information, but the inferential promise of information has yet to be fully tapped. Typically, the effects of glucocorticoids (GCs) in the context of stressors are investigated in indirect ways such that correlations are sought between hormone concentrations and phenotypic form or function. For instance, both in biomedicine (i.e., allostasis) and evolutionary endocrinology (i.e., the GC-fitness hypothesis), stress is studied by seeking links between single or a few hormone measurements and individual health or fitness. Whereas a focus on GC concentrations has been partially successful, it oversimplifies the role and form of information in endocrine systems, tacitly assuming that concentrations are the difference makers. In this paper, we highlight the need to study hormones as conduits of information. (A) According to the free-energy principle (FEP), Bayesian brains perceive and transduce syntactic information about stressors into hormone concentrations such as GCs. Importantly, though, information in GCs only becomes semiotic (i.e., meaningful) once it binds to receptors. The Bayesian body therefore plays a major role in the use of endocrine information. (B) As one important step towards an information framework in stress endocrinology, a useful step given the technical difficulties of describing the Bayesian body, we propose a focus on hormonal regulatory flexibility. Different stressors elicit different stress responses (differently colored lines), but whether individual animals are highly or minimally flexible in how they regulate GCs in response to various stressors is little studied (green ellipses). We hypothesize that such hypothalamic–pituitary–adrenal (HPA) flexibility varies among individuals because the scope of syntactic and semiotic information that brains can encode in GCs differs depending on genetics, epigenetics, and environmental factors. (C) In addition to simply describing HPA flexibility among and within species, we must also resolve whether and how changes in concentrations relate to GC information content. We predict that only some variation in GC concentrations will make a phenotypic difference (i.e., encode semiotic information); residual concentrations might either persist to reduce noise or be an artifact of steroid synthesis and release. We also expect that at least one neural mechanism (i.e., *FKBP5* expression, dashed vertical line) acts as an organismal band-pass filter, restricting the range of semiotic information GCs can encode within a single individual. (D) Ultimately, we will want to discern how the Bayesian brain interacts with the Bayesian body. All cell types express glucocorticoid receptors (GR) and most express mineralocorticoid receptors (MR), but most cell types can also learn from experience (via epigenetic alterations of their DNA). This additional molecular diversity means that information in GCs could functionally be unique among animals, partly due to evolutionary legacy but also developmental experience. Credit for the possum picture in A: https://www.istockphoto.com/illustrations/possum-cartoon-animal-characters; credit for the possum pictures in B: https://hdclipartall.com/img-1678.html.

activate the release of neurotransmitters, which affects behavior. For GCs, meaning in concentrations is apt to be more complex. The degree and duration of GC elevations affect the amount and form of phenotypic change [36]. GC effects also tend to be nonlinear, hinting that concentrations are probably interpreted in more of an analog than digital manner, at least relative to other systems [44]. Even if GC binding to single receptors is digital, only once a GC binding threshold is surpassed on a cell or cell class (i.e., a given number or fraction of receptors is bound) is an alternative phenotype engaged [45]. We strongly advocate that attention be paid to how GCs encode information, which we expect will be more similar to cardiovascular than to visual or auditory systems [36], but as yet, this issue is unresolved (Box 2).

Box 2. Resolving how hormones encode information

MRs and GRs are probably the most-studied receptors in all of biology [7]. Indeed, GR signaling was the basis of our understanding of the regulation of gene transcription in vertebrate cells [7]. Although we thus have a fairly detailed appreciation of how GCs enter cells, bind to GRs, translocate to the nucleus, dimerize, and find and interact with glucocorticoid response elements in the genome, it remains obscure how information is instantiated by the brain in GC fluctuations. We propose that an important first step to revealing the semiotic information content of GCs for a given cell type would be to describe the mathematical function relating hormonal concentration to phenotypic change (Figure 1C). Already, differences in such GC sensitivity are known to exist [49]. Some of this diversity in GC sensitivity is probably due to variation in the absolute expression of intracellular high-affinity MR and low-affinity GR, as well as the ratio of expression of GR/MR (Figure 2). Although too few data exist to make a definitive statement, these patterns suggest that some fraction of information in GCs will be syntactic, existing simply to accommodate noise as hormones move from the adrenal glands to their target tissues (Figure 1C, Box 1). The remaining fraction, however, will probably be semiotic but in a bespoke manner. Various cell types should be able to extract more meaning from modest concentration changes by virtue of their relatively greater number of GRs or/and lability of GR expression; many cell types will be recruited to stress responses only when GCs reach very high levels. Altogether, we expect GCs help organisms cope with stressors by engaging different cell types, depending on how much and for how long GCs remain elevated (driven by the brain) and how the Markov blankets of each cell type senses, acts, and updates its priors.

Testing these predictions should start with efforts to measure GR and MR expression distributions and inducibility among tissues and over time. Equally important will be work describing the concentration regimes over which cell types are sensitive to GCs. The shapes of such GC performance curves should capture well how semiotic information in GCs manifests to individual cells and cell types. Importantly, too, the parameters describing these GC-performance functions could serve as quantitative metrics used to parameterize mathematical models of stress at the cellular level. A major remaining challenge will obviously be to integrate GC effects across tissues, organs, and whole organisms. However, because natural selection acts on how GCs mediate fitness, not GCs themselves, as a start we should be able to focus on a subset of organs or physiological systems particularly relevant to health and fitness for our focal organism.

Perhaps the major concern about information in endocrinology is that hormones alone cannot contain all meaning; some meaning manifests only once signals are interpreted [46]. Of course, some meaning is imbued to GCs by the brain, otherwise, the hypothalamic–pituitary–adrenal (HPA) axis would not have endured over the evolutionary past [47]. However, some meaning must arise when the Bayesian brain interacts with the Bayesian body. Several observations support this proposition. First, steroid actions on somatic targets are slow to occur, tending to function by altering gene expression over minutes to days [7]. Cells and tissues, therefore, must extract some meaning so phenotypic change occurs over a window of time appropriate to a resolving or otherwise dealing with a stressor [36]. Second, the production and release of GCs will naturally involve some error; such noise could arise via degradation of hormones in the body over time but also via active metabolism (e.g., 11β-HSD), over- or under-activity of hormone-synthesizing cells, and/or cell-to-cell variation in the ability of cells to detect or respond to concentration changes (Box 1). How much of the meaning in circulating hormone concentration as encoded by the brain is just a means to mitigate noise? How much are corticosteroid-binding globulins (CBGs), molecular chaperones such as FKBP5, and other factors somatic mitigators of noise in GCs [48]?

Finally, and perhaps most importantly, information residing in GC concentrations is biologically inconsequential if it is not extracted. A useful way to think about this situation is to distinguish **syntactic information** from **semiotic information** [11]. Syntactic information is agnostic about the meaning of a signal; syntactic information can affect a system, but not in a manner wholly consistent with the intended function of the signal. Semiotic information, by contrast, is a subtype of syntactic information, but one that makes a difference with respect to a particular function. As an example, think about the sound our ears perceive when listening to music. We hear the song we want to hear and the musicians want to play, but we also hear accidents in the playing of instruments, background noise, and all sorts of other putative information that has nothing to do with the meaning of the song. Syntactic is all of the sound we hear; semiotic is the music we want to hear. How does the body extract semiotic from syntactic information in GCs?

Bayesian brains need Bayesian bodies

Somatic cells can generally trust stressor-relevant information in GCs because GCs are regulated by the brain and, as self-evidencing is imperative for complex systems to persist [34], the amounts of GCs in circulation can reliably be interpreted by the body as what the brain intended to put there. The questions remain though: how does the body distinguish signal from noise in GC concentrations [10] and how does it parse semiotic from syntactic information?

We expect that both issues are resolved by the Markov blankets and the internal models of somatic cells themselves. We know that different cells can respond differently to GCs (i.e., GC sensitivity [49]) and we expect that this condition endures so cells are recruited to stress responses based on their utility [36]. When GCs bind to receptors, the amount of receptors bound relative to the amount bound in the otherwise same context without a stressor (i.e., the standing generative model of a given cell type) can be compared to internal model expectations. Depending on experience and context [50], the internal state of the cell will enable cells to respond differently to stressor-relevant information should a model update be the most effective way to minimize free energy [37,51]. Alternatively, or additionally, prediction errors can be used to activate appropriate downstream pathways given GC concentration and other states of the cell as well as other stimuli perceived through sensors [20]. Also, the sensory states of cellular Markov blankets probably also maintain somatic **band-pass filters** that distinguish normal, biorhythmic changes in GC concentrations from those elicited by stressors.

We hypothesize that different cell types, but also different populations and species of vertebrates, will have distinct somatic propensities to extract semiotic information from GCs (i.e., distinct and diverse Bayesian bodies). Figure 2 shows that the tissues of lab mice differ extensively in how

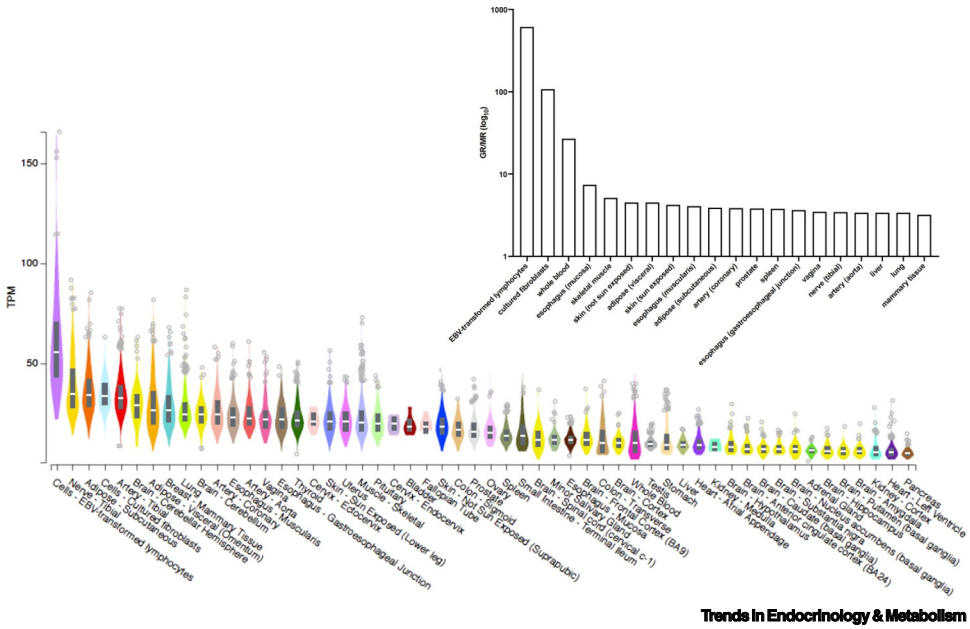

Figure 2. Glucocorticoid receptor distribution among murine tissues. Tissue distribution based on data from https://www.gtexportal.org/home/gene/NR3C1. Inset figure is glucocorticoid receptor (GR)/mineralocorticoid receptor (MR) ratio (log_{10} transformed for visibility) in the top 20 most GR-biased tissues. These figures depict the propensity of various cell types to respond to the salient information content of glucocorticoids (GCs). For instance, even modest increases in GC concentrations in response to stressors should be semiotic for lymphocytes and fibroblasts. By contrast, mammary and lung tissues should detect little to no semiotic information content of stressor-associated pulses in GCs. See also Box 2. Abbreviations: EBV, Epstein-Barr virus; TPM.transcripts per million.

much glucocorticoid receptor (GR) and GR relative to mineralocorticoid receptor (MR) they express. We expect that with exposure to every subsequent stressor, DNA methylation and other epigenetic mechanisms can further alter the meaning of GCs to mice, and probably most other species, by modifying the Bayesian body contingent on the evolutionary history, life history strategy, and ecology of the species [52]. Some cell types and species will probably be exceptionally flexible, whereas others will not. In support, the transcriptional effects of GCs are tissue- and cell type-specific [49], with variation largely conferred by differences in the chromatin landscape of each tissue [37]. We predict that there is also a master band-pass filter in the brains of all species (i.e., FKBP5, Figure 1C) that sets an upper bound on meaningful GC concentrations circulating in the body through its role in negative feedback [53] (but see [54]). To us, any model of stress that does not explicitly account for role of the Bayesian body in GC regulation (i.e., how information is encoded to make a difference), will be incomplete [55].

The empirical value of information theory to stress endocrinology

Presently, it is challenging to describe GR sensitivity and receptor dynamics in the cells of live animals, although some options exist for the former [49]. In the short term, we propose a focus on the regulatory nimbleness of the HPA axis, what we call **HPA flexibility** [56]. We think that HPA flexibility captures the scope of information content that can be encoded in GCs by the brain. As with any form of phenotypic flexibility [57], HPA flexibility should enable organisms to match their whole phenotype adaptively but reversibly to changing environments [8]. In regard to information, we expect that HPA flexibility represents the propensity of an animal to use centrally derived GCs as an information conduit (Figure 1B): individuals that can achieve the most diverse forms of GC elevations and negative feedback control should cope best with stressors, novel or not [58]. These organisms would have the greatest latitude and flexibility to recruit and call off various cell types as stress builds and is resolved.

We advocate for the study of HPA flexibility over measurements of single GC concentrations or even stress responses (i.e., GC release induced by brief psychological duress), as HPA flexibility captures something critical that popular approaches do not: that all individuals will cope with many and varied stressors across their lifetimes (Figure 1B). Responsiveness to stressors, generally, seems to be what we seek to describe when we quantify repeatability in baseline, post-stressor, and post-negative-feedback GCs [59]. Indeed, this directive partly explains why GC **reaction norms** [8] have become popular to measure [60–62]. We think, however, that HPA flexibility is more informative than reaction norms, as it represents a more holistic form of GC regulatory performance while embracing more directly the important tenets of information theory, although reaction norms in HPA plasticity, in principle, could also be measured.

A shortcoming of HPA flexibility as a focal trait is that it is time-consuming to describe. To do it well, organisms must be exposed to various stressors over time and GC concentrations measured repeatedly. One option that might circumvent this challenge entails measurements of the expression of *FKBP5* [56]. In the hypothalamus, *FKBP5* influences how GR regulates negative feedback on GCs (Figure 1C). In house sparrows (*Passer domesticus*), many lab rodent strains, and humans, *FKBP5* expression is also correlated to HPA flexibility or something akin to it [56]. In house sparrows, too, hypothalamic *FKBP5* expression is correlated to expression in whole blood [63]. Practically then, peripheral *FKBP5* measurements might inform us of HPA flexibility without having to measure HPA flexibility directly.

Concluding remarks

We think we are now asking too much of GC concentrations as proxies of stress [64,65]; indeed, GC concentrations typically relate only loosely to health and evolutionary fitness [14,16,66]. Many scientists have proposed that new and important insights about stress will come from measuring

Outstanding questions

How are syntactic and semiotic information encoded in GCs?

How does information in GCs accommodate the different time scales on which the brain and body operate? Neurotransmitter effects largely arise in seconds, whereas most steroid effects span minutes to hours or even days.

Does HPA flexibility capture the scope of semiotic information that can be communicated to the body by the brain via GCs?

How does the body inform the brain about its struggle with or resolution of stressors? Is negative feedback ever delayed or it is always initiated once circulating GCs surpass some threshold?

What form of information, if any, is encoded in GC circadian rhythms?

Can we apply information theory to the regulation of other pleiotropic hormones such as androgens and estrogens?

How might information theory be used to generate basic operating principles for endocrine systems in synthetic or artificial organisms?

more HPA elements more thoroughly [67]. Although we agree in a general sense, more data alone will not suffice [68]. We need to couple more and better data with theoretical efforts directed at revealing how GCs encode information [69] (Box 2). When the field of neuroscience began to use information theory [43], it was transformed from a niche field into an influential subdiscipline of biology. We expect the same for endocrinology.

The most conspicuous promise of the integration of information theory into stress endocrinology is that it will foster quantitative parametrization of the determinants of stress, as has occurred in related fields [38,70–72], including robotics [73]. Endocrinologists will eventually be able to 'formulate, explore, and reject models at a pace that no experimental program can match' [43]. Such mathematical models might even point us to novel computational biomarkers of stress [36]. By conceiving of hormones as parts of an information control system [27,28], quantitative models, grounded in data, can be developed that cast GCs as one of many factors that mediate intra-organismal struggles for resources over a lifetime [26,74]. This perspective, in turn, will drive us to think about stress as a system-level process [75].

In this light, we can already make a few systems-style predictions about stress. We predict that the semiotic information content of GCs will instigate reductions in local cellular or tissue-level entropy by transiently or permanently reducing the number of physiological states that systems can take [12]. When GCs surge in the blood in response to stressors, phenotypes probably get switched into these less entropic states relative to the environment in which they occur (i.e., an **emergency life history state** [6,76]). Such decreased entropy (e.g., allocating fewer resources to reproduction or growth in the short term) likely manifests at the molecular level as simplified regulatory network complexity. Network simplicity could take many forms, including lower internode connectivity or higher centrality for the average node (i.e., fewer nodes connected to many other nodes). In the short term, modest adjustments to regulatory networks are expected in preparation for future stressors [13,75]. As stress becomes chronic, though, regulatory relationships could become permanently canalized to simpler states [77], which might underpin many diseases associated with chronic stress (Box 1).

Ultimately, we expect the lens of information theory to reveal GCs as one part of a complex physiological network evolved to optimize organismal performance in an adverse, unpredictable, or uncontrollable context [41,75,78,79]. Contrast this perspective with the allostasis model, arguably the currently most popular model of vertebrate stress. In that model, adaptive shifts in set points of homeostatic molecules occur to match anticipated changes in the environment or the organism's internal state [1,2]. Although homeostatic mediators including GCs do indeed have normal ranges, termed reactive scope [3], and homeostasis is without question integral to life [55], models of the molecules alone lack mechanisms to explain when/why/how GCs promote fitness, cause pathological damage [80], or compromise health [38]. In other words, homeostasis-oriented models do not focus on the GC differences that make a difference [49].

Many readers will appreciate that our perspective is in a way a restatement of Selye's general adaptation syndrome [81]. The key differences are that it leverages modern ideas from systems theory and GR and MR expression data collected in just the last few years [49]. Perhaps the distribution of GC receptors (or myriad other processes affecting information extraction across the soma [37,82]) is a major mechanism by which organisms respond in a surprisingly consistent, general way to adversity (Box 2). To us, GCs (in the context of stress) are best understood as endocrine signals that enable individual animals to become what the environment hints that they should be [83–86]. Information theory might help move us away from simple models of stress focused on changes in hormone concentrations to evolutionarily informed, systems-focused

models based on information as perceived and encoded by the brain and body [59,87] (see Outstanding questions).

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Declaration of interests

No interests are declared.

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