Published in final edited form as:

Dev Psychobiol. 2015 September ; 57(6): 705–718. doi:10.1002/dev.21231.

Coupling of the HPA and HPG Axes in the Context of Early Life Adversity in Incarcerated Male Adolescents

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Abstract

The effects of early life adversity can be observed across the lifespan, and the Hypothalamic-Pituitary-Adrenal (HPA) and Hypothalamic-Pituitary-Gonadal (HPG) axes could be mechanistic intermediaries underlying this phenomenon. The current study examined fifty adolescent males aged 12–18 in a maximum-security correctional and treatment setting. Saliva samples were collected five times a day for two day and assayed for cortisol, testosterone and DHEA. Youth completed semi-structured life stress interviews and self-reports of child maltreatment to index adversity. When youth had higher testosterone levels, they had higher cortisol and DHEA levels, indicating positive “coupling” of the HPA- HPG axes. In addition, children experiencing greater life adversity had tighter coupling of the HPA-HPG axes. Additional analyses hint that coupling may be driven largely by HPG axis functioning. Results indicate that positive coupling of the HPA-HPG axis is observed within incarcerated adolescents, especially for those with the greatest life stress.

DESCRIPTIVE KEYWORDS

Cortisol; Testosterone; DHEA; HPA; HPG; dual-axis; HLM; Stress; Adolescence

INTRODUCTION

Early life adversity is associated with a number of adverse health outcomes, including increased risk for cardiovascular disease, more frequent hospitalizations, increased prevalence of obesity, greater drug abuse, increased risk for poor physical health (Batten, Aslan, Maciejewski, & Mazure, 2004; Flaherty et al., 2006; Hussey, Chang, & Kotch, 2006) and poor mental health as well (Bremner, 1999; Kaufman & Charney, 2001). Furthermore,

the context of incarceration can be inherently stressful, engendering a reactive response from endocrine axes. The reactive, malleable nature of endocrine axes suggest these might play a role in the transmission of life adversity and incarceration effects to ‘get under the skin’ (Shirtcliff & Ruttle, 2010) and impact the way an organism adapts to its environment.

Alterations in Hypothalamic-Pituitary-Adrenal (HPA) axis functioning is implicated as an outcome of early life adversity (Cicchetti & Rogosch, 2001; Gunnar & Vazquez, 2001). The impact of early life adversity may extend to other endocrine axes as well (Lupien et al., 2006). Less is known about the effects of life adversity on the hypothalamic-pituitary-gonadal (HPG) axis. Research indirectly points to the HPG axis through the role of testosterone and other sex hormones in advancing puberty. Early life adversity is related to early pubertal timing and tempo, indicating that the HPG axis may also be reactive and malleable in the context of adversity (Ellis & Garber, 2000).

The present study considers that the HPA and HPG axes develop differentially based on the presence of life adversity, and examines whether early *adversity is capable of altering the crosstalk between these axes*. As with other articles in this special issue, cross-talk between the axes is described as “coupling” of the axes. Below, we describe how these axes typically communicate in order to establish that it is physiologically plausible for HPA-HPG coupling to be moderated by early adversity. We pay particular attention to the neural regulation of these axes through both top-down and bottom-up regulation of both axes.

Regulation of Sex and Stress Hormones

Cortisol is an end-product of the HPA axis, and the majority of single nucleated cells in the human body are potential targets of cortisol action. By the same token, the HPG axis results in the production of testosterone, whose androgenic effects differ based on developmental stage, but are also widespread throughout the human body. These axes are regulated by the brain (top-down processes), inter and intra-axis communication, and feedback on those same regions that initiate each respective endocrine cascade (bottom-up processes).

Top-down Processes: Neural regulation of the HPA and HPG axis

Before either the HPA or HPG axes are stimulated, emotion-related limbic circuits are implicated, such as the hippocampus, amygdala, and mPFC. The hippocampus is largely inhibitory on the HPA axis (Herman & Cullinan, 1997; Jacobson & Sapolsky, 1991); for example, lesions to the hippocampus increase HPA axis activity (Herman, Ostrander, Mueller, & Figueiredo, 2005; Sapolsky, Krey, & McEwen, 1984). The amygdala plays a largely stimulatory role on the HPA axis (Herman et al., 2005). Lesions to the amygdala reduce HPA axis activity (Allen & Allen, 1974; Feldman, Conforti, Itzik, & Weidenfeld, 1994) and stimulation of the amygdala increases HPA axis activity (Matheson, Branch, & Taylor, 1971). This is consistent with the function of the amygdala for activating fight-or-flight autonomic responses (Gray, 1993) and involvement with fear and anxiety potentiation (Davis, 1992; Herman et al., 2005). The mPFC has multiple roles in regulation of the HPA axis. The mPFC can be both activating and inhibiting on the HPA, responding differentially both in terms of efferent projections and contextual transduction of incoming stimuli. Thus,

limbic and paralimbic structures coordinate top-down regulation of the HPA axis, and this regulation largely involves emotion related neural circuitry.

Less is understood about the way the brain activates the HPG axis, with most imaging studies involving testosterone administration (reviewed below in bottom-up section). Developmentally oriented literature delineates the organizational – activational effects of testosterone and the rise in this and other sex hormones when the HPG axis is activated at puberty. Much of this recent research focuses on protein expression and receptors such as kisspeptin which act as a principal activating agent for the hypothalamus to initiate pulsatile release of GnRH release (Greives et al., 2007; Popa, Clifton, & Steiner, 2008) and trigger downstream release of sex hormones. This literature illustrates that multiple neural systems are involved in activating the HPG axis, but does not directly bear on acute or momentary reactive regulation of the HPG axis given the protracted time-course for initiation and maturation of the GnRH pulse generator within adolescents.

To gain insight into acute or momentary initiation of the HPG axis by the brain, some studies look at neural regulation in the context of behavioral outcomes for which testosterone is implicated, but not measured. Both human and animal research has examined the influence of the amygdala and prefrontal cortex, for example, in relation to outcomes of aggression and violence (Davidson, 2000). Lesions to the amygdala cause a decrease in aggressive behavior in rats (Vochtloo & Koolhaas, 1987). The prefrontal cortex functions as a regulatory structure for aggressive behavior (Giancola, 2006). Because the HPG axis is often an intermediary in this behavioral phenotype, it is not unreasonable to think that amygdala or PFC lesions could alter downstream regulation of the HPG axis, and thus alter aggressive behavior. Providing further evidence for a link between top-down acute HPG activation and aggressive behavioral outcomes, Marceau (2012) found testosterone response to challenge was associated with negative emotionality and family problems in boys. In further support, Denson (2012) found higher levels of testosterone after participation in a modified Taylor aggression paradigm for participants in the winner condition. Suarez (1998) found greater testosterone response to challenge in high hostility men than in low hostility men. Nonetheless, HPG functioning is not the only possible intermediary and demonstrating a neural link to aggression does not necessitate involvement of the HPG axis. Nonetheless, the HPG is likely initiated and regulated by limbic structures, though evidence for this is indirect, and future research in this area is vital.

It is notable that there is overlap between the structures that initiate the HPA axis and those that likely initiate the HPG axis. It is not possible to infer whether these higher-order structures inhibit or activate each axis in parallel or in opposition. It is possible that some structures may activate the HPA but inhibit the HPG (i.e., amygdala) whereas other structures may not show a clear direction of effect within either axis (e.g., PFC). Additional higher-order structures or circuits are also likely involved in initiating both axes, such as the anterior cingulate cortex (Cohen et al., 2006; MacLulich et al., 2006), insula (Wang et al., 2005), or hippocampus. Collectively, structures implicated in the initiation of either axis include higher-order structures largely implicated in processing emotional and social information. Downstream initiation of the HPA or HPG axis may aid the individual's ability to manage or cope with salient social and emotional information processing.

The HPA and HPG Axes

The hypothalamus and the pituitary form the first leg of the post-limbic HPA and HPG axes, and communicate with one another via a closed portal system (Papa & Fielding, 1930). The paraventricular nucleus (PVN) of the medial anterior lobe of the hypothalamus is primarily responsible for the secretion of corticotropin-releasing hormone (CRH) to the pituitary gland via the closed portal system (Weinstock, 2005). For the HPG axis, the preoptic nucleus of the hypothalamus releases Gonadotropin Releasing Hormone (GnRH) into the same portal system to activate the pituitary (MacLusky, Naftolin, & Leranth, 1988).

The anterior pituitary serves as the main target for CRH and GnRH. In the case of the HPA axis, CRH stimulates release of adrenocorticotrophic hormone (ACTH) from corticotrophic cells. ACTH acts on the middle cortical layer of the adrenal cortex along the perimeter of the adrenal gland to stimulate the release of glucocorticoids, and the initial HPA response to environmental threat occurs on the order of seconds (Sapolsky, Romero, & Munck, 2000). In the case of the HPG axis, gonadotrope cells within the anterior pituitary are stimulated by GnRH to secrete Luteinizing Hormone (LH) and Follicle-stimulating Hormone (FSH) into the bloodstream where they interact with Leydig cells in the testis to produce testosterone in males, and theca cells in the ovaries in females. In sum, though different subnuclei are responsible for initiating each axis, the origins of the top-down processing of the HPA and HPG axes, respectively, run in parallel.

Bottom-up Processes: HPA & HPG

Both the HPA and HPG axes feed back to the brain, exerting actions at glucocorticoid or androgen receptors in relevant structures. These cytosolic nuclear receptors (NR's), in turn, act as transcription factors. Once a steroid hormone binds to the NR, a conformational shift is induced and the receptor complex binds directly to DNA, which in turn regulates gene expression. The effects of testosterone and cortisol on neural structure is described below; as of yet, the effects of DHEA on specific structures involved with regulation of the HPA and HPG axes are unknown but likely to be large given DHEA's property as a neurosteroid (Dubrovsky, 2005).

The Hippocampus

The hippocampus contains a number of glucocorticoid receptors (Aronsson et al., 1988), and binds cortisol to influence limbic activation, such that decreased hippocampal glucocorticoid signaling has been associated with HPA axis inhibition (Issa, Rowe, Gauthier, & Meaney, 1990; Sapolsky, 1986). Within humans for example, cortisol administration affects hippocampal responses to memory tasks (Abercrombie et al, 2011). Alternatively, testosterone has been shown to increase activity in the hippocampus (Smith, Jones, & Wilson, 2002) and is possibly protective against stress (Mizoguchi, Kunishita, Chui, & Tabira, 1992), at least in animal models. Within humans, performance on tasks that rely on the hippocampus for performance is related to testosterone (Driscoll et al, 2005) and testosterone administration modulated hippocampal activation during memory tasks (van Wingen et al, 2008), suggesting testosterone-hippocampal links may translate to humans. More importantly, these studies illustrate overlap of neurocircuitry that receives information from the HPA and HPG axes.

The Amygdala

Both central and medial amygdaloid nuclei contain glucocorticoid receptors, and respond to glucocorticoids. The main effects of glucocorticoids on amygdala receptors is to stimulate CRH production (Herman et al., 2005). Testosterone has been shown to act on the amygdala to influence dominance behavior in animal models (Delville, Mansour, & Ferris, 1996; Stanton, Beehner, Saini, Kuhn, & LaBar, 2009). In humans, testosterone has been shown to increase the activity of the amygdala (Van Wingen, Ossewaarde, Bäckström, Hermans, & Fernandez, 2011). For example, exogenous testosterone administration has been shown to increase amygdala reactivity to happy and fearful faces (Bos, van Honk, Ramsey, Stein, & Hermans, 2012). In another fMRI investigation, greater right amygdala activity was found in response to angry faces after testosterone administration (Hermans, Ramsey, & van Honk, 2012). In a related study, testosterone selectively increased amygdala activation in response to angry and fearful faces (Derntl et al., 2009). This finding is not ubiquitous, however, and the relationship between testosterone and the amygdala is likely mediated by whether or not an individual perceives an angry face as socially threatening or dominant (Stanton, Wirth, Waugh, & Schultheiss, 2009). Furthermore, it has been postulated that age-related declines in testosterone are linked to decreased amygdala activity, and in one study, exogenous administration of testosterone to middle-aged women increased amygdala activity to that which would be characteristic of young adult women (van Wingen et al., 2008).

The Medial Prefrontal Cortex

Just like the amygdala and the hippocampus, the medial prefrontal cortex also contains a large number of GR receptors (Ahima & Harlan, 1990), and stressful stimuli tend to promote feedback to this region (Herman et al., 2003). This feedback has a variety of effects, including memory consolidation, working memory impairment (Barseganyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010) and regarding the HPA axis, can be down-regulatory (Diorio, Viau, & Meaney, 1993). It is important to note that the impact of cortisol on the medial prefrontal cortex is likely gender dependent, with males being more susceptible to impairment in conditioning than females (Stark et al., 2006). Testosterone impacts the vmPFC, lowering the threshold for engaging in dominance and behavioral aggression (Ambar & Chiavegatto, 2009). Testosterone can also increase pituitary volume (Peper et al., 2010). While the nuances of feedback of cortisol and testosterone on limbic structures still evade us, it is clear that these hormones do act in the limbic brain, and largely on the same structures that are involved with the top-down activation of the HPA and HPG axes.

Coupling of the HPA and HPG Axes

The prevailing viewpoint has been that the secretory end products and functional intermediaries of one axis negatively feed back on the other axis (Viau, 2002). For example, animal studies have indicated that HPA hormones down-regulate the HPG axis at all levels, and act primarily on the intermediaries (GnRH, LH, FSH) (Rivier & Rivest, 1991; Tilbrook, Turner, & Clarke, 2000). In rodents, CRH limits synthesis of LH (Porter, Lincoln, & Naylor, 1990). Similarly, testosterone has been shown to down-regulate the HPA axis (Viau, 2002), possibly mediated by androgen receptors, especially in the context of stress (Viau, 2002).

However, there is evidence to support the idea of the HPA and HPG axes as parallel processes that are continually influencing each other, and not necessarily mutually antagonistic axes. We refer to this possibility of co-regulation through top-down activation, bottom-up feedback, and inter and intra-axis communication as “coupling” of the HPA and HPG. Based on the literature above and the time-course for acute or momentary hormone fluctuations, we suspect that coupling may be derived through parallel top-down involvement of relevant social- and emotion-relevant circuitry leading to parallel activation of HPA and HPG axes in salient social contexts.

While relatively novel, this dual axis approach has precedence. First, a potent example of the highly intertwined architectures of these two axes is DHEA production. DHEA is produced adrenally, in the gonads, and also in the brain. DHEA and its sulfated analog DHEA-S are the most abundant hormones in the body, and as an adrenal androgen, DHEA operates as an end-product of both HPA and HPG axes (Shirtcliff, Zahn-Waxler, Klimes-Dougan, & Slattery, 2007). Second, a small body of research finds that both HPA and HPG hormones are reactive at the same time within participants (Bateup, Booth, Shirtcliff, & Granger, 2002; Eatough, Shirtcliff, Hanson, & Pollak, 2009; Marceau, Dorn, & Susman, 2012), indirectly suggesting that these hormones may be elevating within the same individuals (Marceau et al., 2013). Outside of this special issue, some prior research has also examined HPA and HPG axes simultaneously in humans, and has not necessarily found that these axes inhibit one another. Glenn and colleagues (2011) found the ratio of baseline testosterone to cortisol stress reactivity was related to psychopathy. Mehta and colleagues (2008) found that, after losing a competition, men who were high in testosterone and lost a competition tended to have a drop in cortisol, and men who were high in testosterone and succeeded in a competition tended to have a rise in cortisol (Mehta, Jones, & Josephs, 2008). These findings illustrate the axes can act distinctly, depending on how an individual interprets their social context (Mehta, 2008; see also Mehta 2010), and this role for appraisal may implicate top-down modulation of cross-axis activation. Gettler and colleagues (2011) found that waking and evening samples of cortisol and testosterone were co-elevated, especially within males who were actively seeking a romantic partner. Co-activation may be beneficial and adaptive in this context where the challenge of mate-seeking may require both axes to up-regulate.

Project Overview

This study examines how life adversity modulates HPA and HPG dual axis functioning for several reasons. First, the review above emphasized that the nature of HPA and HPG activation can be moderated by appraisal and cognitive factors prior to initiation of each axis. Life adversity is highly personally relevant and may be salient enough to influence how the individual initiates cross-axis communication. Second, life adversity is linked with both axes, so it is plausible that it could be linked with coupling of the axes. Third, research which does consider cross-axis communication consistently finds that the direction and strength of the effects is dependent on the individual’s social context, motivations, and functional goals. Following life history theory (Ellis, 2004), life adversity is one setting in which the individual’s stressful social context (i.e., child maltreatment and extreme stress)

and functional motivations (i.e., to advance development and maturation) would lend to the prediction that these axes may work together to achieve those goals.

Incarcerated adolescent males represent a unique and desirable population within which to examine the long-term effects of life adversity. In our sample, 65 percent of participants experienced child maltreatment of any kind and rates of early adversity are high. Such high risk populations are difficult to obtain, and with real-world collection it is difficult to determine whether the youth adheres to rigorous data collection protocols. Saliva samples were collected at precisely proscribed times, with little variation in sampling. Beyond data collection, however, the chaos and stress of daily lives may render daily schedules and patterns of activity to be disorganized and this may impact the nature of the circadian rhythms. The rigid schedule and structure of a youth detention center allows for many zeitgebers (e.g., meal-times, bed-times) to be standardized across youth within the facility.

Moreover, the context of incarceration is likely to be important for both HPA and HPG functioning insofar as it could be a context where there is increased plasticity or flexibility in the axes to facilitate adaptation to this potentially stressful environment. This proximal context may be an environment where it makes sense for both axes to activate together. Dominance hierarchies exist within prisons, and are associated with elevated testosterone levels (Dabbs, 1991; Dabbs & Hargrove, 1997). Competition and status seeking behaviors are pervasive aspects of prison life. At the same time, prison is inherently stressful, rife with social evaluative threat and uncontrollability (Kupers, 1996). We use a dual-axis approach to examine HPA and HPG coupling across the day within incarcerated youth, and consider whether coupling is modulated by life adversity.

METHODS

Participants

Participants included 50 male incarcerated adolescents (M age=16.08, SD =1.06, range 14–18 yrs) from Mendota Juvenile Treatment Center (MJTC), a maximum-security detention and treatment facility located in Madison, Wisconsin. MJTC receives youth referred for extreme behavior problems from two juvenile correctional facilities located in the state of Wisconsin. The sample was diverse and included participants who were African-American (60%), Caucasian (26%), Hispanic (12%), and other (2%) ethnic groups. 65% of responders met criteria for any maltreatment (abuse and/or neglect), with 37.3% reporting physical abuse and 41% reporting neglect by one or more parents, and 52% reporting any form of abuse (physical, sexual or emotional). Psychiatric difficulties were highly prevalent, with 92% and 88% of youth having at least one internalizing or externalizing disorder, respectively; these include Conduct Disorder (96%), ADHD (63%), PTSD (31%), Substance Abuse (57%), Attachment Disorder (9.8%) and Mood Disorder (84%). Thirty-eight participants were administered one or more medications to manage behavior and/or symptoms of mental disorders. The impacts of these medications were statistically assessed and controlled.

Procedure

Informed assent was obtained from each participant before testing. Saliva collections were conducted 1–2 weeks after admission to preclude treatment effects. Testing occurred over 3 days, including two consecutive days for collecting saliva samples (five samples per day) and one for conducting the Life Stress Interview and administering self-report measures of abuse and maltreatment and demographic information.

Measures

Saliva Collection—Researchers collected saliva samples (a) upon waking ($M=7:07\text{am}$, $SD=11\text{min}$, range=6:10–7:53am); (b) 45 minutes later to capture the response to awakening ($M=7:46\text{am}$, $SD=15\text{min}$, 7:10–8:25am) (Wust, Federenko, Hellhammer, & Kirschbaum, 2000); (c) before lunch to minimize the influences of mealtimes ($M=11:31\text{am}$, $SD=5\text{min}$, 11:19–11:47am); (d) before dinner ($M=5:33\text{pm}$, $SD=9\text{min}$, 5:10–6:38pm); and (e) immediately before bedtime to capture the entire rhythm ($M=10:00\text{pm}$, $SD=16\text{min}$, 9:30–11:55pm). Saliva was collected following published protocols (Schwartz, Granger, Susman, Gunnar, & Laird, 1998) and frozen immediately (-80°C).

On the day of assay, each saliva sample was thawed and assayed within 24 hours for cortisol, DHEA and testosterone in duplicate, using well-established enzyme immunoassay kits (www.salimetrics.com). All samples from an individual were assayed on the same kit to minimize measurement error. Mean intra-assay coefficients of variation (CVs) were less than 3.8%, 6.7% and 5.8% for cortisol, testosterone, and DHEA, respectively. Mean inter-assay CVs were less than 7.4% and 14% for cortisol and testosterone, respectively. For each hormone, the sample was reanalyzed if the CV for the duplicate measurements was greater than 7%. Raw hormones were skewed (range 1.6–2.5). Hormones were log-transformed and extreme values were winsorized (skew range -4 to -2) in order to normalize distributions (see table 1 for mean values).

Life Adversity—Maltreatment was measured through a combination of self-report measures and interviews. The Life Stress Interview (LSI) is a semi-structured interview administered one-on-one with each participant, and is highly sensitive to stress in adolescent environments. The LSI measures stress across several domains; we focus on peer and family domains as they are largely interpersonal stressors and still pertinent with incarcerated youth, but also examine a summation of chronic stress across domains (academic, behavioral, cross-gender, parental). Participants describe challenges and buffers in each domain as well as episodes of major stressors within the prior year to the interviewer. After the interview, an independent rating team of three or more raters blinded to the child rates the stressfulness of the events, providing a consensual judgment of severity of stress within each domain. Higher ratings correspond to more stressful events. In addition, at the end of the study, LSI lifetime stressors were then aggregated and ranked on a 10-point scale by trained raters. The Life Stress Interview (LSI) has been found to be a valid and reliable measure of stress (Adrian & Hammen, 1993).

In addition, participants provided self-report measures of maltreatment. The Childhood Trauma Questionnaire (CTQ) is a well-validated, sensitive and specific measure of abuse

even within in adolescent populations (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997). Subscales include emotional abuse, emotional neglect, sexual abuse, physical abuse, and physical neglect. The Conflict Tactics Scale (CTS) assesses frequency, prevalence and severity of physiological or psychological aggression and discipline instances in the child-parent relationship, and has been widely utilized in research involving violent or potentially violent relationships (Straus, 1998). We focus on subscales for physical abuse and neglect with the mother, as paternal data is often missing.

A principal component analysis of the centered LSI, CTS, and CTQ subscales was conducted to provide an aggregate vantage point for the heterogeneous construct of adversity and to establish an overarching relationship of coupling with adversity. The first principal component accounted for 49% of the variance in the abuse measures, and was coded as an overall 'adversity factor'.

RESULTS

Analytic Strategy

Missing data were minimal. Out of 500 samples, 443 (89%) were obtained in sufficient quantity for assay. Analyses were conducted using Hierarchical Linear Modeling (HLM) (Raudenbush, 2004) to account for the inherent nesting of samples collected within individuals (level-1) across 50 participants (level-2). HLM is an optimal analytic tool for analyses such as these because it allows for modeling of the diurnal rhythm, as well as assessing the nature of the coupling, or co-activation, that occurs between hormone axes. In the first set of analyses run, cortisol was the outcome of interest, and the base model was established to index the level of coupling between the sex (testosterone) and stress (cortisol) hormones. In order to best capture the diurnal rhythm of cortisol across the day, four additional variables were loaded on to the level 1 model. A dummy coded variable to capture the cortisol awakening response (CAR) was added; time since waking (TSW, in minutes) was added to capture the diurnal slope; two dummy coded time points were introduced due to the non-linear slope of the diurnal rhythm before lunch and before bedtime, respectively. Because we are interested in modeling the interaction between HPA and HPG end products, a sex hormone variable was added as the final predictor on the level 1 model. At level 1, this can be interpreted as momentary fluctuations in one hormone being correlated with the other hormone, beyond the influence of the diurnal rhythm or CAR, within the individual. Potential effects of medication (a level 1 variable) were assessed by adding each medication category as a level-1 predictor in a well-established manner (Essex et al., 2011; Shirtcliff et al., 2012). No significant interactions occurred for any medication category.

The level 1 model is represented by the equation:

$$Y_{\text{CORT}} = \beta_0 + \beta_{1\text{CAR}} + \beta_{2\text{TSW}} + \beta_{3\text{testosterone}} + \beta_{4\text{after-lunch}} + \beta_{5\text{pre-dinner}} + R$$

With the level 1 model established, HLM allows level 2 equations to be set up with the slope coefficients of the level 1 predictors as the outcome of interest for the level 2 predictors. The present study focused on life adversity as a between-subjects variable that could influence

the coupling parameter between sex and stress hormones. For example, the Level 2 equation for coupling is represented by the equation:

$$\beta_{2\text{Testosterone}} = \gamma_{30} + \gamma_{31}(\text{Abuse measure}) + U_2$$

Several potential control variables were examined as level 2 predictors in order to assess their impact on hormone functioning. Age, race and BMI were self-reported. Pubertal status was measured with the Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988), and timing was derived by residualizing age-for-stage. SES was measured with the Hollingshead index (Hollingshead, 1975). None of these covariates had significant effects on cortisol.

HLM Analysis

The level 1 model with no level 2 predictors was first run to establish the coupling parameter and to model the diurnal rhythm. In the morning, Cortisol rose sharply according to the CAR ($B = .59, p < .001$). After this initial spike, cortisol exhibited a steady drop over the course of the day ($B = -.09, p < .001$). The lunch time measurement of cortisol was not significantly different than that predicted by the diurnal rhythm ($B = -.05, p = .51$), but the pre-dinner sample was higher than would be expected by the diurnal rhythm ($B = .70, p < .001$).

Testosterone was positively coupled to cortisol rhythm ($B = .61, p < .001$) in this sample, such that, in moments when individuals had higher testosterone, they also had higher cortisol release. This relationship can be seen in Figure 1. Thus, over the course of a stressful prison day, moments when testosterone is elevated are coupled to moments when cortisol is elevated as well.

When adversity factor was loaded as a level 2 predictor, waking cortisol levels were lower ($B = -.81, p < .05$), and the CAR was significantly steeper ($B = .16, p < .01$) in males with higher abuse factor scores. Beyond these time-locked effects, the coupling parameter between testosterone and cortisol was also positive and significant ($B = .16, p < .05$), indicating that, in adolescents who had experienced higher levels of abuse the coupling between testosterone and cortisol was greater than in those with less life adversity (see figure 1). To understand which type of adversity was driving this effect, individual subscales were loaded on to the model as level 2 predictors. Consistently across subscales, positive (tighter) coupling was observed between cortisol and testosterone, as indicated by the coupling coefficient (β_3) in individuals who had greater life adversity (see table 2).

Next, we were interested in understanding whether the positive coupling of cortisol-testosterone were driven by the HPA or the HPG axis. First, we examined whether the adrenal androgen DHEA predicted cortisol. These hormones were positively coupled, and this was moderated by adversity (see figure 2 and table 2), potentially indicating that DHEA is acting as a stress hormone within incarcerated youth. Next, we examined whether DHEA and testosterone were coupled. These two sex hormones were positively coupled as well, and that this was moderated by adversity, potentially indicating that DHEA is acting as a sex hormone and implicating the HPG axis in these bivariate analyses. Next, to further disentangle the axes, we conducted a separate set of analyses loading both DHEA and

testosterone onto the dependent variable cortisol. The purpose of these analyses was to assess whether the influence of prior life stress is related to DHEA operating more androgenically or adrenally, given that DHEA can have effects on both the HPA and HPG axes. The trivariate model partials out the degree to which DHEA is acting adrenally (coefficient with cortisol) or androgenically (coefficient with testosterone). Interestingly, while Table 2 reflects strong coupling between cortisol and DHEA in the bivariate analyses (suggesting that DHEA is acting as a stress hormone), the trivariate model in Table 3 reflects that the majority of the variance found for the relationship between DHEA and cortisol gets partialled out when accounting for testosterone. The overall pattern of switch in beta weight for DHEA (moving from positive to negative) in the bivariate compared to the trivariate model suggests that DHEA is in fact operating more androgenically than adrenally, and that the positive correlation between DHEA and cortisol initially found in the bivariate models is likely only reflecting the degree to which stress and sex (DHEA in this case) hormones are coupled together. Thus, it appears that in the face of early life stress, sex hormones become even more strongly coupled with stress hormones, and potentially cause DHEA to operate even more androgenic in function than it otherwise would be in adolescent males.

DISCUSSION

The present study takes the approach that, during certain developmental points, the HPA and HPG axes are not necessarily operating as mechanistically antagonistic systems, but instead as co-operative, or coupled, processes. This positive link was demonstrated within incarcerated adolescent males, a unique population and context. This empirical finding is largely contrary to the prevailing viewpoint that these two axes are de-coupled or exhibit inverse feedback dynamics. We suspect that one reason for this emerging finding of coupled HPA and HPG axis profiles is that these axes are both instantiated in parallel structures in the brain. This 'brain-first' perspective of the HPA axis expands it to a dynamic, coordinated and constantly fluctuating mechanism for continually integrating environmental information and adapting to that information. The HPG axis is proposed to work in a similar fashion, with a high degree of overlap in structural intermediaries that are communicating on all levels. These axes can work competitively, or can coordinate, depending on the environmental needs of the moment.

Co-activation could have a number of mechanistically permissive pathways. The amygdala, hippocampus, and pre-frontal cortex all feed to and back from the hypothalamus, and could moderate activity of both axes. Communication between the two axes, in the form of mechanistic intermediaries, could be moderated by receptor sensitivity. The rate of metabolism or aromatization of axis end-products could be accelerated, thus altering feedback dynamics.

The limbic regulatory architecture that we suspect supports HPA and HPG axis coupling is well-suited to respond in acute settings, and most prior studies have indicated elevations of both axes in an acute, reactive setting (Bateup et al., 2002; Eatough et al., 2009). We suspect that the sophisticated neural architecture which could allow for acute coupling in humans is not limited to an acute time-course, however. The body possesses the ability to adapt over

multiple time courses. If stressors are more chronic, the physiological response will likely be more ingrained as we indirectly evidence with the diurnal coupling of sex and stress hormones. Incarceration is a stable, but often stressful environment, replete with uncontrollable and threatening challenges that can arise at many different times. At the same time, prison life is status-oriented, and dominance hierarchies are quick to form and be defended. Competition, challenge and even violence are routine parts of daily life. These challenges are historically associated with elevated testosterone levels in inmates (Dabbs, Carr, Frady, & Riad, 1995) which dynamically change as the inmate confronts these challenges (Thompson, Dabbs, & Frady, 1990). In support of this interpretation, Johnson and colleagues (2013) found increased coupling of the HPA and HPG axes within this same population, in the context of elevated interpersonal psychopathy symptoms; the authors interpret this finding as being indicative of high social dominance and manipulative traits, with the HPG recruiting the HPA to operate in an androgenic manner. Moreover, the challenges that the inmate must face are not delimited to discrete moments but rather it may be adaptive for both axes to be activated in anticipation of status-opportunities or stressful challenges as we observe across two days between wakeup and bedtime. Longer-term cross-axis coupling was also observed by Gettler and colleagues (2011) who found relationship status and fatherhood moderated coupling. An even longer term adaptation to context may underlie the ability of early adversity to moderate coupling. In sum, prison is a context where, mechanistically, both sex and stress hormones are expected to be activated, jointly contributing to the best adaptive functioning of the individual for that setting.

Further insight into the mechanisms underlying this dual axis approach can be gained from examining life adversity as a modulator of HPA – HPG coupling. Early adversity can alter the HPG axis, indirectly evidenced as accelerated pubertal timing (Ellis, 2004). Early adversity further represents a highly stressful context in which one would often have an altered stress response (Cicchetti & Rogosch, 2001; Harkness, Stewart, & Wynne-Edwards, 2011), suggesting both axes must alter in order for the individual to adapt to adversity. It stands to reason the body would develop a mechanism to allow permissive co-activation in contexts such as this one. Stemming from the evolutionary psychology field, this can be thought of as a faster life history trajectory in which early adversity advances maturation of the HPG axis and pubertal timing.

One question that emerges from the suggestion that early life adversity can initiate a ‘faster’ life history trajectory is whether the HPA or HPG axis is driving the adaptive changes. The present analyses hint toward the activating effects of the HPG axis as being central to the observation of positive coupling. Testosterone becomes even more strongly coupled with cortisol in individuals with greater early adversity. This correlation is substantiated by the trivariate model which partials the variance in the association of DHEA with cortisol while accounting for testosterone’s relationship with cortisol. In this model, it became clear that DHEA was behaving more androgenically in the face of early life stress. That is, the beta-weight that reflected the relationship between DHEA and cortisol became negative when accounting for testosterone. Thus, it appears that not only is early life stress associated with increased mutual up-regulation of cortisol and testosterone, but also that DHEA acts as a more masculinizing agent in the body to promote growth and development rather than align more closely with cortisol as a stress hormone.

Limitations and Future Directions

There are several limitations to the current study. The study is restricted to male participants, and it is possible that there are gender differences that could affect the coupling parameter. Replicating the study with females is an important next step, and primary data collection in a similar project with females has been completed. Secondly, another limitation is that we observed momentary coupling of the HPA and HPG axes across the day, but did not induce such a change through the use of a stress task. However, reactive coupling between cortisol and testosterone has been observed in Marceau et al. 2014 (see this issue). This possibility does not diminish the importance of examining coupling across the day in incarcerated youth, but does raise the challenge of distinguishing diurnal from acute coupling of these axes. Third, there are important concerns about generalizability of findings to normal populations, as the current investigation was conducted with incarcerated youth. There is evidence that coupling may be observed across a wider range of adversity, both in terms of timing and type of experience (see Ruttle, Simmons, Bobadilla this issue). Findings should be replicated in different populations in diverse context. For example, examining abused children relocated into supportive homes would represent a useful direction as it would involve contextual shifts without (presumably) large acute challenges. Given its role as a mental health-oriented treatment facility, the institutional effects of Mendota Juvenile Treatment Facility are somewhat diminished and may exert a stabilizing influence upon the participants.

Given the review's emphasis on neural underpinnings of HPA-HPG coupling, future studies will benefit from a thorough and holistic investigation into the structural underpinnings of coupling. What is currently understood about cross-axis communication is insufficient to fully capture the width and breadth of the interactions that occur through these axes, as they communicate with one another, and how they are initiated within the brain. This is especially true in the case of the HPG axis, where very little is known about how environmental stimuli invoke responsivity. Instead, many studies use exogenous administration of testosterone, largely in females, to study the *effects* of testosterone, and consequently under-emphasize the initiation and regulation of endogenous testosterone as an contextually-reactive cascade. The initiation and regulation of DHEA as a neuroendocrine end-product of both axes is even more poorly understood. Better elucidation of neuro-regulatory forces will bring clarity to the role of cross-axis communication in the production of testosterone, cortisol, and DHEA.

Lastly, there are a number of individual differences and environmental contexts that could impact the coupling parameter. We do not consider coupling to be a universal, 'always-on' phenomenon; instead, we view coupling as an adaptive strategy sometimes employed to best situate the participant to his or her unique environment. The challenge of incarceration may be such a context. There are many other contexts where it might not make sense to have a co-elevated sex and stress hormone axis, and as such, this pattern of activity would not be expected. Despite these limitations, the present study illustrates the diverse challenges of incarceration for adolescent males, shows that physiological systems such as the HPA and HPG axis can work together to adapt to these mutually status-oriented and stressful challenges. Long before incarceration, however, this process of adaptation through cross-

axis communication may be initiated early and in response to equally challenging experiences, namely, early adverse experiences such as child maltreatment.

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Figure 1.

Predicted cortisol values for 1 standard deviation above and below the mean on abuse factor.

The high T moment and the Low T moment indicate changes in cortisol predicted by changing testosterone by 1 standard deviation above and below the mean.

Figure 2.

Figure 1: Predicted cortisol values for 1 standard deviation above and below the mean on abuse factor. The high T moment and the Low T moment indicate changes in cortisol predicted by changing DHEA by 1 standard deviation above and below the mean.

Table 1

Means and standard deviations of raw hormone values

Hormone	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
Cortisol	.29720 (.21486)	.42960 (.26284)	.14260 (.17365)	.15540 (.16373)	.05940 (.14718)
Testosterone	176.65 (82.315)	131.76 (62.478)	100.94 (47.356)	76.782 (33.509)	69.357 (31.849)
DHEA	408.37 (271.80)	329.89 (229.78)	219.69 (192.66)	159.31 (103.03)	158.23 (155.61)

Table 2

The Impact of Abuse on Bivariate Coupling

BIVARIATE COUPLING OF CORTISOL WITH TESTO AND DHEA											
	Cortisol as Outcome			Cortisol as Outcome			DHEA as Outcome				
	Level	CAR	Slope	DHEA	Level	CAR	Slope	Testo	Level	Slope	Testo
Adversity Factor	—	.118**	—	.531***	-.816*	.158**	.005	.160*	—	-.006*	.026 ⁺
CTQ-Sexual Abuse	.222**	.005	-.005*	-.031*	-.124	—	—	.029 ⁺	-.111**	—	.027**
CTQ-Physical abuse	—	.025+	—	-.003	-.201	.036 ⁺	.002	.035	-.090*	—	.020*
CTQ-Emotional Abuse	—	—	—	.001	-.203*	.026 ⁺	.002	.041*	—	—	.005
CTQ-physical neglect	—	—	.002	.001	-.272*	.008	.006*	.052*	-.055	—	.013
CTQ-Emotional Neglect	—	—	—	.005 ⁺	-.258*	.026	.004 ⁺	.054**	-.082 ⁺	—	.017
CTS-Maternal Abuse	1.586*	.053	-.043*	-.297	—	—	—	-.037	—	—	.079*
CTS-Maternal Neglect	—	—	—	.040	-1.34	-.010	.020	.302 ⁺	-.318	—	.065
LSI - Peer	—	.231*	—	-.019	-.822*	.219*	—	.161*	—	—	.038*
LSI -Family	—	—	—	—	—	—	-.007	.024*	—	-.006 ⁺	.010
LSI - Life Rank	—	—	—	—	-.369***	.036	.002	.073***	—	—	—
LSI - Chronic	—	.204*	-.018*	.016	—	.253*	-.021*	.039 ⁺	—	—	.036

⁺ p<.10;

* p<.05;

** p<.01;

*** p<.001.

Note:

^alevel=basal cortisol level represented by the intercept upon awakening

Table 3

The Impact of Abuse on Trivariate Coupling

TRIVARIATE COUPLING OF CORTISOL WITH TESTOSTERONE AND DHEA					
Cortisol as Outcome					
	level	CAR	Slope	DHEA	Testo
Adversity Factor	-.418 *	.149 **	—	-.151 *	.252 ***
CTQ - Sexual Abuse	-.011	.011	-.002	-.054 ***	.067 **
CTQ - Physical Abuse	—	.034 *	—	-.048 +	.051
CTQ - Emotional Abuse	-.070	.030 *	—	-.041 *	.061 **
CTQ - Physical Neglect	-.201 +	.009	.005 *	-.009	.050 +
CTQ - Emotional Neglect	-.073	.021	—	-.027	.052 *
CTS - Maternal Abuse	—	.217	-.014	-.340 *	.328 *
CTS - Maternal Neglect	-.158	.015	.007	-.484 *	.634 ***
LSI - Peer	-.997 ***	.219 *	—	-.036	.225 +
LSI - Family	—	—	—	-.029	.045
LSI - Life Rank	-.234 *	.040 +	.001	-.072 *	.126 ***
LSI - Chronic	-.465	.271 **	-.021 *	.023	.001

+ p<.10;

* p<.05;

** p<.01;

*** p<.001.

Note:

^alevel=basal cortisol level represented by the intercept upon awakening