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HORMONES: COMMENTARY

RIDING THE PHYSIOLOGICAL ROLLER COASTER: ADAPTIVE SIGNIFICANCE OF CORTISOL STRESS REACTIVITY TO SOCIAL CONTEXTS

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The authors conjecture that to understand normal stress regulation, including cortisol stress reactivity, it is important to understand why these biomarkers are released and what they function to accomplish within the individual. This perspective holds that high (or rising) cortisol has advantages and disadvantages that must be understood within a context to understand how individual differences unfold. This perspective is juxtaposed with a popular vantage point of this stress hormone or of stress exposure that emphasizes the deleterious consequences or problems of this hormone. While the costs and benefits of cortisol are emphasized for normal stress regulation, this dynamic context-dependent purpose of stress hormones should extend to the development of psychopathology as well. This functional and dynamic view of cortisol is helpful for interpreting why Tackett and colleagues (2014) appear to observe advantageous cortisol recovery from stress in individuals with elevated personality disorder symptoms.

The steroid hormone cortisol is a physiological end-product of the hypothalamic-pituitary-adrenal (HPA) axis and has been considered as a biomarker of stress exposure since the 1950s when Selye coined the term *stress* (Selye, 1976). Borrowing from the field of engineering, Selye defined stress as the nonspecific response of the body to any demand for change. This terminology emphasizes that stress is an internal response that orients the organism to the challenges and difficulties of the external environment. Selye distinguished stress from the external environment or stressful context, on the other hand, by terming this *stressor*. External stressors, internal stress responses, and behavioral propensities reciprocally interact over time to calibrate individuals to their environment. This engineering-inspired, physiologically motivated definition has largely been lost as this term has been popularized.

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A popular view of stressors is that they are identifiable, overwhelming, undesirable, and clearly aversive. No one would want to be under stress; such contexts can quickly lead to a variety of adverse cognitive, emotional, physical, and behavioral symptoms such as moodiness, irritability, general unhappiness, aches and pains, diarrhea, chest pains, frequent colds, memory problems, poor judgments, racing thoughts, and constant worrying (McEwen & Schmeck, 1994; Sapolsky, 1998). Some contradictions within this arsenal of negative consequences are hinted toward given that people under stress can eat too much or too little, experience hypersomnia or insomnia, and demonstrate elevated or depressed activity levels. Even within this popular view, then, some questions emerge as to whether being under stress captures everything bad with your day.

By extension, the quintessential stress hormone cortisol and other stress-responsive biomarkers came to be synonymous with the negative consequences of stressors. Cortisol is therefore described in the popular literature as being aversive and maladaptive—the silent killer, which will make you obese, sick, and depressed, and contributes to early morbidity and mortality. Cortisol is thought to contribute to cell death and senescence, cancer and depression, and a myriad of mental health problems (Bauer, Jeckel, & Luz, 2009; Cacioppo et al., 2000; Goodman, McEwen, Huang, Dolan, & Adler, 2005; Shonkoff & Bales, 2011).

Nonetheless, there are paradoxes about cortisol that suggest that this stress hormone is complex and must be considered contextually to determine if the stress hormone is healthy, unhealthy, or both. Three problems emerge with the prevailing popular view, even with a folk understanding of cortisol and its physiological effects. First, in all likelihood, each of us has at one time or another willingly applied or ingested cortisol. Hydrocortisone cream, a synthetic cortisol, is a powerful antipruritic medicine that is safe enough to take over the counter and is commonly used for the treatment of a variety of rashes and skin irritations (Verbov, 1976) as well as for the systemic administration for other sorts of inflammation (Schofer & Simonsen, 2010). Second, sometimes treatment with cortisol (as prednisone) may be the only available treatment for chronic or life-threatening problems such as Crohn's disease (Irving, Gearry, Sparrow, & Gibson, 2007; Zlatanic, Fleisher, Sasson, Kim, & Korelitz, 1996) or rheumatoid arthritis (Kirwan & Buttgereit, 2012). Third, the most powerful illustration of the benefits of cortisol is with children, illustrating its potent effects and relative safety. Synthetic cortisol is a useful treatment in the form of inhaled or systemic steroids for treatment of asthma (Derendorf, Nave, Drollmann, Cerasoli, & Wurst, 2006; Manser, Reid, & Abramson, 2001) and other breathing concerns (Waddell, Patel, Toma, & Maw, 2003), or for life-saving high-dose application with preterm infants to aid in lung maturation and physical development (Subhedar, Duffy, & Ibrahim, 2007; Ward, 1994).

Paradoxes extend to the psychological literature, as demonstrated by studies that find that declining cortisol is not necessarily good and rising cortisol is not necessarily bad. For example, several investigations have found that cortisol can acutely decline during stressors. Klimes-Dougan, Hastings, Granger, Usher, and Zahn-Waxler (2001) observed acute cortisol declines in

parent-child conflict in adolescents (Shirtcliff, Zahn-Waxler, & Klimes-Dougan, 2005). Similar acute cortisol declines apply to marital conflict (Kiecolt-Glaser, Bane, Glaser, & Malarkey, 2003; Kiecolt-Glaser et al., 1997). This could indicate that these contexts were not stressful for these individuals, and do not fit with the aversive notion of cortisol. However, acute cortisol declines have been observed in response to contexts that are unequivocally stressful, such as an ice storm (Anisman, Griffiths, Matheson, Ravindran, & Merali, 2001), the death of a child from cancer (Hofer, Wolff, Friedman, & Mason, 1972), or the day of an attack by Special Forces soldiers (Bourne, Rose, & Mason, 1968). Conversely, cortisol can acutely rise in response to contexts that participants describe as fun and exciting such as skydiving (Chatterton, Vogelsong, Lu, & Hudgens, 1997; Shirtcliff, Allison, Peres, Boettger, & Leonbacher, under review; Thatcher, Reeves, Dorling, & Palmer, 2003), sports competition (Bateup, Booth, Shirtcliff, & Granger, 2002; Carre, Muir, Belanger, & Putnam, 2006; Filaire, Sagnol, Ferrand, Maso, & Lac, 2001; Gonzalez-Bono, Salvador, Serrano, & Ricart, 1998), Christmas eve (Flinn, 2006), video games (Mazur, Susman, & Edelbrock, 1997), or social drinking (Bottger, Shirtcliff, Curtin, Skinner, & Moberg, under review; Lovallo, 2006).

Beyond cortisol reactivity, there are paradoxical findings regarding high (or low) basal cortisol levels. Cortisol levels have been found to be highest in girls who were the most social and had lots of friends (Booth, Granger, & Shirtcliff, 2008), in mothers who were sensitive to their child's needs (Papp, Pendry, & Adam, 2009; Ruttle, Serbin, Stack, Schwartzman, & Shirtcliff, 2011; Sethre-Hofstad, Stansbury, & Rice, 2002; Shirtcliff, Skinner, Obasi, & Haggerty, under review), in observers who connected emotionally with others (Buchanan, Bagley, Stansfield, & Preston, 2012), in family members who provide saliva samples together (Schreiber et al., 2006), and in a variety of situations in which individuals bond and socially connect (Taylor, 2002; Taylor et al., 2000). Conversely, the notion that low cortisol is beneficial is challenged by research findings that individuals with low cortisol have elevated mental health symptoms (Essex et al., 2011; Shirtcliff & Essex, 2008) such as externalizing problems (Shirtcliff, Granger, Booth, & Johnson, 2005) and callous-unemotional traits (Shirtcliff et al., 2009).

Such paradoxes readily appear in the article by Tackett and colleagues (2014) insofar as seemingly maladaptive personality traits were related to a good profile of cortisol recovery from the Trier Social Stress Test (TSST). Closer inspection of the findings showed that cortisol was reactive to the TSST in most participants, but this did not consistently interact with personality disorder symptoms. Real individual differences emerged 35 min after the stressor terminated. This time period can be conceptualized as HPA recovery, when HPA axis activity terminates itself through negative feedback. Efficient recovery may be characterized as a good thing (Dienstbier, 1989), because this latter profile might characterize individuals who realized that the stressor was not as bad as they thought it would be, or who had the psychosocial resources to cope with the challenge. For example, several studies cited earlier that found acute cortisol declines during stress exposure observed the greatest acute drops in individuals who coped well with conflict or who had

good relationship quality (Kiecolt-Glaser et al., 2003; Kiecolt-Glaser et al., 1997; Shirtcliff, Zahn-Waxler, et al., 2005). Nonetheless, it is also possible that this declining cortisol has drawbacks, reflecting an early termination of the HPA axis regardless of whether the individual still needed elevated cortisol to mobilize resources for the situation. Early termination might convey a certain physiological disengagement with the social context or passive coping (Delahanty, Raimonde, & Spoonster, 2000; Yehuda, McFarlane, & Shalev, 1998), allowing the individual to avoid or ignore the social cues in his or her environment (Anisman et al., 2001; Hofer et al., 1972) and to behave in a manner commensurate with this physiological disengagement from salient social cues (Snoek, Van Goozen, Matthys, Buitelaar, & van Engeland, 2004; van de Wiel, van Goozen, Matthys, Snoek, & van Engeland, 2004). This flat-affect or emotionless response fits with finding acute cortisol declines in Special Forces soldiers or bereaved parents.

What the reader is left with after exploring the cortisol literature is the temptation to elicit a stress response by just trying to make sense of the literature. Indeed, even within the same population it is possible to find high HPA functioning being linked with both more *and* fewer problems, depending on the context for when cortisol is measured (Essex et al., 2011; Ruttle, Shirtcliff, et al., 2011; Shirtcliff & Essex, 2008). Nonetheless, this roller coaster is commensurate with long-standing notions of stress physiology and adaptation. For example, Selye (1976) termed this situation the General Adaptation Syndrome (GAS) to emphasize that the stress response was an adaptation to a stressor and illustrated that stress hormones could be low or high, depending on the stage of GAS being observed (it isn't hard to imagine why the term *stress* caught on, but GAS did not). Building from this perspective, McEwen describes allostasis as the process of achieving stability through change (McEwen, 1998; McEwen & Wingfield, 2003) and suggests that the pathway to disease and illness can be characterized as repeated hits or lack of adaptation where rising cortisol or declining cortisol reactivity and recovery is problematic, respectively, or where a prolonged elevated level or an inadequately low cortisol level, respectively, is problematic. Koob and Le Moal (2008a, 2008b) use the allostasis framework to describe regulation and counterregulation processes that build on each other over time until what was once problematic (elevated cortisol) completely reverses (low or declining cortisol) to predict drug addiction and mental health problems. In parallel, Miller, Chen, and Zhou (2007) and Miller, Chen, and Cole (2009) and Weems and Carrion (2007, 2009) describe how both high and low cortisol may be linked with stressors, depending on the timecourse since a traumatic event or extreme stressor. Finally, Boyce and Ellis (2005) use a U-shaped curve to describe how elevated biological sensitivity can be associated with the best and the worst of outcomes, depending on the early psychosocial stress and adversity of the child. Taken together, the major theories and theorists in the stress field acknowledge that there is not a good or a bad cortisol profile, but rather both high and low cortisol could be advantageous (or problematic), depending on a multitude of factors such as timing, context, prior stressors, and life history. Tackett and colleagues (2014) further suggest that intrinsic traits such as

personality disorder symptoms add an important individual difference factor that should be considered to understand the physiological roller-coaster ride.

Del Giudice, Ellis, and Shirtcliff (2011) build from these aforementioned theories to emphasize the adaptive significance of different physiological profiles of stress responsivity in their theory, the Adaptive Calibration Model (ACM) of stress responsivity. The ACM diverges from Allostatic Load, which suggests that maladaptation culminates as a wear-and-tear on the stress responsive system (SRS). The ACM emphasizes that up-regulation and down-regulation of the SRS can be adaptive with trade-offs inherent for high and low cortisol (Del Giudice, Ellis, & Shirtcliff, 2013; Ellis, Del Giudice, & Shirtcliff, 2013). The SRS, including the HPA axis as well as autonomic nervous system functioning, serves a purpose: It encodes and amplifies information in the environment, mediating openness of the individual to environmental inputs. When cortisol levels are high, the individual appears open to environmental stimuli; when low, the individual is more likely to filter nonessential information from the environment. This is a mechanism of conditional adaptation in which no single profile is adaptive, but rather multiple profiles are adaptive, depending on the environment. Whether a pattern of SRS activity is adaptive is conditional on the environment, especially in the first years of life and again at certain developmental stages or "switch-points." Each component of the SRS has different thresholds of activation. The HPA axis has an especially high threshold for activation and, in parallel, long-lasting effects (Shirtcliff et al., 2012). These effects may be more pronounced for some individuals than others, with sex differences expected to be larger in high- than in low-stress contexts.

What becomes apparent in this and other theories of stress regulation is that the prevailing notion that high cortisol is good (or bad) or that rising cortisol is good (or bad) or even that stress is good (or bad) is simplistic at best. At worst, this unidirectional, valenced viewpoint is intuitive and straightforward; consequently, it risks being adopted for its ease of interpretation, while more complex yet realistic findings and nuanced conceptual models are dismissed as intractable or tautological. Nonetheless, if we as a field pause to consider what we mean when we say stress regulation, we would see the obvious problems with the popular, simplistic view.

There are at least three basic tenets of a regulatory system (Siever & Davis, 1985). First, *regulation* implies change, fluctuation, and calibration to context. Physiological systems will respond to meet the demands of the environment and terminate that response once the demands are met (Gunnar, Bruce, & Donzella, 2000). Depending on the moment in which cortisol is measured in relation to a challenge, regulation could mean rising or falling cortisol as Tackett and colleagues (2014) describe with regard to cortisol reactivity and recovery after the TSST. Hidden within their protocol, however, is another detail that illustrates appreciation of the timecourse for regulation. Each participant was in the laboratory for a standardized 30-min period before the onset of the TSST. This helps minimize the arrival effect (Balodis, Wynne-Edwards, & Olmstead, 2010; Battaglia et al., 1997; Hastings, Ruttle, et al., 2011; Ruttle, Serbin, et al., 2011) in which the HPA axis responds to the arrival of the participant to the laboratory (or experimenters

to the child's home) rather than the planned stressor task. Without this experimental rigor, the early recovery could have meant that individuals with elevated personality disorder symptoms had mounted a stress response to the arrival effect and were well into the negative-feedback driven recovery phase by the time the TSST terminated. It is important for future work to ensure with experimental rigor that what the experimenter plans to be stressful or not actually matches the participant's representation of stress and challenge, as Tackett and colleagues (2014) have done here.

Second, regulation implies coordination across systems. This coordination is dynamic, and positive correlations across SRS components may not be observed (Hastings, Shirtcliff, et al., 2011). If the stressor is minor, this could entail fast withdrawal of parasympathetic inhibition on arousal or a brief rise in heart rate to stimulate the fight-or-flight response without an HPA response; by the time the HPA axis peaks, the autonomic system could be terminated (Sapolsky, Romero, & Munck, 2000). This explains why many stressors succeed in stimulating other stress-responsive physiological systems (Gordis, Granger, Susman, & Trickett, 2006) but not the HPA axis (Cohen et al., 2000). Even more interestingly, failure to demonstrate an HPA response could mean that the individual is able to cope prior to initiating a peripheral stress response. Taylor and colleagues (2008) found that individuals with substantial psychosocial resources often did not show cortisol reactivity to the TSST; reduced amygdala activity during threat mediated the apparently adaptive TSST nonresponse. Similarly, Kern and colleagues (2008) found that enhanced activation of the medial prefrontal cortex, an important site for voluntary down-regulation of emotion, was associated with lower TSST responsivity. Thus, some individuals may appear as TSST nonresponders when they appraise the challenge, but successfully regulate responsivity prior to crossing the relatively high stress threshold of the HPA axis (Bosch et al., 2009). Conversely, it may be indicative of dysregulation for some individuals to appear as nonresponders (Petrowski, Herold, Joraschky, Wittchen, & Kirschbaum, 2010). In this case, failure to show an HPA stress response signifies that the individual maintains a low capacity to mount a stress response even in situations that call for it. This lack of malleability in the HPA axis could be problematic because such individuals would not be able to recalibrate their physiological functioning to meet the demands of a changing environment. Given that one of the main functions of the HPA axis is to terminate a diversity of stress responses, these individuals may be at heightened risk for stress-related diseases associated with impaired negative feedback (Miller et al., 2007; Raubenheimer, Young, Andrew, & Seckl, 2006; Susman, 2006; Yehuda, 2000). The importance of malleability and flexibility is emphasized by Tackett and colleagues (2014) regarding inflexibility with patterns of thinking, feeling, and behaving in individuals with personality disorders.

Third, regulation implies that these changes in the SRS are made in response to a context in which a response is appropriate. It follows that the direction of effects of HPA axis is unlikely to distinguish good from bad responsivity profiles, but rather the types of contexts and behavioral outcomes are more informative for illustrating individual differences. Del Giudice and

colleagues (2011), following an evolutionary psychology model, describe these as life-history relevant dimensions. They propose that the SRS amplifies information in the environment about resource availability, extrinsic morbidity-mortality cues, and unpredictability. Extrinsic morbidity-mortality cues include proximal danger cues such as exposure to violence, threats, or danger as well as absence of protective factors such as warm, supportive caregivers and loved ones. Similarly, unpredictability also includes caregiving information related to stability in family composition and parental behaviors such as warmth and sensitivity. Contrary to the popular notion that people often feel totally stressed out, it has actually proven difficult to capture acute cortisol reactivity (Gunnar, Talge, & Herrera, 2009). The appeal of the TSST is that it reliably produces cortisol reactivity in 70% of participants on average (Kirschbaum, Pirke, & Hellhammer, 1993) because it uses the key dimensions of the SRS, namely, unpredictability and social evaluative threat (SET; Dickerson & Kemeny, 2004). Social evaluative threat taps into both extrinsic morbidity-mortality and unpredictability as it signals whether conspecifics in the environment are supportive (or threatening) and whether they can be relied on as a stable source of social support (Dickerson, Gruenewald, & Kemeny, 2004; Dickerson, Mycek, & Zaldivar, 2008; Taylor et al., 2010). Tackett and colleagues (2014) thus capture significant cortisol reactivity to a well-validated stressor, but it will be important for the next generation of studies to disentangle these life-history relevant key dimensions to understand individual differences in stress calibration to unpredictability, extrinsic morbidity-mortaility, and resource availability. In sum, stress regulation implies a dynamic response in which the timing, duration, context, and coordination across systems must be considered in order to understand whether a response is good or bad, adaptive or maladaptive.

In conclusion, the function of the HPA axis should be considered when interpreting behavioral correlates of stress regulation. Following Del Giudice et al. (2011), cortisol is related to openness to experience, functioning to amplify or enhance salient social cues in the environment. Cortisol is an adaptive and regulatory stress agent: It is both good and bad with inherent trade-offs. High (or rising) cortisol is expected when individuals are social, engaged with their environment, in a context that is personally relevant, or when they are facing a difficult but surmountable challenge (Fries, Shirtcliff, & Pollak, 2008). High cortisol is good because it allows us to be open to social information processing, enhances our ability to be socially connected with others, promotes feelings of empathy and attunement, and facilitates sharing warmth and sensitivity together. Yet high cortisol is bad because it also leaves us open to be hurt, amplifying feelings of social evaluation, disapproval, and judgment. On the other hand, low (or declining) cortisol is expected when the individual is socially—or emotionally—disengaged from his or her environment or others (Shirtcliff et al., 2012; Shirtcliff et al., 2009), or when the challenge is insurmountable or no longer novel (Shirtcliff & Essex, 2008; Skinner, Shirtcliff, Haggerty, Coe, & Catalano, 2011). Low cortisol is good because it allows us to be buffered from the vagaries of acquaintances and minor day-to-day hassles. Yet low cortisol can be bad because it can prevent us from connecting emotionally with others and can lead us

to see our friends and loved ones' emotions or stressors as unimportant and inconsequential. Sharing in each other's stressors is the root of bonding and attachment, so low cortisol can prevent us from feeling rewards and pleasures that come from bonding with others (Acevedo, Aron, Fisher, & Brown, 2012; Fisher, 1998). Up or down, rising or falling: What is important about cortisol regulation is that this molecule is functioning to do something, for that individual, at that time, and in that context. The adaptive significance of cortisol stress reactivity may appear like a physiological roller coaster, but the pattern is lawful and understandable. It will be exciting and thrilling to see whether the next generation of researchers and theorists can embrace the complexity and enjoy the ride.

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