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A dual-axis approach to understanding neuroendocrine development

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Abstract

This paper on 'a dual-axis approach to understanding neuroendocrine development' sets out to introduce a series of paper about a novel perspective regarding stress and sex hormones, or what the authors within this special issue term 'coupling' of hypothalamic-pituitary-adrenal and –gonadal axes. This view postulates that these axes do not necessarily operate in opposition, but can operate together as evidenced empirically as a positive within-person association between stress hormones like cortisol or sex hormones like testosterone. A wealth of papers within the special issue demonstrate positive coupling across acute, diurnal, basal, and longitudinal timeframes and across several different types of contexts. Reviews were meant to challenge whether this was physiologically plausible. Consistently, sophisticated statistical models were utilized in order to show a template for how to model positive coupling and to ensure that coupling was a within-person phenomenon. We cautiously considered positive coupling until the consistency of observing positive coupling was robust enough for us to consider challenging the prevailing oppositional view of these axes. We do so to acknowledge that there are contexts, moments and stages in which the function of these axes should work together: for example when contexts are both stressful and challenging or at developmental stages (like adolescence) in which the youth must grow up despite the storm and stress of youth. We hope that by putting forward a functional dual-axis approach, the field will be able to consider when and how a dual-axis approach is useful.

Keywords

cortisol; testosterone; dehydroepiandrosterone (DHEA); HPA-axis; HPG-axis; coupling; adolescence; life history theory

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Introduction

It is difficult to imagine a construct more frequently used and yet poorly defined as the term stress (Selye, 1976). There is an unacceptable amount of ambiguity for such a ubiquitous term, yet popular agreement does emerge in that the connotation of stress is overwhelmingly and undeniably negative. By extension, stress hormones, like cortisol, are commonly described as a "silent-killer" in popular press (Shirtcliff, Peres, Dismukes, Lee, & Phan, 2014). This poor reputation persists despite the hormone's potential lifesaving clinical utility (Frey & Frey, 1990) and increasing recognition of its' adaptive physiological value (Del Giudice, Ellis, & Shirtcliff, 2011). Calls for action to "move beyond" the popular notion of stress occur within various scientific disciplines (Del Giudice, Ellis, & Shirtcliff, 2013; Ellis, Del Giudice, & Shirtcliff, 2012; Lupien et al., 2006; McEwen & Lasley, 2002) but the struggle to "re-brand" this hormone more broadly persists despite herculean efforts within the scientific community (Shonkoff, 2000, 2010). Put simply, the bad reputation of cortisol and stress precede them. Evidence to the contrary is viewed as counter-intuitive; research which tries to argue otherwise risks being over simplified and reduced to straw-man claims that are incorrectly and easily refuted (Lyons & Parker, 2007).

Like others, the authors in this special issue put forward the notion that the reputation of cortisol needs to be reconsidered. It is beyond the scope of a single special issue to challenge all assumptions about stress. Instead, the special issue represents a substantial challenge to a very small piece of the stress puzzle: the prevailing wisdom that sex and stress hormones necessarily inhibit on another. To do so, we dovetail another misconception about sex hormones and adolescent development. We focus on sex hormones like testosterone because they are, arguably, as misunderstood as testosterone in popular press (Sapolsky, 1997) and folk wisdom (Eisenegger, Naef, Snozzi, Heinrichs, & Fehr, 2010). We utilize this empirical challenge to more broadly challenge the notion that stress and reproduction are inhibitory developmental processes. Below, we describe why we challenge this particular paradox and end by introducing the reader to initial empirical tests of a dual-axis approach to understanding neuroendocrine development.

Two Axes in Parallel

The hypothalamic-pituitary-adrenal axis (HPA) acts in response to stress, helping to govern an individuals' response to stress exposure (Essex, Klein, Cho, & Kalin, 2002; Tarullo & Gunnar, 2006). Stress is initiated in the brain (Pruessner et al., 2010), as limbic and related neural circuits are activated as the first stage of stress appraisal and coping. This neural activation initiates the release of corticotropin releasing hormone (CRH) from the hypothalamus (Papadimitriou & Priftis, 2009) into a limited blood supply into the anterior pituitary; pro-opiomelanocortin is stored in the anterior pituitary, but CRH causes it to be cleaved into adrenocorticotropic hormone (ACTH) which then stimulates release of cortisol and other hormones from the adrenal gland. Most cortisol is bound to serum proteins especially in blood to aid in transfer; the small amount of cortisol that remains free (10–15%) is biologically active and able to directly enter a cell nucleus to alter gene-expression. The end-product cortisol can cross the blood brain barrier to bind to mineralocorticoid in

largely basal or preparatory states as well as glucocorticoid receptors which terminate the stress response through negative feedback.

The hypothalamic-pituitary-gonadal (HPG) follows a similar neuroendocrine cascade. Hypothalamic neurons initiate release of gonadotropin releasing hormone (GnRH) which, in turn, stimulates the release of hormones from the anterior pituitary (leutenizing hormone, LH; follicle stimulating hormone, FSH) and subsequently these pituitary hormones travel through the blood and eventually stimulate the release of androgens from the gonads and adrenal gland. Here we focus on testosterone although we acknowledge that a suite of androgens, progestogens, and estrogens act as end-products of the HPG axis. Below, we will also focus on an adrenal androgen, dehydroepiandrosterone or DHEA, to further advance understanding of cross-axis communication. Like cortisol, androgens like testosterone are steroid hormones capable of crossing the blood brain barrier to influence neural functioning in limbic and related neural circuits (Op de Macks et al., 2011; Peper, Hulshoff Pol, Crone, & van Honk, 2011). Thus, while the hormones themselves diverge, the structures of the HPA and HPG axes are largely parallel in how their ‘top-down’ cascade flow from brain to periphery.

The review by Marceau and colleagues (Marceau, Ruttle, Shirtcliff, Essex, & Susman, 2014a) in this issue describes the parallels between these two hormonal cascades in the acute, top-down activation of these axes (Marceau et al., 2014b). Several other studies support this top-down view by showing that, like the HPA axis and its end product cortisol, HPG hormones are also stress-reactive (Bateup, Booth, Shirtcliff, & Granger, 2002; Eatough, Shirtcliff, Hanson, & Pollak, 2009; Marceau, Dorn, & Susman, 2012). Bobadilla and colleagues (Bobadilla, Asberg, Johnson, & Shirtcliff, 2014) show acute cross-axis coupling to a frustration task. This is important to note as it suggests that the parallel initiation of these two neuroendocrine cascades and subsequent feedback to the brain may not be coincidental; instead, parallel activation points to shared regulation and counter-regulation by similar neurocircuitries. Next, the review by Marceau and colleagues (Marceau, et al., 2014a) as well as prior studies (Ruttle, Shirtcliff, Armstrong, Klein, & Essex, 2013; Shirtcliff & Ruttle, 2010) describe the developmental parallels of the HPA and HPG axes across the lifespan. For both the HPG and HPA, this pattern is typified as being active in early development, actively inhibited during juvenile development, and reactivated during adolescence as the youth must adjust to their new hormonal state. This developmental profile has been appreciated for decades by sex hormone researchers interested in the organizational-activational hypothesis (Goel & Bale, 2008; Romeo, 2003; Schulz, Molenda-Figueira, & Sisk, 2009)and more recently has been described for stress hormones as well (Gunnar, Talge, & Herrera, 2009a; Shirtcliff & Ruttle, 2010) which enter into a juvenile stress hyporesponsive period(Vazquez, 1998). Such a curiously close developmental profile is directly considered by two papers in the special issue (Han, Miller, Cole, Zahn-Waxler, & Hastings, 2015; Ruttle, et al., 2013). Across a much smaller time frame, it is also notable that these axes – like most other steroid endproducts whose pattern of release is controlled centrally by the suprachiasmatic nuclei – both show a circadian rhythm in which hormone levels decline across the daytime hours(Marceau, et al., 2014a). Within the special issue, several papers highlight the shared circadian profiles of stress and sex hormones and consider these as interactive and not just parallel diurnal drops

(Dismukes, Johnson, Vitacco, Iturri, & Shirtcliff, 2014; Marceau et al., 2013). Pointing to shared diurnal declines is important because it shows that the top-down control of these axes from brain to periphery does not begin in the hypothalamus, but rather begins at much higher neural levels. Next, Marceau and colleagues (Marceau, et al., 2014a) challenge the notion of two axes operating in parallel by reviewing the tight metabolic connections of these hormones, beginning from the precursor cholesterol and shared prohormone progesterone. These metabolic starting points are shared by most steroid hormones; the number of enzymatic steps between HPA and HPG hormones is surprisingly few. This metabolic connection is notable for the purpose of the special issue because it illustrates that the cross-axis communication is not only centrally-driven, but can also occur within the periphery. Furthermore, the unique role of dehydroepiandrosterone (DHEA) as an endproduct of both the HPA and HPG axes highlights that parallels of these axes are surprisingly close. DHEA, like cortisol, is responsive to stress (Eatough, et al., 2009) and is stimulated by ACTH release (Parker, 1999). But, like other androgens, DHEA functions in the body primarily as an androgen. DHEA's dual role as a stress and sex hormone strongly suggests that a solely inhibitory relationship between HPA and HPG functioning is untenable (Kroboth, Salek, Pittenger, Faban, & Frye, 1999; Shirtcliff & Ruttle, 2010). The fact that testosterone within females is primarily of adrenal, rather than gonadal, origin provides another challenge to the idea that the HPA and HPG axes work in isolation (Granger, Shirtcliff, Booth, Kivlighan, & Schwartz, 2004). In sum, the many parallels of these two axes are striking and cannot be ignored. Nonetheless, HPG and HPA biomarkers are typically examined in isolation in human research.

Given these parallels of these axes, it would seem difficult to conclude that these axes do not operate together. These parallels and possible intersections have long been recognized within the literature, especially within animal studies (see review by (Viau, 2002)). This research demonstrates inhibition of the HPA axis or stress on gonadal functioning and reproduction (Pierce et al., 2008; Rivest, Plotsky, & Rivier, 1993; Rivest & Rivier, 1993; Rivier & Rivest, 1991; Stackpole et al., 2006; Tilbrook, Turner, & Clarke, 2000) and mutual inhibition of the HPA axis by androgens (Kerr, Allore, Beck, & Handa, 1995; Kerr, Beck, & Handa, 1996; Viau & Meaney, 1996, 2004). This cross-talk is recognized as being functional (Viau, 2002). Many investigations within human research begins with a statement about mutual inhibition of these respective axes and then proceed to examine these hormones in isolation or probe their overlap using a cortisol/DHEA (Christeff et al., 1999; Cruess et al., 1999; Goodyer, Herbert, & Altham, 1998; Khanfer, Lord, & Phillips, 2011) or cortisol/testosterone ratio (Doan, Newton, Kraemer, Kwon, & Scheet, 2007; Elloumi, Maso, Michaux, Robert, & Lac, 2003; Glenn, Raine, Schug, Gao, & Granger, 2011; Romero-Martinez, Gonzalez-Bono, Lila, & Moya-Albiol, 2013; Terburg, Morgan, & van Honk, 2009). The ratio is advantageous for combining these biomarkers, but unfortunately, on a statistical level, is most meaningful for informing about mutual inhibition (i.e., a ratio is large when one hormone is substantially higher than another). Consequently, the possibility of mutual activation would be under-emphasized by this analytical approach (see (Marceau, et al., 2013) for a more extensive description of statistical issues). Perhaps more importantly, cross-axis i*nhibition* is assumed to be a robust phenomenon, and largely accepted without critical evaluation of the contexts in which cross-axis *activation* may be adaptive or

advantageous. If cross-talk between HPA and HPG axes is functional, are there contexts in which cross-axis activation serves a function? What are the contexts in which the functional response would be for dual-axis activation rather than inhibition? Challenging the prevailing notion of mutual inhibition has served researchers interested in understanding autonomic nervous system function exceptionally well (Beauchaine, 2001; Hastings et al., 2011) and here we put forward a similar cautious challenge that probing the concept mutual inhibition is of value for HPA and HPG axes.

Below, we describe one context in which the stress of life is expected to be reflected in the HPA axis and gonadal maturation is expected to be reflected in the HPG axis; furthermore, we argue that life stress may be a context in which the functional purpose of these axis is for one of dual-axis activation. This lack of mutual inhibition across HPA and HPG axes has been described before in this context in animal research (Wingfield & Sapolsky, 2003) in order to avoid a "ironic possibility" of stress-suppressed gonadal functioning in dominant animals during the breeding season (Sapolsky, 2005). Within the human, we focus on adolescence.

Adolescence as an Awkward Developmental Stage

With one exception (Bobadilla, et al., 2014), the papers in this special issue focus on adolescence, because it is a developmental switch point (Del Giudice, 2006) during which stress and reproductive development take center stage (Dorn & Chrousos, 1997; Foilb, Lui, & Romeo, 2011; Walker, Sabuwalla, & Huot, 2004). Adolescence is an awkward developmental stage – where the individual is mismatched between childhood and adulthood (Dahl, 2004). This awkward stage is not surprisingly characterized by many seemingly paradoxical findings regarding behavioral, neural, social and emotional development (Buchanan, Eccles, & Becker, 1992; Susman, 1997). Like stress, the popular notion of adolescence is also fraught with misunderstandings (Dahl, 2004). Adolescence as a life stage is characterized, and even defined by "storm and stress." Although this contention stands on shaky ground (Hollenstein & Lougheed, 2013), there is some agreement that adolescence is an awkward stage because it is stressful (Steinberg, 2000). We take advantage of this awkward stage to apply the dual-axis paradox to a developmental phenomenon.

Adolescents go through puberty, and this illustrates another paradox. Stress should suppress gonadal functioning and the release of sex hormones, as evidenced by non-human animal research (Rivier, Rivier, & Vale, 1986; Viau, 2002). Nonetheless, adolescents traverse this stressful developmental stage culminating with gonads fully functional and with sex hormones readily released. The primary end-product of the HPG axis is testosterone in boys (and there are also testosterone changes in girls) (Ojeda & Terasawa, 2002), which advances gonadal development, pubertal growth spurt, muscle-development, voice changes and other masculinizing effects most apparent in boys (though it masculinizes in both sexes) (Hiort, 2002; Sisk & Foster, 2004). Like testosterone, DHEA functions as an androgen like testosterone (Havelock, Auchus, & Rainey, 2004; McKenna, Fearon, Clarke, & Cunningham, 1997; Shirtcliff, Zahn-Waxler, Klimes-Dougan, & Slattery, 2007) which controls many aspects of puberty such as acne, body odor, and pubic hair (Shirtcliff, Dahl, & Pollak, 2009) despite its adrenal origin. During adolescence, the HPA axis also is more

responsive to stress than at other developmental stages (Dahl & Gunnar, 2009; Gunnar, Wewerka, Frenn, Long, & Griggs, 2009b; Quevedo, Benning, Gunnar, & Dahl, 2009; Stroud et al., 2009). Prior to the past few years, a small handful of studies have illustrated that an inverse association between cortisol and testosterone may not be apparent in adolescents (Matchock, Dorn, & Susman, 2007; Popma et al., 2006; Roy, Kirschbaum, & Steptoe, 2003; Scerbo & Kolko, 1994). Stress and puberty can, and frequently do, co-occur.

We can speculate that an inhibitory role of HPG-HPA axes during sensitive stages such as adolescence serves an underlying developmental purpose. In adults, mutually inhibitory sex and stress axes may be adaptive as reproduction during stressful times may result in a loss of offspring or mortality (Ellis, 2004). Yet, adolescence is a developmental stage that by its very nature is stressful (Andersen & Teicher, 2009), and comprises the first stage where both stressful experiences and strong sexual/romantic interests are present (McClintock & Herdt, 1996). For a limited period, it may be functional for sex and stress hormone activation to co-exist during normative development (Dahl et al., 1989; Ellis, 2004; Nelson, Leibenluft, McClure, & Pine, 2005).

Probing the Developmental Switch Point with Life History Relevant Information

One easy critique of the above developmental argument is that the authors are making the ecological fallacy – drawing a conclusion about processes within an individual based on population level statistics. This critique would state, for example, that it is possible that the stress of adolescence could trigger HPG suppression, but this inhibition would be minimal enough for puberty to be advanced. The critique's prediction would be that cortisol and/or stress exposure would be associated with later/slower puberty or HPG functioning, but the opposite is typically seen. Below, we explore a viewpoint that these axes are mutually activated within individuals by drawing from Life History Theory. Largely, the evidence is indirectly capturing hormone-related processes as the dual-axis approach is still very novel. Notably, this viewpoint is highly functional which allows us to make specific predictions about which individuals will experience the greatest dual-axis activation during adolescence. Efforts have been made to understand the developmental paradox of stress and puberty in two ways.

First, by decomposing the construct of "stress" into functional parts (Del Giudice, et al., 2011; Del Giudice, et al., 2013) life history theory makes it easier to disentangle the mechanisms for why stress impacts development. Not every environmental signal is salient. The stress response system is expected to encode and enhance information that is important and filter out other information distractions from what matters. Key dimensions of the environment (i.e., stressors) include (a) resource availability, (b) extrinsic morbidity-mortality cues and (c) instability and unpredictability. Environmental cues that include these three key dimensions shape the stress response system and alter the development of life history strategies. This developmental shift is functional as it allows the individual to adapt to their environment and "make the best of the situation" (Ellis, et al., 2012; Ellis, Figueredo, Brumbach, & Schlomer, 2009). This developmental shift is conditional in that developmental maturation is shaped by these key dimensions of the environment and would

thus differ from one individual to another depending on their environmental cues and biological sensitivity.

Second, life history theory allows the developmental paradox of adolescence to be partially addressed by using the timing of pubertal maturation as an index of gonadal maturation (Ellis, 2004) and considering why pubertal timing shows individual differences. Life History theory suggests that there are trade-offs to competing life functions, and these trade-offs can be conceptualized as a balance between quality (i.e., added time spent on growth and development of current assets of one's self or current offspring for example) vs. quantity (i.e., time and energy devoted to a new asset such as future offspring). Life History trajectories are shaped by resource availability; across our evolutionary heritage, resources were likeliest to refer to caloric intake and metabolic resources. The energetics theory of timing of pubertal development suggests that individuals with chronically low energy availability would slow down growth and maturation and experience later development (see review by Ellis (Ellis, 2004)). Delayed puberty within ballet dancers(Warren et al., 2002), gymnasts (Rogol, Clark, & Roemmich, 2000), extreme athletes(Constantini & Warren, 1995; Roemmich, Richmond, & Rogol, 2001), and individuals with anorexia(Kholy, Job, & Chaussain, 1986) or malnourishment (Martorell, 2010) can be recast as the impact of low caloric intake on growth and reproductive development. Early maturation within overweight or obese youth also illustrates the impact of caloric intake on developmental trajectories (Castilho, Pinheiro, Bento, Barros-Filho Ade, & Cocetti, 2012; Wronka, 2010). The secular trend for earlier puberty across the past 150 years in westernized societies adds evidence to the removal of the energetics-based delay of maturation (Worthman, 1999). Some animal model research has found that stress exposure exerts a differentiated impact on development depending on whether the individual is pre- or late-pubertal (Gomez, Houshyar, & Dallman, 2002). Framed within the present special issue, this provides evidence that the HPG axis can take center stage rather than the HPA axis depending on the functional needs of the individual. If maturation is already well under-way, stress exerts a smaller impact, suggesting that the HPG, in turn, can inhibit the HPA axis.

Unfortunately, energetics is not an applicable definition of stress for much of human research. The "Stress Suppression Theory" attempted to broaden the energetic definition to more human-specific stressors by arguing that stress exposure more typical of the human condition (i.e., psychosocial stress like maltreatment, poverty and psychosocial stress) would also suppress puberty; this view failed to receive much empirical support because it conceptualized "stress" too broadly. Instead, much of the literature emphasizes the paradox of stress and puberty by finding that stress exposure *heightens* gonadal functioning. Taking a more functional perspective and nuanced definition of stress helps resolve the paradox. Ellis (Ellis, 2004) describes inter-related Child Development Theories wherein, essentially, the second two key dimensions of the environment -- Extrinsic Morbidity-Mortality cues and Unpredictability/Instability – are shown to accelerate maturation (especially reproductive maturation) toward a fast Life History trajectory which favors early development (see also (Belsky, Steinberg, & Draper, 1991; Ellis & Garber, 2000; Ellis, McFadyen-Ketchum, Dodge, Pettit, & Bates, 1999; Ellis, Shirtcliff, Boyce, Deardorff, & Essex, 2011; Moffitt, Caspi, Belsky, & Silva, 1992)). In environments with many cues of stability and safety, the

duration of childhood is lengthened to permit more time for learning, developing skills, gaining status and growth(Bjorklund, 1997); there are few costs to delaying reproductive development in such protective environments. In unstable or unsafe environments, however, the tradeoffs shift to favor shorter or faster reproductive life spans. When applied to puberty, acceleration of child development theory provides pivotal empirical and theoretical support for the notion that stress exposure – particularly psychosocial stress – can speed up maturation. By extension, this theory outlines an important conceptual and functional model to explain why stress and puberty can coexist within the individual and help resolve a developmental paradox; assuming hormonal mechanisms of stress and sex hormones underlie stress and gonadal maturation, respectively, life history theory provides the foundation for why, when and for whom we might predict HPA-HPG activation.

In sum, adolescence is a life-stage in which both HPA and HPG axes are important. The implications of the special issue may extend across the lifespan, but we largely focus on adolescence as it represents a clear functional developmental stage for both axes. How and when an individual traverses adolescence is influenced by stress and reproduction. We propose that environments in which stress is best conceptualized as energetic stress may produce HPA-HPG axis opposition. As an aside, much of the animal research which empirically supports mutual HPA-HPG inhibition fit within this definition of stress rather than psychosocial stress. Environments in which stress more closely tracks psychosocial processes – including extrinsic morbidity-mortality cues of threat and unpredictability/unstability – should instead align with the paradox of HPA-HPG axis correspondence. Put another way, environments with many stress cues will not only shape the HPA axis, but will also shift the balance of these two axes toward HPG-related processes. We hope that direct examination of both HPA and HPG hormones will shed light on the underlying biobehavioral mechanisms whereby stress exposure heightens gonadal functioning rather than suppresses it during salient developmental stages.

Inhibiting the Notion of Inhibition

Most of the evidence regarding stress accelerating child development in humans is indirect, relying on pubertal maturation as an index of gonadal functioning. While useful, a direct biomarker of gonadal functioning can add further to our understanding of HPG functioning (Dorn, Dahl, Woodward, & Biro, 2006), just as studies of the HPA axis have considerably advanced understanding of the physiological impact of stressors (Gunnar, et al., 2009a). Identifying a mechanism for *how* stress exposure advances puberty and adolescent development is important for the fields of developmental psychobiology and evolutionary psychology. Investigations of this nature have been hampered by the prevailing notion of HPA-HPG axis inhibition; setting aside that *a priori* assumption can allow for refinement of our theories of adolescent development.

Turning to the special issue, with alarming consistency, studies found support for the utility of the dual-axis approach, illustrating a robust association of HPA and HPG axes especially within adolescent populations. The phenomenon of co-activation is described as “coupling”, where cortisol and testosterone (and dehydroepiandrosterone) are positively linked within an individual. We hesitated to introduce new jargon to the field, but ended up with this term to

emphasize the shared intra-individual nature of HPA-HPG axis communication and the possibility that coupling can be positive or negative. The investigations converge on positive coupling in the special issue (Bobadilla, et al., 2014; Dismukes, et al., 2014; Dismukes, Shirtcliff, Hanson, & Pollak, in press; Han, et al., 2015; Marceau, et al., 2013; Ruttle, et al., 2013). This suggests that coupling is a robust phenomenon and adds insight to other studies which have investigated the interplay between the HPA and HPG axes (Denson, Mehta, & Ho Tan, 2013; Johnson et al., 2013; Marceau, et al., 2014b; Mehta & Josephs, 2010; Zilioli & Watson, 2012, 2013). Importantly, studies found that HPA-HPG coupling had implications for mental health in adolescents, with notable longitudinal predictive utility (Han, et al., 2015; Ruttle, et al., 2013). The investigations converge on the use of sophisticated statistics to capture within-individual hormone processes (see especially (Marceau, et al., 2013)); on a practical level, these statistical models can be easily used within a broad range of archival studies which have measured multiple biomarkers but which have analyzed them in isolation. The Life History model's prediction that HPA-HPG axis interplay would be shaped by early stress exposure was clearly supported in one study (Dismukes, et al., 2014), but a nuanced picture was more typical. For example, Ruttle and colleagues (Ruttle, et al., 2013) found tight HPA-HPG coupling within early adolescents, but found an early longitudinal switch to an adult-like pattern within those with early life stress (Ruttle, et al., 2013). Simmons and colleagues found positive coupling or 'covariation' of the axes within male adolescents exposed to high levels of maternal aggression but did not find the same pattern within females or traumatized youth (Simmons et al., 2015). Dismukes and colleagues likewise did not find that maltreated youth displayed different HPA-HPG axis coupling than non-maltreated youth (Dismukes, et al., in press). Thus, our goal is not to reject the notion of HPA-HPG axis inhibition, but rather to systematically begin to consider when and for whom positive coupling occurs; consistent with this caveat are several papers from Mehta's group (Denson, et al., 2013; Mehta & Josephs, 2010; Zilioli & Watson, 2012) as well as others (Johnson, et al., 2013) which can be re-interpreted as evidence of positive coupling overall but not within subgroups of primary interest. A consistent picture emerged for HPA-HPG coupling with more proximal stressors, such that coupling was stronger within those exposed to greater stress defined by: a difficult laboratory-day (Dismukes, et al., in press), during acute laboratory stressors (Han, et al., 2015; Marceau, et al., 2014b), or as combat experiences in adulthood within military veterans (Bobadilla, et al., 2014). In sum, the studies in the special issue build off the basic finding of positive coupling in unique ways which are complementary and allow the phenomenon of "HPA-HPG coupling" to extend across basal, diurnal, and reactive hormones; early, extreme, and concurrent stress exposure; and across a range of behavioral outcomes.

Conclusion

The special issue presents converging data on positive coupling across several independent datasets, populations and time-series. We do not propose that this is a substantial challenge to the field where (a) developmental switchpoints finally have a biological index, (b) the entire field of stress research must be dismissed, or (c) animal research do not translate to human research. It is beyond the scope and overly ambitious to challenge the stress field so extensively.

Staking claim to a modest challenge of the prevailing viewpoint in the field has, throughout the course of putting together this special issue, raised as many questions as we have answered and caused the first author many sleepless nights and grey hairs. Is positive coupling an artifact of saliva sampling (we don't think so (Marceau, et al., 2014b))? If this is all about Life History, why wasn't early stress more consistent? What would we find with the gonadal hormones like estrogen or progesterone? Do we really have the guts to go against pharmacological studies (we think coupling is consistent insofar as pharmacological inhibition would also be predicted within as well as across axis because of negative feedback)? Would animal research that is designed to capture psychosocial stress converge with these human findings (we think so (Sapolsky, 2005; Wobber et al., 2010))? If we're talking about sex and stress hormones, where do we put gender (is early life stress more consistent within males (Simmons, et al., 2015)or females (Ruttle, et al., 2013)?).

Instead of making grand premature claims, we put forward much more modest goals that hopefully will gain traction. By taking a functional viewpoint of the HPA and HPG axes, we suggest there are times one would predict dual-axis activation. This may appear within certain developmental stages and we emphasize adolescence as developmental stages in which both axes may work together. Dual-axis activation or "coupling" may appear within certain salient contexts. As described by (Dismukes, et al., in press), we suspect this can be captured as contexts in which "stress" stimulates the HPA axis through psychosocial or evaluative mechanisms and when "challenge" stimulates the HPG axis through motivation to achieve goals or threat of status loss. This functional viewpoint is supported by (Bobadilla, et al., 2014) in an acute frustration task outside of the adolescent time-period. Beyond the context of dual-axis coupling, our modest long-term goal is to encourage future studies to advance this functional mechanistic view of both HPA and HPG axes. Staking claim to this long term ambition is stressful, but we hope that the next generation of researchers are up to the challenge.

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