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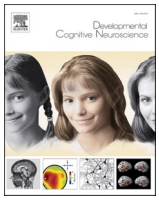

A dual-system, machine-learning approach reveals how daily pubertal hormones relate to psychological well-being in everyday life

Julia E. Chafkin [a,*,1], Joseph M. O'Brien [a,2], Fortunato N. Medrano [a], Hae Yeon Lee [b,3], Robert A. Josephs [a,4], David S. Yeager [a,5]

[a] Department of Psychology, University of Texas at Austin, Austin, TX, USA
[b] Department of Psychology, Yale-NUS, Singapore

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ABSTRACT

The two studies presented in this paper seek to resolve mixed findings in research linking activity of pubertal hormones to daily adolescent outcomes. In study 1 we used a series of Confirmatory Factor Analyses to compare the fit of one and two-factor models of seven steroid hormones (n = 994 participants, 8084 samples) of the HPA and HPG axes, using data from a field study (https://www.icpsr.umich.edu/web/ICPSR/studies/38180) collected over ten consecutive weekdays in a representative sample of teens starting high school. In study 2, we fit a Bayesian model to our large dataset to explore how hormone activity was related to outcomes that have been demonstrated to be linked to mental health and wellbeing (self-reports of daily affect and stress coping). Results reveal, first that a two-factor solution of adolescent hormones showed good fit to our data, and second, that HPG activity, rather than the more often examined HPA activity, was associated with improved daily affect ratios and stress coping. These findings suggest that field research, when it is combined with powerful statistical techniques, may help to improve our understanding of the relationship between adolescent hormones and daily measures of well-being.

1. Introduction

How are pubertal hormones related to adolescents' psychological well-being in everyday life? This question has fascinated researchers for decades. Answering it is important in part because there is a great need for better, basic knowledge about the etiology of internalizing psychopathology in adolescence, considering the recent three-fold increase in internalizing symptoms that has been called a "mental health pandemic" (=Moyer, 2022; Racine et al., 2021; Hill et al., 2021; Holland et al., 2021; Santomauro et al., 2021; Loades et al., 2020; Taquet et al., 2021; Elmer et al., 2020; Ellis, 2021; Keeter, 2021; Bor et al., 2014; Andersen and Teicher, 2008; Pine et al., 1998). As such, projects that increase our understanding of how pubertal processes are linked with everyday affective regulation (e.g., coping with stress, positive and negative affect) are vital. This is especially true as certain patterns of affective regulation are well-known precursors to internalizing disorders (Scott et al., 2020; Sperry et al., 2020; Joseph et al., 2021; Bailen et al., 2019; Matias et al., 2011; Stanton and Watson, 2014). Here we offer several advances on past research to provide answers to this question. These include (a) a new conceptualization and operationalization of daily activation of two pubertal hormone axes; (b) the largest known database of adolescents' repeated, naturalistic, daily hormone levels and well-being assessments; and (c) an application of a powerful, non-parametric, machine-learning approach—Bayesian Additive Regression Trees (BART)—to make sense of possibly complex interaction effects.

We asked two main research questions. The first was a measurement question: *do naturalistic, daily levels of adolescent steroid hormones map onto variables representing the Hypothalamic Pituitary Adrenal (HPA) and Hypothalamic Pituitary Gonadal (HPG) systems, as expected by theory, and, if so, how?* The second question used measures of axis activation

* Correspondence to: 1202 North Duke Street, Durham, NC 27701, USA.
E-mail address: Julia.Chafkin@utexas.edu (J.E. Chafkin).
[1] ORCID 0000-0003-0257-5476
[2] ORCID 0000-0001-9851-5077
[3] ORCID 0000-0002-8155-6400
[4] ORCID 0000-0002-2422-0150
[5] ORCID 0000-0002-8522-9503

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obtained from answering the first question, and asked: *how are HPA and HPG system activity associated with real-world, daily adolescent affective experiences?*

Study 1 used a series of Confirmatory Factor Analyses (CFAs) to compare the fit of one and two-factor models of seven steroid hormones of the HPA and HPG axes collected over ten consecutive weekdays (see https://osf.io/hxq6w for preregistration), using data from the Texas Longitudinal Study of Adolescent Stress Resilience (TLSASR, Yeager, 2022), a new, public-use database designed for basic and applied research linking adolescent hormones to well-being over time (https://www.icpsr.umich.edu/web/ICPSR/studies/38180). Study 2 used the same dataset to explore how the two axes were related to outcomes (self-reports of daily affect and stress coping) using the modeling technique BART, which applies machine learning methods and conservative, Bayesian priors to avoid over-fitting the data. This makes it uniquely suited for cases in which there are multiple, competing, potentially non-linear interaction effect hypotheses, as in the present case when we expect two hormone systems to interact with each other and with biological sex to predict outcomes. These steps were taken using a careful, sequential pre-registration that kept the research team blind from the relevant variables before each analytic step had been decided on, which helps guard against spurious findings resulting from excess researcher degrees of freedom (https://osf.io/hdxje).

In summary, by using an empirical approach to modeling hormones that is grounded in the biological realities of the HPA and HPG axes, and applying advanced, machine-learning methods to a large and unique dataset, we were able to conduct a comprehensive analysis that might allow for an improved understanding of the relationship between adolescent hormones and daily measures of well-being.

2. Contribution of Study 1: one or two factor solution?

A central contribution of Study 1 to the literature comes from its potential to resolve uncertainty around the *competitive* versus *cooperative/coupling* views of daily levels of HPA and HPG hormones. HPG and HPA axis hormones (usually, testosterone and cortisol, respectively), are often thought to suppress or to be inversely related to one another especially under circumstances of acute or prolonged stress exposure (Mehta and Josephs, 2010; Tackett et al., 2014, 2015; Hermans et al., 2007; van Honk et al., 2010). This *competitive* view has been influential in the field and has often been associated with seminal papers such as Viau's (2002) work which described and synthesized findings in the literature suggesting mutual suppression by hormones from each axis on one another. A more recent and nuanced view of the competitive relationship between hormones produced by the HPA and HPG systems can be found in the *Dual Hormone Hypothesis* (DHH), which does not claim that positive correlations between hormone systems do not occur, but rather posits that gonadal hormones (testosterone and estradiol) will be positively related to status-relevant behaviors, but only when cortisol levels are low (Mehta and Josephs, 2010; Mehta and Prasad, 2015; Tackett et al., 2015). Further, the DHH literature has expanded in the decade-plus since its inception, with some findings suggesting that different circumstances may produce differing patterns of suppression or cooperation between HPA and HPG axis hormones (Mehta et al., 2008; Dekkers et al., 2019; Welker et al., 2014; Mehta and Prasad, 2015; Dismukes et al., 2015; Grebe et al., 2019; Chafkin et al., 2021; Denson et al., 2013).

Research directly examining positive hormone *coupling (*aka the *cooperative* view), suggests that adolescence may signal a unique developmental shift toward overall increased synchrony between HPA and HPG hormones (Dismukes et al., 2015; Marceau et al., 2015a, 2015b; Zakreski et al., 2018; Shirtcliff et al., 2009). This synchrony results from coordination in top-down systems controlling release of HPA and HPG hormones: the hypothalamus and pituitary (Dismukes et al., 2015). Before pubertal maturation, by contrast, these two systems are thought to be more competitive. Evidence for the coupling hypothesis comes from studies showing that, over the course of the day, in response to laboratory or environmental stressors, and over longer developmental time frames, hormones of the HPA and HPG axes such as testosterone, cortisol, and DHEA-s, are positively correlated with one another (Marceau et al., 2014, 2015a, 2015b; Bateup et al., 2002; Turan et al., 2015; Ruttle et al., 2015; Dismukes et al., 2015; Shirtcliff et al., 2015).

The DHH and coupling literatures provide a breadth of work from which to hypothesize about the best latent variable model to represent the hormones of the HPA and HPG axes. There are arguments in favor of both one-factor and two-factor solutions. In favor of a one-factor solution, steroid hormones all share multiple precursor molecules and are all synthesized from cholesterol. As such, they are each small, lipophilic, and capable of crossing the blood brain barrier. In addition, the signaling pathways that synthesize and release HPA and HPG hormones both begin in the hypothalamus and anterior pituitary. These similarities in structure and function suggest that HPA and HPG axis hormones could plausibly be modeled as a single factor representing steroid hormones. In favor of a two-factor solution, both the DHH and coupling hypotheses suggest that HPA and HPG hormones are likely best represented with two separate latent variables. Additionally, HPA and HPG hormones are synthesized and released mostly from different organs in the body (though there is some overlap), and research describing competitive behavior between cortisol and testosterone suggests that these systems work side-by-side but separately (Oyola and Handa, 2017; Viau, 2002). Further, hormones from the HPA and HPG systems often act to self-regulate their own release (Green and McCormick, 2016). This tendency toward self-regulation suggests that these systems are ultimately best modeled as distinct from one another.

If the better model contains two factors, an important question remains: where should DHEA-s fit? As a hormone without a specific receptor, DHEA-s produces downstream effects by binding to both HPA- and HPG-specific hormone receptors (Webb et al., 2006; Widstrom and Dillon, 2004). Additionally, studies in adolescent samples have repeatedly shown a tight, positive coupling between DHEA or DHEA-s and *both* cortisol (Howland et al., 2020; Ruttle et al., 2015; Simmons et al., 2015) and testosterone (Han et al., 2015; Ruttle et al., 2015). However, like other hormones of the HPA axis, a high proportion of circulating DHEA-s is produced by the adrenal cortex (Rainey et al., 2002). Therefore, it is an open question whether DHEA-s should be modeled as a part of the HPA or HPG axis in daily, naturalistic data.

3. Contribution of Study 2: links to stress coping and daily emotion

Study 2 of this manuscript contributes to the literature by better clarifying the magnitude and direction of the potential relationships between adolescent hormones and daily mental health outcomes (daily affect and stress coping). Here, we examine whether HPG hormones are positively associated with better mental health, HPA hormones are negatively associated with better mental health, and whether HPA hormones interact with HPG hormones in predicting outcomes. As much of the adolescent mental health literature has focused on HPA hormones, this study provides a much needed dual focus on hormones from both the HPA *and* HPG axes.

*Hormones and daily positive/negative affect. A*dolescents in high school tend to report more positive than negative emotions throughout the day, and tend to experience more intense emotions than adults (Bailen et al., 2019; Flook, 2011; Diener et al., 1985; Charles et al., 2013; Stawski et al., 2013). Ecological momentary assessment (EMA) studies (in which emotion states are assessed repeatedly from participants often at multiple times per day) with an ambulatory hormone assessment component have demonstrated that self-reports of affect appear to be correlated with hormone profiles (Joseph et al., 2021; Bailen et al., 2019; Doane and Zeiders, 2014; Matias et al., 2011). For instance, a recent meta-analysis and review showed that ambulatory cortisol assessments were positively correlated with EMA reports of negative affect and

negatively correlated with EMA reports of positive affect (Joseph et al., 2021) regardless of the technique used to model the association.

The link between HPG axis hormones and daily affect has received less attention than the link between cortisol and affect. This may be due to the focus, both colloquially and in the literature, on adolescence as a period dominated by negative affective states and moods (Coe-Odess et al., 2019). This 'storm and stress,' conceptualization of adolescence has often been challenged, and a view of adolescence as a period of social growth has been proposed instead (Stirrups, 2018; Payne, 2012; Dahl and Hariri, 2005; Arnett, 1999). Nevertheless, very few studies have rigorously tested a central prediction from this more optimistic view of pubertal maturation: that higher levels of HPG hormones (which are linked to many of the most pronounced physical changes during puberty) are associated with positive affective well-being. The little research that does exist has shown that negative affect and affective instability are associated with low levels of HPG hormones such as testosterone and estradiol (Susman et al., 1991; Buchanan et al., 1992). Thus, there is a gap between the rhetoric of adolescence and the findings in the data, which we seek to fill here.

This study used an affect ratio to account for the (often) simultaneous existence of positive and negative affective states (An et al., 2017; Miyamoto et al., 2010). Negative affect during adolescence is not only unavoidable, it is also sometimes desirable, because it can be the natural consequence of embracing and overcoming the challenges of healthy development. This has led scholars to argue that strong negative affect *and the relative absence of positive affect* indicates poor well-being, while negative affect co-existing with an equal or greater amount of positive affect can indicate better well-being. Operationally, this refers to the *ratio* of positive to negative affect. Although affect ratios have been critiqued (Fredrickson and Losada, 2005, 2013; Brown et al., 2013), the basis of these critiques mostly was methodological, not conceptual, and stems from past authors' arbitrary choices of an optimal ratio (e.g. three positive emotions for each negative emotion). Therefore we calculated the overall ratio of positive to negative affect on each day and allowed this measure to vary freely, thus avoiding the (legitimate) criticisms of an arbitrary positivity ratio threshold. We call the resulting measure the *affect ratio*.

Stress coping. Adolescents' physiological stress response systems undergo tremendous neural and hormonal maturation during pubertal development (Roberts and Lopez-Duran, 2019). Additionally, this period in a young person's life is notorious for its diverse social stressors (Dahl and Gunnar, 2009). Adolescents' behavioral and biological responses to stressors are thought to be linked to the emergence of psychopathology during adolescence (Romeo, 2010). Here, we use the term 'stress coping' as it relates to adolescents' self-reports of their beliefs about the adequacy of their resources to meet the challenges of naturalistic stressors or negative events in their daily lives (Susman et al., 1988). We use this approach based on findings from smaller-scale studies showing that people who think they cannot handle their stressors, and who ruminate about their stressors, differ in their hormone profiles, especially in HPA-axis profiles (e.g. cortisol), from those who believe they can handle their stressors (Aldao et al., 2014; Sladek et al., 2016; Stewart et al., 2013).

Cortisol levels are the most commonly-studied covariate of stress coping. Far less research to date has examined how other hormones of the HPA axis may be related to daily, ecologically valid stress responses and stress coping in humans (Dagnino-Subiabre, 2022; Vanaelst et al., 2013; de Kloet, 2004). In addition, much research has neglected the links between HPG axis activation and daily stress coping patterns. Studies that do examine how HPG hormones respond during periods of stress tend to focus on the extent of coupling between HPG and HPA hormones during laboratory-induced stressors, or on HPG hormone responses to stress more generally, as opposed to focusing on how HPG hormones may move in relation to an individual's perceptions of their stress coping (Marceau et al., 2015a, 2015b, 2014; Dismukes et al., 2015; Shirtcliff et al., 2015; Phan et al., 2021). Hormones of the HPG axis are related to adolescent neural plasticity (Takesian and Hensch, 2013), and yet the role of the HPG axis in daily stress coping remains under-researched—a state of affairs that we aim to address here.

The value of naturalistic hormone data. As we have been suggesting, most studies linking adolescent hormones to teenage stress and well-being take place in a laboratory in response to a controlled stressor, or measure hormone levels immediately after waking (Stalder et al., 2016; Fries et al., 2009; Kirschbaum et al., 1993). These methods are valuable for certain purposes–for instance, studying the responsiveness of the HPA axis to known, acute stressors, or studying circulating levels of hormones, which can be influenced by early life stress (Ruttle et al., 2015; Marceau et al., 2015a, 2015b). But the laboratory and waking cortisol levels are not optimized for our research questions, which involve the relation of daily hormones to ecologically-valid (but unmeasured) stressors inherent in everyday adolescent life (Armario et al., 2012). Therefore, a strength of our study is its collection of hormone data later in the day (and, in almost 80% of cases, after noon) so that hormone levels will better reflect reactivity to the accumulation of social and academic difficulties, big and small, on a given day in high school.

4. Study 1 methods

Participants. Data for the present research come from the TLSASR students who participated in the fall or winter of 2016 and 2017. Participants were ninth graders at the time of data collection (age range = 13 – 16). This dataset is unique for its large size (n = 994 ninth grade boys and girls, 52.1% female, 8084 daily observations), which can increase reliability of results, the diverse identities reported by sample participants (Asian 4.72%, Black 3.82%, Hispanic 30.78%, Native Hawaiian/Pacific Islander, American Indian or Alaskan Native, or reporting "Two or More Races" 4.12%, White 47.99%), which are reflective of the geographic area, and therefore increase generalizability, and its ecological validity (data collected in schools about teenagers' real-life experiences). See supplement for information on missing data patterns for all hormone and non-hormone variables. This is the first manuscript to use the full TLSASR dataset for hormone analyses.

4.1. Procedures

Salivary Sample Collection and Analysis. All data collection procedures for the TLSASR were developed and approved by an advisory board of psychoneuroendocrinologists, affective scientists, and clinical psychologists. A total of 8084 salivary samples were collected in school classrooms for ten consecutive school days in the first six months of the 9th grade year. Samples were collected, where possible, between the hours of 12PM and 4:30PM to reduce variability due to diurnal changes in steroid hormone levels (Rose et al., 1972). N = 1942 (24%) samples were collected between 9:48AM and 12PM due to constraints in the school partner's schedules. Time of sample collection was automatically recorded in an electronic daily intake questionnaire, and variability due to time of day of collection was controlled for using procedures described below (also see analyses in the supplemental material). After collection, salivary samples were frozen and later shipped to Dresden, Germany in October of 2018 and June of 2019 for analysis with Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) (for cortisol, cortisone, corticosterone, testosterone, progesterone, and DHEA-sulfate (DHEA-s)) or Chemiluminescent Immunoassay (CLIA) (for estradiol) at Dresden Lab Services (PI, C. Kirschbaum). Detailed methods for LC-MS/MS procedures can be found in Gao et al. (2015). Samples were aliquoted first for estradiol quantification using CLIA before using LC-MS/MS to quantify the remaining six hormones. In 42 cases, there was not sufficient sample left after analysis with CLIA to quantify the remaining hormones. These 42 cases were removed from the final analyses, leaving a total of 8042 samples in the final analysis. For more information on salivary sample collection, see the supplement.

Hormone data preparation. All data cleaning and preparation was

completed in R (version 4.2) and Mplus version 8 (Muthén and Muthén, 2017). Some concentrations for each hormone were too low to be detectable using LC-MS/MS. 1 (0.01%) cortisol concentration was not detectable, 3 (0.04%) cortisone concentrations were not detectable, 6189 (77%) corticosterone concentrations were not detectable, 1614 (20%) progesterone concentrations were not detectable, 256 (3.2%) testosterone concentrations were not detectable, and 92 (1.1%) DHEA-s concentrations were not detectable. In addition, 7 (0.09%) estradiol concentrations were not detectable using CLIA (see supplemental tables for more details).

Removing artifacts using Bayesian Additive Regression Trees (BART). To remove variability in hormone concentrations due to theoretically irrelevant factors (such as time of day or behaviors that artificially alter hormone levels), Bayesian Additive Regression Trees (BART) models were used (Chipman et al., 2010). The primary reason for using BART is to allow for non-linear and complex, interactive effects of extraneous variables, so that only the theoretically-relevant variation remained in our primary analyses. BART is a non-parametric Bayesian approach to regression that uses many constrained regression trees (decision trees with small numbers of branches) to estimate outcome variable values based on predictor inputs into a model. CFA results prior to BART are included in the supplement. The list of day-level covariates included time of day of sample collection, self-reports of exercise in the past two hours ("Have you exercised (ran or sweated) in the past 2 h?") self-reports of caffeine intake in the past two hours ("Did you have any caffeine (e.g., coffee, tea, energy drinks, coke, or chocolate) in the past 2 h?"), self-reports of dairy intake in the past two hours ("Did you eat any YOGURT or dairy products (e.g., milk, cheese) in the past 2 h?"), menstrual cycle stage (see supplemental section titled "Menstrual cycle coding procedures" for details), daily reports of medication ("Have you taken any medicine today?"), and daily reports of illness ("Did you feel sick today?"). For more information on BART analysis, and covariate processing, see supplement.

Analysis. Skew, kurtosis, and distribution characteristics of all hormones were assessed (see supplement for descriptive statistics and histograms of hormones). As population distributions of steroid hormones naturally produce right skew, log transformations were performed on hormone values to reduce skew and increase normality of residuals, as pre-registered. Hormones were then separated by biological sex assigned at birth (obtained from administrative demographic data) and winsorized within sex and hour of day of collection such that outliers were set to the highest value falling within 3 standard deviations of the mean for each hormone. Hormone values were winsorized using both sex and time of day in order to account for high or low hormone values due to variations in time of day of collection. Using this pre-registered procedure, values were replaced as follows: for cortisol, 23 values in boys and 29 values in girls were replaced, for cortisone, 33 values in boys and 33 values in girls were replaced, for corticosterone, 5 values in boys and 4 values in girls were replaced, for DHEA-s, 43 values in boys and 44 values in girls were replaced, for testosterone, 12 values in boys and 49 values in girls were replaced, for estradiol 46 values in boys and 45 values in girls were replaced, and for progesterone, 30 values in boys and 6 values in girls were replaced. Finally, BART models, referenced above, were run to remove variation due to daily potential confound variables, yielding a predicted value for each measurement occasion for each individual.

Confirmatory Factor Analysis. After applying this pre-registered data cleaning pipeline to the hormone values, the resultant hormone values were used to fit CFA models. Sequential models compared the fit statistics of one-factor versus-two-factor models, including all seven hormones. This was done in Mplus (version 8). Models were estimated separately for each biological sex because of orders-of-magnitude differences in relative hormone concentrations in adolescent boys and girls. Robust Maximum Likelihood estimation (MLR) was used as all variables included in the CFA analysis were continuous (Kline, 2015). Missing values were estimated with Full Information Maximum Likelihood (FIML) estimation in order to produce low bias in model estimates (Kline, 2015). Models were clustered by participant ID. For one-factor models, all hormones were included in a single factor. Fit statistics (Root Mean Square Error of Approximation, or RMSEA, Comparative Fit Index, or CFI, and Tucker-Lewis Index, or TLI) of one-factor models were compared to fit statistics of two-factor models in which hormones of the HPA axis (cortisol, cortisone, corticosterone, and DHEA-s) were assigned to one factor (HPA), and hormones of the HPG axis (DHEA-s, testosterone, estradiol, and progesterone) were assigned to a second factor (HPG). DHEA-s was cross-loaded and then subsequently loaded onto the HPA factor only and the HPG factor only and model fits were compared. Additionally, a series of exploratory models were fit to examine variability in model fit based on included variables, and to examine the importance of certain residual covariances. In particular, one set of exploratory models removed corticosterone due to high missingness, and one set of exploratory models in boys only removed estradiol, as estradiol was non-significantly correlated with latent variables. Exploratory models were fit in boys and girls with each set of hormone variables (all hormones, corticosterone removed, and estradiol removed), in which residual variances of estradiol and progesterone (only in models with estradiol included) and of cortisol and DHEA-s were allowed to be correlated. Models with a CFI above.95 were considered to have good fit, while models with a CFI above.90 were considered to have moderately good fit. Models with an RMSEA below.05 were considered to be a close fit of the model to the covariance matrix relative to the degrees of freedom (Chen et al., 2009). Path model structures can be seen in Fig. 1.1.

5. Study 1 results

Primary findings. Our main findings are consistent with the *coupling*, and not the *competitive*, view of adolescent hormones. Findings clearly supported the existence of two separate, positively correlated hormone systems.

Table 1.1a and b contain fit statistics of one and two-factor solutions for the seven hormones included in this analysis in boys and girls. Results show improved fit, lower RMSEA and higher CFI and TLI, when a two-factor model, as compared to a one-factor model (girls: RMSEA.093, CFI.845 TLI.768, boys: RMSEA.086 CFI.866 TLI.784), was used to explain the data.

Role of DHEA-s. Where did DHEA-s belong—with the HPA axis or the HPG axis? In our data, DHEA-s fit best when loaded onto the HPG axis. Statistics from Table 1.1a and b indicate improved fit in two-factor models when DHEA-s was loaded onto the HPG factor (girls: RMSEA.058, CFI.945 TLI.91, boys: RMSEA.056 CFI.94 TLI.91) or cross-loaded onto both factors (girls: RMSEA.061, CFI.942 TLI.899, boys: RMSEA.059 CFI.942 TLI.898) compared to when DHEA-s was loaded onto the HPA factor alone (girls: RMSEA.093, CFI.855 TLI.766, boys: RMSEA.086 CFI.866 TLI.784). However, closer inspection of models in which DHEA-s was cross-loaded onto the HPA and HPG factors revealed that DHEA-s did not load significantly onto the HPA factor.

Additional findings. Exploratory models allowing correlations between residual variances of cortisol and DHEA-s and between estradiol and progesterone (in girls only) displayed the best fit statistics. In girls, the best fitting model was a two-factor solution in which DHEA-s was loaded onto the HPG factor, and residual variances of cortisol and DHEA-s, and of estradiol and progesterone, were allowed to be correlated (RMSEA 0.042 CFI 0.975 TLI 0.952). In boys, the model with the best fit statistics in which all variables significantly loaded onto latent variables was a two-factor solution with estradiol removed in which DHEA-s was loaded onto the HPG factor, and residual variances of cortisol and DHEA-s were allowed to be correlated (RMSEA 0.032 CFI 0.989 TLI 0.976).

Summary. This pre-registered, complex analysis showed that for both girls and boys in our study, a two-factor structure of hormones of the HPA and HPG axes fit the data better than a one-factor structure

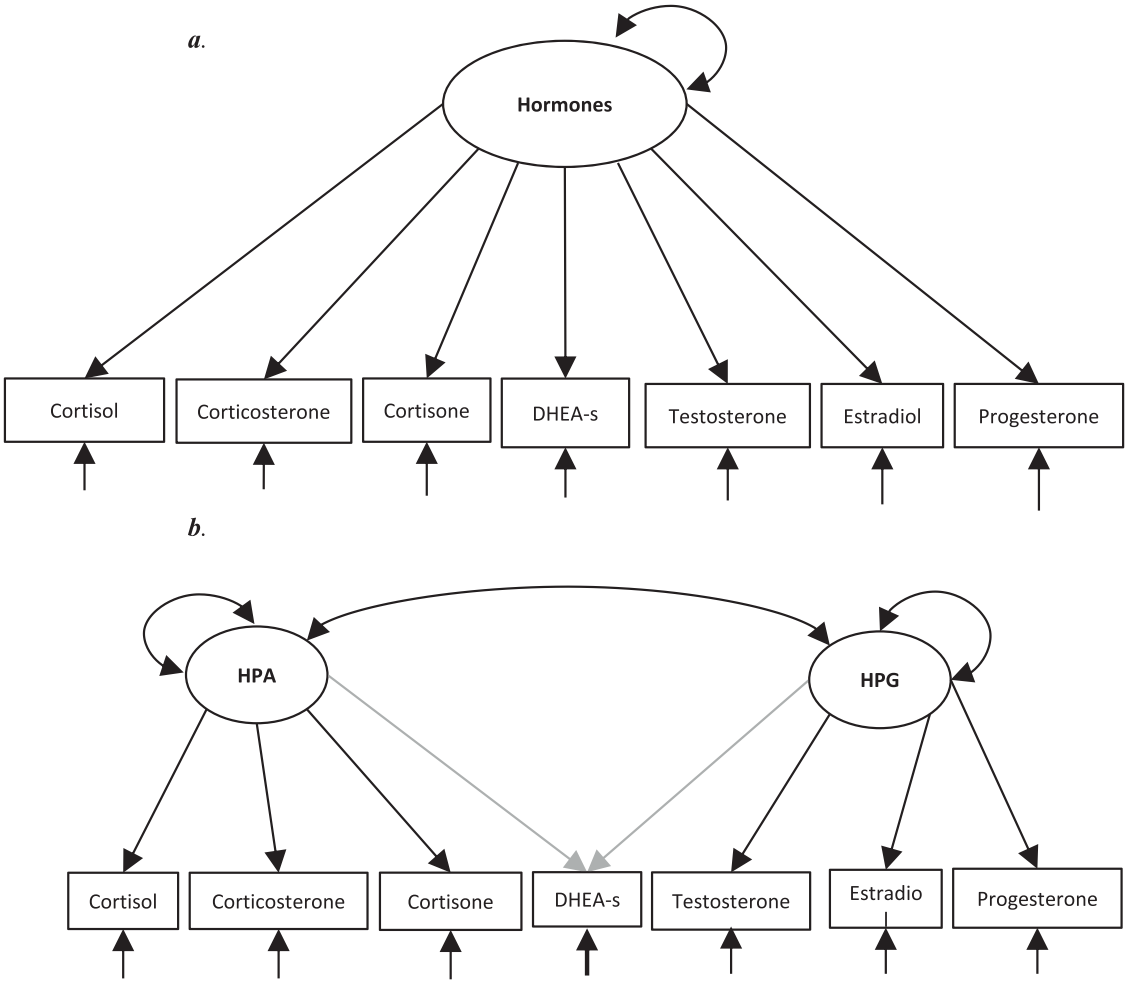

Fig. 1.1. Hypothesized path models. Path models comparing the fit of one (a) and two (b) factor models for the seven steroids of the HPA and HPG axis measured were compared. Latent variables are represented in circles. Arrows pointing from latent variables to observed variables (hormones) represent factor loadings of each steroid hormone. Arrows pointing up to hormones represent residual variances. Double headed arrows connecting latent variables represent correlation between latent variables. Recursive double headed arrows represent variance of latent variables, which was fixes at 1 in all cases. Models were considered to have improved fit when they contained lower Root Mean Square Error of Approximation (RMSEA), higher Comparative Fit Index (CFI), and higher Tucker Lewis Index (TLI). Gray lines linking DHEA-s to HPA and HPG factors in model b represent exploratory analyses examining fit of DHEA-s to the HPA factor, the HPG factor, and both factors, respectively. Two-factor model latent factors were allowed to covary.

(Table 1.1a and b, Figs. 1.2 and 1.3). Interestingly, the best fitting model in girls was a two-factor solution with DHEA-s loaded onto the HPG factor in which residual variances of both cortisol and DHEA-s and of estradiol and progesterone were allowed to be correlated (RMSEA 0.042 CFI 0.975 TLI 0.952). The best fitting model in boys was a two-factor solution with estradiol removed in which DHEA-s was loaded onto the HPG factor, and residual variances of cortisol and DHEA-s were allowed to be correlated (RMSEA 0.032 CFI 0.989 TLI 0.976). Factor scores (i.e. predicted values of the two axes) were extracted from the fitted models. Then, these values were used in Study 2, which linked these dual hormone axes to daily well-being using the Bayesian, machine-learning BART method.

6. Study 2 methods

To understand how our novel measure of hormone activity related to outcomes, we fit BART models predicting two focal, pre-registered dependent measures: 1) daily affect ratios and 2) daily stress coping by HPA and HPG activity (operationalized as daily deviations from mean HPA and HPG activity, person-level mean HPA and HPG activity, and between-person correlation between HPA and HPG activity, or coupling). These BART models furthermore accounted for the potentially confounding effects of variables that could be correlated with hormone levels and daily well-being outcomes: Body Mass Index (BMI), sleep quality and duration, race/ethnicity, or socioeconomic status (for information on covariate processing, see supplement). Each model accounted for all of these covariates (described below) by including a propensity score (described below), consistent with best practices in machine-learning approaches to causal inference (Hahn et al., 2020; Dorie et al., 2019; Cearns et al., 2019), which allowed us to examine main and interactive associations between the relevant variation in HPA and HPG axis hormones and the daily well-being outcomes. (Table 2.1).

6.1. Measures

Measures of hormone activity. Factor scores created by models from Study 1 were translated into analytic variables. These variables assessed within- and between-person variation in each axis' hormone activity, and include: the person-level mean (i.e. average of HPA over the 10 days, and the same for HPG), the day-level deviation from the mean (i.e. the difference between the day's value and the person-level mean for each day), and each person's amount of coupling between the two axes (i.e., for each person, how correlated their HPA and HPG values were

Table 1.1a
CFA Fit Statistics.

Females:								Factor loadings								Correlations		
Factors	*Sex*	*DHEAs*	*RMSEA*	*CFI*	*TLI*	*Residual covariances*	*Removed variables*	*Cortisol*	*Cortisone*	*Corticosterone*	*dheas (hpa/ 1F)*	*dheas (hpg)*	*Testosterone*	*Estradiol*	*Progesterone*	*HPA-HPG*	*csl-dhe*	*est-pro*
HPA HPG	F	HPG	0.058(0.051 0.065)	0.945	0.91	none	none	0.880***	0.908***	0.301***		0.584***	0.627***	0.141***	0.162***	0.471***		
HPA HPG	F	HPG	0.066(0.057 0.076)	0.947	0.902	none	ccs	0.867***	0.923***			0.577***	0.633***	0.144***	0.161***	0.469***		
HPA HPG	F	HPG	**0.042(0.034 0.050)**	**0.975**	**0.952**	csl-dhe, est-pro	none	0.822***	0.972***	0.279***		0.542***	0.678***	0.147***	0.136***	0.439***	0.174***	0.125***
HPA HPG	F	HPG	0.040(0.029 0.051)	0.986	0.964	csl-dhe, est-pro	ccs	0.790***	1.012***			0.538***	0.675***	0.150***	0.135***	0.427***	0.179***	0.125***
HPA HPG	F	Cross-loaded	0.061(0.054 0.069)	0.942	0.899	none	none	0.884***	0.905***	0.302***	0.064 NS	0.506***	0.683***	0.151***	0.154***	0.428***		
HPA HPG	F	Cross-loaded	0.073(0.064 0.083)	0.944	0.88	none	ccs	0.870***	0.919***		0.056 NS	0.510***	0.681***	0.151***	0.154***	0.433***		
HPA HPG	F	Cross-loaded	**0.047(0.039 0.055)**	**0.972**	0.942	csl-dhe, est-pro	none	0.823***	0.972***	0.279***	0.018 NS	0.519***	0.697***	0.149***	0.133***	0.427***	0.172***	0.125***
HPA HPG	F	Cross-loaded	**0.047(0.036 0.059)**	**0.984**	**0.951**	csl-dhe, est-pro	ccs	0.790***	1.012***		0.016 NS	0.518***	0.692***	0.151***	0.132***	0.416***	0.177***	0.125***
HPA HPG	F	HPA	0.093(0.086 0.100)	0.855	0.766	none	none	0.884***	0.903***	0.302***	0.292***		0.692***	0.178***	0.115**	0.439***		
HPA HPG	F	HPA	0.111(0.102 0.120)	0.852	0.723	none	ccs	0.878***	0.910***		0.290***		0.687***	0.179***	0.116**	0.444***		
HPA HPG	F	HPA	0.096(0.088 0.104)	0.871	0.753	csl-dhe, est-pro	none	0.829***	0.965***	0.282***	0.247***		0.720***	0.169***	0.087**	0.419***	0.129***	0.130***
HPA HPG	F	HPA	0.118(0.108 0.129)	0.875	0.688	csl-dhe, est-pro	ccs	0.794***	1.008***		0.229***		0.690***	0.177***	0.087**	0.421***	0.157***	0.130***
1 factor	F	NA	0.093(0.086 0.100)	0.845	0.768	none	none	0.882***	0.905***	0.302***	0.291***		0.309***	0.065**	0.042 NS			
1 factor	F	NA	0.108(0.100 0.117)	0.842	0.737	none	ccs	0.875***	0.912***		0.290***		0.309***	0.067***	0.042 NS			
1 factor	F	NA	0.095(0.087 0.102)	0.862	0.759	csl-dhe, est-pro	none	0.825***	0.969***	0.280***	0.246***		0.301***	0.076***	0.030 NS		0.131***	0.141***
1 factor	F	NA	0.113(0.104 0.123)	0.866	0.713	csl-dhe, est-pro	ccs	0.792***	1.009***		0.228***		0.289***	0.078***	0.024 NS		0.158***	0.141***

Table 1.1b
CFA Fit Statistics.

Males:								Factor loadings								Correlations		
Factors	*Sex*	*DHEAs*	*RMSEA*	*CFI*	*TLI*	*Residual covariances*	*Removed variables*	*Cortisol*	*Cortisone*	*Corticosterone*	*dheas (hpa/1F)*	*dheas (hpg)*	*Testosterone*	*Estradiol*	*Progesterone*	*HPA-HPG*	*csl-dhe*	*est-pro*
HPA HPG	M	HPG	0.056 (0.048 0.063)	0.944	0.91	none	none	0.914***	0.869***	0.239***		0.571***	0.691***	0.035 NS	0.148***	0.591***		
HPA HPG	M	HPG	0.066 (0.057 0.076)	0.943	0.894	none	ccs	0.907***	0.875***			0.568***	0.694***	0.036 NS	0.148***	0.592***		
HPA HPG	M	HPG	0.056 (0.047 0.065)	0.96	0.926	none	est	0.915***	0.867***	0.239***		0.573***	0.689***		0.146***	0.592***		
HPA HPG	M	HPG	**0.030 (0.021 0.038)**	**0.987**	**0.975**	csl-dhe, est-pro	none	0.861***	0.922***	0.225***		0.508***	0.776***	0.039 NS	0.124***	0.537***	0.237***	0.145***
HPA HPG	M	HPG	**0.032 (0.021 0.044)**	**0.99**	**0.975**	csl-dhe, est-pro	ccs	0.851***	0.933***			0.507***	0.775***	0.040 NS	0.125***	0.536***	0.235***	0.145***
HPA HPG	M	HPG	**0.032 (0.022 0.042)**	**0.989**	**0.976**	csl-dhe	est	0.862***	0.922***	0.225***		0.510***	0.775***		0.123***	0.538***	0.237***	
HPA HPG	M	Cross-loaded	0.059 (0.052 0.067)	0.942	0.898	none	none	0.911***	0.871***	0.238***	-1.787 NS	2.416 NS	0.469***	-0.002 NS	0.135**	0.876***		
HPA HPG	M	Cross-loaded	0.074 (0.064 0.085)	0.938	0.867	none	ccs	0.904***	0.878***		-1.788 NS	2.413 NS	0.471***	-0.001 NS	0.136**	0.877***		
HPA HPG	M	Cross-loaded	0.056 (0.047 0.067)	0.965	0.924	none	est	0.911***	0.872***	0.238***	-1.632 NS	2.259 NS	0.473***		0.136***	0.868***		
HPA HPG	M	Cross-loaded	**0.024 (0.015 0.033)**	**0.992**	**0.984**	csl-dhe, est-pro	none	0.863***	0.920***	0.225***	-1.751 NS	2.333 NS	0.485***	0.012 NS	0.135***	0.863***	999.000 NS	0.148***
HPA HPG	M	Cross-loaded	**0.023 (0.010 0.036)**	**0.996**	**0.987**	csl-dhe, est-pro	ccs	0.853***	0.930***		-1.651 NS	2.230 NS	0.487***	0.013 NS	0.136***	0.857***	999.000 NS	0.147***
HPA HPG	M	Cross-loaded	**0.020 (0.008 0.033)**	**0.996**	**0.99**	csl-dhe	est	0.863***	0.920***	0.225***	-1.835 NS	2.418 NS	0.483***		0.134***	0.867***	999.000 NS	
HPA HPG	M	HPA	0.086 (0.079 0.093)	0.866	0.784	none	none	0.909***	0.870***	0.237***	0.344***		0.556***	0.040 NS	0.136***	0.766***		
HPA HPG	M	HPA	0.102 (0.093 0.111)	0.866	0.75	none	ccs	0.906***	0.873***		0.344***		0.554***	0.040 NS	0.136***	0.771***		
HPA HPG	M	HPA	0.096 (0.087 0.105)	0.883	0.781	none	est	0.910***	0.869***	0.237***	0.344***		0.499***		0.126***	0.853***		
HPA HPG	M	HPA	0.088 (0.080 0.096)	0.882	0.774	csl-dhe, est-pro	none	0.860***	0.922***	0.222***	0.284***		0.540***	0.039 NS	0.128***	0.780***	0.170***	0.144***
HPA HPG	M	HPA	0.109 (0.098 0.120)	0.885	0.714	csl-dhe, est-pro	ccs	0.850***	0.934***		0.277***		0.540***	0.042 NS	0.128***	0.776***	0.181***	0.144***

(*continued on next page*)

Table 1.1b (*continued*)

Males:								Factor loadings								Correlations		
Factors	*Sex*	*DHEAs*	*RMSEA*	*CFI*	*TLI*	*Residual covariances*	*Removed variables*	*Cortisol*	*Cortisone*	*Corticosterone*	*dheas (hpa/1F)*	*dheas (hpg)*	*Testosterone*	*Estradiol*	*Progesterone*	*HPA-HPG*	*csl-dhe*	*est-pro*
HPA HPG	M	HPA	0.105 (0.095 0.115)	0.877	0.736	csl-dhe	est	0.862***	0.920***	0.223***	0.286***		0.509***		0.123***	0.828***	0.167***	
1 factor	M	NA	0.081 (0.074 0.089)	0.871	0.806	none	none	0.870***	0.909***	0.236***	0.344***		0.427***	0.015 NS	0.109***			
1 factor	M	NA	0.094 (0.086 0.103)	0.871	0.785	none	ccs	0.873***	0.906***		0.344***		0.428***	0.016 NS	0.110***			
1 factor	M	NA	0.091 (0.082 0.099)	0.883	0.805	none	est	0.869***	0.910***	0.237***	0.344***		0.426***		0.109***			
1 factor	M	NA	0.083 (0.075 0.091)	0.885	0.799	csl-dhe, est-pro	none	0.861***	0.921***	0.222***	0.285***		0.422***	0.024 NS	0.104***		0.168***	0.146***
1 factor	M	NA	0.100 (0.090 0.110)	0.888	0.761	csl-dhe, est-pro	ccs	0.851***	0.932***		0.279***		0.420***	0.026 NS	0.103***		0.179***	0.145***
1 factor	M	NA	0.098 (0.089 0.107)	0.878	0.771	csl-dhe	est	0.863***	0.920***	0.223***	0.286***		0.422***		0.104***		0.166***	

Table 1.4. *Female (a) and Male (b) CFA Fit statistics.* Tables a and b above contain fit statistics of one and two factor models of seven steroid hormones produced by the HPA and HPG axes. P value <0.001 = ***, p value <0.01 **, p value <0.05 *, p value > 0.05 = NS. Factors contained in each model are listed under "Factors" column, with 2-factor models containing HPA and HPG factors and 1-factor models listed as "1 factor". DHEAs column contains information on location of loading of DHEAs in a given model (HPA, HPG, or cross-loaded on both axes?). RMSEA (Root Mean Square Error of Approximation) values contain s.e. in parentheses. Comparative Fit Index = CFI, Tucker Lewis Index = TLI. Residual covariances column lists residual variances that were allowed to covary in a given model. Removed variables lists variables removed from a given model. Factor loadings of all hormones are listed under columns containing hormone names. Correlations of latent variables are listed under HPA-HPG column. Residual covariances listed under csl-dhe and est-pro columns.

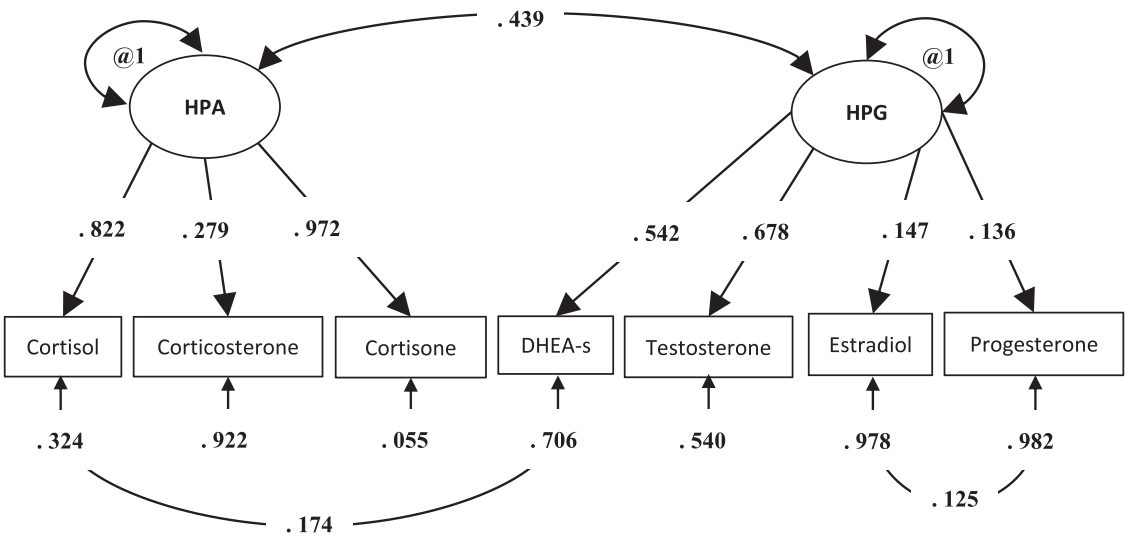

Fig. 1.2. Final Path Model of Two-Factor Hormone Structure in Females. The final path model of female hormones can be viewed above. Factor loadings were standardized and are presented along arrows pointing down from latent HPA and HPG variables. Residual variances are presented below boxes with hormone names. All hormones were retained in the final model, and error terms of cortisol and DHEA-s and of estradiol and progesterone were allowed to be correlated. Cortisol, cortisone, DHEA-s, and testosterone showed the strongest loadings onto HPA and HPG latent variables, while corticosterone, estradiol, and progesterone showed the weakest loadings. Latent variables were positively correlated, in line with the hormone coupling hypothesis.

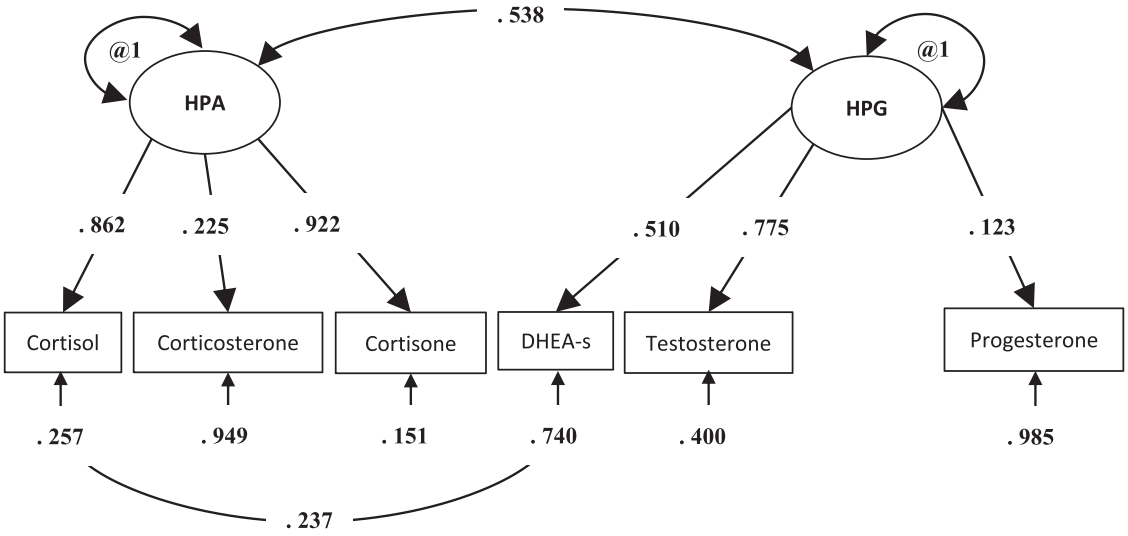

Fig. 1.3. Final Path Model of Two-Factor Hormone Structure in Males. The final path model of male hormones can be viewed above. Factor loadings were standardized and are presented along arrows pointing down from latent HPA and HPG variables. Residual variances are presented below boxes with hormone names. Estradiol was removed from the final model fit, due to a non-significant loading in all model iterations. Additionally, error terms of cortisol and DHEA-s were allowed to be correlated. Like in females, cortisol, cortisone, DHEA-s, and testosterone showed the strongest loadings onto HPA and HPG latent variables, while corticosterone and progesterone showed the weakest loadings. Latent variables were positively correlated (0.538), in line with the hormone coupling hypothesis.

over the 10 days). Thus, the model could examine the differential predictive effects of adolescents' overall hormone levels, their daily fluctuations from their means, and their overall tendency to have coupled HPA and HPG hormones.

Hormone propensity score. To account for potentially confounding effects of Body Mass Index (BMI), sleep quality and duration, race/ethnicity, and socioeconomic status, random forest models were run and included as covariate predictors in the final BART model.

Affect Ratio. Latent variables representing measures of daily affect ratio were calculated using measures collected from participants asking about the extent to which respondents endorsed a list of feelings ("RIGHT NOW how much are you feeling…"). Participants were asked to rate on a 5-point Likert scale the extent to which they felt each one of 10 feelings. Feelings were grouped into *positive* (happy[M: 3.14, SD: 1.31], grateful[M: 2.89, SD: 1.45], thrilled[M: 1.98, SD: 1.27], enthusiastic[M: 2.25, SD: 1.34], optimistic[M: 2.51, SD: 1.36]) and *negative* (sad[M: 1.56, SD: 0.98], angry[M: 1.44, SD: 0.89], lonely[M: 1.58, SD: 1.02], dumb[M: 1.54, SD: 0.99], anxious[M: 2.16, SD: 1.28]) variables, which were allowed to covary. Factor scores were created from latent variable models for each person for each day. Affect ratios were calculated by dividing factor scores of daily positive emotions by factor scores of daily negative emotions to create a daily variable of affect ratio.

Table 2.1
A C plots. HPG Activity Predicts Affect Ratio at High and Low HPA Activity B D plots. HPG Activity Predicts Coping at High and Low HPA Activity.

Girls				Boys				Girls				Boys			
Group Means: Affect Ratio				Group Means: Affect Ratio				Group Means: Coping				Group Means: Coping			
Plot A		Quantiles		Plot A		Quantiles		Plot B		Quantiles		Plot B		Quantiles	
HPA	HPG	Median	10th	90th	HPA	HPG	Median	10th	90th	HPA	HPG	Median	10th	90th	HPA	HPG	Median	10th	90th
high	high	1.0563	[1.0379	1.0719]	high	high	1.0466	[1.0317	1.0620]	high	high	-0.0161	-[0.0751	0.0363]	high	high	0.0885	[0.0355	0.1447]
	low	1.0005	[0.9816	1.0170]		low	1.0163	[1.0011	1.0306]		low	-0.1298	-[0.1943	-0.0760]		low	0.0201	-[0.0339	0.0697]
low	high	1.0466	[1.0279	1.0635]	low	high	1.0410	[1.0256	1.0556]	low	high	-0.0065	-[0.0677	0.0465]	low	high	0.0801	[0.0269	0.1323]
	low	1.0006	[0.9823	1.0168]		low	1.0224	[1.0077	1.0362]		low	-0.1301	-[0.1928	-0.0775]		low	-0.0295	-[0.0867	0.0202]
Simple Slopes				Simple Slopes				Simple Slopes				Simple Slopes			
Plot C		Quantiles		Plot C		Quantiles		Plot D		Quantiles		Plot D		Quantiles	
HPA		Median	10th	90th	HPA		Median	10th	90th	HPA		Median	10th	90th	HPA		Median	10th	90th
high		0.0556	[0.0453	0.0656]	high		0.0307	[0.0216	0.0394]	high		0.1146	[0.0838	0.1465]	high		0.0690	[0.0321	0.1085]
low		0.0458	[0.0369	0.0549]	low		0.0185	[0.0096	0.0273]	low		0.1240	[0.0922	0.1558]	low		0.1115	[0.0727	0.1519]

Notes. Table 2.1 summarizes results of BART analyses by providing median, 10th and 90th quantile values of boxplots depicted in Fig. 2.5. Analyses relate latent HPA and HPG hormone models to daily affect ratios (left side columns) and stress coping (right side columns) in boys and girls. Lack of overlap of quantile ranges between high and low HPG activity at high HPA activity (plot A in girls, 90th quantile of high HPA, low HPG activity group = 1.0170, while 10th quantile of high HPA, high HPG activity group = 1.0379) suggests that changes in HPG activity are related to significant differences in affect ratios. Similar significant differences were observed in all A and B plots except B plot in boys predicting stress coping, where slight overlap between boxes was observed. As BART analyses do not use p values to determine specific cut points of significance, likely group differences are determined by examining differences between inter-quartile ranges in Fig. 2.5, and more stringent group differences are determined by examining 10th to 90th quantile ranges here.

Supplemental analyses were conducted to explore links between hormone variables and positive and negative affect scores separately. As the direction of findings was the same as those observed with affect ratios, the simpler unified affect ratio was retained in the main text.

On an exploratory basis, a separate model was created in which affect ratios were calculated according to methods described in Fredrickson & Losada's original 2005 paper on the positivity ratio. Likert scales ranging from 1 to 5 of daily positive and negative emotions were examined. Positive emotions greater than or equal to 3 and negative emotions greater than or equal to 2 were kept and used to create daily scores of positive and negative emotions. Positive emotion scores were then divided by negative emotion scores. BART models were run and results, presented in the supplemental section, showed the same patterns as results obtained using factor scores. Therefore, results using factor score models, which are more statistically defensible, will be presented in the main body of this text.

Stress Coping. Latent variables representing measures of daily stress responses were calculated using measures collected from participants to assess stress responding to daily negative life events. Participants reported up to two negative life events each day of data collection ("please write about one NEGATIVE thing that happened today or that you thought a lot about today"). Participants were then asked to rate, on a 1–7 Likert scale (1 = strongly disagree, 7 = strongly agree) how much they agreed with a series of statements assessing their reactions to the daily negative events they wrote about. Stress responses were grouped into *positive coping* responses ("I felt like I could handle the negative things that happened to me today"[M: 5.15, SD: 1.52], and "Today, I felt confident that I could handle the stresses that I experienced"[M: 5.15, SD: 1.42], "Overall, how good or bad did you feel about yourself today?"[M: 5.1, SD: 1.56]) and *negative coping* responses ("I felt overwhelmed by the negative things that happened to me today"[M: 3.28, SD: 1.82], "I can't stop thinking about the negative things that happened to me"[M: 3.33, SD: 1.82], "The negative things that happened to me will probably never get better"[M: 2.63, SD: 1.57]).

Latent variable models of adaptive and poor stress coping (Figs. 2.1 and 2.2), which were allowed to covary, were created based on correlation matrices of stress coping items (supplement), and daily factor scores were saved and used to calculate an overall measure of stress coping ranging from adaptive to poor.

6.2. Analysis

Latent variable models of outcomes. Latent variables models of daily stress coping and affect were produced with Mplus version 8 (Múthen and Múthen, 2017). Data were kept separated by sex (models were run for boys and girls separately) in order to allow for detection of sex differences across multiple variables (Zucker et al., 2022). Robust Maximum Likelihood estimation (MLR) was used and missing values were estimated with Full Information Maximum Likelihood (FIML) estimation in order to produce low bias in model estimates (Kline, 2015). Models were clustered by participant ID to account for the multi-level structure of the data. For path models of variables, see Figs. 2.1 and 2.2. Correlation matrices of daily stress coping and affect measures (see supplement) suggested strong correlations between specific variables (positive emotions: feeling thrilled, feeling enthusiastic, and feeling optimistic, and negative stress coping: feeling overwhelmed and not feeling able to stop thinking about a negative event), therefore, residual variances for those variables were allowed to be correlated. Fit statistics were used to assess fit of models to the covariance matrix of the data. Factor scores were saved for the models of stress coping and positive and negative affect (Study 2).

Bayesian Additive Regression Trees (BART). A combined measure of stress coping, and measure of affect ratio as described above were used as outcomes in BART models in which the hormone values (person-level means, daily deviations, and coupling, along with the hormone propensity score) were the predictors. We fit a multi-level BART model,

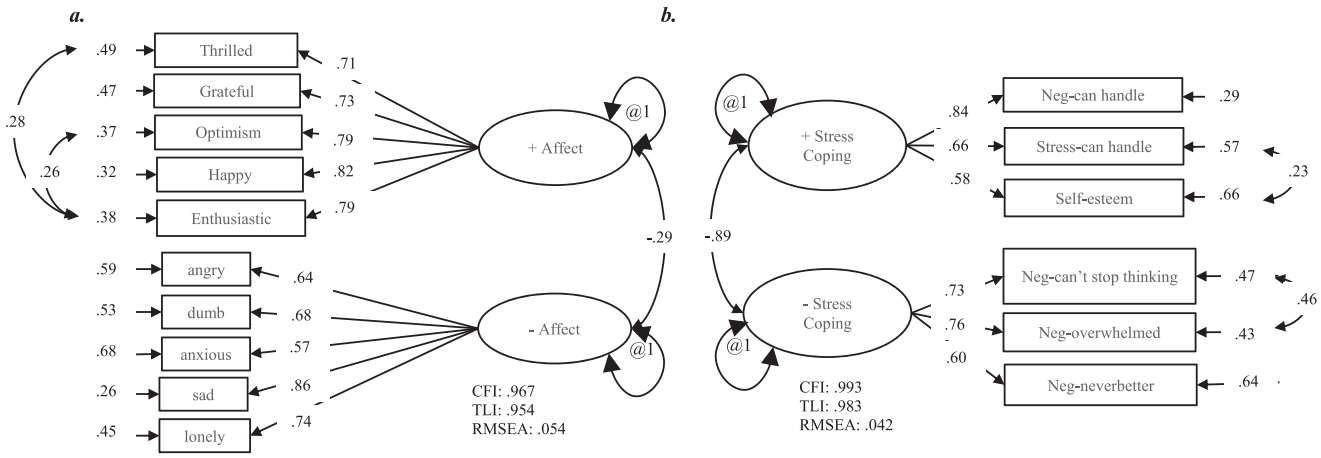

Fig. 2.1. Path models describing positive and negative affect (a) and stress coping (b) latent variables in females. Positive and negative affect and positive and negative stress coping in females were measured daily for the 10 days of daily diary collection. Latent variables were clustered by ID and created to represent underlying constructs of positive and negative affect and positive and negative stress coping.

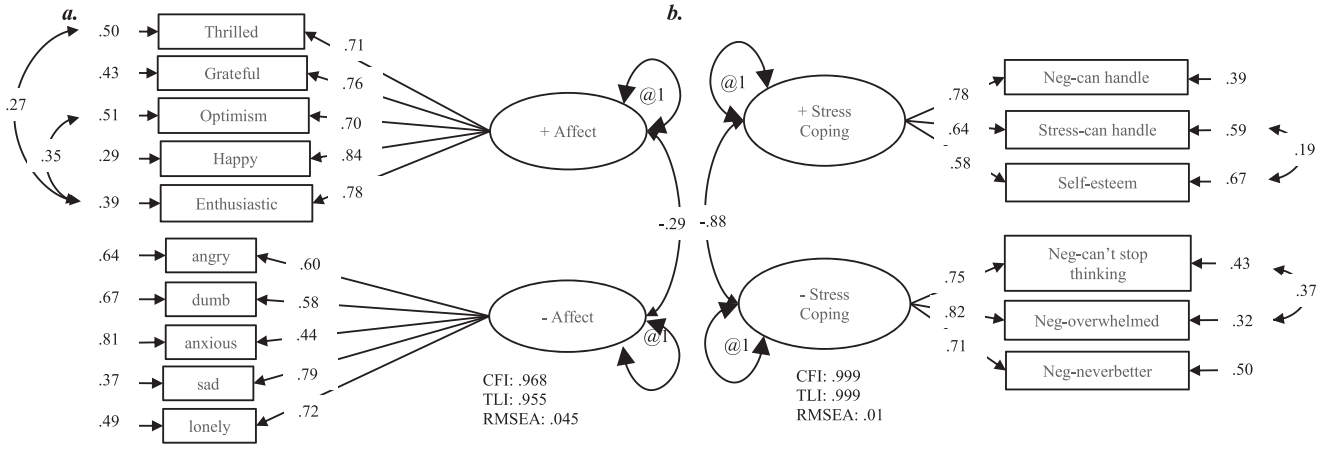

Fig. 2.2. Path models describing positive and negative affect (a) and stress coping (b) latent variables in males. Positive and negative affect and positive and negative stress coping in males were measured daily for the 10 days of daily diary collection. Latent variables were clustered by ID and created to represent underlying constructs of positive and negative affect and positive and negative stress coping.

with observations nested within individuals, and a random effect for individual, thereby allowing for partial pooling and adjusting uncertainty intervals for the nested structure of the data.

The Bayesian analysis approach used here has the potential to address the limitations of conventional analyses and therefore resolve controversies about the many mixed findings in the literature concerning the links between hormones, and affective outcomes. The conventional regression-based approach, which involves fitting and refitting many regression models to find complex interactions with many possible functional forms, is flawed (Green and Kern, 2012; Gelman, 2015). Even with strong pre-registration, it could lead to false positive results due to over-fitting the data, and false negatives due to under-searching the model specification space. Instead, BART models natively correct for multiple comparisons by building uncertainty into the model's posterior distribution, rendering the typical post-hoc p-value adjustment unnecessary (Green and Kern, 2012).

Here we use a pre-registered BART analysis to analyze this large and comprehensive dataset, and therefore prevent both the false positive and false negatives that might be prominent in the literature. The BART machine-learning algorithm is known to reduce false positives because the regression tree algorithm allows models which contain many predictors and moderators to be statistically penalized by conservative prior distributions that avoid over-fitting the data. Meanwhile, the regression tree algorithm also reduces false negatives by allowing for complex, non-linear interactions that might be missed by a conventional regression model that would have focused only on typical polynomial functional forms (e.g. squared or cubic). Notably, the final model is a weighted sum of the potential models, weighted by their fit to the data, unlike the conventional approach that assumes there is only one optimal regression model fit.

In addition, by using a Bayesian rather than a classical approach to hypothesis testing, we can reduce false positives and negatives even further. In the Bayesian approach we use the data in a disciplined way: to move from the prior distribution to the posterior distribution by estimating the likelihood function. The results are summarized by inspecting draws from the posterior distribution of the model fit. Plotting the posterior distribution of the regression coefficients, even when doing so many different ways, does not change the posterior distribution; further, the possibility that statistical noise is driving the results has already been accounted for with the conservative algorithm by widening the posterior distribution in spaces where there is less certainty. This is in contrast with the classical approach, in which the data are used many times, and each time the model is re-fit, with variables centered at different points to estimate different simple effects and test different specifications of predictors, covariates, and moderators. The classical approach is a problem because the analyst is using the data to inform

additional model fits. With each model fit in the conventional analysis, the analyst would be changing the standard errors and probabilities in the hypothesis tests in a way that is not authentic to their actual prior knowledge, invalidating p-values (McShane et al., 2019). In summary, with the Bayesian approach, the analyst can inspect many different regression coefficients—dozens or hundreds, and their interactions with many factors—without worrying about the concerns with multiple hypothesis that loom large in conventional regression analysis, because the model is fit only once, without knowledge of results.

Bayesian model parameters were set according to recommendations in the literature (Woody et al., 2020a, 2020b, 2021; Hill et al., 2020; Carvalho et al., 2019). Models were set to create 200 trees with 200 cuts for each run. Each model fit began by running 10,000 draws, called burn-in draws, prior to beginning to keep information from draws. Subsequent to the burn-in period, models were set to run 8000 draws, of which one of every 4 draws was kept to create the final posterior distribution. This was done in order to protect against autocorrelation in the residuals that might occur when keeping consecutive iterations of a Monte Carlo Markov Chain. Additive summary plots depicting relationships between model predictors and the posterior distributions of sample draws were inspected, and trends in these summary plots were used to create plots depicting average effects of our predictors of interest on our outcomes of interest. Visual inspection of additive summary plots for this analysis suggested that a median split of main predictors and moderators would allow for appropriate inspection of main and moderation effects of model variables on outcomes. Again, dichotomizing continuous variables is a statistically kosher to simplify the results for interpretation because the Bayesian model uses the entire continuous variable when fitting the model, and dichotomizing during summarization does not change the underlying posterior distributions.

How to interpret BART results. Results of BART analyses are summarized using both additive summary plots and subgroup plots. Additive summary plots describe how a given outcome variable (affect ratio or stress coping) differs over the distribution of a given predictor variable while holding other predictors constant. Each additive summary figure contains plots of every predictor in the model, and contains a variable controlling for possible hormone confounds (in our models, control variables are called 'hpahat' and 'hpghat').

Subgroup plots allow us to examine variability in the predicted distributions of affect and coping outcomes for different groupings of variables. BART analysis provides a probability distribution of the full predicted surface of a dependent variable from all independent variables and moderators. Therefore, we are able to examine direct (average) and interactive (conditional) effects of variables by looking at the distribution of expected outcomes for different groups of predictor variables. In particular, we were interested in examining how HPA and HPG activity predicted affect ratios and stress coping.

A and B plots in Fig. 2.5 display probability distributions of predicted outcome measures under differing variable conditions in girls and boys. For example, the subgroup low HPG activity, low HPA activity in girls is represented in the leftmost box in Fig. 2.5 plot A. All A and B plots can be thought of as depicting the average outcomes (of affect ratios or stress coping) associated with different subgroups of predictors. We will call these plots 'group mean' plots. C and D plots can be thought of as displaying probability distributions of simple slopes of HPG activity under differing HPA conditions (such as low HPA activity in girls. This group is

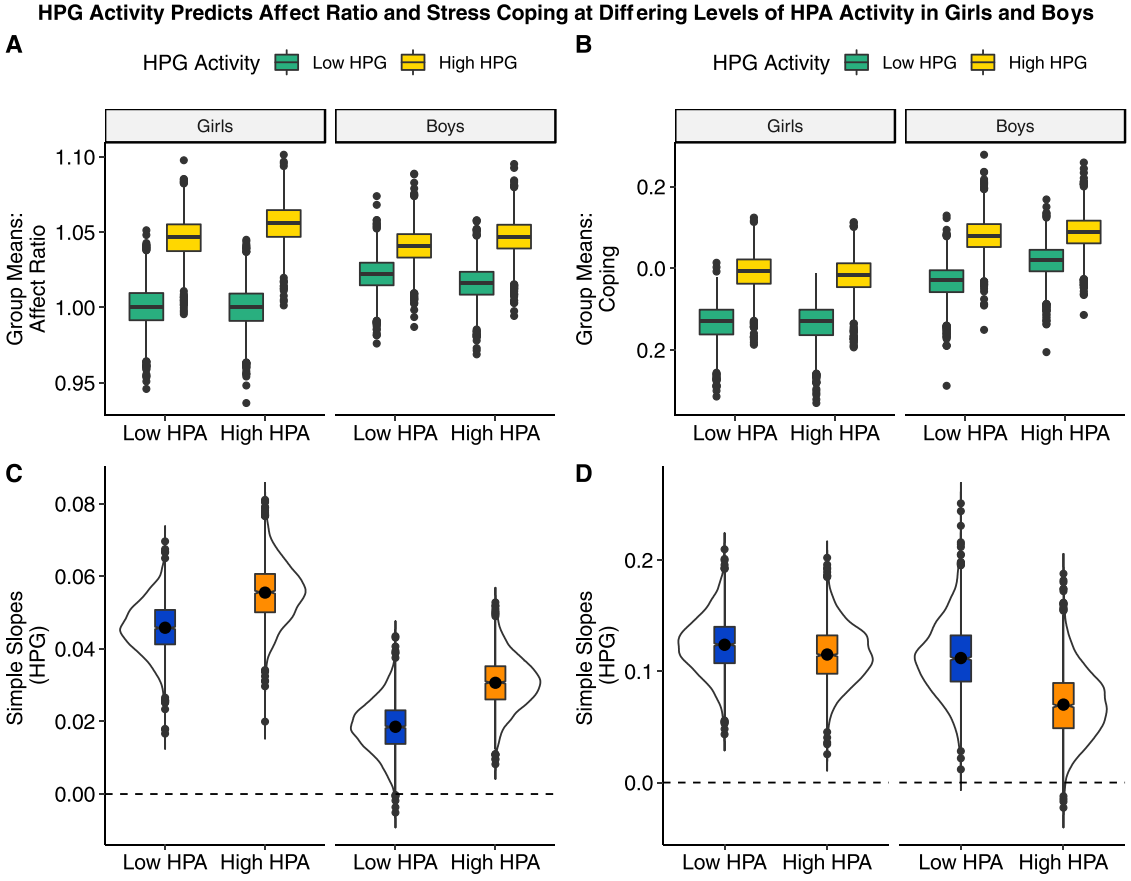

Fig. 2.5. High HPG activity confers protective effects for affect ratio and stress coping in girls and boys. Plots exploring the effect of HPG activity on affect ratios (left) and stress coping (right) suggest a general protective effect of high HPG activity (yellow boxes in A and B plots). Additionally, HPA activity appeared to moderate the slope of HPG activity predicting affect ratio, such that high HPA activity was associated with *more* positive HPG slopes than low HPA activity in girls and boys (plot C). HPA activity also appeared to moderate the slope of HPG activity predicting stress coping, but in boys only, such that high HPA activity was associated with *less* positive HPG slopes than low HPA activity (plot D boys only).

represented in the leftmost box in Fig. 2.5 plot C). In other words, all C and D plots display the effect of HPG activity under different HPA conditions in girls and boys. We will call these plots 'simple slope' plots.

It should be noted that the 'effects' we will discuss should be considered non-directional. In this analysis, while we are able to examine associations between variables, the method of data collection for this study, in which we collected salivary hormone samples once per day for repeated days, precludes us from making directional claims. When we use the term 'effect' here, we are instead referring to the difference in the probability distribution of an outcome for 'low' vs. 'high' levels of subgroups of dichotomized predictors. Unlike traditional boxplots, boxplots presented here display draws from a posterior, and should therefore be considered to differ significantly from one another when there is no overlap in interquartile range (IQR). Finally, before presenting the results, please note that y axes on all plots were allowed to vary. We allowed y axes to vary for each plot in order to be able to see IQR ranges clearly for each plot.

7. Results

Summary of Results. Overall, the results of study 2 were consistent with the *coupling* hypothesis when linking hormones to adolescent affect, and were consistent with the *competitive* view when linking hormones to stress coping. Specifically, we observed that HPG activity was broadly associated with higher affect ratios and more adaptive stress coping in girls and boys. That is, the hormones typically associated with greater gonadal maturation were generally protective against mental health problems, consistent with popular asset-based theories of puberty (Dahl and Hariri, 2005). In addition, we observed a positive relationship between HPG activity and affect ratios that increased in slope when HPA activity was high, especially in boys. While we also observed a positive relationship between HPG activity and stress coping, this slope did not increase when HPA activity was high, and in fact tended to become less positive in boys with high HPA activity. In summary, our results show that HPG system activity appears to confer a positive effect on daily affect ratios and stress coping in adolescent girls and boys. In line with the coupling hypothesis, this positive effect on affect ratios is greater when HPA activation is also high. Conversely, in line with the competitive view of hormones, this positive effect on stress coping is significantly buffered (but still positive) when HPA activation is also high in boys. In the remainder of the results section, we will walk through a detailed review of the findings in Figs. 2.3, 2.4, and 2.5.

Additive Summary Plots. Summary plots presented here (Figs. 2.3 and 2.4) show results of analyses predicting affect ratios on the y axis. Plots showing stress coping can be found in the supplement, as patterns were similar across outcomes. In girls (Fig. 2.3), person-level HPA system activity ('HPA_mean') was, broadly, *negatively* associated with affect ratio and stress coping. In other words, in our sample, higher mean HPA activity was associated with lower affect ratios and poorer stress coping. Conversely, person-level HPG system activity in girls was *positively* associated with these same outcomes, such that higher mean HPG activity was associated with higher affect ratios and adaptive stress coping. In boys (Fig. 2.4), medium levels of mean HPA activity were associated with higher affect ratios and more adaptive stress coping (very high and very low mean HPA activity was also associated with higher affect ratios and adaptive stress coping, though these portions of the distribution represented a small portion of participants and should be handled with caution). Low and medium HPG activity in boys, like mean HPG activity in girls, showed a positive association with outcomes. However, unlike in girls, high mean HPG activity in boys displayed a negative association

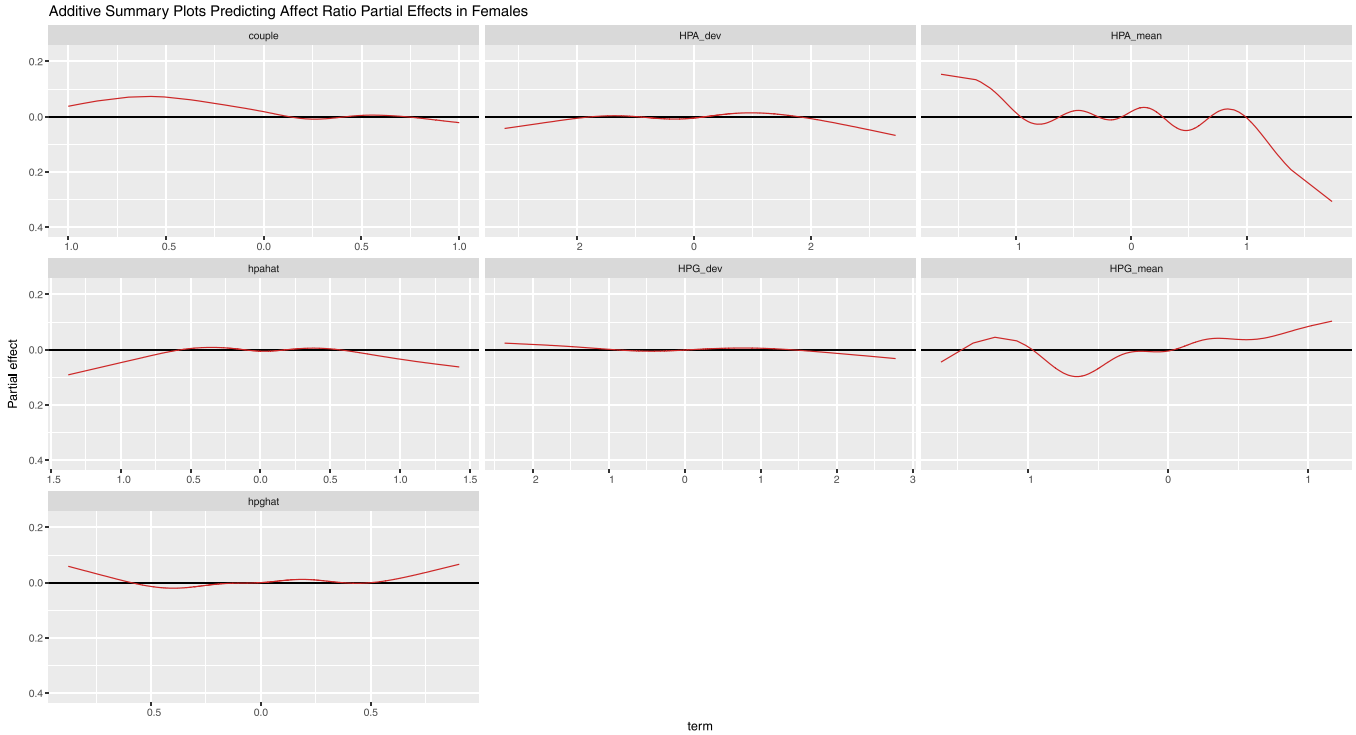

Fig. 2.3. Additive Summary Plots Predict Affect Ratio in Females. Additive summary plots show BART posterior summarization of affect ratio (on the y axis) for each predictor while controlling for all other predictors in females. Rug plots on all x axes show presence and absence of data along the distribution of x. Positive links between mean HPG axis activity (HPG_mean) and affect ratio were observed, such that as HPG axis activity went up, affect ratios became more positive. Conversely, negative links between mean HPA axis activity (HPA_mean) and affect ratio were observed. HPA_dev and HPG_dev plots describe how daily deviations from mean values predict affect ratio. Nearly flat lines demonstrate no strong impact of daily deviations from mean HPA or HPG values. HPAhat and HPGhat values describe impacts of hormone confounds on positive and negative affect, describing variability removed from final estimates. Finally, possible links between coupling of HPA and HPG values and affect ratio is described in plot labeled 'couple.' Distribution of extend of coupling was uneven, with most values closer to 1 on the x axis. Where data was present, coupling did not appear to be related to affect ratio.

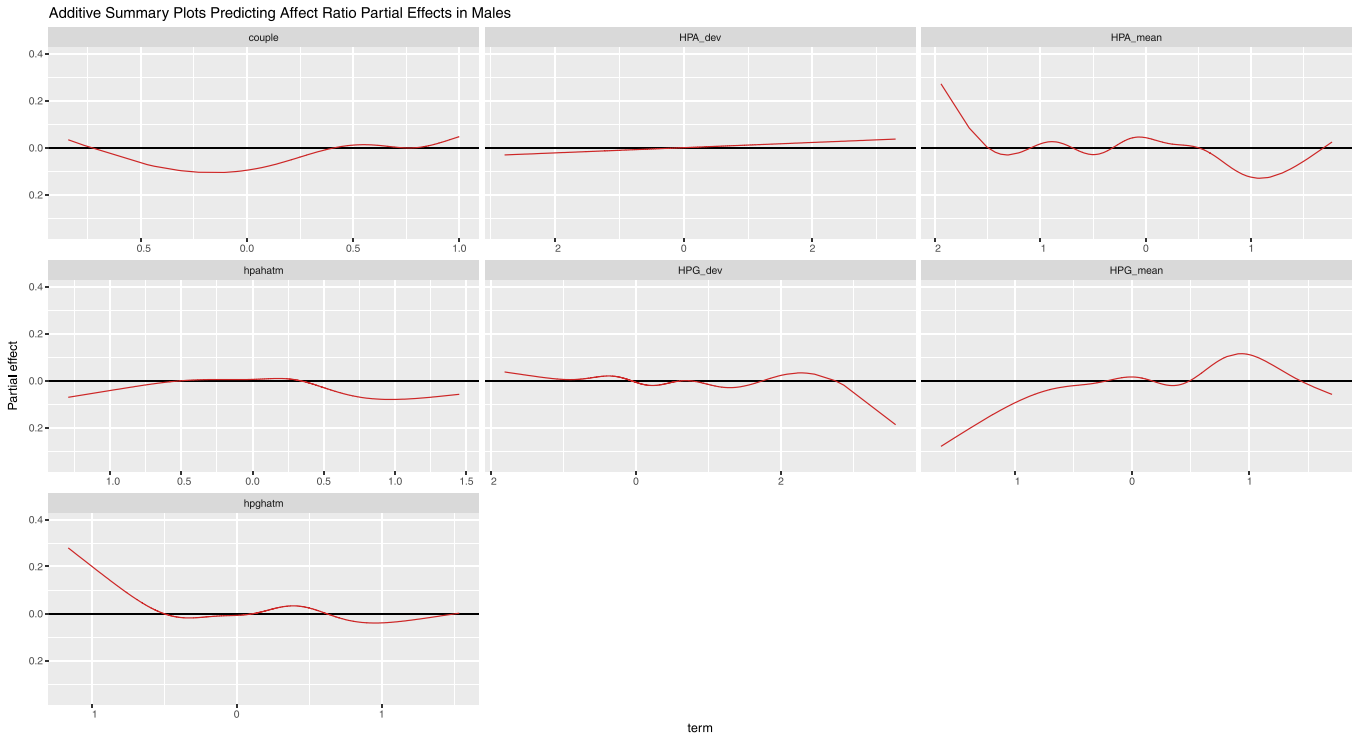

Fig. 2.4. Additive Summary Plots Predict Affect Ratio in Males. Additive summary plots show BART posterior summarization of affect ratio (on the y axis) for each predictor while controlling for all other predictors in males. Rug plots on all x axes show presence and absence of data along the distribution of x. Positive links between mean HPG axis activity (HPG_mean) and affect ratio were observed, such that as HPG axis activity went up, affect ratios became more positive. Conversely, negative links between mean HPA axis activity (HPA_mean) and affect ratio were observed, though negative trend was less prominent in male plots than female plots. HPA_dev and HPG_dev plots describe how daily deviations from mean values predict affect ratio. Nearly flat lines demonstrate no strong impact of daily deviations from mean HPA or HPG values. HPAhat and HPGhat values describe impacts of hormone confounds on positive and negative affect, describing variability removed from final estimates. Finally, possible links between coupling of HPA and HPG values and affect ratio is described in plot labeled 'couple.' Distribution of extend of coupling was uneven, with most values closer to 1 on the x axis. Where data was present, increased coupling appeared to be marginally related to increases in affect ratio, though this relationship was mostly flat.

with both affect ratios and stress coping (again, this portion of the distribution represented a small portion of participants and so should be handled with caution).

Group Mean Plots. Group mean plots (A and B plots) showed a broad protective effect of HPG activity on outcomes, such that high HPG activity (yellow boxes in all A and B plots) was associated with higher affect ratios and more adaptive stress coping (higher y axis values) than low HPG activity (green boxes).

Simple Slope Plots. Simple slope plots examining affect ratios and stress coping (C and D plots) showed that HPG activity evinced a *positive* relationship with outcomes under all conditions (all C and D plot boxplots were *above* the dotted horizontal line). This effect was somewhat moderated by HPA activity in models predicting affect ratios (plot C) such that high HPA activity was associated with more positive HPG slopes than low HPA activity in girls and boys. In models predicting stress coping (plot D), a positive relationship between HPG activity and outcomes was also observed in all cases. This effect was also slightly moderated by HPA activity, but in the opposite direction as models predicting affect ratio and only in boys, so that in boys with high HPA activity, HPG slopes were *less* positive (but still positive) than in boys with low HPA activity.

8. Discussion

The analyses in this manuscript suggest three main take home messages. First, we saw that *HPA and HPG hormones belong to two, separate, positively correlated latent variables*. We also saw that *HPG activity appears to confer protective effects on daily affect and stress coping*. Finally, we observed that HPA activity appears to *enhance* HPG's protective effect on affect ratios, and to *suppress* HPG's protective effect on stress coping. This manuscript sought to establish and test a novel model of adolescent hormones, and to explore whether and how hormonal system activity is linked to daily adolescent experiences. Given the robustness of the findings, this work can be taken as a kind of descriptive benchmark that can be the basis of future theorizing. Furthermore, these results definitively show that adolescent hormones *are* linked to the precursors to internalizing psychopathology in real-life, naturalistic settings. This is the strongest evidence that we know of in support of the conclusion that models of the etiology of internalizing disorders are incomplete if they do not account for levels of pubertal hormones in the HPA and HPG axes, and their coupling.

Results of study 1 support a cooperative view of adolescent hormone systems, showing that in both boys and girls, HPA and HPG hormones were best modeled in two separate, *positively* correlated, latent factors. These findings align with past hormone coupling research (Shirtcliff et al., 2015; Black et al., 2018; Ruttle et al., 2015; Marceau et al., 2014). Additionally, we observed that DHEA-s fit best when modeled as a part of the HPG axis. Importantly, this study reveals a rather striking discrepancy between hormone research with adults and naturalistic hormone research with adolescents.

The presence of hormone coupling in our adolescent data is not novel, per se. By expanding the number of hormones representing HPA and HPG systems, however, our novel hormone model may allow for a broader exploration of the variables that moderate hormone system activity and coupling across each of the contexts reviewed above. Systematic comparisons between coupling of single hormone pairs and of broader hormone systems may provide a new lens through which to examine how coupling progresses during adolescence and what factors

impact coupling at both specific (single hormone pair) and broad (latent variable pair) levels. Additionally, by expanding our focus to a system-level exploration of hormonal patterns, we were able to clarify that DHEA-s is best modeled as a part of the HPG axis. It is important to note here that, given our study design, we were only able to focus on modeling basal hormone levels, and were unable to assess questions of hormone reactivity. These questions are an important future direction for this work, and may prove particularly interesting as a test of the fidelity of DHEA-s to the HPG axis under differing circumstances, such as those involving exposure to a stressor. Given, for instance, the affinity of DHEA-s for HPG hormone receptors (Webb et al., 2006), it may be the case that social stressors, which are highly salient to teens and have been shown to produce upregulation in cortisol and DHEA-s (Mazurka et al., 2018; Shirtcliff et al., 2007), are linked to a latent variable hormone model in which DHEA-s maps more strongly onto the HPA axis or loads equally onto the HPG and HPA axes.

In Study 2, we examined links between our novel models of HPA and HPG activity and meaningful, daily adolescent outcomes and saw evidence of both *cooperative* and *competitive* hormone relationships predicting outcomes. We saw a broadly protective effect of HPG activity that persisted across girls and boys at high and low levels of HPA activity. For affect ratio only, the protective effects of HPG hormones were greater when HPA activity was also high, for both boys and girls. Conversely, for stress coping, the protective effects of HPG hormones were slightly buffered when HPA activity was also high, but only in boys. These findings come from the most comprehensive such analysis to date, using advanced analytic methods (BART), a careful, sequential preregistration, and a large and diverse sample.

We note that our observed *protective* effect of high HPG system activity on daily stress responses and affect in boys and girls stands is in contrast with both the colloquial stereotypes associated with HPG hormones and with portions of the adolescent HPG hormone literature, which when not specifically examining testosterone and estradiol in relation to pubertal development, has tended to examine how HPG hormones are related to externalizing symptoms and risk-taking behaviors that increase during puberty (Duke et al., 2014; Tackett et al., 2014). This work has often suffered from relatively small numbers of observations and statistical methods that risk false conclusions. This literature has also focused on the positive association between estradiol and mood disorders in girls (Balzer et al., 2015), though a more recent finding suggests that *deficiency* of testosterone and estradiol is associated with depressive states (Bashkatov and Garipova, 2022). Conversely, much of the stress literature in adolescents has focused on HPA hormone activity, showing that high baseline levels of hormones such as cortisol, and specific patterns of cortisol responses to stressors, may be associated with negative mental health outcomes. While our study confirmed this basic effect, our work suggests an important nuance in showing the role of HPG hormones as protective barriers against daily negative affect and poor stress coping. This is in line with research suggesting that, while storm and stress may very well occur in some cases, and may even be a *part* of the teenage experience for many, for the majority of teens, much of adolescence is a time of approach-oriented growth and learning (Dahl et al., 2018).

Our findings are particularly interesting in light of the method of collection of salivary hormones for this study. By collecting hormones in the field in a diverse sample of adolescents starting high school, and measuring high schoolers own self-reports of their daily experiences and responses to those experiences, we were able to examine how hormones relate to naturalistic rhythms of daily high school life. While it is true that field studies present myriad challenges, these findings show some of the benefits of meeting those challenges for studies seeking to capture patterns in adolescent development and wellbeing.

Summary and limitations. There are a few noteworthy limitations to this study. First, in our CFA analyses, it was interesting to observe that estradiol did not load significantly onto the HPG latent variable in boys. This lack of a significant loading in estradiol on the HPG latent variable was not unexpected, as estradiol was measured using Chemiluminescent Immunoassay whereas all other hormones included in this analysis were measured using Liquid Chromatography Dual Mass Spectrometry (LC-MS/MS). Estradiol was measured using a different method to avoid issues related to the intensive sample preparation and errors introduced by derivatization that can occur when estradiol is measured with LC-MS/MS (note that these methods have advanced significantly since our samples were quantified in 2018). Despite the expected low loading of estradiol, the nonsignificant loading we observed in boys, and our decision to remove estradiol from the final model of steroid hormones in boys, may have impacted the predictive validity of HPG axis measures in ways we were unable to assess in this study. Additionally, the low loading we observed in girls (0.147) was also likely due to the use of CLIA for estradiol (rather than LC-MS/MS), and may have led to an underestimation of the true loading of estradiol on the HPG system latent variable.

We also had a large amount of missing corticosterone values across our samples (almost 77%) in boys and girls, and a far smaller, but still significant, amount of missing progesterone data (16.7%). Corticosterone values in human saliva are often too low to be detectable (Saracino et al., 2014) even when the most rigorous methods are used. Likewise, progesterone has been shown to evince values too low to be detectable in boys (Ney et al., 2020). Blood serum samples could have avoided this issue, but that is impractical for a large, community-based field study that sought to optimize response rates and reduce biased attrition.

With our novel hormone model, we have identified something of a universal hormone system lever, but it may still be the case that this lever is best conceptualized as a measure of pubertal development over time, or of broad allostatic and homeostatic system load. In order to test the true utility of this hormone system model, a larger longitudinal study designed to systematically test relationships between single and system-level measures of hormones would need to be conducted.

Turning to the larger goal of this study, the relationships we sought to uncover in these analyses, between hormone activity and daily measures of stress coping and affect, allowed us to look at estimates of the relationship between these variables in a cross-sectional manner. While this analysis has uncovered fascinating trends, we cannot support any inferences about the causal direction of effects (e.g. whether hormones cause affect or coping, or vice versa). However, work from other groups, such as Adam and colleagues, suggests that the use of time-lagged modeling may allow for the detection of causal links between variables, suggesting an intriguing future direction for this and other similar studies (Hittner and Adam, 2020; Hoyt et al., 2016).

Another drawback of the daily diary design of this study, which allowed for collection of information about daily adolescent stressors and affect simultaneously with salivary sample collection, relates to the diurnal and menstrual cycle-related rhythms of hormones and the challenge of incorporating information about these diurnal and menstrual rhythms in samples collected during the same school days in all participants. Research has shown that in many cases, especially those in which genetic influences on hormone levels are a part of the research question, salivary hormone samples should ideally be collected at the start of the day to capture the awakening response, or should be collected at the same time across individuals, or at the same time within individuals. Time of day and time since waking have effects on most hormone concentrations (Brambilla et al., 2009; Dabbs, 1990; Liening et al., 2010; Pruessner et al., 1997; Smyth et al., 2013), with the possible exception of progesterone in boys and girls and testosterone in girls (Parikh et al., 2018). It is true that in this study, we were not interested in more stable, genetic influences on salivary hormone levels, but rather on the compounding effects of the daily experience on hormone levels, making afternoon sample collection a better method for our research question. However, due to the restrictions of collecting during the school day, we were not able to prioritize collecting samples at consistent times of day either across individuals or within individuals across days. Additionally, in controlling for time of day of collection, we were unable

to examine time since waking and instead used clock time as a covariate. While collecting during the school day meant that, in most cases, we were able to have relative confidence that students woke up prior to the start of school, the impact of using clock time may have resulted in increased error in our analyses (Liening et al., 2010). In order to combat this, we included sleep duration and quality as covariates. Turning to the effect of menstrual cycles, many studies incorporating measures of hormones in women control the time of the menstrual cycle during which participants are asked to provide salivary samples, usually asking questions to help participants identify their midluteal phase, when hormone concentrations are high and stable, or using complex methods, which are still in development, to account for the many variables that can impact menstrual cycles and the hormone levels that drive them (Shea and Vitzthum, 2020; Thiyagarajan et al., 2022). In this sample, where the goal was a broadly generalizable, universal, community-based sample from a large sample in naturalistic settings, it was not advisable to increase respondent burden and risk losing a school partner (due to the logistical challenges of interrupting multiple classes per day for hundreds of students over 10 days). In addition, as our participants were at a stage in development during which menstrual cyclicity is still stabilizing, as they are almost all within 3 years of menarche, menstrual cycle data poses even more challenges and necessitates the use of a pubertal development assessment like that included in this set of studies (Schmalenberger et al., 2021). Our method of using random forest statistical models to take out the effects of diurnal and menstrual cycle rhythms, therefore, represented the best possible compromise between measurement error in the hormones and ecological validity / generalizability of the sample. Still, it prevented us from asking questions about within-person variation in diurnal rhythms.

Speaking more broadly to the nature of this field study, the volume and complexity of the data collected for this study necessitated a tremendous amount of data processing that may be difficult to reproduce for researchers interested in these topics who may not have computational resources. Therefore, we have made our dataset publicly available via ICPSR, so that future researchers can access the data and bypass the years of data processing required to have clean and valid hormone values.

Conclusions. Overall, this research suggests that hormones are both developmentally coupled across axes and that the activity of hormonal systems is related to daily experiences adolescents are having in the naturalistic environment of high school. Unexpectedly, we observed that HPG activity, rather than the more often examined HPA activity, was positively associated with positive affect and more adaptive stress coping. This finding fits into the broader narrative that adolescent hormones, far from being exclusively a liability, may often be a part of a system that guides teenagers through healthy development. While we are unable to make causal claims here, the robustness of our descriptive findings in this study will hopefully open the door to myriad future research questions and closer inspection of the possible adaptive role of HPG hormones during adolescence.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data is available on the ICPSR website as indicated in the text of the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2022.101158.

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