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Stress hypothesis overload: 131 hypotheses exploring the role of stress in tradeoffs, transitions, and health

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ABSTRACT

Stress is ubiquitous and thus, not surprisingly, many hypotheses and models have been created to better study the role stress plays in life. Stress spans fields and is found in the literature of biology, psychology, psychophysiology, sociology, economics, and medicine, just to name a few. Stress, and the hypothalamic-pituitary-adrenal/interrenal (HPA/I) axis and sympathetic nervous system (SNS), are involved in a multitude of behaviors and physiological processes, including life-history and ecological tradeoffs, developmental transitions, health, and survival. The goal of this review is to highlight and summarize the large number of available hypotheses and models, to aid in comparative and interdisciplinary thinking, and to increase reproducibility by a) discouraging hypothesizing after results are known (HARKing) and b) encouraging *a priori* hypothesis testing. For this review I collected 214 published hypotheses or models dealing broadly with stress. In the main paper, I summarized and categorized 131 of those hypotheses and models which made direct connections among stress and/or HPA/I and SNS, tradeoffs, transitions, and health. Of those 131, the majority made predictions about reproduction (n = 43), the transition from health to disease (n = 38), development (n = 23), and stress coping (n = 18). Additional hypotheses were classified as stage-spanning or models (n = 37). The additional 83 hypotheses found during searches were tangentially related, or pertained to immune function or oxidative stress, and these are listed separately. Many of the hypotheses share underlying rationale and suggest similar, if not identical, predictions, and are thus not mutually exclusive; some hypotheses spanned classification categories. Some of the hypotheses have been tested multiple times, whereas others have only been examined a few times. It is the hope that multi-disciplinary stress researchers will begin to harmonize their naming of hypotheses in the literature so as to build a clearer picture of how stress impacts various outcomes across fields. The paper concludes with some considerations and recommendations for robust testing of stress hypotheses.

1. Introduction

It has been nearly 85 years since Hans Selye brought the term stress to the field of physiology (Selye, 1936; see Viner, 1999 for history). The concept of stress has been a major boon (Fink, 2016a) for physiology, medicine, ecology, and evolution as is evidenced by the multitude of studies linking stress to behavior, health, tradeoffs, survival, and fitness. Stress, broadly defined, can impact all life, ranging from unicellular organisms, to plants, to vertebrates, and thus the role of stress in shaping selection, evolution, and tradeoffs is likely. Selye defined stress as "a state manifested by a specific syndrome which consists of all the non-specifically induced changes in a biologic system" (Selye, 1959) and, later, the "the nonspecific response of the body to any demand made upon it" (Selye, 1973). He went on to highlight the ubiquity of stress by stating "stress is not simply nervous tension; stress reactions do occur in lower animals, which have no nervous system, and even in plants" (Selye, 1973). But, despite these writings, and given Selye's initial work, stress is often operationalized as activity of the hypothalamic–pituitary-adrenal (HPA) axis, namely glucocorticoid hormone release, and to a lesser extent by the sympathetic nervous system (SNS) (Jackson, 2014). However, it should be noted that stress is not synonymous with the HPA axis or with glucocorticoids, and the terms are not interchangeable (MacDougall-Shackleton et al., 2019). Since Selye's initial introduction, there have been many refinements to and discussions on the concept and definition of stress (see: Yates and Maran, 1974; Vigas, 1980; Stott, 1981; Levine, 1985; Lazarus, 1993; Dhabhar and McEwen, 1997; Chrousos and Gold, 1992; Chrousos, 1998a; Lima, 1998; Buchanan, 2000; Creel, 2001; Kim and Diamond, 2002; Dallman,

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2003; McEwen and Wingfield, 2003, 2010; Romero, 2004; Levine, 2005; Armario, 2006; Monroe, 2008; Romero et al., 2009; Koolhaas et al., 2011; Johnstone et al., 2012; de Kloet, 2014; Oken et al., 2015; Fink, 2016b; Del Giudice et al., 2018; Epel et al., 2018), but there is still no consensus on a single, universal definition.

Even from the beginning, Selye noted the importance of stress and the stress response in adaptation (Selye, 1950, 1959), and for the role of stress in the transition from health to disease (e.g., the sickness syndrome and diseases of adaptation, Selye, 1946, 1973, 1976). For example, he stated "Indeed, there is perhaps even a certain parallelism between the degree of aliveness and the extent of adaptability in every animal and man." (Selye, 1950). This idea of stress and adaptation has continued and the stress response systems – mainly the HPA/I (interrenal) axis and to a lesser extent the SNS – have been prime targets for understanding how stressors can shape physiology, behavior, and evolution.

These two physiological systems have been expected targets for investigation given their complex and important roles in shaping many behaviors and physiological processes and because they are phylogenetically conserved (Denver, 2009a). They are particularly important as the SNS and HPA/I axis can integrate environmental and internal information about a broad range of challenges (or stressors) and thus can serve as a similar end point to many types of challenge (but see Romero and Gormally, 2019). We now know that the stress response is not non-specific, as Selye originally proposed: different stressors can lead to differential activity of stress mediators (McCarty et al., 1992; Levine, 2005; Fink, 2016b), responses can vary depending on time-of-day, situation, sex, age, species, or life-history (Romero, 2002; DeVries et al., 2003; Kudielka and Kirschbaum, 2005; Harris et al., 2012; Harris and Saltzman, 2013; Niedbala et al., 2018; Heck and Handa, 2018; Zhao et al., 2019). Additionally, the neural pathways relaying sensory information about stressors to the hypothalamus differ (see Herman and Cullinan, 1997; Harris and Carr, 2016), but HPA/I axis and SNS activation does occur in response to a wide variety of challenges. The basal, daily activity of these systems are critical for maintaining homeostasis and baseline hormone levels have important preparative effects (Yates and Maran, 1974; Sapolsky et al., 2000; Gjerstad et al., 2018).

Bidirectional interactions between the HPA/I axis and behaviors also exist, as axis activation and release of glucocorticoids can influence behavior, and behaviors can influence axis activity (Packard et al., 2016). Thus, unsurprisingly, many authors have devised hypotheses about how aspects of stress endocrinology underpin tradeoffs and life history stage transitions. But, the physiological mediators that will be highlighted as playing a major role in vertebrates (and in this review), namely the HPA/I axis and the SNS, are not universally necessary for organism to respond to stressors. For example, plants, bacteria, and multiple invertebrates can all behaviorally and physiologically respond and adapt to various stressors (e.g., Salmon et al., 2001; Nyström, 2002; Adamo, 2008, 2012; Hawlena and Schmitz, 2010; Verma et al., 2016) and they lack HPA/I axes and SNS. All cells of all organisms are capable of mounting cellular stress responses which are driven by a conserved set of proteins, collectively called the minimal stress proteome of cells (Kültz, 2005). This cellular stress response is thought to work with a separate but interconnected cellular homeostatic response to aid in cell survival (Kültz, 2005). Heat shock proteins are part of this minimal stress proteome, they function as molecular chaperones and are important for responding to thermal, as well as multiple other types of stresors (Kültz, 2005). For example, recent work in drosophila suggests that the cellular stress response (heat shock and associated proteins) can help to increase genetic variability in germ cells by creating de novo mutations, via increased activation of transposable elements, which would be beneficial for evolutionary responses to environmental stressors (Cappucci et al., 2019; Maggert, 2019). Heat shock proteins are also involved in the stability and regulation of glucocorticoid receptors in vertebrates (Kirschke et al., 2014; Rubin et al., 2014). Additionally, "stress granules" or membraneless organelles comprised of RNA and RNA binding proteins form in response to acute challenges (stressors) and are important drivers of cell function (Wolozin and Ivanov, 2019); they are also found across eukaryotic taxa (see Buchan et al., 2013). Invertebrates lack an HPA/I axis but still mount a neuroendocrine response to stressors, including the release of biogenic amines, some of which are similar to or the same as those involved in the SNS in vertebrates (e.g., dopamine, epinephrine, norepinephrine, octopamine [structurally similar to norepinephrine], and/or serotonin; reviewed in Adamo, 2012). Additionally, CRF- and POMC/ACTH-like molecules are fond in a variety of invertebrates and may help them cope with stressors (Ottaviani and Franceschi, 1996; Stefano et al., 2002). Thus while the HPA/I axis and SNS are no doubt important for vertebrate species, and conserved functioning of axis hormone precursors may be beneficial in other species, they are by no means the only way in which organisms can respond to and cope with changes in the environment. In all organisms, multiple interactions among molecular, genetic, cellular, neuroendocrine, and behavioral components are likely important to adequately respond to stressors (Ottaviani and Franceschi, 1996; Kültz, 2005; Adamo, 2012; Wada, 2019).

The aims of this special issue of *General and Comparative Endocrinology* are to 1) review the evidence that ecological tradeoffs lead to changes in endocrine function in wild animals and 2) address the possibility that ecological tradeoffs have shaped the evolution of endocrine axes. Although it is incredibly likely that bidirectional relationships between tradeoffs and stress (and the physiological stress response) have influenced evolution and selection, there exists a cause and consequence issue. Part of this issue is due to the nebulous definition of stress (see citations above) and the other is due to the complexity of endocrine systems (e.g., what aspect of regulation is selected for? – plasticity of response, magnitude of response, circulating hormone levels, receptor number or function, speed of feedback, etc.) and the determination of selection for adaptations vs exaptations (see Ketterson and Nolan, 1999 for a good discussion of this topic). Additionally, when asking how proximate mechanisms might support ultimate explanations, it is not clear if stress physiology directly determines outcomes (e.g., phenotype), if there is correlational selection pressure on stress physiology and related outcomes, or if outcomes determine stress physiology (Carere et al., 2010). Lastly, using hormonal phenotype-fitness relationships to answer questions about evolutionary endocrinology can be problematic (Bonier and Martin, 2016). The current review will not tackle the evolution of endocrine axes, per se, but will address the hypothesized relationships among stress, the endocrine stress response systems, and ecological and life-history tradeoffs as well as life-history transitions in vertebrates.

The hypotheses and models contained in this review span multiple scientific fields and address both proximate (how) and ultimate (why) questions. The goal of this paper is to provide a framework for comparing and contrasting predictions about stress tradeoffs, transitions, and overall survival. Additionally, it is the hope that multi-disciplinary stress researchers will begin to harmonize their definitions and hypotheses so as to build a clearer picture of how stress impacts various outcomes across fields. The layout of the manuscript is as follows: before discussing the hypotheses, I briefly describe the role of stress and stress mediators in tradeoffs (Section 2) and transitions (Section 3). I then describe and categorize the hypotheses found in the literature (Section 4; Fig. 1; Table 1) and briefly review the framework surrounding hypotheses related to reproduction (Section 4.1), development (Section 4.2), stress coping and variability (Section 4.3), health to disease (Section 4.4), and then cover stage-spanning hypotheses or models (Section 4.5). Lastly, I summarize why *a priori* hypothesis formation and testing is important (Section 5) and provide some practical concerns and caveats for testing stress hypotheses (Section 6).

2. Stress, stress mediators, and tradeoffs

Tradeoffs, or "fitness costs that occur when a beneficial change in

one trait is linked to a detrimental change in another" (Stearns, 1989; but see Zera and Harshman, 2001), are a central tenet of life-history and ecological theory (Stearns, 1989; Garland, 2014; Healy et al., 2019). Tradeoffs have also been recognized to play a role in the ecomorphological paradigm and for evolution of complex phenotypes (e.g., whole-organism performance; Garland and Carter, 1994; Lailvaux and Husak, 2014). Tradeoffs typically operate under the general assumption that resources are limited and available organismal resources (energy) are diverted to the processes or behaviors that are most beneficial in order to maximize lifetime reproductive success, but that this diversion comes at a cost (the Y model; Wasser and Barash, 1983; Bronson, 1989; Reznick et al., 1990; Roff, 1992; Stearns, 1992, 2000; Zera and Harshman, 2001). The necessity for organisms to partition limited resources has led to several proposed tradeoffs (Stearns, 1992, 2000). Examples include balances between current vs. future reproduction, reproduction vs. survival, reproduction vs. growth, offspring number vs. offspring size, age/size at maturity vs. lifespan, feeding vs. fleeing behavior, sexual selection vs. predation (extravagance handicap), interbrood/-birth interval and offspring survival, solitary vs. social living, as well as many others (Hamilton and Zuk, 1982; Stearns, 1989, 1992, 2000; Lima and Dill, 1990; Roff 1992; Blumstein et al., 2010). The stress response is thought to be costly (Lankford et al., 2005; Vermeulen and Loeschcke, 2007), making it likely to be involved in these types of tradeoffs.

The mechanisms that drive and support tradeoffs can be classified as genetic, phenotypic, or intermediate (Stearns, 1989). Traditionally, tradeoffs at the genetic and phenotypic levels have received the most attention and empirical testing, however, the role of intermediate structures (e.g., physiological and developmental mechanisms under hormone control) in linking genotype to phenotype are incredibly relevant but have received relatively little attention and are largely unknown (Stearns, 1989, 2000; Ketterson and Nolan, 1999; Ricklefs and Wikelski, 2002; Moore and Hopkins, 2009). Specifically, the role of the endocrine system is likely critical as hormones coordinate many physiological and behavioral endpoints and can have pleiotropic effects (Williams, 1957; Ketterson and Nolan, 1999; Zera and Harshman, 2001; Ricklefs and Wikelski, 2002; Moore and Hopkins, 2009; Lailvaux and Husak, 2014; Cox et al., 2016; Garland et al., 2016), making them prime candidates for linking multiple traits, and connecting genotype to phenotype (Stearns, 1989).

The hormonal cascades associated with the endocrine stress response, that is activation of the hypothalamic-pituitaryadrenal/interrenal (HPA/I) axis and sympathoadrenomedullary system, have been suggested to mediate various tradeoffs. Due to the multiple functions of the glucocorticoid hormones (Sapolsky et al., 2000; Hau et al., 2016), and the relative ease with which these hormones can be measured, the HPA/I axis has received the most attention. Baseline levels of glucocorticoids are necessary for metabolic, brain, and homeostatic regulation on a daily basis (Sapolsky et al., 2000), as these hormones are released in a circadian pattern, with the endogenous glucocorticoid peak occurring just prior to the onset of daily activity (Dallman et al., 1987, 1993; Chrousos, 1998b; Sapolsky et al., 2000; Landys et al., 2006; Harris et al., 2012; Lightman, 2016). The HPA/I axis and the glucocorticoids are also critically important in the organismal response to stressors and can have permissive, suppressive, stimulatory, or preparative effects, depending on the location, time course, tissue type, and receptors involved (Sapolsky et al., 2000; Sapolsky, 2002). Glucocorticoids act on numerous cell types and physiological systems and affect a large number of organismal functions, including multiple behaviors, emotion, cognition, immunity, energy partitioning, metabolism (via suppression of insulin secretion and stimulation of gluconeogenesis, lipolysis, glycogenolysis, and proteolysis), feeding, locomotion, and reproduction (Dallman et al., 1993; Stratakis and Chrousos, 1995; Chrousos, 1998a; Sapolsky et al, 2000; Sapolsky, 2002; Wingfield and Sapolsky, 2003; Boonstra, 2005; Reeder and Kramer, 2005; Ferin, 2006), all of which make these hormones prime candidates as mediators of resource allocation and tradeoffs.

While life-history theory mainly focuses on the distribution of limited resources (Reznick et al., 1990; Roff, 1992; Stearns, 1992, 2000), life-history and ecological tradeoffs can also appear when a physiological constraint exists within an organism (Ricklefs and Wikelski, 2002). For example, according to Ketterson and Nolan (1999), hormonal tradeoffs are "costs to potential fitness that occur when some but not all of the traits mediated by a hormone are beneficial." Given that hormones, and particularly the glucocorticoids, can control a suite of responses (i.e., have pleiotropic effects) this seems particularly fitting. It might be true that glucocorticoids influence both the acquisition of resources and the allocation of resources (Sapolsky et al., 2000), but glucocorticoid-mediated resource allocation may not be the only way in which a tradeoff is maintained. For example, just as physiological and hormonal constraints on behavior are observed in differing life-history states (Jacobs and Wingfield, 2000), activation of the stress-responsive systems (e.g., SNS and HPA/I axis) may produce scenarios that are no longer conducive to the expression of specific behaviors, regardless of energy availability. Thus, these hormones may play more direct, energy-mediating roles in tradeoffs or may have more indirect influences by making different behavioral or physiological states incompatible, regardless of energy status.

3. Stress, stress mediators, and transitions

Just as ecological and life-history tradeoffs are important for understanding organismal function, so too are daily, situational, ontogenetic, and life history stage transitions. All species undergo developmental changes from conception to maturity. For some species, these changes are rapid and maturation occurs quickly; for others, the process is slower, but in all species these transitions are critical. Developmental transitions for vertebrates can include fetal growth (either in utero or in egg), parturition or hatching, smoltification (salmonids), reproductive maturity, and dispersal from natal nest or territory. Repetitive life history stage transitions include those that occur cyclically and define the life cycle of an organism, such as migration, breeding, offspring rearing, and molting. These transitions are necessary, adaptive, and, in vertebrates, are driven, at least in part, by glucocorticoids (de Kloet et al., 1988; Romero, 2002; Landys et al., 2006; Wada, 2008; Denver, 2009b; Crespi et al., 2013; Buchholz, 2015; Fowden and Forhead, 2015; Fowden et al., 2016). In addition to the cyclical transitions, Wingfield and colleagues (1998) proposed a new transition to an emergency life history stage which can occur when current labile perturbation factors (challenges) have reached a critical threshold and the organism can no longer continue in the current life history stage. This emergency stage is likely driven by the HPA axis and glucocorticoids, and follows a set of behavioral and physiological adjustments to help the organism deal with the perturbations and increase survival (Wingfield et al., 1998; Wingfield and Kitaysky, 2002; Wingfield and Romero, 2010). Thus, glucocorticoids aid in the adaptive temporary suppression of the current life history stage.

Glucocorticoids play important roles in ontogenetic and life history stage transitions, but understanding how variation in the stress response correlates with coping and resilience, and how the stress response influences aging, senescence, and disease is not as clear. Stress in general, and glucocorticoids specifically, can absolutely impact aspects of mental and physical health, and the behavioral and physiological response to stressors (coping) can be an important link for the transition from health to disease. Both baseline and post-stressor levels of glucocorticoids can increase with age and impact the transition to senescence (Sapolsky et al., 1986; Masoro, 1995; Otte et al., 2005; Deuschle et al., 1997), and along with other stress mediators, glucocorticoids can shift an individual from a state of health to one of disease (Selye, 1973; McEwen and Wingfield, 2003; McEwen, 2008; Juster et al., 2010).

4. The stress hypotheses

Stress is ubiquitous and thus, not surprisingly, many hypotheses have been created to better study the role stress plays in life. Stress spans fields and is found in the literature of biology, psychology, psychophysiology, sociology, economics, and medicine, just to name a few. This review includes 214 different named hypotheses discussed in the literature, 131 of them are categorized and described in the main text (Table 1); the additional 83 hypotheses are included separately (Table 2). This is likely not an exhaustive list of all stress-related hypotheses, although every attempt was made to be extremely thorough. Importantly, effort was made to incorporate hypotheses that span disciplines with the goal of making work more integrative, comparative, and translational. To find papers I used Google Scholar and PubMed to search relevant terms (e.g., stress hypothesis, cort hypothesis, GC hypothesis, reproductive tradeoff, stress and health, etc.). I searched my own computer files and scanned social media for new papers. I also searched pertinent references of the sources I found. When searching for papers to include in the main body of this review, I narrowed my focus to those that mentioned the word stress specifically and/or included the role of classical stress mediators (HPA/I axis and SNS). Given the different fields included, and the ongoing debates within each field, about what, exactly, we mean by stress (see Section 1), here I will not attempt to provide a unifying definition. Instead, I will let the individual authors describe what they mean by stress within each paper. I did not categorize or expand on hypotheses related to immune function and oxidative stress due to their own extensive literatures (e.g., see Demas and Nelson, 2012; Costantini, 2014; Cain and Cidlowski, 2017), but the (non-exhaustive) list of hypotheses related to those topics can be found in Table 2. Table 2 also contains hypotheses that were tangentially related to the focus of the paper and were thus not included in Table 1. Additional reviews compiling stress literature, hypotheses, and predictions on immunity and oxidative stress would certainly be useful. In this paper I make no effort to review the legitimacy or the support for or against each hypothesis, unless this information was explicitly stated in the reference, as doing so would be too much for one paper.

The described hypotheses are categorized by the tradeoff or transition they most closely explain and major topics include: development (n = 23), reproduction (n = 43), health to disease (n = 38), stress coping (n = 18), and stage spanning hypotheses or models (n = 37). In addition to these major categories, some hypotheses also pertain to other or secondary topics (e.g., survival, social interaction, hormone regulation, performance, aging): these secondary topics are listed in parentheses in the Stage or Transition column of Table 1. Within in each major category, I tried to further organize the hypotheses into themes. Some themes were more cohesive and allowed me to match hypotheses by prediction, other themes were looser or more broad as I could not find a way to present totally unified predictions. Please see Supplemental Table 1 for an editable version of the Table 1 included here as readers may want to organize themes in a different manner.

Fig. 1 lists the hypotheses by major category, it should be noted that some hypotheses fit into more than one category and are thus listed more than once. However, when organizing Fig. 1, hypotheses that fit into the category of stage-spanning hypotheses or models were not listed in other categories as they could likely have been listed in every one. Thus, there could be much more overlap of hypotheses among categories than is currently listed.

Table 1 contains an alphabetized and more in-depth description of each hypothesis, including definition; predictions; stage or transition; taxon specificity; proposed mediators – categorized as HPA/I axis (glucocorticoids; GCs), autonomic nervous system, or other; and if relevant, baseline or post-stress GCs; and any additional notes. Out of the 131 hypotheses, 111 include specific mention of the HPA/I axis as a mediator with the most common dependent variable being the glucocorticoids. Of those that listed specific glucocorticoid predictions, 14 hypotheses addressed baseline glucocorticoid level only, 40 addressed post-stress levels only, and 52 additional hypotheses mentioned both baseline and post-stress levels. When possible to do so without losing meaning, the wording from the original text was shortened, in other cases, original text is used. I tried not to take away from the initial authors' writing and therefore terminology is not entirely consistent across Table 1 as I did not attempt to standardize word usage. This table is meant to be used as a reference and compilation, not an exhaustive work of each hypothesis. In all cases please see the original source for longer discussions of each hypothesis, and their background and rationale. It should be noted that the sources used are not always the first to propose the framework but were chosen because they were the first to formally name the hypothesis, to provide a great description of the hypothesis, or to make a major contribution to highlighting or reviewing the hypothesis. Some hypotheses are very detailed, specifying thorough predictions for direct mediators and likely moderators, whereas others are more general in their predictions. Some of the hypotheses listed are actually defined as models (e.g., Allostatic Load Model, Biological Sensitivity to Context Model, Reactive Scope Model, Traditional Model) and are much more comprehensive than straight hypotheses, thus not all items listed in Table 1 are equal in their descriptive and predictive power. Moreover, some hypotheses have been tested multiple times and others only a few (at least based on searches of the hypothesis name – the concept may very well have been tested in other papers). Future critical investigation of studies supporting or failing to support each hypothesis, or family of hypotheses, would certainly be illuminating. Additionally, several of the hypotheses are similar or nearly identical to one another in description and/or in predictions. I included them all to highlight how many hypotheses exist in the literature. Thus, the hypotheses listed here are not necessarily mutually exclusive. Lastly, many of the hypotheses from different fields have parallel ideas, or in some cases nearly identical ideas with different names. My hope is that overtime hypotheses will be tested, consolidated, and streamlined as the broad field of stress physiology moves forward. Below in Sections 4.1 through 4.4, I have outlined the basics of the literature framework for each of the hypothesis major categories listed in Fig. 1 and Table 1.

4.1. Reproduction: stress, GCs, and reproduction framework

The most prominent life-history and ecological tradeoffs are those surrounding the cost of reproduction (i.e., the marginal increase in adult mortality incurred by investing resources in reproduction; Stearns, 1976). In the 1930s, Fisher proposed that each individual has a reproductive value, or the mean amount of future reproductive success, and this reproductive value changes with age (Fisher, 1930). The "cost of reproduction" framework for life-history tradeoffs was formalized by Williams (1966) and states reproduction is costly and therefore a tradeoff between investment in reproduction vs self (maintenance or growth) exists. The Asset Protection Principle for ecological tradeoffs was proposed by Clark (1994) and states the larger the current reproductive asset, the more important it becomes to protect it. Thus, in general, reproductive tradeoffs have two major costs – those paid to survival and those paid to future reproduction (Stearns, 1989).

Investing too heavily in a current reproductive bout, specifically under challenging conditions, could lead to decreases in parental body condition (e.g., energy reserves, immune function), which could ultimately impact survival and future reproductive opportunities (Wasser and Barash, 1983; Roskaft, 1985; Bronson, 1989; Daan et al., 1990; Wingfield and Sapolsky, 2003). Which breeding option (current vs. future) is more favorable depends on a variety of organismal and environmental factors, including, but not limited to, nutritional and health status, somatic growth/body condition, social cues, abiotic and biotic resources, residual reproductive value, and current life-history state (Bronson, 1989; Stearns, 1992). Frequently, suppressing or triaging reproduction under currently unfavorable (stressful) conditions is more advantageous than wasting precious energy and resources on

Fig. 1. Categorization of HPA/SNS/stress hypotheses included in this review. Hypotheses may be listed in more than one category, depending on predictions (note: hypotheses listed under stage spanning or models do not appear in more than one category on this figure due to space). Descriptions, predictions, and additional details for each hypothesis can be found in Table 1 (superscript numbers refer to entry on Table 1).

reproductive attempts that are likely to fail (Wasser and Barash, 1983; Reznick, 1985; Bronson, 1989; Wingfield and Sapolsky, 2003; Harshman and Zera, 2007). Current dogma suggests that stress, and HPA/I hormones, promote fitness during challenging times by suppressing current reproduction (physiology and/or behavior) and shifting resources and behaviors to survival or future reproductive efforts (Wingfield and Sapolsky, 2003; Crespi et al., 2013). Using this framework, several hypotheses predict that during stressful times, organisms will favor self-maintenance and future reproductive opportunities at the cost to current breeding (Crossin et al., 2016). But, recent work has challenged this simplified view (see Breuner et al., 2008; Bonier et al., 2009a,b) and suggests the relationship between stress and reproduction is much more complicated and nuanced. Under specific conditions, however, organisms are expected to invest more heavily in current reproduction and thus show a blunted response to stress in order to protect reproductive effort (see Tables 1 and 2 in Wingfield and Sapolsky, 2003); this tradeoff often depends on an organism's ecology, environment, and/or life history stage.

Many of the proposed hypotheses covered in this review (n = 43 out of 131) address how, when, and by what mechanism these value of reproduction tradeoffs occur. The majority of these hypotheses make the assumption that elevation in stress mediators (mainly glucocorticoids) has a negative impact on current reproductive investment. In order to aid in comparing these hypotheses, I chose to classify them into one of five themes: 1) Increased stress/ GCs impair reproduction (25 hypotheses: Brood Value Hypothesis; Capricious Conditions Hypothesis; Christian (non-adaptive) Stress Hypothesis; Chronic Stress Hypothesis; Constraint Hypothesis; Cort (GC)-Adaptation Hypothesis; Cort-Fitness Hypothesis; Cort-Flexibility Hypothesis; Cort-trade-off Hypothesis; Current Reproduction vs. Survival Hypothesis; Parental Care Hypothesis; Predation Stress Hypothesis; Predation-Sensitive Foraging Hypothesis; Predator-Induced Breeding Suppression (PIBS) Hypothesis; Prudent Parent Hypothesis; Restraint Hypothesis; Senescence Hypothesis; Short-Season Hypothesis; Stress Hyporesponsiveness Period[2]; Stress of Subordination; Stress-Suppression Hypothesis; Terminal Restraint Hypothesis; Trade-off Hypothesis; Value of Reproduction Hypothesis; Workload Hypothesis), 2) Increased stress/GCs facilitate reproduction (5 hypotheses: Adaptive Stress Hypothesis; Energetics-Hormone Vocalization Model; Facilitation Hypothesis; (GC-Induced) Reproductive Conflict Hypothesis; Match-Mismatch Hypothesis[1]), 3) Increased GCs can either inhibit or facilitate reproduction (3 hypothesis: Context-Dependent Hypothesis; Cortisol Buffering Hypothesis; Current Condition Hypothesis), 4) Increased GCs are an honest signal for reproductive programming (6 hypotheses: Adaptive Theory Hypothesis; Developmental Stress Hypothesis; Economic Stress Hypothesis; Maternal/Offspring Match Hypothesis; Maternal-Match Hypothesis; Nutritional Stress Hypothesis), and 5) GCs are related to reproductive energetic status (5 hypotheses: Lean and Fit Hypothesis; Fat and Fit Hypothesis; Reproductive Stress Hypothesis; Energetic Stress Hypothesis). Supplemental Fig. 1 shows themed arrangement of the hypotheses. Please note, these hypotheses could likely be arranged in a variety of ways besides the way in which they are

Table 1
Summary of hypotheses and models included in the manuscript. When possible to do so without losing meaning, the wording from the original text was shortened, in other cases, original text is used. Readers interested in testing any of the hypotheses or models listed here are highly encouraged to read the cited paper(s) for more complete information. The sources used are not always the first to propose the framework but were the first to either name the hypothesis/model or to make a major contribution to highlighting or reviewing the hypothesis. In some cases hypotheses are nearly identical, either in name or in description/prediction, all are listed here to showcase the number of proposed hypotheses. ANS = autonomic nervous system; SNS = sympathetic nervous system; PNS = peripheral nervous system; HPA = hypothalamic–pituitaryadrenal; GCs = glucocorticoids; Cort = corticosterone or cortisol; MR = mineralocorticoid receptor; GC = glucocorticoid receptor. For Proposed Mediators, X = major variable, x = minor variable, no mediator is listed if the hypothesis just said "stress" but did not mention a specific factor. For hypotheses and models that clearly mentioned baseline or post-stress glucocorticoids, that is noted; column is blank it this information was not specified. (Please see Supplemental Table 1 for an editable/sortable version of this table).

#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
1	Adaptive Calibration Model (ACM)	Individual differences in stress responsivity are largely (though not exclusively) the result of conditional adaptation – the evolved ability of an organism to modify its developmental trajectory (and the resulting phenotype) to match the local conditions of the social and physical environment (see Fig. 1 in Del Giudice et al., 2011).	Information is encoded by the stress response system (ANS and HPA axis) during development and feeds back on the long-term calibration of the system itself, resulting in adaptive patterns and individual differences in life-history-related behavior. Suggests four (Sensitive, Buffered, Vigilant, Unemotional) prototypical responsivity patterns (see Table 1 & Fig. 2 in Del Giudice et al., 2011).	Model (Development; Stress Coping)	Yes, humans	X	X	X	baseline and post-stress	To explain humans but takes an evolutionary and life-history strategy approach. A well-developed form of the Adaptive Tuning Hypothesis. Expansion and refinement of the BSC (see section 1.2.1 in Del Giudice et al., 2011)	Del Giudice et al., 2011; 2012
2	Adaptive Stress Hypothesis	Reproductive success and fitness come at a cost to self-maintenance and survival (e.g., semelparous marsupials).	Increased GCs are associated with increased reproductive investment and fitness (and likely with age), but come at a cost to self-maintenance and future survival. Elevated GCs levels allow organisms with short lifespans to mobilize energy and reduce the need to forage, thus allowing animals to invest time in reproductive efforts.	Reproduction	No (but for species with short life-spans and early reproduction)	X			baseline	Originally developed to describe stress/GCs and reproduction in semelparous species. Rejected by study in meadow voles (Boonstra and Boag, 1992) Similar to Energy Mobilization Hypothesis and to the Survival vs. Fitness hypothesis.	Lee and Cockburn, 1985; Boonstra and Boag, 1992; Bradley, 1997; Wingfield and Sapolsky, 2003; Crespi et al., 2013
3	Adaptive Theory (aka Trivers-Willard Hypothesis)	In order to maximize future reproduction and fitness, stressed populations will adjust the sex ratio to favor the production of female over male offspring.	Increased levels of stress, and presumably GCs, should alter sex ratio to favor females over males. This could occur at various levels (e.g., sperm, fertilization, implantation, survival to term) and the mechanism by which stress (and GCs) impact sex ratio is not clear (see Figs. 1 & 2 in Navara, 2010).	Reproduction	No	x			post-stress	Initial papers say stressed populations, Navara (2010) summarizes the role of GCs in this phenomenon.	Trivers and Willard, 1973; Cameron, 2004; Navara, 2010
4	Adaptive Tuning Model				No	x		x			

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
		Except when the early environment is catastrophically stressful, the early environment is adaptive in preparing organisms for success in their later environment. Assumes early environment is a good signal of future environment.	Low and moderate early life stress helps to shape the adaptive ability to cope with future stressors. Parental care likely plays a role as does sex (See Figs. 4 & 6 in Sachser et al., 2011).	Model (Development; Stress Coping)					baseline and/or post-stress (of mother)	Similar to Inoculation Stress Hypothesis, but Adaptive Tuning predicts that all but the highest levels of stress produce an adaptive phenotype.	Del Giudice et al., 2011; Sachser et al., 2011; Sih, 2011
5	Alcohol Stress Response Dampening Hypothesis	Alcohol consumption buffers the effects of subsequent stressors.	The increase in negative affect in response to a stressor should be less for intoxicated individuals than sober individuals. Intoxication should also reduce HPA and SNS responses to stress.	Health to Disease; Stress Coping	Yes, humans	x	x		post-stress	Mixed findings as alcohol can increase HPA function but can also block increase in HPA activation following a stressor. Context and time course likely matter.	See Bresin, 2019
6	Allostatic Load Model	Allostasis can be defined as "stability through change." Organisms are able to cope with stressors for a given period of time and may even adjust physiologically to those stressors (allostatic state). If the energetic demand becomes too great (allostatic overload), the organism can no longer cope and several behaviors and processes will fail.	Severely elevated stress-mediators (GCs), or prolonged elevation of stress mediators (GCs), disrupt energy balance and behavioral and physiological investment (See Fig. 1 in McEwen and Wingfield, 2003; Fig. 1 in McEwen et al., 2015; and Fig. 3 in McEwen, 1998b, and see Fig. 4 in Juster et al., 2010 for list of mediators).	Model; Stage Spanning (Health to Disease)	No (but energetic thresholds may differ for ectotherms)	X	X	X	baseline and/or post-stress	Problems can occur after longer-term or repeated activation of stress systems, so changes in both baseline and post-response mediators may occur. Energy availability is important.	Sterling and Eyer, 1988; McEwen, 1998b; Schulkin, 2003; McEwen & Wingfield, 2003, 2010; Korte et al., 2005; Juster et al., 2010; McEwen et al., 2015
7	Anna Karenina Hypothesis	Exposure to stressors reduces the ability to regulate the microbiota community leading to greater variation in the microbiota of stressed individuals compared to non-stressed or healthy ones.	Upon exposure to a stressor, microbiota communities will respond by becoming more varied and unstable, and thus healthy microbiota communities will be more similar to one another than will stressed communities.	Health to Disease	Yes, microbiota					Every unhealthy microbiome is unhealthy in its own way. Implications for multiple species, ranging from corals to mammals.	Zaneveld et al., 2017
8	Attenuation Hypothesis	An individuals' neurobiological-psychological-behavioral systems is closely connected with the character of the physical and sociocultural environment in which the individual is embedded. All of this plays a role in establishment and maintenance of persistent antisocial behavior.	Biological vulnerability and early adverse family environments (e.g., inadequate care, frequent pain or distress) will impact the developing brain and stress system, increasing risk for persistent antisocial behavior. Later in life, attenuation of stress system physiology (ANS and HPA axis) under novel and	Development; Health to Disease; (Social Interaction)	Yes, humans	X	X	x	baseline and post-stress	In this context, the word antisocial refers to the wide range of socially unacceptable or deviant behaviors that persist from at least childhood to young adulthood (Susman, 2006)	Susman, 2006

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
			threatening situations is predicted.								
9	Behavior Hypothesis	GCs and behavioral expression are linked, and the need to express specific behavior drives reproductive changes in HPA axis function and GC release. Thus, the need to seasonally regulate GC-mediated behaviors is what drives GC rhythms.	If elevated GCs typically inhibit (or enhance) a particular behavior, seasonal changes in GC regulation are driven by the need to inhibit (or enhance) a life-history-stage- or season-specific behavior. For instance, if elevated GCs inhibit reproductive effort, GC levels (baseline and likely post-stress) should be lower during the breeding season.	Stage Spanning	No	X			baseline and/or post-stress	Initially an attempt to explain seasonal regulation of HPA axis. Likely useful for describing GC changes within a single season but not across seasons.	Romero, 2002; Lattin and Romero, 2013
10	Behavioral Resiliency Hypothesis	Animals can maintain consistent, adaptive behavioral phenotypes in the face of significant physiological challenges.	The maintenance of steady-state behavior or comparable behavioral phenotypes even under chronically-elevated plasma GC levels. The magnitude and direction of the responses should hold across various contexts (e.g., predation threats, social interactions, foraging activity, etc.).	Stage Spanning	No	X			baseline and post-stress	Comparisons should be set up carefully so as not to predict the null hypothesis of no difference.	Lawrence et al., 2019
11	Biological Sensitivity to Context Model (BSC)	Heightened stress reactivity may reflect, not simply exaggerated arousal under challenge, but rather increased biological sensitivity to context, with potential for negative health effects under conditions of adversity and positive effects under conditions of support and protection.	High reactivity phenotypes disproportionately emerging within both highly stressful and highly protected early social environments (U-shaped relationship between adversity and stress-reactive profile; see page 289 in Boyce and Ellis, 2005). Variation in stress reactivity is maintained by natural selection because differences in reactivity produce different fitness outcomes in different scenarios.	Model (Development; Stress Coping)	Yes, humans	X	X	X	post-stress	To explain humans but takes an evolutionary approach and uses supporting data from animals.	Boyce and Ellis, 2005; Ellis et al., 2005
12	Body Condition Hypothesis	Elevated GCs should disrupt current life history stage, but the GC response to stress is dependent on body condition.	If an organism's body condition is high enough to resist or cope with situation, elevation of GCs will be low, if the organism is in	Stage Spanning	No	X			post-stress	Body condition must be able to be adequately monitored by the organism.	Lynn et al., 2003

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						HPA/GCs	ANS (SNS)	other			
			poor condition, GC response to the challenge will be higher.								
13	Brood Value Hypothesis	Individuals actively modulate their GC stress response (either up or down) with respect to the value of the of the current reproductive bout.	Elevation of GCs in response to a stressors should inhibit reproduction if the contribution of the current brood to lifetime reproductive fitness is low and probability of parental survival and future reproduction is high.	Reproduction	No (but for species with parental care)	X			post-stress	Hinges on knowing whether potential for future breeding is high or low. Was supported over the workload hypothesis in original study.	Lendvai and Chastel, 2008; Crespi et al., 2013
14	Burn-Out Hypothesis	Chronic or intense job stressors (or demands) can become overwhelming and lead to burn-out. Burn-out is noted as a behavioral response to high levels of stress and leads to emotional exhaustion, depersonalization, detachment, cynicism, rigidity, and professional inefficiency.	It is thus far unclear as to what exactly triggers burn-out and better biomarkers and clinical definitions would be useful. Recent work has looked at SNS and HPA axis function in relation to facets of burn-out (see de Vente et al., 2003; Marchand et al., 2014).	Health to Disease	Yes, humans	x	x		baseline and/or post-stress	Burnout, as per the dictionary: to fail, wear out, or become exhausted by making excessive demands on energy, strength, or resources. Term was originally coined to describe outcomes in community workers.	Freudenberger, 1974; Zastrow, 1984; de Vente et al., 2003; Iacovides et al., 2003; Marchand et al., 2014;
15	Capricious Conditions Hypothesis	Increased GCs can derail reproduction. Species breeding under harsh conditions should secrete less GCs in response to a stressor, or be behaviorally insensitive to elevated GCs during the parental care phase to prevent nest abandonment.	Under harsh conditions, breeding birds should show lower stress-induced GCs or higher CGB levels than non-breeding birds (or non-breeding season in same bird). Alternatively, breeding birds may not be behaviorally sensitive to elevated GCs, thus behavioral sensitivity to GCs will differ in breeding vs. non-breeding season (or by season within the same bird).	Reproduction	No, but focus is on birds	X			post-stress	Survival vs. reproduction framework.	Cornelius et al., 2012
16	Christian Stress Hypothesis (aka non-adaptive stress hypothesis)	The stress response in small mammals is ultimately non-adaptive, causing increased mortality and decreased reproduction. Increases in population density lead to increased antagonistic interactions which increases GC release, increased GCs impair immune function and reproduction.	Magnitude of GC response should correlate with density. At increased population density, organisms have larger adrenal glands (proxy for increased HPA axis function), and the (presumably elevated GCs) will negatively impact survival and reproduction.	Reproduction (Survival)	Yes, small mammals (rodents)	X		X	post-stress	Only in some populations; early work done on captive animals. Using more refined methods (other than adrenals) seems warranted (Krebs, 2013)	Christian, 1950, 1980; Boonstra and Boag, 1992; Krebs, 2013
17					No	X			post-stress		

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						HPA/GCs	ANS (SNS)	other			
	Chronic Stress Hypothesis	Organisms are constantly negotiating finding food and avoiding predation, therefore animals are likely always subject to inseparable effects of both food and predation. Extension of the Predator(Predation)-Sensitive-Foraging hypothesis, stress effects can be interpreted as the lasting 'imprint' of 'predator-sensitive foraging'.	Clinchy and colleagues (2004) suggested two main predictions: 1) an animal's stress profile will be a simultaneous function of both food and predator pressures, and 2) the inseparable effects of food and predators on physiology will result in inseparable effects on demography owing to the long-term adverse health effects of chronic stress.	Reproduction (Survival)						Hinges on predator cues increasing HPA axis activity, data on this connection are mixed (see Boonstra, 2013; Harris and Carr, 2016 for reviews).	Boonstra et al., 1998; Clinchy et al., 2004
18	Compensation Hypothesis	Early life stress is aversive and not preparative for later life.	Early (developmental) stress is problematic but later life experiences can reduce the negative impact of early stressors.	Development	No					Form of environmental match/mismatch	Groothuis and Taborsky, 2015
19	Conditioning Hormesis Hypothesis (Priming)	Environmental stressors can have beneficial effects at low exposure levels but can be toxic at higher levels, and that environmental "priming" of certain physiological processes can result in their improved functioning in later life.	Early exposure to a low level of a particular stressor primes or conditions the organism, such that when tested with a higher level of that same stressor at a later time period, the early-exposed individuals do better than those not initially exposed.	Development	No					Definition of hormesis is important; expanded to include eco/evo variables and examples. Overlap with stress-hardening (Kültz, 2005).	Costantini et al., 2010
20	Constraint Hypothesis	Both old and young animals may have reduced reproductive success due to lack of experience or physical capacity.	Elliot and colleagues (2014) propose that stress response declines with age and is similar among reproductive and non-reproductive (pre-breeding) individuals and this could be due to habituation or to adrenal decay (stress response declines with age following ACTH injection).	Reproduction (Survival)	No (but for iteroparous species)	X			post-stress	Predicted specifically free GCs. Seems to be opposite to Coping Hypothesis of Aging.	Elliott et al., 2014
21	Context-Dependent Hypothesis	Reproductive success and fitness come at a cost to self-maintenance and survival. When the fitness value of current reproduction is high, increased GCs direct resources toward reproduction; when value of reproduction is low, increased GCs reduce allocation to reproduction.	Elevated baseline GC levels can either facilitate or inhibit reproductive investment. High GCs promote investment in high-fitness-potential reproductive bouts but reduce investment in low-fitness-potential reproductive bouts.	Reproduction	No	X			baseline	Hypothesis seems to be so far untested. Hinges on knowing whether a current reproductive bout is of high or low fitness potential.	Bonier et al., 2011

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						HPA/GCs	ANS (SNS)	other			
22	Coping Hypothesis of Aging	The ability to cope with challenges is reduced in old individuals due to senescent changes in the activity of the hypothalamic–pituitaryadrenal (HPA) axis, leading to increased GCs.	During times of high energetic demand, aged individuals are predicted to have elevated GCs above those in young individuals under the same energetic conditions (interaction between age and demand). These GC changes should relate to markers of allostatic load and body condition.	Health to Disease; Stress Coping (Aging)	No	X			baseline and post-stress	Seems to be opposite to Constraint Hypothesis.	Hamalainen et al., 2015
23	Cort (GC)-Adaptation Hypothesis	Reproduction itself is an environmental challenge and those individuals in good condition can invest the most resources to reproduction.	Positive relationship between baseline GCs and reproductive effort and fitness (especially pronounced in individuals in good condition). (See Box 1 in Bonier et al., 2009b).	Reproduction	No (but most work done in birds)	X			baseline	An expansion of the Cort-Fitness hypothesis to include the allostatic costs associated with reproductive effort.	Bonier et al., 2009b; Crossin et al., 2016
24	Cort-Activity Hypothesis	Baseline GCs increase in response to environmental challenges and these increases are helpful for physiological and behavioral coping and ultimately survival and fitness.	Increased levels of baseline GCs should be associated with increased survival, possibly due to increase locomotor and anti-predator activity.	Stage Spanning (Stress Coping)	No	X			baseline		Rivers et al., 2012
25	Cort-Fitness Hypothesis	Higher baseline cort is associated with individuals or populations in worse condition and those individuals have decreased reproductive investment and decreased fitness.	Baseline cort (GCs) should increase with increasing levels of environmental challenges, and fitness (and survival) should decline with increasing challenges. (See Fig. 1 in Bonier et al., 2009b).	Reproduction	No (but most work done in birds)	X			baseline	A review of the literature did not find overwhelming support for this hypothesis (Bonier et al., 2009b). Not supported in Patterson et al., 2014.	Bonier et al., 2009a,b
26	Cort-Flexibility Hypothesis	Pre-breeding is a special period characterized by the priming of GC function, which allows animals to response flexibly to non-optimal environments. A pre-breeding animal has enhanced sensitivity to the GC system and if a negative factor is encountered the animal can respond strongly and therefore pause reproductive behavior and physiology.	Lattin and colleagues provide six predictions for ways in which pre-breeding birds increase the effect of GCs: 1) increase GC release, 2) decrease negative feedback, 3) rapidly decreased concentrations of CBG, 4) alter enzyme activity, 5) increase receptor density, and 6) alter activity of other hormone systems	Reproduction	Yes, birds in the pre-breeding period	X		X	baseline and post-stress		Lattin et al., 2016
27	Corticosteroid Receptor Hypothesis of Depression	Impaired central stress hormone regulation is causally involved in the development and course of	Intracellular signaling of GCs is impaired in specific areas of the brain, resulting in a number of changes in	Health to Disease	No	X		X	baseline and post-stress	Ultimate goal is to understand human depression but data from	Holsboer, 2000

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						HPA/GCs	ANS (SNS)	other			
		depression, and antidepressants work in part by normalizing the HPA axis.	gene activity and neurotransmitter production involved in causality of depression. Depressed individuals are predicted to have elevated baseline HPA activity and decreased response to dexamethasone.							animal models is discussed. Mental health – depression.	
28	Cortisol Buffering Hypothesis	Elevated GCs are typically thought to inhibit reproduction, and developmental GC exposure can impact offspring. In reproductive female fish GCs are elevated and some level of cortisol is likely essential for embryogenesis and oogenesis. Cortisol buffering in the ovary may help to modulate hormone levels to promote oogenesis.	Initial exposure to of early stage oocytes to GCs results in developing follicles with a cortisol buffering system (likely via increase in 11beta-HSD2). (See Figs. 1, 2, & 3 in Faught and Vijayan, 2018).	Development; Reproduction	Yes, fish	X		x	baseline and/or post-stress (of mother)	GCs source is likely exogenous (e.g., female fish, environment, or environmental contaminants that inhibit 11beta-HSD2).	Michael and Cooke, 1994; Faught and Vijayan, 2018
29	Cort-trade-off Hypothesis	Short-term (stress-induced) GC elevation helps to mediate the trade-off between survival and reproduction by redirecting resources to survival.	Positive association between GCs and survival, but negative association between GCs and reproductive success	Reproduction	No (but most work done in birds)	X			post-stress	This hypothesis was supported over Cort-fitness and Cort-adaptation when tested in Patterson et al., 2014	Patterson et al., 2014; Wingfield and Sapolsky, 2003
30	CRF Hypothesis of Depression	CRF hypersecretion is responsible for the HPA axis hyperactivity noted in depressed patients. CRF acting on extra-pituitary sites produces many of the signs and symptoms of depression.	Depression is characterized by elevated CRF release, in the hypothalamus and supra-hypothalamic sites, and drives increased HPA function, decreased appetite, disrupted sleep, decreased libido and psychomotor alterations. (See Binder and Nemeroff, 2010 for more).	Health to Disease	Yes, humans	X			baseline and post-stress	Mental health – depression.	Nemeroff, 1996; Binder and Nemeroff, 2010
31	CRF-HPA Dysregulation Hypothesis	HPA dysregulation, specifically driven via hypersecretion of CRF, initiates a wide-range of psychiatric disabilities.	Increased activity of CRF releasing neurons in the amygdala, PVN, and pituitary result in increased ACTH and elevated GCs, this profile is associated with psychiatric disabilities.	Health to Disease	No	X			baseline and/or post-stress	Mental health – affective disorders and substance abuse	Keller et al., 2006
32	Cumulative Stress Hypothesis	Effects of stress over a lifetime are cumulative and lead to allostatic load (overload) which increases likelihood of disease onset. Aversive experiences early in life predispose individuals to be more vulnerable to aversive challenges later in life.	Individuals that experience the most frequent and/or severe stress will have the greatest likelihood of disease or psychopathology. (See Fig. 1a in Nederhof and Schmidt, 2012; the authors aim to integrate the	Development; Health to Disease	No	x	x	x	baseline and/or post-stress	Also sometimes called the 2-hit hypothesis, but this is a misnomer because it implies that only 2 specific events are needed and/or relevant (Nederhof and Schmidt, 2012).	Nederhof and Schmidt, 2012

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						HPA/GCs	ANS (SNS)	other			
			cumulative stress with the mismatch hypothesis).								
33	Current Condition Hypothesis	Elevated baseline GC levels are indicative of poor condition that may translate into reduced performance or reduced fitness of either an individual or a population.	Thomas and colleagues (2017) state baseline GCs should be negatively related to health (body condition), and post-stress GCs should be positively related to health (body condition).	Reproduction (Performance)	No	X			baseline and post-stress	Related to the Cort-Fitness Hypothesis	Thomas et al., 2017
34	Current Reproduction vs. Survival Hypothesis	Reproductive success and fitness come at a cost to self-maintenance and survival. Chronic stress and prolonged GC elevations disrupt current reproduction but increase overall lifetime fitness.	A good stress response is adaptive because it increases lifetime fitness. Confusion over what constitutes a "good" stress response is problematic. As reviewed by Breuner and colleagues (2008) current opinion posits that a combination of low baseline, fast increase, and rapid induction of negative feedback represents a 'good' HPA response and is adaptive.	Reproduction (Survival)	No (but most work done in birds)	X			post-stress	Empirical evidence is limited, data on fitness effects of acute, vs. chronic, stress response are needed, but see recent work by Vitousek lab. Most data to test this hypothesis rely on chronic stress studies and not on baseline or acute stress response and HPA changes.	Wingfield and Kitaysky, 2002; Wingfield and Sapolsky, 2003; Breuner et al., 2008; Crossin et al., 2016; Vitousek et al., 2018; Zimmer et al., 2019
35	Damage-Fitness Model	An integration of stress responses from cellular to organismal levels; shifts focus to damage instead of response. Any mechanism that minimizes or avoids persistent damage to a cell or tissue is an anti-damage regulator. Here, a stressor is a stimulus that has the potential to inflict measurable damage at molecular, cellular, organ, or organismal levels.	A negative relationship between the extent of persistent damage or dysregulation of physiological systems and reproductive success and survival. (See Figs. 1, 2, and 3 in Wada, 2019 for more detail).	Model; Stage Spanning	No	x	x	X	baseline and post-stress	Interdisciplinary approach that is also meant to be taxa-spanning, including more than just vertebrates.	Wada, 2019
36	Deakin/Graeff Hypothesis	The serotonergic system plays important roles in conserved responses to aversive stimuli ("stresses"), compromises to this system could lead to anxiety disorders.	Serotonergic systems facilitate anxiety-liked processes but constrain panic processes (Table 1, Deakin and Graeff, 1991; see Paul and Lowry, 2013 for more specific brain region predictions).	Health to Disease	No			X		Mental health – anxiety.	Deakin and Graeff, 1991; Paul and Lowry, 2013
37	Developmental Hypothesis	Inter-specific variation in the GC response to stress of hatchlings reflects the species-specific degree of altricial development.	HPA function and GC release should increase with age. Young altricial animals (birds) may not be able to respond fully (behaviorally, physiologically) to stressors due to their state of being reliant on parental care.	Development	Yes, for birds	X			baseline and post-stress	Useful for comparison across species but less so within a species. In some species, elevated GCs in chicks increases begging but impairs future cognitive function, so likely trade-offs involved.	Schwabl, 1999; Sims and Holberton, 2000; Kitaysky et al., 2003; Blas et al., 2006

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						HPA/GCs	ANS (SNS)	other			
			Elevated GCs in response to stressors will likely not be beneficial and could induce harmful effects (e.g., cognitive decline, reduced growth).								
38	Developmental Stress Hypothesis	The honesty of bird song as a signal may be maintained by costs incurred during development. May be a general example of how indicators of developmental stability become sexually selected traits.	Correlations among adult traits may result from stressors during development and impacts likely depend on when in development stressor was experienced (see Fig. 1 in Spencer and MacDougall-Shackleton, 2011).	Development; Reproduction	No (but example is for male song birds)	X		x	post-stress	Expansion of the Nutritional Stress Hypothesis (Nowicki et al., 1998); not just limited to nutritional stress; focus on pleiotropic effects of physiological mediators.	MacDougall-Shackleton et al., 2009; Spencer and MacDougall-Shackleton, 2011
39	Developmental Origins of Health and Disease (DOHaD) (a.k.a, Fetal Origins Hypothesis)	Early life experiences can alter later disease risk. Environmental factors encountered by a developmentally plastic organism early in life influence health and disease outcomes throughout adulthood.	A developing organism senses its metabolic milieu and adjusts its physiological homeostatic setpoints according to the expected future environment. Alterations in response to developmental cues may be subtle and not be apparent under future basal conditions, may only appear in response to challenge. (See Fig. 2, 3, & 4 in Gluckman et al., 2007).	Model/ Framework (Development; Health to Disease)	No (but focus here is on humans)	x		x	baseline and/or post-stress (of mother or offspring)	Part of this framework is the "match-mismatch model" (see Fig. 2 in Gluckman et al., 2007). Large emphasis on maternal nutrition and nutrient availability for developing fetus.	Gluckman et al., 2007; Whirledge and Cidlowski, 2017
40	Diathesis Stress Hypothesis	Diathesis–stress models of psychopathology assert that all people have some level of predisposing risk factors, or diatheses, for any given mental disorder. The point at which each individual develops a given disorder varies depending on the interaction between the degree of risk factors and the degree of stress experienced by the individual in question.	There is a threshold above which people would develop a given disorder. Interactions among factors influencing onset of pathology is not yet clear. (See various path models in Monroe and Simons, 1991; see Fig. 1 in McKeever and Huff, 2003).	Health to Disease	No (but focus is on humans)	x	x			Developed originally for schizophrenia but now applied to other psychopathologies. Mental health.	Monroe and Simons, 1991; McKeever and Huff, 2003
41	Differential Susceptibility Hypothesis	Individuals are differentially vulnerable to the effects of stress and environmental influence. Individuals might not just be differentially vulnerable to stressors but also to the positive effects of environmental support and enrichment. This risk phenotype might be better classified as plasticity phenotypes ("for better and for worse" framework).	Phenotypic temperament, endophenotypic attributes, and genes can interact to be plasticity factors which can render individuals more susceptible to positive and negative environmental stimuli. The ANS and HPA axis are likely endophenotypic attributes	Health to Disease	No (but focus is on humans)	X	X	X	baseline and post-stress	Expansion of the Diathesis-Stress Model and the Biological Sensitivity to Context hypothesis. Lots of focus on gene × environment studies.	Belsky and Pluess, 2009; Belsky et al., 2009

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						HPA/GCs	ANS (SNS)	other			
			but no directional hypotheses are provided.								
42	Double-Hit or Two(2)-Hit Hypothesis	Psychopathologies are likely influenced by genes and environmental contributions. The first hit is a dysfunctional gene (inherited or spontaneously acquired), the second hit is some environmental factor (e.g., infection, birth complication, social stressors).	The disease-regulating genes are involved in brain development and maturation and the function of the genes can be modulated by future hits. The second (or more) hits can occur during development or later in life, and impact of hits may depend on time or developmental stage. Need both factors for development of disease.	Development; Health to Disease	No (but focus is on humans)					First proposed for schizophrenia, but has been applied more broadly. Mental health.	Bayer et al., 1999; Yee et al., 2011
43	Dual Hormone Hypothesis	Elevated testosterone is often associated with aggressive behavior, dominance, and social status. High baseline testosterone will only be associated with increased dominance, risk-taking, and status-seeking behavior if baseline GCs are low.	High baseline GCs will block the effect of elevated testosterone on dominance, status-seeking, or risk-taking behavior in both males and females.	Stage Spanning (Social Interactions; Performance)	No (but developed from work in humans)	X		X	baseline	Analysis using post-stress hormone values was conducted but baseline values were a better predictor (see Mehta et al., 2015).	Mehta and Prasad, 2015
44	Ecology of Fear Framework	Prey are under near continual (non-lethal) threat from predators. This chronic threat, or fear, is a form of sustained psychological stress as prey species are not in immediate danger of predation but are continually wary of possible attack. This sustained psychological stress impacts physiology, behavior, and population dynamics.	The presence of predators, or honest predator-threat signals, should elicit physiological and behavioral responses in prey animals. This should occur under acute and chronic conditions with chronic exposure resulting in pronounced changes in behavior, physiology, and population dynamics (e.g., increased fear response, increased HPA and SNS activity, decrease in population numbers). Removal of predators, or predator signals, should reduce stress and increase population size.	Model/ Framework; Stage Spanning	No	X	X		baseline and post-stress	Similarities to PIBS hypothesis. Hypothesis aims to bridge human and animal studies (e.g., is predator-induced stress similar to chronic stress and/or psychopathology in humans?)	Brown et al., 1999; Preisser et al., 2005; Clinchy et al., 2011, 2013
45	Economic Stress Hypothesis	Uses the economy as a stressor model (adapting to changes in the social, organizational, and physical environment can induce physiological stress responses in humans) to suggest that economic decline influences human sex ratio.	As markers of economic stress or instability increase the sex ratio of newborn babies should skew towards more females than males. This could occur at various levels (e.g., sperm,	Reproduction	Yes, humans	x			post-stress	This is the Adaptive (Trivers-Willard) Hypothesis specific to economic stressors in humans.	Catalano, 2003; Catalano et al., 2005; Navara, 2010

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Table 1 (*continued*)

#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
			fertilization, implantation, survival to term) and the mechanism by which stress (and GCs) impact sex ratio is not clear (see Figs. 1 & 2 in Navara, 2010 and see Catalano et al., 2005).								
46	Emergency Life History Stage (ELHS)	Exposure to labile perturbation factors (LPFs; stressors) causes animals to mount a physiological stress response (including HPA activation), and the resulting increase in HPA hormones can push organisms from the current life history stage to an emergency life history stage.	Exact predictions can depend on current life history stage, but three general strategies are predicted: 1) Leave-it: move away from LPS, 2) Take-it: switch to an alternate set of energy conserving behavioral and physiological traits, 3) Take at first and then leave-it: switch to energy conserving mode first and then move away if conditions do not improve. (Also, see pages 192–193 of Wingfield et al., 1998).	Stage Spanning	No (but most work done in birds)	X			post-stress	General framework: Acute stress-induced GC elevation suppresses investment, and chronic GC elevation inhibits investment.	Wingfield et al., 1998; Wingfield and Romero, 2010; Landys et al, 2006
47	Endocannabinoid Deficiency Hypothesis of PTSD	Deficiencies in endocannabinoid signaling can result in impaired stress response regulation and increased emotionality, mirroring findings in those with PTSD.	A state of endocannabinoid deficiency could represent a stress susceptibility endophenotype predisposing individuals to the development of trauma-related psychopathology (see Fig. 3 in Hill et al., 2018, and corresponding text).	Health to Disease	No (but focus on humans)	x		X	post-stress	Mental health – post-traumatic stress disorder	Hill et al., 2018
48	Energetic Stress Hypothesis	Reproduction is physiologically stressful. Female birds lose body mass during breeding due to energetic deficit.	Mass loss in females should be due to increased demands of reproduction and should not occur if food is made readily available (via supplementation or years of good food supply)	Reproduction	Yes, birds (females)					Same thing as Reproductive Stress Hypothesis. Tested with the Wing-Loading Hypothesis and supported in that comparison..	Nagy et al., 2007
49	Energetics-Hormone Vocalization Model	In male anurans, calling behavior drives an increase in plasma testosterone and that is accompanied by an increase in GCs to due high energetic demand. GCs and reproductive investment should be positively correlated if reproduction is energetically expensive.	Elevated GCs are helpful initially as they help maintain the energetically expensive calling behavior, but become detrimental to reproduction when levels get too high (elevated GCs suppress T, which is necessary for calling).	Reproduction	Yes, anurans (male)	X			baseline	An expansion of Emerson and Hess (2001), which stated that calling in male anurans increases testosterone and GC levels due to the energetically expensive nature of this behavior.	Emerson and Hess, 2001; Moore and Jessop, 2003

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						HPA/GCs	ANS (SNS)	other			
50	Energy Mobilization Hypothesis	GC concentrations will be highest during energetically costly times of the year.	Species, sex, and life-history strategy, but GCs should be elevated when energetic costs are highest. Relies on need to know energetic cost and ways in which organisms gather, store, and use energy.	Stage Spanning	No	X			baseline	An attempt to explain seasonal regulation of HPA axis; not much support when applied broadly across taxonomic groups.	Romero, 2002
51	Everyday Stress Resilience Hypothesis	Everyday coping experiences develop regulatory capability and capacity or a "regulatory resilience". The best way to prepare for future stress is to experience a moderate amount of "training" stress (analogy of training for a marathon is used - no training is bad, but so is overtraining).	Coping with everyday stressors influences infants' regulatory capacities for these typical stressors and prepares them to cope with later, more taxing stressors. Critically dependent on infant-caretaker relationship. (See Figs. 1 & 2 in DiCorcia and Tronick, 2011).	Development; Stress Coping	Yes, humans	x	x		post-stress	Similar to the Inoculation Stress Hypothesis but this one is not all-or-none and is an ontogenetic model. Also similar to Conditioning Hormesis or Priming Hypothesis.	DiCorcia and Tronick, 2011
52	Facilitation Hypothesis	Predicts that plasma GCs would be positively correlated with energetically costly functions during non-challenging (baseline) times.	According to Thomas and colleagues (2017), both baseline and post-stress GCs should be positively related to reproduction/immunity	Reproduction	No	X			baseline and post-stress	Also known as the (Cort) Adaptation Hypothesis. Similar to Energy Mobilization Hypothesis.	Thomas et al., 2017
53	Fat and Fit Hypothesis	At times of low allostatic load and low GC levels, it is better to store more energy and bulk up in order to provide an energy-store cushion for when allostatic load increases. Benefits of bulking up would have to outweigh the costs (e.g., decreased maneuverability, maintain large body mass, etc.).	Circulating GCs drive energy accumulation and are negatively and linearly related with energy reserves. (See Fig. 2 in Schultner et al., 2013).	Reproduction (Survival)	No	X			baseline	Uses the Allostatic Load Model. "Lean and fit" was supported over "fat and fit" when using data from an Arctic seabird.	Schultner et al., 2013
54	Fight or Flight	Animals react to general threats via discharge of the sympathetic-adrenal system. This aids in redistribution of resources.	SNS dominates following threats, results in increase in catecholamines and activation of multiple target tissues.	Model/ Framework; Stage Spanning	Yes, vertebrates		X			Initially mammals but includes vertebrates and even invertebrates (Adamo, 2012)	Cannon, 1929; 1936; 1942
55	Free-hormone Hypothesis	GCs travel through the blood bound to corticosteroid-binding globulin (CBG; bound), loosely attached to other proteins or unbound (free). CBG does not enter cells and thus the free fraction is the biological active measure of GCs.	Measures of free GCs should be performed to get an accurate picture of how GCs are related to study question.	Stage Spanning (GC Regulation)	No (but most work done in birds)	X			baseline and post-stress	See paper by Schoech and colleagues (2013) for some concerns and potential limitations of CBG analysis. Also note, some species do not have CBG.	Mendel 1989, 1992; Malisch and Breuner, 2010; Schoech et al., 2013
56	GALF Hypothesis	Gut bacteria play an important role in physiology and health. In certain cases, gut microbes metabolize organismal GCs to a variety of glycerrhetinic acid-like factors	GALFs will inhibit or reduce function of 11beta-HSD2 and lead to increased hypertension. (See Table 2	Health to Disease (GC Regulation)	No	X		X	baseline and post-stress		Morris and Ridlon, 2017

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
		(GALFs) which inhibit the function of 11beta-HSD2, leading to excessive MR binding and hypertension.	in Morris and Ridlon, 2017 for likely bacterial culprits).								
57	General Adaptation Syndrome (GAS) (Selye's Syndrome)	The GAS is a coordinated syndrome with objectively measurable manifestations, is nonspecific, and is a response to (noxious) stimuli. It has three phases: alarm (aka Fight or Flight), resistance, and exhaustion. Also see mention of local adaptation syndrome (LAS; Selye, 1959).	Initial general alarm stage (typically SNS driven) and then moves into GAS with longer term challenge. Long-term stress leads to health problems and "diseases of adaptation" (e.g., ulcers, high blood pressure, immunosuppression).	Model/ Framework; Stage Spanning	No	X	x	x	post-stress	Stress mediators are not limited to HPA axis and SNS, but those got initial attention due to technical reasons. Ideas have been refined and three phases of GAS are not supported; also stress response is not non-specific.	Selye, 1936; 1959; 1973; Fink, 2009
58	(GC-Induced) Reproductive Conflict Hypothesis	In birds, elevated GCs aid in energy balance but can also result in nest abandonment. These two outcomes produce a conflict for breeding birds in how to physiologically balance effects of elevated GCs. This apparent conflict can be explained by measuring free (unbound) and total GCs.	During energetically demanding reproductive stages, CBG levels should decrease and free GC levels should increase without an overall change in total GCs.	Reproduction	No (but best for non-mammal tetrapods)	X			baseline	Elevated GCs may be a necessary component of reproduction in birds (and reptiles and amphibians).	Moore and Jessop, 2003; Love et al., 2004; Crossin et al., 2016;
59	Glucocorticoid (overexposure) Hypothesis	One of the key hypotheses to explain early life programming (changes made by the fetus in response to intra-uterine environment impact physiology, structure, and metabolism). Placental 11beta-HSD2 helps to protect the developing fetus from elevated GCs, but if this enzyme is overcome (or does not function properly), increased GCs will negatively alter fetal development and programming.	Elevated GCs program the fetus and result in low birth weight, increased HPA axis function, and altered metabolic and behavioral profiles. (See Fig. 1 in Reynold, 2013; Fig. 2 in Whirledge and Cidlowski, 2017; and Fig. 1 in Seckl and Holmes, 2007).	Development	Yes, placental mammals	X		x		GCs source is likely exogenous (e.g., mother, environment, or factor that inhibit 11beta-HSD2). Extension of the DOHaD Hypothesis. Other hypothesis used to explain fetal programming is fetal malnutrition (but this is likely linked to GC exposure). Similar to Cortisol Buffering Hypothesis.	Edwards et al., 1993; Seckl and Holmes, 2007; Reynolds, 2013; Whirledge and Cidlowski, 2017
60	Glucocorticoid Cascade Hypothesis	Increased stress with age leads to some form of altered feedback regulation at the level of the hippocampus (either via decrease in GC receptors and/or in loss of neurons), this leads to decreased inhibitory tone on the HPA axis and increased GCs. The increased GCs create a positive feedback cycle of hippocampal damage and HPA axis dysregulation with ultimate negative impacts on other health outcomes.	Aged individuals are predicted to have 1) elevated baseline GCs, 2) decreased sensitivity to negative feedback, and 3) prolonged HPA response following stressor exposure. These HPA changes should be positively related to markers of aging and senescence. (See Fig. 4 in Sapolsky et al., 1986; and Figs. 1 & 2 in Landfield et al., 2007).	Health to Disease (Aging)	No	X			baseline and post-stress	Original hypothesis (coined by Sapolsky et al., 1986) has been modified and expanded by Landfield and colleagues (2007). Also see Glucocorticoid Vulnerability Hypothesis.	Sapolsky et al., 1986; Landfield et al., 2007
61				Health to Disease		X			post-stress		Conrad, 2008

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
	Glucocorticoid Vulnerability Hypothesis	A history of chronic stress, which includes repeated elevation of glucocorticoids, may make the hippocampus vulnerable to potential injury by causing dendritic retraction.	Conditions of chronic stress or prolonged exposure to GCs produce dendritic retraction which makes the hippocampus vulnerable to neurotoxic or metabolic challenges. Dendritic retraction may persist for long periods after the stressor (or GCs) are removed and thus there exists a window of hippocampal vulnerability.		No (but focus is on humans)					An expansion of the Glucocorticoid Cascade Hypothesis. Particularly relevant for Cushing's, post-traumatic stress disorder, and major depressive disorder. Mental health.	
62	Glutamate Hypothesis of Depression	Glutamatergic neurons make up the bulk of the cortex. Thus,the glutamatergic system is a primary mediator of psychiatric pathology and, potentially, also a final common pathway for the therapeutic action of antidepressant agents.	Malfunction in the mechanisms regulating clearance and metabolism of glutamate, and maladaptive morphological changes in a number of brain areas mediating cognitive and emotional behaviors. Several of these changes can be caused by stress and GCs (see Fig. 3 in Sanacora et al., 2012).	Health to Disease	No	X		X	post-stress	Shift from a monoamine hypothesis of mood/ anxiety disorders to neuroplasticity hypothesis focused on glutamate. This hypothesis is a corollary of the Neuroplasticity Hypothesis.	Sanacora et al., 2012
63	Goodness-of-Fit Hypothesis	Stress depends on a number of subjective cognitive judgments that arise from the dynamic interplay between person and environment. No event or situation is inherently stressful. Rather, the individual's subjective judgment of the situation is what defines a stressor.	The effects of problem-focused versus emotion-focused coping are moderated by the appraised controllability of the stressor.	Stress Coping	Yes, humans					Teasing apart the transactional model by Lazarus and Folkman, 1984. Alternate to Main-Effects Hypothesis.	Zakowski et al., 2001
64	Hawk-Dove Model (Bold-Shy Continuum; Cort-Risk Hypothesis)	Natural selection has maintained populations of organisms that differ in behavioral and hormonal response to challenges. Hormones can have pleiotropic effects and hormones associated with stressors are likely linked to other physiological responses and to stress-coping behavior, resulting in animals that reliably differ in endocrine, neuroendocrine, behavioral, and physiological responses to stressors and to disease susceptibility.	The general framework is that hawk (bold, risky, aggressive, proactive) individuals have decreased HPA and increased SNS responses whereas dove (shy, risk-averse, non-aggressive, reactive) have increased HPA and decreased SNS responses. Several authors have more detailed predictions for this model: see Tables 1, 2, 3, & 5 in Korte et al., 2005; Figs. 1 & 2 in Carere et al., 2010; Table 1 and Fig. 6 in Cockrem, 2007. (Also see	Model; Stage Spanning	No	X	X	X	baseline and post-stress	Brings in ideas of animal personalities and of hormonal pleiotropy.	Korte et al., 2005; Cockrem, 2007; Carere et al., 2010; Baugh et al., 2017

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
			page 100 in Baugh et al., 2017).								
65	Hormesis	An adaptive response to a moderate and typically acute stress. The hormetic response is also called preconditioning or adaptive stress response.	Exposure to a low dose of an environmental agent (e.g., stressor, chemical, toxin) will have priming effects on the system (cell, organism) which will enhance ability to cope with future challenges. (See specifics in Fig. 1 in Calabrese et al., 2007 and Fig. 2 in Mattson, 2008).	Stage Spanning	No	x		X	baseline and post-stress	Various issues with exact terminology and cross-discipline differences in meaning of terms exist (Calabrese et al., 2007). Also see Chapman, 2002.	Chapman, 2002; Calabrese and Baldwin, 2002; Lupien et al., 2005; Calabrese et al., 2007; Mattson, 2008; Schreck, 2010
66	Inoculation Stress Model	Like a vaccine will protect against future infection, mild stressors will provide tools for coping with future stressors. This model posits an upside-down U-shaped relationship between early life stress and later life resilience.	Exposure to (mild) early life stressors along with positive and adaptive coping responses will prime an organism for enhanced future responses and resilience.	Model (Development; Stress Coping)	No (but most work done on humans)	x			post-stress	Also called immunizing, toughening, or steeling (see Sih, 2011), or cross-tolerance (Kültz, 2005).	Sih, 2011; Crofton et al., 2015
67	Inverted-U Hypothesis	Increases in arousal (stress; anxiety) are associated with concomitant increases in the quality of performance up to a certain point, after which additional increases in arousal (stress; anxiety) result in increasingly inferior performance.	Relationship between arousal and performance measure should follow an inverted U shape, both high and low levels of arousal should produce poorer performance than mid-levels. Arousal can be operationalized as self-reported stress, self-reported anxiety, GCs, or catecholaminergic concentration or output. For GCs, the right side of curve is likely mediated by GR and the left side by MR. (See Fig. 4 in Coates et al., 2010 or Fig. 1 in Herman, 2013 for a schematic).	Stage Spanning (Performance)	No (but initial focus on humans)	X	X		baseline and post-stress	Performance has been measured using various dependent variables ranging from the cellular to organismal level. Versions of this hypothesis have been proposed multiple times over the last 100 years across fields (e.g., Yerkes-Dodson Law).	Malmo, 1959; Martens and Landers, 1970; Nixon, 1976; Anderson, 1990 Diamond et al., 1992; de Kloet et al., 1999; Lupien and Lepage, 2001; Joels, 2006; Salehi et al, 2010; Herman, 2013
68	John Henryism Hypothesis	Prolonged high-effort coping in response to chronic psychosocial stressors, without sufficient socioeconomic support, is associated with risk for negative health outcomes.	Individuals who score high on the John Henryism construct, vs. those that score low, will show more pronounced negative health outcomes. Continuous and active engagement with chronic psychosocial stressors (e.g., occupational or financial demands, discrimination, job	Stress Coping; Health to Disease	Yes, humans,	X	X	X	baseline and post-stress	Developed to study the connection between stress, coping, and health in African Americans as previous hypotheses made decent predictions for Whites but not for Blacks. Similar to Allostatic Load.	Bennett et al., 2004

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						HPA/GCs	ANS (SNS)	other			
			insecurity) will result in elevated physiological markers (e.g., ANS and HPA axis) which over time may lead to health problems. Effects will be particularly pronounced for African-American individuals and for those of low socioeconomic status.								
69	Leaky Gut Hypothesis	The importance of the gut-brain axis in regulating stress-related disorders has long been appreciated but it is not clear exactly how gut-brain connections impact health. One proposed mechanism is disrupted gut barrier function commonly known as the "leaky gut" phenomenon.	The epithelial barrier of the GI tract becomes compromised as a result of psychological or organic stress, leading to increased intestinal permeability and subsequent translocation of gram-negative bacteria across the mucosal lining to access immune cells and the enteric nervous system. This leads to a suite of physiological changes in the organism (See Fig. 2 in Maes et al., 2009).	Health to Disease	No	x		X	baseline and/or post-stress	Lots of factors at play in this framework. Links gut microbes to mental health.	Maes et al., 2009; Foster et al., 2017
70	Lean and Fit Hypothesis	At times of low allostatic load, abundant food, and low GC levels, it is best to maintain energy stores that maximize benefits of a leaner physique (e.g., reduced mobility costs, decreased metabolism, decreased predation risk, etc.).	Circulating GCs have an inverted U relationship to energy accumulation. At high and low GC concentrations animals are lean; at intermediate levels they bulk up/increase energy reserves. (See Fig. 2 in Schultner et al., 2013).	Reproduction (Survival)	No	X			baseline	Uses the Allostatic Load Model. "Lean and fit" was supported over "fat and fit" when using data from an Arctic seabird.	Schultner et al., 2013
71	Lifecourse Health Development Model	A synthesis of ideas developed to incorporate rapidly emerging evidence on the biological, physical, social, and cultural contributors to the development of health and disease.	Multiple predictions about how various factors, including stress, can influence health and disease trajectories. (See Fig. 1 in Halfon et al., 2014).	Model (Development; Health to Disease)	No (but focus on humans)	x				Builds on DOHaD model. Spotlight on maternal and child health.	Halfon et al., 2014
72	Main-Effects Hypothesis	Stress depends on a number of subjective cognitive judgments that arise from the dynamic interplay between person and environment. No event or situation is inherently stressful. Rather, the individual's subjective judgment of the situation is what defines a stressor.	Problem- focused coping is generally more effective in reducing distress regardless of appraisal.	Stress Coping	Yes, humans					Teasing apart the transactional model by Lazarus and Folkman, 1984. Alternate to Goodness-of-Fit Hypothesis.	Zakowski et al., 2001
73	Matching Hypothesis	Stress depends on a number of subjective cognitive judgments that	Coping strategies used tend to match the level of	Stress Coping	Yes, humans						Zakowski et al., 2001

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators HPA/GCs	ANS (SNS)	other	If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
		arise from the dynamic interplay between person and environment. No event or situation is inherently stressful. Rather, the individual's subjective judgment of the situation is what defines a stressor.	appraised controllability of the stressor.							Teasing apart the transactional model by Lazarus and Folkman, 1984	
74	Match-Mismatch Hypothesis[1]	High baseline GCs during pre-breeding can be beneficial for exploitation of limited resource acquisition.	When resources are limited, pre-breeding baseline GCs will be high and will aid in gaining limited resources.	Reproduction	No (but focus on birds)	X			baseline	Similar to Maternal/ Offspring Match Hypothesis, but focus on parent.	Crossin et al., 2016
75	Match-Mismatch Hypothesis (of Disease)[2]	Environmental cues during critical developmental windows program developing offspring for their future environment (match), these depend on genetic and environmental factors. When adult and developmental environments do not match (mismatch), health problems are likely.	If the adult environment is similar to that of the development environment (match) then disease risk will be low, if adult and developmental environments are mismatched, disease risk will be high. (See Fig. 2 in Schmidt, 2011).	Development; Health to disease	No (but focus on human depression)					Relies on the tradeoff between adaptation to current vs. future environment and plasticity. Falls under DOHaD.	Schmidt, 2011
76	Maternal Mediation Hypothesis[1]	Developmental plasticity of HPA and fear responses is mediated by variations in active maternal care.	Stressful or fear-evoking situations for the mother translate to decreased levels of active maternal care and this low level of active maternal care may be used by the offspring as a signal for environmental adversity and would result in altered programming of the neuroendocrine stress and fear axes. (See Fig. 1 of Macrì and Würbel, 2006)	Development	No (but most work done in rodents)	X			baseline and post-stress	See introduction of Macrì and Würbel, 2006 for a general history of the hypothesis	Macrì and Würbel, 2006
77	Maternal Mediation Hypothesis[2]	Cognitive, motivational, and emotional behavior of adult offspring can be altered by genetics and by maternal care, both of which regulate MR and GR expression and HPA axis function.	The MR:GR balance is altered by receptor gene variants and experience-related factors. The maternal environment and maternal care can induce epigenetic changes and play a large role in the expression of receptors.	Development; Health to Disease	No	X		X	baseline and post-stress	Attempt to explain variation in stress coping and how glucocorticoid actions can change from protective to harmful.	Oitzl et al., 2010
78	Maternal/Offspring Match Hypothesis	Maternal GCs are a signal of maternal quality and can reduce offspring growth and survival in stressful conditions. These changes to offspring should match maternal ability to provide resources in stressful environments, increasing long-term	Elevated GCs delivered to the developing offspring (via egg or placenta) should reduce offspring size and growth, matching resulting offspring to mother's ability. Mother should benefit by	Development; Reproduction	No (but focus on female birds)	X			baseline and/or post-stress	Similar to as the Maternal-Match Hypothesis. Work in birds suggests males experience more negative effects of early GC exposure (as males are the more demanding sex).	Breuner, 2008; Breuner et al., 2008

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						HPA/GCs	ANS (SNS)	other			
		survival. Benefit may be primarily for the mother.	increased survival. Unclear if offspring also benefit.								
79	Maternal-Match Hypothesis	Maternal GC signaling is a reliable predictor of the offspring's future environment, maternal programming may be an adaptive mechanism, increasing offspring and maternal fitness.	For offspring, maternal GC signal will program offspring to have lower mass, reduced begging, and decreased energetic cost. But, may be a trade-off with future survival for offspring.	Development; Reproduction	No (but focus on female birds and offspring)	X			baseline and/or post-stress	Like Maternal/ Offspring Match Hypothesis; more emphasis on offspring here. Expansion of environmental-match hypothesis (offspring use cues to match phenotype to expected future environment).	Love et al., 2005; Love and Williams, 2008; Love et al., 2013; Sheriff and Love, 2013
80	Melanocortin Hypothesis	The melanocortin system links morphological, physiological, and behavioral traits.	The relative area of black coloration should be positively correlated with behaviors, but negatively correlated with stress response.	Stage Spanning	Yes, vertebrates	X			baseline and post-stress	This should hold if variation in coloration is driven at the level of melanocortin production and not at the level of specific melanocortin receptors.	Ducrest et al., 2008; McKinnon and Pierotti, 2010; Santostefano, 2019
81	Migration Modulation Hypothesis (MMH)	GCs are involved in hyperphagia, lipogenesis and muscle catabolism. Hypothesis was proposed to explain HPA axis dynamics of birds during the migratory period.	During migration, birds have elevated baseline GC levels, which aid in meeting the metabolic demands of migration. These same birds also have decreased HPA axis responses to stress in order to keep GC levels out of catabolic or damaging ranges.	Stage Spanning (Migration)	Yes, migratory birds	X			baseline and post-stress		Holberton et al., 1996; Holberton, 1999; Long and Holberton, 2004
82	Mismatch hypothesis	Aversive experiences early in life trigger adaptive processes, thereby rendering an individual to be better adapted to aversive challenges later in life.	Disease (psychopathology) occurs when there is a mismatch between current expectations and early-life experiences. Experiencing high (or low) levels of stress early in life will program and individual to deal with high (or low) levels of stress later in life, disease develops more frequently when a mismatch occurs. (See Fig. 1a in Nederhof and Schmidt, 2012).	Development; Health to Disease	No	x	x	x	post-stress	In this paper the focus is on psychosocial stress and psychopathologies. The authors aim to integrate the cumulative stress and mismatch hypotheses.	Nederhof and Schmidt, 2012
83	Mosaic Hypothesis	The mosaic hypothesis attributes sex differences in neuro/psychopathology to sex differences in the direction of change in the brain mosaic following specific environmental events. The brain is highly variable and there is no true “female” or “male” brain.	Joel, 2011, states an example. If high spine density in area X is related to proneness to develop depression, and if acute stress is found to increase spine density in this area in females but decrease it in	Stage Spanning	No, but major implication for humans					Contrasts with the idea that sex differences in disease are due to structural differences in the healthy brain. Stress is not in definition but examples relate to stress.	Joel, 2011

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						HPA/GCs	ANS (SNS)	other			
			males, then we can predict that females would be more prone to develop depression following acute stress than males, even if there is no sex difference in this brain characteristic in the population.								
84	Mosaic Hypothesis of Epigenetics	Maternal stress can impact developmental (uterine) environment for the fetus and predispose the individual to onset of adult disease. Shared placental epigenetic factors may underlie this programming that occurs in response to multiple stressors.	Different maternal stressors can have different impacts on the developing embryo/fetus, but there is likely a shared expression pattern of placental genes which regulates epigenetic programming of adult health and disease (see Figs. 1–6 in Longo and Goyal, 2014).	Developmental; Health to Disease	Yes, species with placenta						Longo and Goyal, 2014
85	(MR/GR) Balance Hypothesis	Homeostasis, adaption, and health depend on the balanced interaction between mediators of the onset and termination of the stress response. An integral limbic MR:GR imbalance is causal to altered processing of information. GCs promotes (via MR) the defense against the stressor, while GR-mediated effects facilitate processing of the stressor and storage of stressful events into memory.	Enhanced vulnerability to disease occurs due to imbalance of MR-activating and GR-suppressing components of the stress reaction. Dynamics, distribution, and coordination of MR and GR in brains regions are not well mapped.	Stress Coping; Health to Disease	No	X			baseline and post-stress	Attempt to explain variation in stress coping and how glucocorticoid actions can change from protective to harmful.	Joëls et al., 2008; Oitzl et al., 2010
86	Neurocognitive Hypothesis	Emotion, stress, stress coping, cognition, and neuroendocrine dysfunction likely interact to mediate vulnerability to develop depression.	Individuals presenting a high anxiety trait are particularly vulnerable to develop depression when facing stress and adversity. (See Figs. 2 and 3 in Sandi and Richter-Levin, 2009).	Health to Disease; Stress Coping	Yes, humans	X		X	baseline and/or post-stress	Mental health – anxiety and depression.	Sandi and Richter-Levin, 2009
87	Neurogenesis Hypothesis	Hippocampal neurogenesis is important for maintenance of mental health. Decrease in post-natal hippocampal neurogenesis underlie depression and treatment for depression should restore neurogenesis.	Decreases in dentate gyrus neurogenesis, including those produced by stress or elevated GCs, should precipitating episodes of depression or a depressive phenotype. (See Table 1 in Miller and Hen, 2015 and Fig. 1 in Petrik et al., 2012).	Health to Disease	No	X		X	baseline or post-stress	Menta health – anxiety and depression.	Jacobs et al., 2000; Petrik et al., 2012; Miller and Hen, 2015;
88	Neuroplasticity Hypothesis (of chronic stress)	Chronic stress exposure alters signaling in the amygdala (and in the hippocampus).	In the amygdala, chronic stress increases glutamatergic signaling, leading to increased brain-	Health to Disease	No (but focus on humans)	X		X	post-stress	Mental health – chronic stress impact on the amygdala	Boyle, 2013

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
			derived neurotrophic factor (BDNF) and dendritic outgrowth. In the hippocampus, glutamatergic signaling decreases BDNF, leading to changes that enhance the stress response. (see Fig. 1 in Boyle, 2013 for more details).								
89	Nutritional Stress Hypothesis	The reliability of song as an indicator of male quality is maintained with developmental costs associated with song learning and production. Links selective factors responsible for evolution of song preference in females to the brain mechanisms underlying song acquisition, development, and production in males.	Males that experience less (nutritional) stress during development, or males that cope with stress better (by having "good" HPA responses), should be able to invest more in brain development and should thus learn and produce the best-quality songs.	Development; Reproduction	Yes, for birds (specifically male song birds)	X			post-stress	Hinges on the assumption that nutritional stress elevates GCs (see Spencer et al., 2003) and that GCs impact song learning and production (see Nowicki et al., 2002). [also see Developmental Stress]	Nowicki et al., 1998; 2002; Spencer et al., 2003
90	Ongoing Selection Hypothesis	An evolutionary hypothesis to explain endocrine trait variability. Individual variation in endocrine traits reflects varying adaptive value, with some individuals expressing suboptimal phenotypes that are selected against.	If variation is traits is due to variation in adaptive value, with some individuals expressing maladaptive phenotypes, manipulating endocrine phenotypes toward a putative optimum should increase fitness. (See Fig. 1b in Bonier and Cox, 2020).	Stage Spanning	No	X		X	baseline	Need to know optimum and to make sure endocrine manipulations fall within correct values. Not just GCs.	Bonier and Cox, 2020
91	Optimal Endocrine Phenotype Hypothesis	An evolutionary hypothesis to explain endocrine trait variability. Adaptive plastic responses to environmental variation generate individual variation in endocrine traits and allow individuals to express near-optimal endocrine phenotypes.	If most individuals express endocrine traits that are optimal or near optimal for their environment, then all hormone manipulations should incur fitness costs as animals are pushed farther from their optimum. (See Fig. 1a in Bonier and Cox, 2020).	Stage Spanning	No	X		X	baseline	This hypothesis supported over Ongoing Selection Hypothesis, but more data are needed. Need to make sure endocrine manipulations fall within correct values. Not just GCs.	Bonier and Cox, 2020
92	Pace-of-Life Syndrome Hypothesis	Provides insights into how and why phenotypic traits might covary and why phenotypic variation may be maintained within populations. Individual differences in behavior should integrate with morphological, physiological, and life-history traits along a slow to fast pace-of-life continuum.	"Slow", vs. "fast", pace-of-life individuals/populations should exhibit relatively slow growth rates, reach sexual maturity later in life, and have long life spans, slower metabolic rates, slower stress reactivity, less response to oxidative stress, higher immune response,	Stage Spanning	No	X		X	post-stress	Originally proposed for variation across species or populations, but now used for within population variation.	Réale et al., 2010; Royauté et al., 2018

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
			less risk-taking and more cautious behavior. (see Fig. 1 in Réale et al., 2010 for specifics).								
93	Parental Care Hypothesis	Elevated GCs should interrupt parental care behaviors, therefore, stress-induced GCs will be suppressed in the sex that provides most of the parental care.	Lower lever of post-stress GCs should correlated with continued care of offspring. If males and females differ in level of care, differences in HPA axis reactivity to stress should differ.	Reproduction	No (but for species with parental care)	X			post-stress	Likely depends on whether obligate or facultative care; uniparental vs. biparental care is an important factor. Similar to Behavior Hypothesis.	Wingfield et al., 1995; Lynn et al., 2003
94	Perseverative Cognition Hypothesis	Worry, rumination, and related phenomena play a large role in human health. These perseverative responses are common in response to and anticipation of stressors and can prolong or activate physiological stress responses. Therefore, perseverative cognition is an important link between the physiological stress response and health.	Perseverative cognition can serve as a mediator or pathway, by which psychosocial stress may produce sustained activation of one or more physiological systems. (See Fig. 1 in Brosschot et al., 2006)	Health to Disease (Aging)	Yes, humans	X	X	X	baseline and post-stress	Similar to the Ecology of Fear concept	Brosschot et al., 2006
95	Polyvagal Theory	Via evolutionary processes mammals have developed a secondary vagal system which is important for responding to threats and for regulating heart rate. This evolutionarily newer system aids in psychological processing and can inhibit more primitive defensive pathways. There are three circuits - safety, danger, and shut down and mammal's ability to sense these is termed neuroception.	Predictions of activation of nervous system in each state are as follows: 1) Safety - dominated by PNS activity, specifically ventral vagus and low tone in dorsal vagus, 2) Danger - SNS activity to facilitate Find (tend and befriend), Fawn, Flee and Fight, 3) Shut Down/Terror - PNS dominant, high tone in the dorsal vagus. (see image by Schlote, 2019).	Stage Spanning	Yes, mammals		X	X		The heart and the vagus nerve are central to this theory. The dorsal vagal complex, SNS, and ventral vagal complex mediate responses to situations.	Porges, 1995; Schlote, 2019
96	Predation Stress Hypothesis	The presence of predators, or honest predator-threat signals, should elicit an HPA axis response, leading to elevated GCs and as a result, anti-predator behavior as well as reduced reproduction and survival.	Fonner & Woodley (2015) suggest several predictions: 1) short-term exposure to predators should increase GCs and elicit predator avoidance behavior, 2) prolonged exposure to predator cues should lead to chronically elevated GCs and constitutive expression of predator avoidance behavior, 3) elevated GCs triggers expression of	Reproduction (Survival)	No	X			baseline and post-stress	Hinges on predator cues increasing HPA axis activity, data on this connection are mixed (see Boonstra, 2013; Harris and Carr, 2016 for reviews). Not supported in salamanders (Fonner and Woodley, 2015).	Boonstra et al., 1998; Creel et al., 2009; Fonner and Woodley, 2015

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators HPA/GCs	ANS (SNS)	other	If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
			predator avoidance behaviors.								
97	Predation-Sensitive Foraging Hypothesis	This hypothesis describes the strategy hares would take to balance behavioral tradeoff between foraging and predator avoidance, under this strategy both survival and condition would decrease.	Hik (1995) writes that predictions are: 1) increased predation risk leads to decreased body mass (and fecundity) and, 2) decreased food levels lead to increased mortality.	Reproduction (Survival)	No (but developed to explain population dynamics in hares)	x			baseline and/or post-stress	Tested with Condition Constraint Hypothesis and the Predator-Avoidance Constraining Hypothesis (see Fig. 2 in Hik, 1995); GCs not directly targeted here but in the Discussion.	McNamara and Houston, 1987; Hik, 1995
98	Predator-Induced Breeding Suppression (PIBS) Hypothesis	During times of high population density there is increased predator pressure and intraspecific competition, this combination is stressful. Female rodents should suppress reproduction under high predation pressure and wait to reproduce under more favorable conditions.	When predation pressure is high reproductive investment will be decreased.	Reproduction	No (but most work done on rodents)					Similar to Chronic Stress Hypothesis. GCs not mentioned directly in either source (for hypothesis discussion, see Boonstra, 2013).	Ylönen and Ronkainen, 1994; Ruxton and Lima, 1997
99	Predictive Adaptation Hypothesis (Predictive Adaptive Response Hypothesis)	This hypothesis blends developmental programming and match-mismatch ideas. The outcome of developmental programming is not always deterministic in nature but rather depends on context in later life. Development under mild circumstances is permissive to phenotypic plasticity from a single genotype. The plastic changes induced by early-life experiences might be adaptive and put in place an expectation of the future environment.	Early-life experiences will impact epigenetic regulations of MR and GR and HPA axis function. The degree of match and mismatch with future environments is fundamental to understanding outcomes of early-life experiences.	Stress Coping; Health to Disease	No	X			baseline and post-stress	Attempt to explain variation in stress coping and how glucocorticoid actions can change from protective to harmful. Similar to developmental programming but this takes an evolutionary perspective.	Oitzl et al., 2010; Bateson et al., 2014
100	Preparative Hypothesis	Predictable annual changes in (potential) exposure to adverse conditions primes GC regulation. Baseline GC changes prepare organism for potential seasonal differences in frequencies of stressful events. An organism does not have to actually experience increased stressors at certain times of year, but the chance of experiencing the increase should be expected.	If baseline GCs are preparative (see Sapolsky et al., 2000), then season-specific increases in baseline GCs may have a priming effect and aid the organism in coping with expected stressors in that season. Thus, seasonal differences in stressor frequency need to be predicable over time.	Stage Spanning	No	X			baseline and/or post-stress	Initially an attempt to explain seasonal regulation of HPA axis. This hypothesis has rarely been tested.	Selye, 1959; Sapolsky et al., 2000; Romero, 2002; Lattin and Romero, 2013
101	Prudent Parent Hypothesis	Organisms should favor self over reproduction when there are multiple future options for reproduction or when the current cost of reproduction is too high (current cost would outweigh future opportunities).	The GC stress response be downregulated when value of current (compared to future) breeding is high, but if future breeding attempts remain then inhibition of breeding by stress is okay.	Reproduction	No (but most work done in birds)	X			post-stress	Generally applies to young animals in long-lived species with multiple breeding opportunities and parental care. Hinges on knowing whether potential	Bokony et al., 2009

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
										for future breeding is high or low.	
102	Reactive Scope Model	Similar to allostatic load, but incorporates more physiological variables (not just energy), and behavioral and cognitive responses to stress. For various physiological endpoints, organisms have a circadian variation, a predictive homeostatic range, and a reactive homeostatic range, and different variables have different scales. Any of these physiological variables can enter a state of homeostatic overload (too high) or homeostatic failure (too low); both overload and failure are detrimental to reproduction and health.	This model removes the reliance on energy and shifts the Y-axis to almost any physiological mediator. Homeostatic ranges for mediators change across seasons and life history stages (predictive homeostasis) and in response to challenges (reactive homeostasis). Together, predictive and reactive homeostasis define the reactive scope. Levels below the predictive homeostasis are homeostatic failure, levels above the reactive homeostasis are homeostatic overload. Both too high and too low are problematic. (See Fig. 1 and Table 1 in Romero et al., 2009 for specifics)	Model; Stage Spanning	No	X	X	X	baseline and/or post-stress		Romero et al., 2009
103	Reactivity Hypothesis	Variation in physiological reactivity to everyday psychosocial stressors should predict disease risk and aging, as mounting a large response to minor stressors is not needed for coping and may negatively impact health.	Regardless of affect and perceptions of coping, individuals with the highest stress reactivity following an in-lab stress challenge will have decreased immune function, poorer health, and advanced aging compared to low-reactivity individuals.	Stress Coping; Health to Disease	Yes, humans	X	X	X	post-stress	Specifically for social and psychological stress in humans	Cacioppo et al., 1998
104	Reproductive Stress Hypothesis	In altricial bird species, females lose body mass after hatching of the young and this is due to the physiological stress associated with egg production, incubation, and feeding young.	Mass loss in females should be due to increased demands of reproduction and should not occur if food is made readily available (via supplementation or years of good food supply). Harding and colleagues (2009) mention role of GCs.	Reproduction	Yes, birds (females)					Not supported when tested with the Adaptation for Flight Hypothesis (decreased mass is beneficial for flight maneuverability and energy savings during foraging).	Slagsvold and Johansen, 1998; Harding et al., 2009
105	Reservoir Hormone Hypothesis	This hypothesis distinguishes between biologically active (free) and biologically relevant (bound to corticosteroid binding globulin; CBG) GCs. The bound component acts as a	Measures of free and bound GCs are incredibly important for fully understanding how GCs are related to study question.	Stage Spanning (GC Regulation)	No (but most work done in birds)	X			baseline and post-stress	This is complementary to the Total Hormone Hypothesis. Also see paper by Schoech and colleagues (2013) for some concerns	Malisch and Breuner, 2010; Schoech et al., 2013

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators HPA/GCs	ANS (SNS)	other	If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
		reservoir of available GCs for times of increased metabolic need.	For example, individuals may not differ in total hormone level but may have very different current MR and GR binding (from free portion) and may have different reservoir capacities for later use (bound portion).							and potential limitations of CBG analysis. Also note, some species do not have CBG.	
106	Restraint Hypothesis	Young animals are expected to invest less in current reproduction due to high prospects for future reproduction.	Reproductive success should increase with age. In terms of stress response, Elliott et al. (2014) propose that the stress response is proportional to residual reproductive success at a given age. Change only occurs in reproductive individuals.	Reproduction (Survival)	No (but for iteroparous species)	X			post-stress	Predicted specifically free GCs; hinges on having an honest signal of residual reproductive success.	Elliott et al., 2014
107	Scope of Flexibility Hypothesis	The magnitude of within-individual changes in endocrine traits across an environmental gradient or in response to a stimulus. Relevant aspects may include the scope of initial response as well as those of subsequent responses, including downregulation.	Individuals that have a greater scope of flexibility are better able to match the optimal endocrine phenotype across diverse conditions, will have higher fitness. (See Figures in Taff and Vitousek, 2016).	Stage Spanning	No	X			baseline and post-stress	As aspect of endocrine flexibility	Taff and Vitousek, 2016; Schoenle et al., 2018
108	Self-Medication Hypothesis	A person uses the abused substance to cope with tension associated with life stressors or to relieve or suppress symptoms of anxiety and depression. Often seen in individuals with PTSD.	Drug (e.g., cocaine) and alcohol use should decrease feeling of life stress.	Health to Disease; Stress Coping	No (but focus on humans)	x			post-stress	Substance abuse. Paper discusses HPA axis but no clear stress mediator predictions for this hypothesis.	Goeders, 2003
109	Senescence Hypothesis	Population declines are driven in part by GC-induced reduction in reproduction in aged microtines. The HPA axis becomes dysregulated due to life-long exposure to GCs and this dysregulation leads to reproductive senescence.	See pages 211–212 of Boonstra, 1994 for predictions.	Reproduction (Aging)	Yes, microtine rodents	X			baseline and post-stress	An extension of the Glucocorticoid Cascade Hypothesis and the Christian Stress Hypothesis. Population age structure is critical here.	Boonstra, 1994
110	Short-Season Hypothesis	To maximize reproductive opportunities, organisms living in severe environments with short breeding seasons will down regulate the GC response to stress during breeding.	HPA axis sensitivity among species should correlate with length of the breeding season; the shorter the season the less reactive the axis.	Reproduction	No (but for severe environments with short breeding seasons)	X			post-stress	Cues for length of breeding season must be detectable and reliable. Suggests elevated GCs should impair reproduction.	Wingfield, 1988; Lynn et al., 2003
111	Silver Spoon Hypothesis	Individuals developing in stable, rich conditions might always outperform those subjected to stressful, unpredictable conditions in traits such	Developmentally stressed individuals should be of lower quality, and less capable of high-quality	Development (Performance)	No					Also called carryover effects.	Boogert et al., 2013; Taborsky, 2017

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
		as learning or other types of performance.	performance than those with a stable development.								
112	Speed of Flexibility Hypothesis	The rapidity with which endocrine trait expression responds to a change in context or exposure to a stimulus. Relevant aspects include speed of initial and subsequent changes.	Changes in environmental conditions will result in a mismatch between optimal and expressed endocrine phenotypes. In moderately dynamic environments, those that can more quickly adjust phenotype will have higher fitness (See Figures in Taff and Vitousek, 2016).	Stage Spanning	No	X			baseline and post-stress	As aspect of endocrine flexibility.	Taff and Vitousek, 2016; Schoenle et al., 2018
113	Stress Acceleration Hypothesis	The quantity and quality of parental care may act as an environmental signal for pace of offspring maturation with circumscribed emotional systems.	Early-life caregiving stress leads to accelerated development of limbic system development (to cope with parental absence) but may have long-term consequences on circuit integrity and function, such as fear-related psychopathology, by altering developmental plasticity. Sex and stress hormones likely play a role.	Development; Stress Coping; Health to Disease	No	x		x		Stress conditions help to shape tradeoff between duration of childhood and age at sexual maturity. Large focus on parent-offspring relationships.	Callaghan and Tottenham, 2016
114	(stress) Buffering Hypothesis	Social support has a benefit on well-being. This hypothesis states psychosocial stress will have deleterious effects on the health and well-being of those with little or no social support, and these effects will be lessened or eliminated for those with stronger support systems.	Individuals with more social support should report less stress and should show lowers SNS and HPA responses to stressors, they should also have decreased incidence of psychopathology.	Stress Coping (Social Interactions)	No (but initial papers in humans)	x	x		post-stress	Should be noted that social interactions can be positive or negative (see DeVries et al., 2007)	Wilcox, 1981; Cohen and McKay, 1984; Cohen and Wills, 1985; Glasper and DeVries, 2005; DeVries et al., 2007; Floyd et al., 2007
115	Stress Gradient Hypothesis	The balance between positive and negative interactions among species will vary along gradients of stress.	Positive interactions will be more important in more stressful environments. (See Fig. 1 and Table 2 in Barrio et al., 2013; see various predictions in Malkinson and Tielbörger, 2010)	Stage Spanning	No					Originally developed for plants	Holmgren and Scheffer, 2010; Malkinson and Tielbörger, 2010; Barrio et al., 2013
116	Stress Generation Hypothesis	There is a bidirectional interplay between depression and life stress, in that negative life events increase one's risk for depression but depression can also lead to increased risk for negative life events.	Depression can be initiated by stressful events outside one's control, but in those that are depression-prone something about their personality, behavior, or stress coping increases their experience (or perception) of stressful event.	Health to Disease; Stress Coping	Yes, humans					Mental health – depression.	Hammen, 1991; Safford et al., 2007
117				Development		X		x	post-stress		

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#	Name	Background and Description	Specific Prediction(s), if available	Stage or transition	Taxon specific?	Proposed Mediators			If GCs, baseline or post-stress levels?	Notes (caveats, assumptions, etc.)	Sources
						HPA/GCs	ANS (SNS)	other			
	Stress Hyporesponsiveness Period[1] (SHRP; previously Stress Non-Responsive Period)	During the first ~ 2 weeks after birth, the HPA axis of rat pups in greatly attenuated in response to stressors. This is thought to protect the developing central nervous system from catabolic impacts of GCs.	Type of stressor (anticipatory vs reactive) likely matters as do maternal care, nutritional status, and tactile stimulation. (See Fig. 2 in Sapolsky and Meaney, 1986 and Fig. 1 in Schmidt, 2010)		Yes, postnatal period in rodents (rats)					Seems the postnatal HPA axis can generally respond to systemic stressors (ether and LPS) but not to those acting via the limbic pathway (saline or novelty).	Sapolsky and Meaney, 1986; Levine, 2001; Schmidt, 2010
118	Stress Hyporesponsiveness Period[2]	In new mothers, the HPA and SNS response to stressors is downregulated. This change helps to protect offspring from elevated GCs as well as for promoting maternal care and survival of offspring. Possibly helpful for maternal mental health.	This change is likely driven by increased levels of oxytocin and prolactin, and reduce activity of excitatory pathways (norepinephrine, corticotrophin-releasing factor, and opioids). (See Fig. 1 in Slattery & Neumann, 2008)	Reproduction	No (but for mothers in the peripartum period, including lactation)	X	X	X	post-stress	Data from rodents, ewes, and humans.	Slattery & Neumann, 2008
119	Stress of Subordination	In animals with dominance hierarchies, dominant animals breed and subordinate animals (usually) do not. Being a subordinate might be a form of chronic stress.	Subordinate animals are chronically stressed and have chronically elevated GCs, this leads to reproductive suppression.	Reproduction	No (but for cooperative breeders)	X			baseline and/or post-stress	In some species dominant animals have higher GCs, so does not hold for all species with cooperative breeding.	Creel, 2001; Sapolsky, 2005; Creel et al., 2013
120	Stress-coping (mis) Match Hypothesis	Nature (genes) and nurture (environmental stimuli) are both important for development of psychiatric conditions. Stress-coping responses are programmed by genes and the developmental stage of stress experience. Responses are adaptive when they match current stress conditions, but maladaptive when they mismatch.	Active stress coping skills learned to deal with an escapable stressor will be beneficial for future escapable stressors, but problematic for inescapable stressors (and vice versa). Individuals that are stress-sensitive by genotype will show the most adverse responses to mismatched coping. (See Figs. 1 & 2 in Homberg, 2012).	Health to Disease; Stress Coping; Development	No (but focus on humans)	x	x	X	receptors	A combination of the "for-better-and-for-worse" and the Match-Mismatch Hypothesis of Disease.	Homberg, 2012
121	Stress-suppression Hypothesis	Physical and social stressors should delay the onset of pubertal maturation in girls and should also disrupt or delay ovulation in reproductively capable women.	Increased activation of the HPA axis and ANS due to stress results in suppression of the hypothalamic-pituitary–gonadal axis (inhibition can occur at various levels).	Reproduction	No	X	X		post-stress	Used to describe human female pubertal maturation but hypothesis is not limited to humans.	Ellis, 2004
122	Stress-vulnerability Hypothesis	Psychosis (disease) will develop due to an interplay between genetic vulnerability and environmental risk factors. The less stress one can endure the higher their vulnerability of disease.	Specific genetic substrates will interact with environmental stressors to trigger changes in mediators of adaptation (i.e., HPA axis, ANS, immune system) which will	Health to Disease	No (but focus is on humans)	X	X	x	post-stress	Based on the idea of allostasis, this example is for psychotic disorders but idea apply to many other "stress-related" diseases. Similar to Stress-coping (mis)Match Hypothesis.	Gispen-de Wied and Jansen, 2002

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						HPA/GCs	ANS (SNS)	other			
			be related to expression of disease state. Vulnerability substrates are probably different for different disorders.								
123	Tend and Befriend Hypothesis	Evolution has shaped the male and female response to stress. Based on evolutionarily conserved gender roles and parental investment, the response to stressors in females should be "tend and befriend" and in males should be "fight or flight".	Following stress, females show nurturing and affiliative behaviors with decreased activation of SNS and HPA axis. Female response to stress is hypothesized to mediated by oxytocin and moderated by estrogen, progesterone, and opioids (see Fig. 1 in Taylor, 2006). Males show fight or flight behaviors and these responses are primarily related to interactions between testosterone and SNS.	Stress Coping (Social Interaction)	No (but focus is on humans)	X	X	X	post-stress	Hypothesis to explain human female behavior. Hinges on the idea that human family dynamics and social patterns were stable across populations of early hominids and drove differential selection of hormonal and behavioral responses to stress.	Taylor et al., 2000; Taylor, 2006
124	Tension-Reduction Hypothesis of Alcoholism	Alcohol serves to reduce tension, anxiety, or stress possibly because of the depressing or tranquillizing effects of alcohol on the nervous system. Drinking is thus reinforced by the tension reduction effects obtained.	Alcohol serves as a negative reinforcer as its consumption results in the removal (alleviation) of an aversive or unpleasant (anxiety) state	Health to Disease; Stress Coping	Yes, humans					Mixed responses with HPA axis as alcohol tends to increase HPA axis output, but time course (acute, chronic, relapse) matters.	Young et al., 1990; Becker, 2017
125	Terminal Restraint Hypothesis	The oldest animals may show reproductive restraint when conditions are sub-optimal because even a small increase in reproductive investment may lead to death.	Reproduction should decrease with biological, as opposed to chronological, age. Older animals should skip reproduction when times are stressful as reproducing would bring them closer to the physiological minimum to support life. In terms of the stress response, Elliot and colleagues (2014) predict the stress response is inversely proportional to average reproductive success at a given age. Change only occurs in reproductive individuals.	Reproduction (Survival)	No (but for iteroparous species)	X			post-stress	Predicted specifically free GCs.	Elliott et al., 2014
126	Three(3)-hit model	Severe depression is linked to disturbed brain function and an overactive HPA axis. Susceptibility of the underlying pathways is regulated	The 'three hit' model suggests that genetic susceptibility and early-life priming experiences influence responses to stress	Development; Health to Disease	No (but focus is on humans)	X			baseline and post-stress	Focus on depression in humans but animals studies would be useful. Focus is on regulation of MR and GR. Mental health – depression.	de Kloet et al., 2007

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						HPA/GCs	ANS (SNS)	other			
		by three factors: genes, early-life priming, and later-life events.	such that they can precipitate depression. (See Fig. 1 in de Kloet et al., 2007).								
127	Total Hormone Hypothesis	GCs travel through the blood bound to corticosteroid-binding globulin (CBG; bound), loosely attached to other proteins or unbound (free). GCs dissociated from CGB rapidly and bound hormone is readily available for delivery to tissues and measures of total GCs are accurate.	Measures of total GCs, without separating bound vs. free fractions, will provide an accurate picture of how GCs relate to study question.	Stage Spanning (GC Regulation)	No (but most work done in birds)	X			baseline and post-stress	Also see paper by Schoech and colleagues (2013) for some concerns and potential limitations of CBG analysis. Also note, some species do not have CBG.	Breuner et al., 2013
128	Trade-off Hypothesis	During time of stress, plasma GC levels are negatively correlated with functions like reproduction or immune processes that are both energetically costly and not necessary for survival of the threat.	According to Thomas and colleagues (2017), both baseline and post-stress GCs should be negatively related to reproduction and immunity.	Reproduction	No	X			baseline and post-stress	Also known as the Energy Re-Allocation Hypothesis	Thomas et al., 2017
129	Traditional Model	Organisms are in a state of dynamic equilibrium and this includes physiological and psychological processes. Dynamic equilibrium is maintained without stress when situations are predictable (e.g., day/night, season, breeding, etc.). Unpredictable changes are noxious stimuli (stressors) and elicit an active, acute stress response to deal with challenge. Unchecked, over-activation or over-compensation of the stress response (chronic stress) leads to disruption of dynamic equilibrium and health problems.	The nature of the stressor and context matter for how the organism responds to the situation and if, in fact, the situation registers as a stressor (habituation is important). (See Fig. 3 and corresponding text in Chapter 3 of Romero and Wingfield, 2015).	Model; Stage Spanning	No	x	x	x	post-stress		Romero and Wingfield, 2015
130	Value of Reproduction Hypothesis	Broad term with several nested additional hypotheses. Based on the premise that reproduction is costly and that the stress response is adaptive as it helps to terminate current reproduction in order to promote survival and future reproduction.	The GC stress response should be suppressed when the value of current reproduction relative to future reproduction and survival is high. If survival and investment in future reproduction is likely, GCs should suppress current reproduction.	Reproduction	No	X			post-stress	Sub hypotheses mentioned include parental care and short season. Hinges on knowing whether a current reproductive bout is of high or low fitness potential.	Wingfield et al., 1995; Lendvai et al., 2006
131	Workload Hypothesis	Raising offspring and mounting a stress response are both energetically expensive. The stress response should be down-regulated during reproduction so resources can be diverted to raising young.	Parents who are actively investing in offspring (have a high workload) should have a decreased response to stress in order to protect resource investment and spend more energy on raising offspring.	Reproduction	No (but for species with parental care)	X			post-stress	Was not supported when tested with the Brood Value Hypothesis.	Lendvai and Chastel, 2008

Table 2
Hypotheses that were found during literature searches or during manuscript writing but were not included in Table 1 as they were deemed tangentially related or dealt with oxidative stress or the immune system.

#	Name	Topic/Notes	Source(s)
1	Adaptation Hypothesis	Health to Disease	Cohen et al., 2019
2	(Antioxidant) Consumption Hypothesis	Oxidative stress	Cohen et al., 2008
3	(Antioxidant) Regulation Hypothesis	Oxidative stress	Cohen et al., 2008
4	Attention Hypothesis	ACTH on memory	Van Riezen et al., 1977
5	Autonomic Imbalance Hypothesis	Stress system and athletes	Lehmann et al., 1998
6	Behaviour-Hypothesis	GC function after psychological stress	Yates and Maran, 1974
7	Beneficial Acclimatization Hypothesis	Thermal stress	Wilson and Franklin, 2002
8	Biopsychosocial Model of Challenge and Threat	Stress Coping	Blascovich and Tomaka, 1996
9	Burden of Adversity Hypothesis	PTSD; Polytrauma	Brenner et al., 2009
10	Catecholamine Hypothesis of Affective Disorders	Health to Disease; Mental Health	Schildkraut, 1965
11	Common Soil Hypothesis	Oxidative stress	Ceriello and Motz, 2004
12	Cognitive Activation Theory of Stress (CATS)	Cognitive response	Ursin and Eriksen, 2010
13	Consolidation Hypothesis	Development; Environmental Match	Groothuis and Taborsky, 2015
14	Constraint Hypothesis	Oxidative stress	Viblanc et al., 2018
15	Cost Hypothesis	Oxidative stress	Viblanc et al., 2018
16	CRF Hypothesis	Cyclical vomiting syndrome	Tache, 1999
17	CRH Excess Hypothesis	Specific to West Syndrome	Brunson et al., 2001
18	Early Illness Amnesia Hypothesis	Mental Health; PTSD	Granja et al., 2008
19	Elongation hypothesis	Oxidative stress/aging	Haussmann and Mauck, 2007
20	Emotional (Stress) Contagion	Factors influencing stress reactivity	Bolger et al., 1989; Gump and Kulik, 1997; Barsade, 2002; Waters et al., 2014; da Silva et al., 2019
21	Energy Crisis Hypothesis	Immune	Adamo, 2008
22	Evolutionary-Development Perspective	Health to Disease (similar to Differential Susceptibility and Adaptive Calibration)	Ellis and Del Giudice, 2019
23	Evolutionary Hypothesis[1]	Oxidative stress/aging	Haussmann and Mauck, 2007
24	Evolutionary Hypothesis[2]	Conserved response to stress in hemocytes	Ottaviani, et al., 1993
25	GABA Disinhibition Hypothesis	Mechanism for stress-induced analgesia	Lau and Vaughan, 2014
26	Habituation Hypothesis	Factors influencing stress reactivity	Kant et al., 1985; Patel and Hillard, 2008; Romero and Wingfield, 2015
27	Hedonia Hypothesis	Reward; Addiction	Berridge, 2007
28	Hervey's Hypothesis (Ponderostat Hypothesis)	HPA control of body weight	Cabanac and Richard,1996
29	Immunoredistribution Hypothesis	Immune	Dhabhar et al., 1995
30	Immunopathology-avoidance Hypothesis	Immune	Bourgeon et al., 2009
31	Incentive Salience Hypothesis of Reward	Reward; Addiction	Berridge, 2007
32	Insect Performance Hypothesis	Plants; Predation Stress	Larsson, 1989
33	Kindling or Behavioral Sensitization Hypothesis	Factors influencing stress reactivity	Post, 1992; Breese et al., 2005; Monroe and Harkness, 2005
34	Koritz-Hall Hypothesis	ACTH release	Koritz and Hall, 1964; Urquhart et al., 1968
35	Inflammatory Hypothesis Model of Depression	Health to Disease; Mental Health; Immune	Gardner and Boles, 2011
36	Interleukin Hypothesis of Major Depression	Immune	Maes, 1995
37	Lee-Boot Effect	GCs as mediators	Ma et al., 1998
38	Marginal Value Theorem	Predation stress and feeding	Pyke et al., 1977
39	Maternal Capital (Maternal Buffering) Hypothesis	Development; Environmental Match	Groothuis and Taborsky, 2015
40	Membrane Stress Syndrome	Lupus	Ames, 1994
41	Metabolic Hypothesis	For psychological disorders with low cortisol	Yehuda and Seckl, 2011
42	Microbiota-Inflammasome Hypothesis of Major Depressive Disorder	Health to Disease; Mental Health; Immune	Inserra et al., 2018
43	Mitochondrial Allostatic Load Hypothesis	Oxidative stress	Picard et al., 2014
44	Mitochondrial Psychiatry Model of Depression	Health to Disease; Mental Health	Gardner and Boles, 2011
45	Mitochondrial Stress Hypothesis	Oxidative stress	Stier et al., 2013
46	MONA-LISA hypothesis	Obesity; Health to Disease	Bray, 1991
47	Multi-predator Hypothesis	Predation stress	Blumstein et al., 2004
48	Monoamine Hypothesis of Depression	Mental health; Health to Disease	Schildkraut, 1965; Hirschfeld, 2000
49	Neurodegeneration and the Accelerated-Aging Hypothesis	Mental Health; PTSD; Oxidative stress	Miller and Sadeh, 2014
50	Neurodegeneration Hypothesis of Depression	Health to Disease; Immune	Myint and Kim, 2003
51	Neuroimmune Network Hypothesis	Health to Disease; Immune	Nusslock and Miller, 2016
52	Over Excitation Hypothesis	Immune	Adamo, 2008
53	Oxidative Shielding Hypothesis	Oxidative stress	Viblanc et al., 2018
54	Oxidation Handicap Hypothesis	Oxidative stress	Alonso-Alvarez et al., 2006
55	Oxidative Stress Hypothesis	Oxidative stress; Alzheimer's Disease	Markesbery, 1997
56	Oxidative Stress Hypothesis of Life History	Oxidative stress	Costantini, 2019
57	Physiological Toughness Theory	Performance; Temperament	Dienstbier, 1989
58	Police Stress Hypothesis	Stress of law enforcement jobs	Malloy and Mays, 1984
59	Predator Recognition Continuum Hypothesis	Predator stress	Ferrari et al., 2008
60	Psychosomatic Hypothesis	Anger; Health to Disease	Smith, 1992
61	Redox Signaling Hypothesis of Life History	Oxidative stress	Costantini, 2019
62	Redox Stress Hypothesis of Aging	Oxidative stress	Sohal and Orr, 2012
63	Resilience Hypothesis	PTSD; Health to Disease	Flach, 1990
64	Resource Crunch Hypothesis	Immune	Adamo, 2008
65	Resource-limitation hypothesis	Immune	Bourgeon et al., 2009
66	Retrieval Hypothesis	ACTH on memory	Van Riezen et al., 1977
67	Reward Learning Hypothesis	Reward; Addiction	Berridge, 2007
68	S-Process Hypothesis	Sleep; Depression	Ehlers and Kupfer, 1987

(*continued on next page*)

Table 2 (*continued*)

#	Name	Topic/Notes	Source(s)
69	Selection Hypothesis	Oxidative stress/aging	Haussmann and Mauck, 2007
70	Sensation-Seeking Hypothesis	Health to Disease; Alcohol and Substance Use	Goeders, 2003
71	Sensitized-Specialization Hypothesis	Development; Memory	Young et al., 2018
72	Serotonin Hypothesis of Depression	Health to Disease; Mental Health	Coppen, 1967; Albert et al., 2012
73	Shift and Focus Hypothesis	Immune	Adamo, 2008
74	Sit and Wait Hypothesis	Pathogens; Stress Resistance; Virulence	Wang et al., 2017
75	Somatic Marker Hypothesis	Decision making; Does not seem well supported	Dunn et al., 2006
76	Stress Appraisal Theory	Stress coping	Lazarus and Folkman, 1984
77	Stress Paradigm Hypothesis	Predator-prey relationships	Hawlena and Schmitz, 2010
78	Stress-Induced Analgesia	Stress and pain phenomenon	Amit and Galina, 1986
79	Stress-Induced Mitochondrial Hyperfusion	Mitochondrial stress	van der Bliek, 2009
80	Stress Sensitization Hypothesis	Applied to bipolar disorder	Dienes et al., 2006
81	Stressor-Disease Specificity Hypothesis	Health to Disease	Cohen et al., 2019
82	Vicious Cycle Hypothesis	Oxidative stress	Frisard and Ravussin, 2006
83	Winter Immunoenhancement Hypothesis	Immune	Nelson and Demas, 1996; Sinclair and Lochmiller, 2000

presented here.

4.2. Development: stress, GC, and developmental framework

The developmental environment from conception to infancy can have pronounced impacts on offspring phenotype including behavior, physiology, and susceptibility to disease, and this holds across species (Gluckman et al., 2007). The role of developmental environment impacts on adult phenotype and disease risk in humans was formalized by Barker and Osmond (1986) and Hales and colleagues (1991) . Early work was based on epidemiological data connecting low birth weight to later cardiovascular, renal, and metabolic diseases. Hales and Barker coined the Thrifty Phenotype Hypothesis (Hales and Barker, 1992; 2001) to describe their data on early-life conditions and insulin resistance with later development of Type II diabetes mellitus; this has also been termed fetal stress syndrome (Lou et al., 1994). The Thrifty Phenotype Hypothesis posits that when developmental (intrauterine) conditions are nutrient poor the physiological changes that occur in response, namely small size and insulin resistance, make an organism better suited for a poor postnatal environment (i.e., thrifty). This hypothesis slightly contrasted the Thrifty Genotype Hypothesis (Neel, 1962) which suggested that selection favored the acquisition of thrifty genotypes in humans and these genotypes are no longer advantageous in environments with abundant nutritional resources (see refinement to Drifty Gene Hypothesis; Speakman, 2008). Recently, the role of brain energy usage during childhood in shaping the adiposity reserve and obesity risk has been proposed to help explain the link between early life experiences in later (metabolic) disease risk (Kuzawa and Blair, 2019). These hypotheses differ in some aspects, but overall suggest that an adult organism would do well in environments with limited nutrients and would be more susceptible to metabolic disease in nutrient-rich environments (see Gluckman et al., 2007). This idea forms the basis of the Match-Mismatch hypotheses which broadly posit that early life programming is beneficial if the postnatal (nutrient) environment is similar to that of the developmental environment (see Fig. 2 in Gluckman et al., 2007).

The term Developmental Origins of Health and Disease (DOHaD), also known as the Fetal Origins Hypothesis and the Barker Hypothesis, was created to describe the relationship between adverse influences in early life and the resulting changes in physiology, structure, behavior, and/or metabolism that lead to increased disease risk (de Boo and Harding, 2006). This concept of early life stressors, occurring during a critical window, relating to later changes in physiology and metabolism is also known as metabolic priming or metabolic imprinting (Dyer and Rosenfeld, 2011). Several hypotheses that fall under the broad category of DOHaD have been proposed (Gluckman et al., 2007). For example, DOHaD has been conceptualized in the health literature as variations of the (Environmental) (mis) Match Hypothesis, the Predictive Adaptive (or Adaptation) Hypothesis, the Glucocorticoid (overexposure) Hypothesis, the Cumulative Stress Hypothesis, the “hit” hypotheses, and expansion to the Lifecourse Health Development framework (Halfon et al., 2014). The environmental match-mismatch/maternal-offspring match framework has also been extensively applied to ecological studies (Love et al., 2005, 2013; Breuner, 2008; Crossin et al., 2016; Groothuis and Taborsky, 2015; Sheriff et al., 2017) and Sheriff and colleagues have recently proposed using the Error Management Theory to test some of these ideas (Sheriff et al., 2018).

The mediators signaling quality of the developmental environment are not entirely known but glucocorticoids and catecholamines can act as potent signals and these hormones help regulate several aspects of gestation. For example, in mammals, SNS activity and glucocorticoid concentrations in the fetus increase in the days prior to delivery, but the time course and mechanism by which this occurs differs by species (Fowden et al., 1998; Li et al., 2014; Whirledge and Cidlowski, 2017; Mulkey et al., 2019). In humans, glucocorticoids prepare the fetus for birth and for life outside the womb by driving maturation of the lungs, production of glucose in the liver, and increasing production of thyroid hormones and catecholamines (Liggins, 1994). These physiological changes allow the fetus to transition from dependence on the placenta for oxygen, glucose, and heat (Liggins, 1994). In the developing fetus, glucocorticoids also shift the process from cell proliferation to cell differentiation and increase the production of several key enzymes that will be needed to sustain life outside the womb (Liggins, 1994). Thus, many of the DOHaD hypotheses make predictions about the way in early exposure to challenges, and increased glucocorticoids, will alter phenotype, including adult activity and reactivity of the HPA axis and glucocorticoid regulatory systems (Glover et al., 2010; Graignic-Philippe et al., 2014). One mechanism by which early life stress or nutritional environment (e.g., metabolic imprinting) may alter offspring phenotype is via epigenetic regulation (Cutfield et al., 2007; Waterland and Michels, 2007; Aristizabal et al., 2019). Namely, that various stressors can activate a similar suite of epigenetic changes (Mosaic Hypothesis of Epigenetics; Longo and Goyal, 2014) and that epigenetic modification of the glucocorticoid receptor and other effectors (and their bidirectional interactions) is important for organismal response to challenging environments (Bartlett et al., 2019).

Additionally, the concept and evolution of sensitive periods, or times in which developmental trajectories are (more) vulnerable to perturbation or programming, is important (see Frankenhuis and Walasek, 2019). The idea of early (organizational) and later (activational) glucocorticoid effects is similar to the organizational-activational hypothesis (Phoenix et al., 1959; Arnold, 2009) which described the role of sex steroids, mainly androgens, in prenatal brain masculinization (organization) and future (e.g., after puberty) behavior (activation of masculinized neural pathways) in rodents. This organizational-activational concept has been expanded to other species and to

other steroid hormones including the glucocorticoids (McEwen, 1991; Schoech et al., 2009), and adds complexity to determining sensitive periods. Thus, the period in the developmental environment at which signals/stressors occur (e.g., prior to conception, after conception, postnatally, etc.) and the timing/pattern of glucocorticoid release are likely important for programming an individual, but the critical periods and mechanisms are not entirely clear. Moreover, these specifics likely differ by species, physiological systems, and intrinsic factors (Schoech et al., 2011; Hau et al., 2016; Novais et al., 2017; Whirledge and Cidlowski, 2017), and, epigenetic regulation (Champagne, 2019), specific gene × environment interactions (e.g., with single nucleotide polymorphisms; Zannas and Binder, 2014; Gluckman et al., 2007; Noguera and Velando, 2019), maternal investment (Nesan and Vijayan, 2013), (allo)parental factors (Curry, 2019), and interactions with other hormonal systems seem to play a role (Fowden et al., 2016). Many of the hypotheses included make predictions about the mechanism and/or time course for how developmental environment can impact adult phenotype.

Out of the 131 hypotheses included here, a total of 29 make predictions that broadly involve development. Note this number is six higher than that listed on Fig. 1 as it includes six items from the stage spanning or models section that have strong ties to development (Adaptive Tuning Model; Adaptive Calibration Model; Biological Sensitivity to Context; Developmental Origins of Health and Disease; Inoculation Stress; and Lifecourse Health Development Model). I chose to classify development hypotheses into one of six themes: 1) Elevated stress/GCs is bad for offspring development and/or survival (9 hypotheses: Attenuation Hypothesis; Compensation Hypothesis; Cortisol Buffering Hypothesis; Cumulative Stress Hypothesis; Developmental Hypothesis; Glucocorticoid (Overexposure) Hypothesis; Maternal/Offspring Match Hypothesis; Silver Spoon Hypothesis; Stress Hyporesponsiveness Period[1]), 2) Increased stress/GCs during development can help program honest signals of fitness (2 hypotheses: Developmental Stress Hypothesis; Nutritional Stress Hypothesis), 3) Developmental stress/GC exposure shapes the offspring phenotype for survival in the current environment (9 hypotheses: Adaptive Calibration Model; Developmental Origins of Health and Disease; Lifecourse Health Development Model; Match-Mismatch Hypothesis (of Disease)[2]; Maternal Mediation Hypothesis[1]; Maternal-Match Hypothesis; Mismatch Hypothesis; Mosaic Hypothesis of Epigenetics; Stress Acceleration Hypothesis), 4) Increased or decreased stress/GCs during development is problematic (inverted U relationship; 3 hypotheses: Biological Sensitivity to Context Model; Conditioning Hormesis Hypothesis; Inoculation Stress Model), 5) Increased stress/GCs during development interact with genes to influence adult phenotype (interaction effects; 4 hypotheses: Double-hit or Two(2)-hit Hypothesis; Maternal Mediation Hypothesis[2]; Stress-coping (mis) Match Hypothesis); Three(3)-hit Model), and 6) (moderately) Increased stress/GCs during development is helpful (2 hypotheses: Adaptive Tuning Model; Everyday Stress Resilience Hypothesis). Supplemental Fig. 2 shows a themed arrangement of the hypotheses. Please note, these hypotheses could likely be arranged in a variety of ways besides the way in which they are presented here.

4.3. Stress coping, interindividual variation, (Animal) personalities, and resilience

Interindividual variation in behavior and (stress) physiology is well documented in multiple species. Differences in behavior, physiology, and stress coping are important for biomedicine and for ecology/evolution studies (Korte et al., 2005; Williams, 2008; Carere et al., 2010; Stamps and Biro, 2016; Zänkert et al., 2019). For example, one goal of biomedical stress research is to determine why certain individuals are resistant to stress or show resilience following stressors whereas other individuals are susceptible and transition from a state of health to one of disease (Radley et al., 2011; Fink, 2016b; Carcone and Ruocco, 2017; Perneczky et al., 2019). Additionally, while Selye took a physiological and psychobiological approach to stress, in the 1960s, Richard Lazarus thought of stress as “hardship or adversity” and pushed a psychological approach to stress theory, which emphasized the roles of appraisal (evaluation of the event) and coping (individual efforts to manage event) in dealing with stressors (Lazarus, 1993; Krohne, 2002; Biggs et al., 2017). Thus, from a psychological viewpoint, understanding stress coping is a critical component for stress research.

Behavioral differences are often stable and coupled with physiological responses, creating what has been termed animal personalities, also called behavioral syndromes, coping style, predispositions, or temperaments (Carere and Maestripieri, 2013). The classifications of animal personalities has developed to include several behavior- (stress) physiology connections. Initially, Cannon first described the connection between sympathetic activity and behavior (fight or flight or active coping; Cannon, 1915). Later, consistent physiological differences among mice engaging in social conflict were noticed, with winners showing higher sympathetic activity and losers showing higher HPA activity (Henry and Stephens, 1977). The loser/subordinate animals with high HPA axis activity showed the behavioral withdrawal-conservation response (Engle and Schmale, 1972). Around this same time, game theory or the Hawk-Dove framework was introduced to explain the maintenance of rare behavioral variants in frequency-dependent selection (Maynard Smith and Price, 1973). Koolhaas and colleagues compiled multiple studies and classified animals as having either a proactive strategy or a reactive strategy for stress coping (Koolhaas et al., 1999). Physiologically, a proactive strategy is generally associated with low HPA activity and reactivity, low parasympathetic reactivity, and high sympathetic reactivity and high testosterone activity; the reactive strategy shows the opposite pattern. This personality terminology has expanded and animals are typically classified as shy/slow/passive/reactive or bold/fast/active/proactive in their stress-coping responses (Cockrem, 2007). Personalities are often used to describe risk-taking/aversion and SNS and HPA axis dynamics (baseline, stress response, negative feedback, and axis sensitivity; Baugh et al., 2017). Korte and colleagues (Korte et al., 2005) use the Maynard Smith terms of Hawk and Dove for broader descriptions of overall survival strategies, with personality, behavioral, and physiological responses nested within the Hawk or Dove classification. These Hawk/Dove or Proactive/Reactive personality types are reminiscent of the (now seemingly unsupported) Type A and Type B personalities of early biomedical studies which were first described by Friedman and Rosenman in connection to cardiovascular disease (Rosenman and Friedman, 1981; also see Sher, 2005). Many (behavioral) endocrinology papers discuss animals at opposite ends of a spectrum (e.g., shy or bold), as lab-based selection experiments can drive extremes, but in the wild it is important to note that behavioral and physiological responses are shown across a spectrum.

Animal personalities have been used to describe consistent and linked responses between hormones and behavior. The ultimate and proximate drivers of persistent differences in behavior and stress physiology phenotypes are not entirely clear, but possible ultimate explanations include lack of fitness consequences of behavior (not likely), fluctuations in selection pressure, state-dependent behavior (phenotypic plasticity), and/or frequency-depend selection (Carere et al., 2010). When asking how proximate mechanisms might connect stress physiology and behavior, it is not clear if stress physiology directly determines behavior, if additional factors jointly impact stress physiology and behavior (and thus drive correlational selection pressure), or if behavior directly determines stress physiology (Carere et al., 2010; Wolf et al., 2013). It is likely that these three scenarios are not mutually exclusive and that the specific behavior and species under investigation matters. Difference in animal personalities and stress coping are likely at least partially heritable as selection studies can produce lines that differ in behavioral and physiological response (Marin and Satterlee, 2003; Gulevich et al., 2004; Steimer and Driscoll, 2005; Evans et al.,

2006; Malisch et al., 2009). Additionally, gene × environment interactions are important and several lines of evidence show that early life programming (see Section 4.2; Liu et al., 1997; Sapolsky, 2004) can alter long-term changes in stress coping. Regardless of the mechanism, or whether the term personality is used, multiple studies have found that interindividual variation in stress coping (i.e., the behavioral and physiological responses to stressors) is likely an important driver for survival and for selection (Wingfield and Romero, 2010; Carere et al., 2010; Romero and Wingfield, 2015; Sih et al., 2015). But, it is important to note that animals and humans can habituate to stressors and therefore behavioral and physiological responses to the same stressor may change over time (see Romero and Wingfield, 2015), however the process of how rapidly or successfully animals habituation may be linked to personality.

Variability in stress coping is likely related to fitness and may be a way that natural selection maintains populations with heterogenous physiological and behavioral responses to stressors (Korte et al., 2005; Wingfield and Romero, 2010; but also see Stamps and Biro, 2016), and thus this variation may be especially important for maintaining populations in changing environments and for allowing organisms to spread to new habitats (Angelier and Wingfield, 2013). For example, dispersal differs with personality and this is likely mediated, at least in part, by differences in the HPA axis (Cote et al., 2010). Additionally, the likelihood to try novel food sources and to inhabit urban environments may be related to personality (Bokony et al., 2012) and HPA axis function (Prasher et al., 2019). And, in some populations, birds living in more urbanized locations have decrease HPA axis reactivity and are bolder and more risky than birds in less urbanized areas, but more studies are needed (Bonier, 2012).

The ecology of fear framework posits that animals are almost continually under psychosocial stress due the presence of predators (Clinchy et al 2011, 2013; Preisser et al., 2005). For example, Suraci and colleagues have shown that auditory predator cues (dog; sea lion; human voices) are enough to induce behavioral and physiological changes across the ecological landscape (Suraci et al., 2016; 2019). Predators or predator cues tend to increase HPA/I axis activity, but this is not a universal phenomenon (see discussion in Harris and Carr, 2016), organisms can habituate to predators (or predator cues), and interindividual variation still persists. The need for different stress coping strategies also helps to explain why determining what is a "good" response to stress proves so difficult (Breuner et al., 2008; Dhabhar, 2018; Vitousek et al., 2018; Zimmer et al., 2019) as what is good likely depends on multiple organismal and environmental factors (Patterson et al., 2014; Romero and Wingfield, 2015; Schoenle et al., 2019).

Various hypotheses included in Table 1 make predictions about the mechanisms by which interindividual variation in stress physiology and behavior (coping) arises, the proximate mechanisms driving stress coping differences, and the predicted adaptive benefit of successful stress coping (resilience). There are likely several mechanisms that influence resilience and susceptibility (Herman et al., 2011; Southwick and Charney, 2012), including early life experiences (Schmidt, 2010; Glover, 2011), underlying genetic differences/polymorphisms (Puglisi-Allegra and Andolina, 2015), gene × environment interactions and epigenetics (Harris and Seckl, 2011; Touma et al., 2011; Cavalli and Heard, 2019; Dunn et al., 2019), (social) environment and support (Seeman and McEwen, 1996; Ozbay et al., 2007), and interactions with microorganisms (Smith et al., 2019).

Many of the hypotheses that are included in this paper are attempts to understand the complex and intertwined phenomena listed above. Out of the 131 hypotheses included here, a total of 26 make predictions that broadly involve stress coping, variability, and resilience. Note this is eight higher than the number listed on Fig. 1 as it includes items from the stage spanning or models section that have strong ties to stress coping (Adaptive Calibration Model; Adaptive Tuning Model; Behavioral Resiliency Hypothesis; Biological Sensitivity to Context Model; Cort-Activity Hypothesis; Hawk-Dove Model; Inoculation Stress Model; and Pace-of-Life Syndrome). I chose to organize the stress coping hypotheses into one of six themes: 1) Early-life experiences and stressors/GCs shape future stress coping (8 hypotheses: Adaptive Calibration Model; Adaptive Tuning Model; Biological Sensitivity to Context Model; Everyday Stress Resilience Hypothesis; Inoculation Stress Model; Predictive Adaptation Hypothesis; Stress Acceleration Hypothesis; Stress-coping (mis)Match Hypothesis), 2) Individual appraisal of events is important for determining level of stress and coping (5 hypotheses: Goodness-of-Fit Hypothesis; Main-Effects Hypothesis; Matching Hypothesis; Neurocognitive Hypothesis; Stress Generation Hypothesis), 3) Ineffective or prolonged stress coping can lead to disease (5 hypotheses: Coping Hypothesis of Aging; Cort-Activity Hypothesis; (MR/GR) Balance Hypothesis; John Henryism Hypothesis; (stress) Buffering Hypothesis), 4) Evolutionary pressure drives differences in copying style (4 hypotheses: Behavioral Resiliency Hypothesis; Hawk-Dove Model; Pace-of-Life Syndrome Hypothesis; Tend and Befriend Hypothesis), 5) Substance use stems (partially) from need to cope with stress (3 hypotheses: Alcohol Stress Response Dampening Hypothesis; Self-Medication Hypothesis; Tension-Reduction Hypothesis of Alcoholism), and 6) Stress coping behavior cannot override impacts of physiological stress response (1 hypothesis; Reactivity Hypothesis). Supplemental Fig. 3 shows a themed arrangement of the hypotheses. Please note, these hypotheses could likely be arranged in a variety of ways besides the way in which they are presented here.

4.4. Health to disease: stress, GCs, and the health to disease transition

Stress and glucocorticoids play important roles in homeostatic (allostatic) regulation and coordination of many behavioral and physiological processes (see Section 2). Given this, it is not surprising that stress and glucocorticoids are entwined with transitions from health to disease. Many diseases and psychopathologies, including post-traumatic stress disorder (PTSD), anxiety disorders, depression, obesity, diabetes, cardiovascular disease, Alzheimer's Disease, Parkinson's Disease, alcoholism and other addictions [e.g., opiates, cocaine], and eating disorders are associated with dysregulation of the HPA axis (and other stress mediators), and stress can often precipitate or exacerbate symptoms, hasten recovery, or increase likelihood of relapse (Steptoe, 1991; McEwen, 1998a, 2000; Esch et al., 2002; Brown et al., 2006; Sauro et al., 2008; Herman, 2012; Talley et al., under review). It is not always clear if dysregulation is a cause or consequence of disease, but several studies have shown that exposure to stressors results in changes to stress mediators (including the glucocorticoids) which drive changes in health, providing a way in which stress "gets under the skin" (Seeman et al., 1997; Hyman, 2009; McEwen, 2012). However, the exact mechanisms by which dysregulation occurs are not entirely known (and likely differ by disease type and organism sex) but it seems likely that the CRF system, including hypothalamic and supra-hypothalamic signaling, and MR and GR dynamics are important (Nemeroff, 1996; Korte, 2001; Sanders and Nemeroff, 2016). As are multiple other factors (Lupien et al., 2009), including early life experiences (Herman et al., 2011; Nunez-Estevez et al., 2019), underlying genetic differences/polymorphisms (Binder and Nemeroff, 2010; Harris et al., 2019), gene × environment interactions and epigenetics (Zannas and Binder, 2014; Provençal et al., 2019), stigma and life experiences (Harnett et al., 2019), sex (Bangasser et al., 2010; Hodes and Epperson, 2019; Kokras et al., 2019; Slavich and Sacher, 2019), and interactions with microorganisms (Christian et al., 2006; Moloney et al., 2014; Leclercq et al., 2016; Morris and Ridlon, 2017). Additionally, in the biomedical area, it is not clear if all phenotypes that are currently classified as diseases or disorders are "unnatural" or purely pathological, or if they arise due to tradeoffs or due to some advantage of the state (Allen and Badcock, 2006; Nesse and Ellsworth, 2009; Clinchy et al., 2011; 2013; Varga, 2012; Diamond and Zoladz, 2016; Gibbons, 2018; Holmes and Patrick, 2018; Kozubek, 2018; Lemaitre et al., 2019;

White, 2019). It is possible that stress- and/or glucocorticoid-induced changes operate within a tradeoff or across a spectrum and that what appear as negative outcomes (diseases) at one point in life might be due to benefits (tradeoffs) or programming determined by another point in life.

Many of the hypotheses related to the transition from health to disease focus on the role of developmental environment (see Section 4.2 for framework; e.g., match-mismatch hypotheses; the "hit" hypotheses; Stress Acceleration Hypothesis), stress coping (see Section 4.3 for framework; e.g., Burn-Out Hypothesis; Coping Hypothesis of Aging; Self-Medication Hypothesis; Tension-Reduction Hypothesis), or interactions among neurotransmitters systems (e.g., CRF Hypothesis of Depression; CRF-HPA Dysregulation Hypothesis; Endocannabinoid Deficiency Hypothesis of PTSD). Out of the 131 hypotheses included here, a total of 41 make predictions that broadly involve the transition from health to disease. Note this is three higher than the number listed on Fig. 1 as it includes three items from the stage spanning or models section that have strong ties to health and disease (Allostatic Load; Developmental Origins of Health, and Disease and Lifecourse Health Development Model). I chose to classify health to disease hypotheses into one of six themes: 1) Altered HPA axis feedback and/or receptor function leads to disease (6 hypotheses: Corticosteroid Receptor Hypothesis of Depression; CRF Hypothesis of Depression; CRF-HPA Dysregulation Hypothesis; Glucocorticoid Cascade Hypothesis; (MR/GR) Balance Hypothesis; Stress Generation Hypothesis), 2) Alterations in neurotransmitters or neurons related to the stress response leads to disease (6 hypotheses: Glutamate Hypothesis of Depression; Deakin/Graeff Hypothesis; Endocannabinoid Deficiency Hypothesis of PTSD; Glucocorticoid Vulnerability Hypothesis; Neurogenesis Hypothesis; Neuroplasticity Hypothesis of Chronic Stress), 3) Inadequate or altered physiological or behavioral stress coping leads to disease (12 hypotheses: Allostatic Load Model; Alcohol Stress Response Dampening Hypothesis; Burn-Out Hypothesis; Diathesis Stress Hypothesis; Differential Susceptibility Hypothesis; Coping Hypothesis of Aging; John Henryism Hypothesis; Neurocognitive Hypothesis; Reactivity Hypothesis; Perseverative Cognition Hypothesis; Self-Medication Hypothesis; Tension-Reduction Hypothesis), 4) Developmental Stress/GC Exposure Influences Disease Susceptibility (9 hypotheses: Attenuation Hypothesis; Cumulative Stress Hypothesis; Developmental Origins of Health and Disease; Lifecourse Health Development Model; Match-Mismatch Hypothesis of Disease[2]; Mismatch Hypothesis; Mosaic Hypothesis of Epigenetics; Predictive Adaptation Hypothesis; Stress Acceleration Hypothesis), 5) Increased stress/GCs during development interact with genes to influence disease susceptibility (5 hypotheses: Double-Hit or Two(2)-Hit Hypothesis; Three(3)-Hit Hypothesis; Stress-coping (mis)Match Hypothesis; Maternal Mediation Hypothesis[2]; Stress-Vulnerability Hypothesis), and 6) Interaction between stress/GCs and microbiota influence disease susceptibility (3 hypotheses: GALF Hypothesis; Anna Karenina Hypothesis; Leaky Gut Hypothesis). Supplemental Fig. 4 shows a themed arrangement of the hypotheses. Please note, these hypotheses could likely be arranged in a variety of ways besides the way in which they are presented here.

4.5. Stage-spanning hypotheses and models

A total of 37 hypotheses were classified as stage-spanning or were listed as models. These hypotheses or models describe how stress and glucocorticoids impact many aspects of an organism throughout the lifespan, or provide relationships that should hold across many life history stages. One exception to this framework is the Migration Modulation Hypothesis – this hypothesis is specific to the transition to the migratory state but was included in this section due to lack of clear fit in other categories. Please note that many of the models provide a way to organize results, provide context to results, and allow the generation of new hypotheses, and are thus more encompassing than situation-specific hypotheses. Given that by definition these stage-spanning hypotheses or models should hold in multiple scenarios, they were not cross listed in any other category in Fig. 1, nor were they organized into themes. For more information on each model or stage-spanning hypothesis, please see Table 1 and the corresponding citations. Please also see Supplemental Table 1 for comparison of stage spanning hypotheses and models.

5. Importance and implications for clear hypothesis statement and testing

Hypothesis formulation and testing provides the foundation of empirical scientific research (see Huberty, 1993). Although the way in which hypotheses are handled statistically in ecology and evolution has been discussed (see Johnson and Omland, 2004), support of their utility to address and understand scientific phenomena is nearly universally accepted. However, one area that has recently drawn discussion and criticism is the repeatability of hypothesized results. Over the past 5–10 years, the "reproducibility crisis" has been sweeping through the literature with the field of psychological science currently receiving the most press coverage of the topic (Open Science Collaboration, 2015), however this is not the only field in which this problem has been noted (Kelly, 2006; Ellison, 2010; Freedman et al., 2015; Nakagawa and Parker, 2015; Nichols et al., 2019). The psychological sciences example that has drawn much scrutiny suggests that only 39% of 100 big experimental findings could be replicated when repeated by another group (see Baker, 2015a [in other fields it is often estimated that only 40–50% of results are reproducible; Freedman et al., 2015; Munafo and Smith, 2018]). The severity of this "crisis" and the validity of the methods used to reproduce the research in the psychological sciences have been questioned (see Gilbert et al., 2016; Fidler et al., 2017), but the situation does highlight several important points that can be used across fields to strengthen research and reporting practices. These concerns have also increased momentum in the movement to make science more transparent and open. At the center of the open science discussion is preregistered studies – a practice in which, prior to starting a study, authors register their hypotheses, experimental design, and data analysis plan (for discussion see Bowman and Keene, 2018). In 2018 the first registry for preclinical animal studies was launched (see Baker, 2019) with the aim to reduce bias and increase reproducibility. Preregistration is not limited to just human or clinical trial studies, but can be done for any study as preregistration can increase transparency of the experiment, reduce temptation to search for and only publish significant findings, and to reduce irreproducibility.

Preregistration can also reduce the occurrence of HARKing (hypothesizing after results are known), which is another driver of irreproducibility along with publication bias, low statistical power, confirmation bias, and P-value hacking (Parker et al., 2016; Bishop, 2019). HARKing occurs when a *post hoc* explanation of the data is presented as an *a priori* prediction (see Parker et al., 2016), and can be problematic because this practice often allows researcher to present only the analyses that were supported. Additionally, this practice can weaken the strength of support for the hypothesis as it makes the outcome descriptive instead of prescriptive (Lipton, 2005). As authors, we as (behavioral; comparative) endocrinologists, stress physiologists, psychologists, behavioral ecologists, and physiological ecologists, should make it a goal to explicitly state, up front, which stress-related hypothesis we are testing and why it is a good fit for our study. In the discussion sections of our papers we can determine if our data support or reject the hypothesis, and can then highlight if another hypothesis did a better job of explaining results. If the latter is the case, we should then repeat the experiment with our new hypothesis. As a minimum practice, we should strive to make *a priori* predictions instead of matching a hypothesis to the results that have been collected. I would argue that given the sheer number of available, named hypotheses, *a priori* determination of hypotheses is especially important for stress studies, as this abundance of hypotheses can facilitate HARKing. Additionally, we

can report effect sizes with our statistics, for both significant and non-significant findings, to aid in later meta analytical probing of these hypotheses (Fritz et al., 2012; Open Science Collaboration, 2015). Lastly, we can also preregister our studies, animal and human. As reviewers and editors, we can recommend authors include their *a prior* hypotheses, effect sizes for statistical results – significant or not, and can support publication of rigorously determined null findings and replication studies (see Goodman et al., 2016); this practice can be especially important in big-name journals (see Arceneaux et al., 2019).

In addition to the reduction of HARKing, explicitly naming tested hypotheses, and doing so with consistent terminology, would aid in comparison of results across studies and across species, thus leading to better harmonization and better interpretation of comparative data. The field of stress research has an abundance of hypotheses, some of which have only been tested a few times. The creation of multiple new hypotheses can fracture our knowledge instead of bringing big ideas together. Before we, collectively, develop new hypotheses, we should work to fully test the models and hypotheses that currently exist in the literature. This review is an attempt to bring those hypotheses together for this purpose. The process of data harmonization or consolidation is apparent in multiple areas of research. For example, the National Institutes of Mental Health (NIMH) is pushing for the use of the Research Domain Criteria (RDoC) to develop a bio-marker-driven framework for explanation, diagnosis, and etiology of psychopathology (Cuthbert and Insel, 2013; Cuthbert, 2014), as current diagnostic criteria are heterogenous (Allsopp et al., 2019). Additionally, NIMH has highlighted the need for clear definitions of stress in grant applications and publications, and has called for increased rigor and reproducibility in studies focusing on stress biology (National Institute of Mental Health, NOT-MH-18-058). And in epidemiological and behavioral studies, the National Institutes of Drug Abuse's data-harmonization efforts aim "to promote common measures that can be used by researchers across studies within and across particular research fields. By using common measures, researchers can more easily compare and combine datasets to detect more subtle and complex associations among variables, thereby promoting greater collaboration, efficiency, and return on investment (National Institute of Drug Abuse, 2014)." Lastly, the National Science Foundation is pushing for collaborative, interdisciplinary and transformative ideas that span fields, one way in which to better integrate fields is to use the same terminology when conducting cross-disciplinary studies, especially when fields have hypotheses that make the same predictions by go by different names.

6. Practical concerns and caveats

6.1. Testing hypotheses: models and predictions

Many of the hypotheses included in this review were generated using the same general framework and many are not mutually exclusive, thus making it difficult to fully separate the predictions that would support each one. But, for all experiments, it is important to distinguish the hypothesis from the predictions that would support that hypothesis. It may be helpful to use a single experiment or dataset to test multiple hypotheses, but care should be taken so that data reported are valid and accurate (see Anderson and Burnham, 2002). For example, authors should aim to avoid "salami slicing" – or splitting an experiment into multiple publications that have more or less the same hypotheses, same participants/animals, and same methods – as this can lead to confusion and incorrect assumptions about hypotheses when it is unclear that conclusions are being drawn from the same sample of animals or participants (Jackson et al., 2014; Elsevier FactsSheet: Salami Slicing). Comparing multiple statistical models, instead of a single hypothesis/null hypothesis is becoming increasingly common in behavioral ecology (Dochtermann and Jenkins, 2011). However, in some instances, making careful, mutually exclusive predictions that pertain to different related hypotheses can be incredibly insightful (Jenkins et al., 1995).

No matter the method chosen (e.g., traditional null hypothesis testing, model selection procedures), hypotheses and their corresponding predictions should be made *a prior* as doing so provides more rigorous results (Lipton, 2005; Anderson and Burnham, 2002). This is not to say that data-driven approaches are never useful, as observational, correlational, and *post hoc* exploratory data analysis can certainly be insightful and can aid in the generation of new hypotheses (Anderson and Burnham, 2002; Kell and Oliver, 2004; Dochtermann and Jenkins, 2011), but it should be distinct from data-fishing, p-hacking, or data-dredging (Gelman and Loken, 2013; Jebb et al., 2017). And, this practice should always be explicitly stated in publications and is not a substitution for *a priori* predictions, as confusing *post hoc* data exploration with hypothesis support (HARKing) can undermine general conclusions and applications (Bosco et al., 2016).

6.2. Testing hypotheses: what to measure

All of the hypotheses included in this review are relevant to stress and therefore make some assertion about the role stress plays in organismal function. However, given the broad applicability of the word "stress" and the lack of a standardized definition (see Section 1), it is imperative that dependent variables used in studies to test these hypotheses are carefully chosen and are biologically relevant. The majority of hypotheses listed do make some prediction about glucocorticoids, the HPA axis, and/or the SNS, but when testing hypotheses, it should be clear whether the hypothesis makes predictions about stress, or specifically about glucocorticoids, as they are not the same thing (MacDougall-Shackleton et al., 2019). For example, some hypotheses make broad predictions about stress in general whereas others make predictions about glucocorticoids, and some make even more specific predictions about the dynamics of glucocorticoid receptors in certain tissues. Complexity in the HPA axis is often simplified so that circulating (e.g., plasma or serum) or excreted (e.g., saliva, urine, feces, hair, feathers, baleen, scute, housing water [for aquatic animals]) glucocorticoids are measured as a marker, or the sole marker, of axis function. Not as many studies use SNS markers, but those that do tend to measure heart rate, heart rate variability, sweat conductance, pupil dilation, and salivary alpha amylase as endpoints. Measurement of glucocorticoids is useful and important, and sometimes field or organism constraints make getting additional biomarkers difficult, but the HPA axis is much more than just glucocorticoids.

When testing hypotheses related to stress and/or glucocorticoids, multiple variables are potentially important (Fig. 2), including: baseline, circadian levels of corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), glucocorticoids, and binding globulins (e.g., for CRF and GCs); stressor-induced changes in CRF, ACTH, glucocorticoids, binding globulins, and catecholamines, including time course and level of elevation and time to return to baseline; activity of glucocorticoid-metabolizing enzyme (e.g., 11beta hydroxysteroid dehydrogenase); level and activity of transcription factors (e.g., heat shock proteins, FKPB5, BAG1, P23); affinity, binding dynamics, and signaling of CRF, ACTH, glucocorticoids, and catecholamines receptors, as well as, the presence of single nucleotide polymorphisms and DNA methylation patterns for all players involved. Additionally, expanding analysis outside of the paraventricular nucleus and investigating CRF (or urocortin) and glucocorticoid signaling, and receptor type (e.g., CRFR1, CRFR2) and activation, in regions such as the limbic system and prefrontal cortex would be illuminating. Lastly, adding measures of pituitary adenylate cyclase-activating polypeptide (PACAP), a highly conserved peptide known to influence HPA axis and sympathetic nervous system activity in a variety of species would be interesting (Arimura, 1998; Stroth et al., 2011).

In terms of stressor type, the response to acute vs. chronic stressors, and for repeated exposures, whether the stressor is homotypic or heterotypic matters. Moreover, organismal variables such as age, sex,

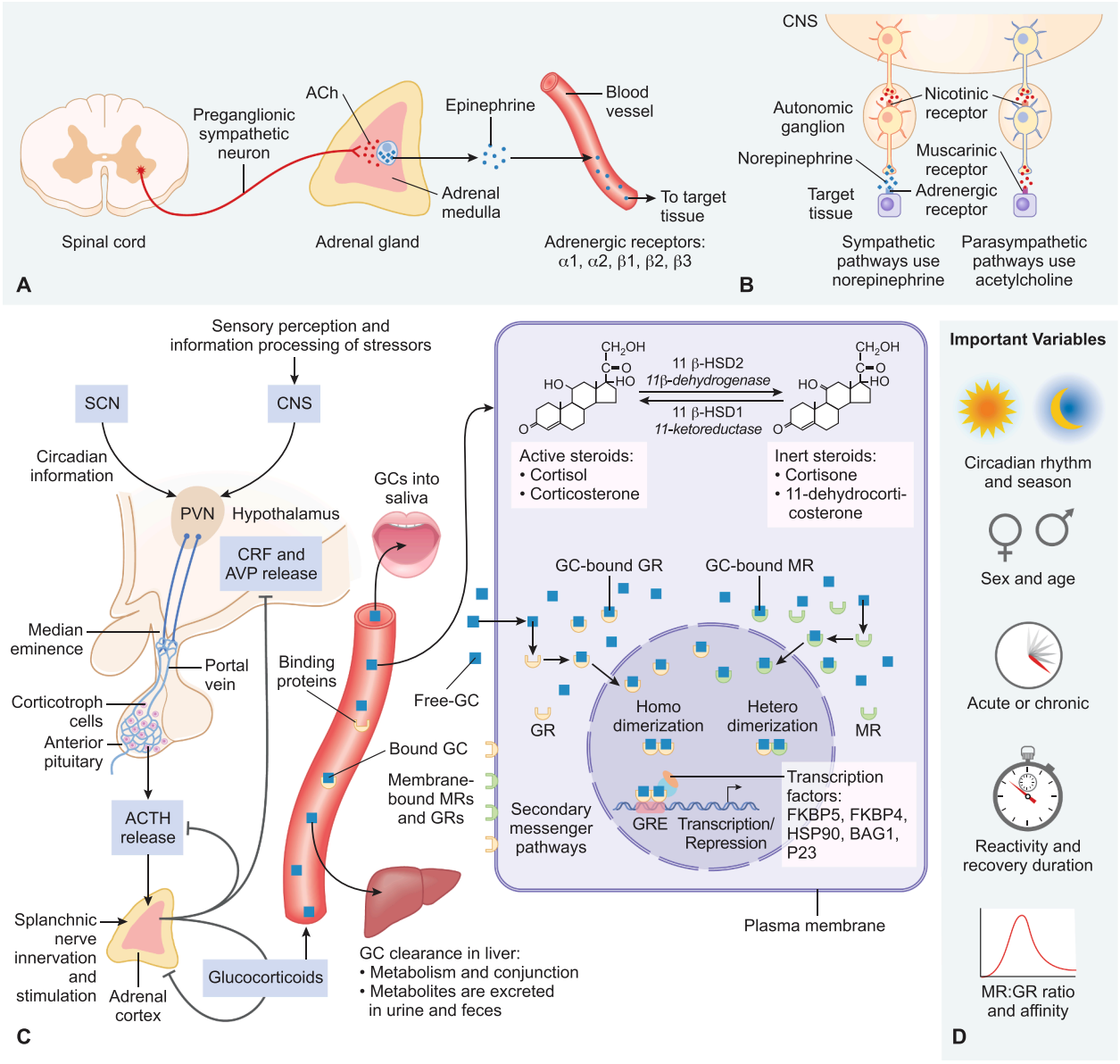

Fig. 2. Schematic highlighting the complexity related to variation in and regulation of the (A, B) autonomic nervous system and (C) HPA axis. HPA axis activity is most commonly measured as total circulating glucocorticoid levels (either in the serum or plasma) or as excreted glucocorticoid (metabolites; e.g., in the saliva, urine, feces, or hair). But, regulation of the HPA axis can occur at supra-hypothalamic, sensory locations in the central nervous system (CNS) or from the suprachiasmatic nucleus (SCN), at the level of the paraventricular nucleus (PVN), or at the adrenal gland itself. Additionally, variability in the production, release, and processing of corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) can have pronounced effects. Glucocorticoids (GCs) can be found bound to peptides (e.g., corticosterone binding globulin, albumin, sex hormone binding globulin) or as free hormones. Once at a target tissue, GCs can bind either membrane-bound or intracellular mineralocorticoid (MR) or glucocorticoid (GR) receptors, or they can be converted to an inactive form by enzymes. Membrane-bound receptors initiation secondary messenger cascades, and intracellular receptors interact with other like (homo-) or different (hetero-dimers) hormone-receptor complexes, and these then interact with transcription factors to regulate gene transcription. At each of these levels, documented variation that influences axis activity and the impact of GCs has been described. Lastly, additional variables (D) play a role in physiological response to challenges.

season, reproductive history, satiety state, housing status (including cage mates and access to toys or exercise), coping skills, and phylogeny can influence SNS and HPA axis measures and should be carefully considered in experimental design. Care should be taken to determine if a hypothesis makes prediction about baseline or post-stressor hormone levels, and in cases where predictions pertain to post-stressor-exposure levels, then it is important to determine if using an acute stressor or a chronic stressor paradigm is more relevant. If a chronic stressor application will be used, what paradigm is best (e.g., mild stress, repeated restraint, a variable stress paradigm)? And, will habituation be an issue? Additionally, determination of the time course from on-set of stressor or stressor paradigm to collection of biomarker samples and behavioral data should be given serious consideration (e.g., for biomarkers, are predictions relevant to peak output? time course of elevation? changes in baseline levels after stressor cessation? time course to return to baseline? etc.; should behavioral changes occur rapidly or after a period of time? Are behavioral changes likely driven by glucocorticoids, acting at either intracellular or membrane-bound receptors, or by other stress mediators? What is the suspected time course needed for that mediator to alter behavior?).

Lastly, the biological significance of the chosen variable for the hypothesis being tested is critical. For example, in the species of interest, is the variable being measured an honest marker? Is it a direct or proxy measure? And if a proxy is chosen, is it accurate? (see Bonier

et al., 2008 for discussion of fitness proxies). If measuring energy status is part of tradeoff studies, is the estimate of energy status useful, valid, and reliable? Additionally, when measuring glucocorticoids, it is important to determine what sample type is needed. For example, is an acute physiological response predicted? If so, blood or saliva would be good options, feces and urine might work, depending on the species and time course. Is a chronic or seasonal effect predicted? In that case, using fur, feathers, baleen, scutes, or feces might be a viable choice. But, it would not make sense, for example, to measure feather or fur glucocorticoids in response to an acute challenge as the short-term increase in hormones would be masked by circadian and seasonal changes captures in those sample types. Is repeated sampling needed? If so, can more than one sample be reliably collected (e.g., can the needed volume of blood be collected within a given timeframe?) or is the collection method terminal (e.g., whole-body glucocorticoids)? If repeated sampling is conducted, has enough time elapsed so that the disturbance induced by collection time 1 will not impact collection time 2? If repeatability is important in the prediction, are hormone levels of interest repeatable? Are they heritable? (see Bonier et al., 2009b for discussion). Repeatability and heritability of baseline and post-stressor levels of glucocorticoids has been investigated, but dynamics likely differ across species (Federenko et al., 2004; Hau et al., 2016; Taff et al., 2018; Beziers et al., 2019). When analyzing data, is mean population level the target? Or is considering individual variation important for the question at hand? (see Williams, 2008; Hau et al., 2016).

Glucocorticoids are the most prominent stress mediators reported in stress biology studies, but using markers other than the glucocorticoids is important. For example, Breuner and colleagues (2013), argue that just using total glucocorticoid concentration is not good enough for chronic stress studies, and they recommend including corticosteroid-binding globulin, glucose, free fatty acids, hematocrit, reproductive hormones, immunosuppression, oxidative stress, telomere length, acute phase proteins, and body mass changes [they give helpful predictions for each variable, too]. Additionally, endocannabinoids, monoamines, oxytocin, vasopressin, brain derived neurotrophic factor, endogenous opiates, melanocortins, ghrelin, leptin, osteocalcin, and many other biomarkers are known to change following exposure to acute and/or chronic stressors (Sapolsky et al., 2000; Juster et al., 2010; Radek, 2010; Dhabhar, 2014; Meyer et al., 2014; Morena et al., 2016; Berger et al., 2019).

6.3. Testing hypotheses: how to measure

Once a hypothesis is chosen a set of relevant predictions and dependent variables is needed. A single hypothesis can have several different and distinct predictions, and directional predictions may differ for various biomarkers (e.g., glucocorticoids will increase, reproductive hormones will decrease). When testing multiple predictions in a given experiment some, all, or none of those predictions may be accurate. Using a specific example from Table 1, Lattin et al. (2016) propose the CORT-Flexibility hypothesis to explain regulation of breeding onset in birds. They provide 6 different mechanisms (predictions) for the way in which HPA axis function may be altered in pre-breeding birds: 1) increasing glucocorticoid release, 2) decreasing glucocorticoid feedback, 3) decreasing plasma corticosteroid-binding globulin, 4) altering enzyme (11 beta HSD1, 2) activity, 5) increasing intracellular MR and GR, and 6) altering other hormones (e.g., gonadotropin-inhibitory hormone). These 6 predictions are not necessarily mutually exclusive, and an ideal, robust probing of the CORT-Flexibility hypothesis would simultaneously test all 6 predictions to determine the appropriate level of analysis for a given organism.

How, exactly, to test those 6 predictions adds another layer of complexity to stress research. Variables such as time from disturbance to collection of blood sample (< 2–3 min for glucocorticoids; Small et al. 2017), sample treatment (e.g., addition of anticoagulant, acid, protease inhibitor, stabilizer; Livesey and Dolamore, 2010) and storage methods (immediately frozen; freeze-thaw cycles; −20 °C vs. −80 °C; Khan et al., 2002) can have profound impacts on sample values. If something other than blood (plasma, serum) is being used for hormone analysis, determining the time course from elevation in blood to elevation in tissue, fluid, or excreta of interest matters (e.g., in humans, ~ 20–22 min from blood to saliva change for glucocorticoids, and ~10–12 min for alpha amylase; Engert et al., 2011; Hohman et al., 2017), as does sample processing (e.g., extraction for fecal steroid analysis or use of hair or feathers; Sheriff et al., 2011; Harris et al., 2012; Palme et al., 2013). For fur, hair, feather, scute, and baleen analysis, knowing the growth and/or molting pattern is incredibly important for matching a sample to a specific timepoint (Lattin et al., 2011; Sheriff et al., 2011; Hunt et al., 2014; Hamilton et al,. 2018). For dependent variables requiring bench analysis, choice of assay kit, reagents, and/or antibodies also matters. Ideally, each assay kit would be biochemically and biologically validated for each species and for each type of sample fluid (e.g., fecal extract may not perform the same way as plasma; Goymann, 2005; Palme, 2005; Touma and Palme, 2005). Sometimes an assay will pass biochemical validation, but not biological validation. For example, an assay can pass accuracy, recovery, and parallelism trials, and provide consistent hormone concentrations (biochemically valid), but those concentration values may not be representative of the biology of the analyte of interest (not biologically valid). This could happen if the analyte, say glucocorticoids, should increase upon exposure to a challenge or change with time of day, but these expected changes do not register using the chosen assay. Or, this can occur when an assay is measuring a metabolite of the analyte of interest and that metabolite does not change in the same manner or over the same time course as the parent analyte, this can be a common issue in fecal glucocorticoid assays (e.g., see Palme, 2005; Touma and Palme, 2005; Harris et al., 2012). Thus both types of validation are important for determining accurate results. Validation of commercially available antibodies for use in immunohistochemistry or in situ hybridization is also necessary (see Fig. 3 in Bordeaux et al., 2010 for a good validation flow chart; Schonbrunn, 2014; Gautron, 2019), as commercially purchased reagents may not function as advertised. Lack of validation can be especially problematic for antibodies against G-protein coupled receptors (Hazell et al., 2012) of which there are many in the hypothalamus and stress axis (e.g., CRFR1 Refojo et al., 2011). Lack of antibody validation, along with poor experimental design, is responsible, at least in part, for the reproducibility crisis in biomedical and preclinical animal data (Baker, 2015b; 2016; Freedman et al., 2015). When collecting tissues for use in immunohistochemistry, in situ hybridization, real time PCR, or other techniques, method of sacrifice (e.g., carbon dioxide, halothane, direct decapitation, etc.), time from death until tissue preservation, as well as preservation technique can all matter when analyzing stress-sensitive biomarkers.

Another consideration when testing stress hypotheses is the appropriate endpoint or dependent variable for the prediction. Take, for example, the thorough studies conducted by Lattin and Romero (Lattin and Romero, 2014; 2015) showing that seasonal and chronic stress impacts on MR and GR are tissue-specific, even within the same bird. Their data suggest that season and tissue type chosen for analysis are important and thus choosing the correct tissue for analysis could make the difference in supporting or failing to support a hypothesis. In addition to being specific about the type of tissue used for analysis, for receptor studies, making specific predictions about the type (MR or GR) and location (intracellular, membrane-bound (Tasker et al., 2006), or tethering role (Ratman et al., 2013)), could be informative. Or for a different example, if a hypothesis predicts that animals should be bolder/less anxious, what is the organism-appropriate operationalization of that measure? For example, there are several behavioral paradigms to measure anxiety-like behavior (e.g., light/dark test; open field), but usefulness and relevance of these paradigms can differ by species (e.g., a test that is valid for mouse behavior may not work for other species; see Coleman et al., 2019). Additionally, for behavioral

endpoints, it is important to include explicit behavioral test arena or apparatus specification, ethogram(s) used to define behaviors, and methods for scoring behavior (see Bohlen et al., 2014). There are several software packages available (e.g., JWatcher, Ethovision, Ethowatcher, BehaviorCloud, TopScan, Biobserve, OpenBehavior, Tracktor, ToxTrac, Actimetrics, etc.) and while the availability of these programs is incredibly useful, they can provide data that are not accurate if settings are not vigorously validated in the lab (e.g., tracking software can lose the location of the animal, can incorrectly identify animal, and can be incredibly sensitive to even minute changes in lighting or glare, but will still provide "numbers" for animals; see Bailoo et al., 2010). Even if careful and valid behavioral scoring is used, the sex of the experimenter can influence hormonal and behavioral responses to stressors (Sorge et al., 2014) and is something that may need to be considered in experimental design. Lastly, if HPA/I axis activity is manipulated via administration of exogenous hormones (e.g., injection(s), in drinking water/food, short- or long-term implants, etc.) the implication on the entire axis and feedback system, including typical circadian rhythm and receptor binding dynamics, needs to be considered (see Landys et al., 2006; Crossin et al., 2016; Spencer and Deak, 2017; Torres-Medina et al., 2018; MacDougall-Shackleton et al., 2019).

6.4. Caveats, considerations, and limitations

To truly test some of these hypotheses it will involve getting into the nitty gritty of the stress response and to make specific, explicit, and directional predictions. Being able to compare results across studies and across species will be important for addressing questions of selection and evolution of endocrine systems in tradeoffs (Ricklefs and Wikelski, 2002; Blumstein et al., 2010). Mechanistic studies using reaction norm (Araya-Ajoy et al., 2015; Bonier and Martin, 2016) and evolutionary physiology approaches (Feder et al., 2000), and implementing a revised ecomorphological paradigm that incorporates tradeoffs, resource allocation, and interactions among performance, other variables (endocrine system), and fitness (Moore and Hopkins, 2009; Lailvaux and Husak, 2014) will be important. Asking questions that address adaptations vs exaptations will able be illuminating (Ketterson and Nolan, 1999), as will those addressing the endocrine plasticity (Taff and Vitousek, 2016) including developmental (Dufty et al., 2002) and genetic underpinnings of plasticity (Lafuente and Beldade, 2019), and, lastly, so will those integrating proximate and ultimate measures within studies (Crespi et al., 2013).

When comparing data across studies and assessing robustness of these hypotheses it is important to remember the role of moderators and variation. Just because data do not align from one study to the next does not necessarily mean the hypothesis is wrong, or that one set of authors' data are not valid, we need to be careful about methods that we know impact markers of stress physiology and then we can begin to get a better picture of universal trends vs. those that are specific to taxa or are perhaps constrained by evolution or ecology. Thus, choosing appropriate dependent variables for each study is important, as is fully and accurately reporting experimental conditions (e.g., feeding, lighting, housing, etc.), tests parameter specifics (e.g., set-up, size, lighting, time of day, etc.), animal or participant information (e.g., sex, age, parity, genotype/strain, etc.), and previous use of data from the same experimental subjects (e.g., avoiding salami slicing). The ARRIVE (Animal Research: Reporting of In Vivo Experiment) guidelines, the National Research Council's Guidance for the Description of Animal Research in Scientific Publications (National Research Council, 2011), and others (see Lee, 2018) provide a good framework for standardizing reporting of experimental variables.

Stressors can range from environmental and social demands (e.g., high population density, social instability, predation) and physical or physiological challenges (e.g., injury, sickness, food or water restriction, extreme ambient temperatures) to psychological stressors (e.g., lack of control, unpredictability, novelty, noise, restraint, predators). Stressor can also be classified as acute (transient) or chronic (prolonged), and as homotypic or heterotypic. Therefore, it is possible, and likely, that physiological and behavioral responses observed in response to one type of stressor may not be identical to those observed in response to a different stressor, even in the same organism or population. In addition, multiple-species testing, and using multi-pronged approaches to address the same hypothesis within a single species (e.g., triangulation; Lawlor et al., 2016) will aid in robustness and reproducibility of effects (Munafo and Smith, 2018). We also need to get beyond just the glucocorticoids and consistently measure many of the other stress mediators (Breuner et al., 2013). When doing so, we should make clear, *a priori* predictions about how various mediators are expected to change, or if it is unclear, state that point upfront in the paper. To enhance harmonization as well as transparency and reproducibility, as authors we can be explicit in the details of methods, including important variables like time of day, time from disturbance until sample, sex, age, housing status, handling, experimental timeline, diet, parasite status (if known), light regimen, and, when applicable, sacrifice method (e.g., CO2, decapitation, halothane, etc.), post-mortem tissue handling, and assay/antibody validation and parameters. We can also being to standardize our terminology (see Epel et al., 2018 for a framework). The 2018 announcement by NIMH highlights that careful handling of these details will be particularly important for funding of stress biology research going forward (National Institute of Mental Health, NOT-MH-18-058).

7. Conclusions

Given the ubiquity of stress, and the breath and complexity that the topic of stress poses, tackling these research questions in a valid and through manner can seem daunting. This paper is not the first to attempt to compile stress hypotheses for comparison as Quarton and colleagues (1955) made an effort to synthesize the hypotheses describing how ACTH and cortisone impact mental disturbance. And, recently, Schoenle and colleagues created a collection of hypotheses related to glucocorticoids and fitness (Schoenle et al., 2018). Some of the caveats and concerns listed by Quarton et al. are still true today (e.g., cause and consequence; complex control of behavior), but others we, as a field, are now better at addressing (e.g., much more is known about how hormones impacts neurons and specific cells, and about biochemical pathways; CRF was discovered by Vale in 1981 [Bale and Chen, 2012]; the availability of advanced statistical software and the rising popularity of *meta*-analyses). Overall, the field has come a long way. By listing *a prior* hypotheses, crafting careful and deliberate predictions, testing predictions using multiple biologically relevant dependent variables, explicitly reporting methods and data, and performing sound replication studies we can move the field of comparative stress endocrinology forward in exciting ways. And, as Selye stated, "*Indeed, complete freedom from stress is death!*" – Hans Selye, 1976

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Appendix A. Supplementary data

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