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Longitudinal Effects of Family Psychopathology and Stress on Pubertal Maturation and Hormone Coupling in Adolescent Twins

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Abstract

Adolescents experience profound neuroendocrine changes, including hormone 'coupling' between cortisol, testosterone, and dehydroepiandrosterone. Emerging research has only begun to elucidate the role of hormone coupling, its genetic and environmental etiology, and the extent to which coupling is impacted by sex, puberty, and family context. We included measures on parent and child mental health, parenting stress, and family conflict of 444 twin pairs and their parents across two timepoints, when target youth were on average 8 and 13 years old, respectively. Structural equation models examined the impact of family context effects on coupling during adolescence. Biometric twin models were then used to probe additive genetic, shared, and non-shared environmental effects on hormone coupling. Hormones were more tightly coupled for females than males, and coupling was *sensitive* to parent depression and co-twin psychopathology symptoms and stress exposure in females. The association between family context and coupling varied across specific neuroendocrine measures and was largely *distinct* from pubertal maturation. Biometric models revealed robust shared and non-shared environmental influences on coupling. We found that family antecedents modify the strength of coupling. Environmental influences account for much of the variation on coupling during puberty. Gender differences were found in genetic influences on coupling.

Keywords

Hormone coupling; Puberty; Family Stress; Twins; Longitudinal

Life history theory guides our understanding of how the trajectory of family factors such as parental depression and stress impacts pubertal development and neuroendocrine hormone functioning as adolescents develop. Life history theory posits that an individual's reproductive strategies or schedules are largely dependent on the allocation of psychological and physiological energy invested early in life (Stearns, 1992; Kaplan & Gangestad, 2005).

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Family factors, such as maternal depression and family stress (Ellis & Garber, 2000), quality of family relationships (Ellis, Shirtcliff, Boyce, Deardorff, & Essex, 2011), father absence (Webster, Graber, Gesselman, Crosier, & Schember, 2014), and parental investment (Ellis & Essex, 2007), impact pubertal development. Thus, family environment has a crucial part to play in adolescent development (Granic, Dishion, & Hollenstein, 2008; Schermerhorn & Mark Cummings, 2008), in addition to genetic factors. Recent studies are beginning to better explain the processes behind the level of environmental (family antecedents) and genetic (e.g., twin covariation) influences on pubertal development and hormone coupling (Grotzinger et al., 2018; Van Hulle, Moore, Shirtcliff, Lemery-Chalfant, & Goldsmith, 2015; Tackett et al., 2015; Harden et al., 2016; Harden & Klump, 2015).

Given that neuroendocrine hormones advance pubertal maturation, adrenal and gonadal hormones are being investigated as mechanisms for how family environment impacts pubertal development. However, extant research has expanded beyond studying individual pubertal hormones to examine the covariation or 'coupling' of hormone levels that derive from the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes, as these axes regulate each other throughout development. Each of these endocrine axes, as well as their coupling, respond to an individual's environment, particularly to change, stress, or challenges (Dismukes, Johnson, Vitacco, Iturri, & Shirtcliff, 2015; Ruttle, Shirtcliff, Armstrong, Klein, & Essex, 2015; Bobadilla, Asberg, Johnson, & Shirtcliff, 2015). The directionality (positive vs. negative correlation) and degree (unit change in association) of HPA-HPG axes coupling (measured by their hormonal outputs) varies based on a youth's family antecedents (Ruttle et al., 2015; Dismukes et al., 2015; King, Graber, Colich, & Gotlib, 2019), suggesting that investigating 'coupling' can help elucidate how early family environments shape children's development and health trajectories at a mechanistic level.

Recent research has begun to examine the genetic and environmental mechanisms of pubertal hormones (Harden & Klump, 2015). Despite evidence for both heritable and environmental influences on testosterone associated with pubertal status (Harden, Kretsch, Tackett, & Tucker-Drob, 2014), only two studies to date, including one from our group, have examined genetic and environmental influences on hormone coupling during puberty (Grotzinger et al., 2018; Van Hulle et al., 2015). Pubertal maturation show strong heritability (Comuzzie et al., 1996; Grotzinger et al., 2018; Van Hulle et al., 2015), but contextual (e.g., family stress) and individual (e.g., gender) factors play a role as well. Unraveling genetic and environmental influences contributing to adolescent developmental changes are important to consider in order to understand youth resiliency and buffering factors that support adolescent development and well-being.

Family Environment and Life Histories

Adolescent development includes sensitive periods (Knudsen, 2004; Fuhrmann, Knoll, & Blakemore, 2015; Fox, Levitt, & Nelson, 2010) when environmental factors may act as a catalyst to accelerate or slow down maturation. Family environments impact one's physiological, biological, and behavioral functions; in other words, family context can "get under the skin" (Fox et al., 2010). Aversive parenting (Papp, Pendry, & Adam, 2009) and

socioeconomic-related stress (Vaghri et al., 2013) impact children's neuroendocrine regulation, and this influence is especially important to monitor during developmental sensitive periods (e.g., puberty). While maternal depression has been found to impact youth's hormone functioning (Ruttle et al., 2014), less is known about paternal depression and its influence on adolescents' development and health outcomes (see exception, Shafer, Fielding, & Wendt, 2017) as well as hormone functioning. Within the family context, depression in either parent or higher psychopathology symptoms in a sibling represents another form of family stress (Mackrell et al., 2014; Marceau & Neiderhiser, 2013). However, it is unclear what processes connect parental depression and/or sibling psychopathology (Ma, Roberts, Winefield, & Furber, 2014), which are part of youths' daily lived experiences, with their development and health. In the present study, we quantify two types of family stressors: (1) family psychopathology, which combines parental depression and co-twin (sibling) psychopathology symptoms; and (2) family stress, which combines family conflict, parenting stress, and socioeconomic status.

Life stress can alter pubertal maturation (Ellis, 2004), which, in turn, can increase risks for later internalizing behaviors (depression, anxiety) and exacerbate externalizing behaviors (aggression, conduct problems, oppositional defiance) in some youths (Zahn-Waxler, Shirtcliff, & Marceau, 2008; Brydges, Best, & Thomas, 2019; Hodes & Epperson, 2019). Antecedents such as family environment and various types of stress modulate cross-communication between stress response systems, which include the HPA and HPG axes (see literature review by Zakreski et al., 2018). In their review, Zakreski and colleagues (2018) discussed various contexts, life histories, genders, and age among several other factors that influence dual axes communication. An example of family context modulating cross-axes communication during puberty is a study by King and colleagues (2019) that used a longitudinal design to examine the effects of early life stress on youths' waking cortisol, DHEA, and testosterone across stages of puberty. The study found that the impact of severe early life stress on hormone coupling patterns depended on pubertal maturation (earlier vs. later puberty), youths' gender, and which hormones were in the coupling associations. In their study, youths who were exposed to higher early life stress showed attenuated hormone coupling in early puberty. Put together, distal and concurrent context and underlying hormone mechanisms exchange information enabling the body to adapt to a given situation as it also transitions from child-like to adolescent-like physiology.

HPA-HPG Axes Hormone Coupling and Puberty

The brain initiates communication with the adrenal cortex and the gonads via a cascade of neurotransmitters and intermediary hormones to flood the bloodstream with hormones that produce secondary sexual characteristics and physical changes to an adolescent body (Marshall & Tanner, 1970; Marshall & Tanner, 1969). These hormones also produce neural changes that shape the adolescent brain (Vijayakumar, Op de Macks, Shirtcliff, & Pfeifer, 2018). During the first stage of puberty, called adrenarche, underlying biologic processes such as manufacturing of dehydroepiandrosterone (DHEA) in the adrenal cortex have begun, though physical changes are not yet visible. Once in the blood, DHEA stimulates pubic hair growth, acne, and a pre-pubertal growth spurt (Shirtcliff, Zahn-Waxler, Klimes-Dougan, & Slattery, 2007). During the second stage of puberty, termed gonadarche, testosterone and

other sex hormones are released from the testes in males and the ovaries and adrenal gland in females (De Oliveira, Fighera, Bianchet, Kulak, & Kulak, 2012). These hormones stimulate breast development in females and testicular growth in males, among other developmental milestones (Emmanuel & Bokor, 2019).

The HPA axis also undergoes developmental shifts during puberty (Matchock, Dorn, & Susman, 2007). Cortisol plays a role in co-regulation of DHEA and vice versa (Kamin & Kertes, 2017; Netherton, Goodyer, Tamplin, & Herbert, 2004; Goodyer, Park, Netherton, Herbert, 2001) and has co-regulatory associations with testosterone, specifically in stressful or challenging contexts (Zilioli & Watson, 2013). Examining cortisol as part of a hormonal triad with DHEA and testosterone helps us to understand its regulatory effects and the degree to which early life antecedents impact coupling during adolescence via the HPA axis (Zakreski et al., 2018; Shirtcliff et al., 2015).

The HPA and HPG axes have regulatory functions that help organisms adapt to their contexts. Traditionally, these systems are thought to inhibit each other in stressful and challenging contexts, and because puberty is stressful physiologically, the HPA axis is thought to inhibit the HPG axis in adolescents (Zakreski et al., 2018). This mutual inhibition is observed as ‘inverse coupling,’ when hormonal outputs such as testosterone and cortisol are inversely (or negatively) correlated. However, researchers have investigated the possibility that positive hormone coupling (or positive correlation) – when rise in a hormone level from one axis is linked to rise in a hormone level from another axis – is both normative and adaptive during adolescence (Shirtcliff et al., 2015; Ruttle et al., 2015). In some cases hormones may be ‘decoupled’ or lose any association positive or negative (Zakreski et al., 2018; Black et al., 2018; Simmons et al., 2015). Given the importance of HPA-HPG co-regulation throughout puberty, and the fact that these associations appear normative, more research is needed on decoupling found in some youth. Empirically, decoupling might be defined by lack of a significant correlation between levels of two hormones. Sometimes, this lack of significant correlation is only apparent when covariates and control variables are included in a regression model. A subtype of decoupling, called ‘less coupling’ in this study, is a decreased but still significant correlation between levels of two hormones when covariates and control variables are accounted.

Given that puberty is a normative developmental process in which HPG axis activation is essential, HPG axis inhibition may be suspended to facilitate puberty and to allow both axes to work together during adolescence. Furthermore, an emergent literature about the role of dual-axes coupling during adolescence illustrates how stressful family antecedents enhance positive coupling during adolescence, also known as tighter coupling or stronger positive correlation (Ruttle, Shirtcliff, Armstrong, Klein, & Essex, 2015; Black, Lerner, Shirtcliff, & Klein, 2018; Simmons et al., 2015). Although the life history view emphasizes that dual axes activation occurs in interaction with early life and concurrent stress exposure, HPA-HPG axes coupling might also be a normative developmental phenomenon initiated with unique genetic underpinnings.

Genetic Underpinnings of Hormone Coupling during Puberty

Genetically informative models (e.g., twin models) can add to our understanding of the mechanisms that underlie HPA-HPG axes coupling during adolescence. Parsing phenotypic variance across additive genetic, shared environmental, and non-shared environmental effects can help clarify what factors drive individual differences in hormone coupling. There is a dearth of empirical studies examining gender differences in the genetic underpinnings of cortisol, testosterone, and DHEA coupling during puberty. To our knowledge, only two studies examined gender differences in genetic and environmental influences on hormone coupling (Van Hulle et al., 2015; Grotzinger et al., 2018). Van Hulle and colleagues (2018) found that for females much of the explained variance in testosterone and DHEA coupling was due to genetic and non-shared environmental influences and the overlapping of puberty, while for males, shared environmental factors explained most of the variance when overlapping with puberty. Grotzinger and colleagues (2018) found higher genetic influences in testosterone and DHEA correlation in males as was found in another study (Harden et al., 2014). In addition, a different study reported gender differences in genetic and environmental influences on cortisol (Schreiber et al., 2006) in which most of the variance in basal cortisol level was due to shared environmental influences.

Study Aims and Hypotheses

We investigate the relationship between family environment and pubertal development, including hormone coupling, to better understand processes that impact adolescent development. First, we established the direction of hormone coupling in this sample. We hypothesized that, controlling for pubertal stage and gender, there would be positive coupling between hormones, as found in Ruttle et al. (2015) in a comparable sample of adolescents. We also expected youth with later pubertal stage to show less coupling and that females would show tighter hormone coupling than males (King, Colich, & Gotlib, 2019). In these analyses, we controlled for youth age and family SES (parent education and family income); these control variables were removed if the effect on hormone coupling was non-significant.

For simplicity, we term family factors (psychopathology and stress at Time 1 and Time 2) as “antecedents” throughout the remainder of the paper. Before examining the impact of family context on hormone coupling, we first examined family antecedent effects on individual morning hormone levels and pubertal status. We tested “family psychopathology” symptoms (parental depression and sibling psychopathology) and family stress at age 8 years (Time 1) and at age 13 years (Time 2), for distal and proximal impacts on morning hormone levels. Next, we examined whether these same family antecedents impact hormone coupling. We expect stability in high family antecedents over time to influence adolescent’s morning hormone levels and their coupling. Morning hormone levels and their coupling may have different patterns based on youth gender; therefore, models were fit to males and females separately. Next, we tested if family antecedents at age 8 years were related to pubertal status. We expected that when family antecedents persisted from childhood to adolescence, youth would have more advanced pubertal status.

Lastly, we hypothesized that gender moderates the associations between additive genetics, shared environmental influences, and non-shared environmental influences on hormone coupling, as we previously found (Van Hulle et al., 2015). Examining the direction and degree of hormone coupling, family antecedent effects on hormone levels and their coupling, and gender-specific genetic and environmental influences on individual differences in hormone coupling adds to the emerging research on cross-talk between the HPA-HPG axes during adolescent development.

Methods

Participants

Families of twins were identified from state birth records and invited to participate in the Wisconsin Twin Project, a longitudinal twin study, at focal age 8 years (Time 1). More information about the Wisconsin Twin Project can be found in our previous work (Schmidt et al., 2019; Schmidt et al., 2013). Families were invited to take part in a second assessment (Time 2) at focal age 13 years. This is a community-based sample. At each testing occasion, parent depressive symptoms, twin psychopathology symptoms, family stress, and socioeconomic status (mother- and father-reported) were assessed. Primary caregivers reported demographic information about race, ethnicity, mother education, father education, and family income. Salivary hormones were collected at the first and second assessment, and puberty measures were collected on twin participants at the second assessment. An Institutional Review Board of the University of Wisconsin–Madison approved all protocols.

A total of N = 888 individuals (444 twin pairs) were included. Children participated at mean age 7.90 years for females (SD = 1.29, range = 6.33 to 11.42) and 8.05 years for males (SD = 1.33, range = 5.67 to 11.42) at Time 1 (T1) and at age 13.12 years for females (SD = 1.39, range = 11.25 to 17.42) and 13.25 years for males (SD = 1.43, range = 11 to 17.75) at Time 2 (T2). At T1, mothers were mean age 38.47 years (SD = 4.71, range = 26.08 to 52.33), and fathers were mean age 40.34 (SD = 5.48, range = 25.08 to 58.92). At T2, mothers were mean age 43.85 years (SD = 4.65, range = 31.58 to 56.67), and fathers were mean age 45.75 years (SD = 5.44, range = 30.00 to 62.92). Family income at T2 was reported in categories; the median income bracket was $50,000 to $60,000. Mothers' mean level of education was 14.50 years (SD = 4.05), and fathers' mean level of education was 13.98 years (SD = 3.93).

Measures

Family Stress.—Three separate questionnaires on family and parenting stress were administered. Mothers completed the Parenting Stress Index -Short form (PSI: Abidin, Austin, & Flens, 2013) at T1 and T2, the Family Conflict Scale (FCS; Porter & O'Leary, 1980) at T1 and T2, and the Stress Index for Parents of Adolescents (SIPA; Eadeh et al., 2019) at T2 only (see descriptive statistics in Table 1). A variable "Family Stress" comprised of (1) the frequency of hostile or arguing behavior in the presence of children; (2) feelings and thoughts about children's behavior that can be stressful (e.g., lack of affection); (3) feelings and thoughts about one's parenting competence or relational stress; and (4) parent education and family income status.

All three measures were averaged across subscales resulting in one variable each for FCS, PSI (at each time point), and SIPA. The PSI, FCS, and SIPA scores were then z-scored. Socioeconomic status was computed as a mean of three z-scores: mother's education, father's education, and family income. Time 1 Family Stress was calculated as the average of z-scored PSI, FCS, and SES; Time 2 Family Stress was calculated as the average of z-scored PSI, FSC, SIPA, and SES.

Family Psychopathology.—Mothers and fathers completed the Beck Depression Inventory (BDI, Vandeputte & de Weerd, 2003; Beck, Steer, & Brown, 1996), a self-report measure of depression. Parents also completed the Health & Behavior Questionnaire (HBQ) separately for each twin (Donovan, Jessor, & Costa, 1993). The Health Behavior Questionnaire had 8 subscales: depression, separation anxiety, conduct disorder, oppositional defiant disorder, impulsivity, inattention, social anxiety, and physical health problems. We then created a composite score for internalizing (depression, separation anxiety, overanxious, social anxiety) and externalizing (conduct disorder, oppositional defiant disorder, overt aggression) behaviors resulting in 2 child psychopathology domains (see Family Psychopathology measures descriptive statistics in Table 1). Parental depression and sibling (co-twin) psychopathology symptoms were then combined as a family variable (see twin siblings' psychopathology symptoms intercorrelations in supplement section Table A4). Family Psychopathology was calculated by, 1) z-scoring all BDI and HBQ variables and 2) averaging mother's and father's BDI, co-twin's internalizing variable [from the HBQ], co-twin's externalizing variable [from the HBQ]. These steps were completed for T1 and T2.

Puberty.—Adolescents self-reported puberty at Time 2 by picking the stage they most closely resembled from images of breast/genital and pubic hair maturation, respectively, for females and males (Morris & Udry, 1980). The Pubertal Development Scale (PDS) was administered to adolescents and their mothers to asses adolescent twins' secondary sexual characteristics (Petersen, Crockett, Richards, & Boxer, 1988). Scores were then combined using an algorithm developed by Shirtcliff, Dahl, and Pollak (2009) to map physical changes onto hormonal developmental processes during puberty, specifically adrenarcheal and gonadarcheal changes, and corresponding with Tanner staging 1 to 5, but permitting fractional stages (see Figures 1a-1c). Regression-based factor scores were then created using principal axis factoring that combined mother- and self-reported PDS and self-reported Tanner stages so that puberty scores were sex-specific and so that adrenarcheal and gonadarcheal pubertal changes received equal weighting. Table 2 displays means and standard deviations of age and Tanner stages at Time 2, split by zygosity and gender. Higher factor scores indicated youth with more advanced pubertal maturation (more developed adrenally, gonadally, and physically).

Morning Hormones.—Saliva was collected at Time 2 by families at home using passive drool. Families were instructed to collect three samples per day across three consecutive days: approximately 30 minutes after waking (M = 8:07am, SD = 0:03), between 4:00-6:00pm central standard time, and before going to bed. Participants were instructed not to eat or drink for at least one hour prior to saliva collection and to refrain from collecting a

sample if they were ill. Participants recorded information about collection time, sleep, medications, and physical symptoms. Samples were initially stored in a sealed zip lock bag in a home freezer. Samples were transported to the laboratory in a cooler with ice bricks and stored immediately in an ultrafreezer at −80°C. A portion of samples were transported through U.S. mail in a padded envelope and then stored at −80°C. Enzyme immunoassays for cortisol, testosterone, and DHEA were conducted using Salimetrics, LLC kits (https://salimetrics.com/; ~90%, N = 712 subjects) and by IBL International (https://www.ibl-international.com/; ~10%, N = 78 subjects). Cortisol was assayed across all 3 days and time points. Details on cortisol assays were reported in our previous studies (Van Hulle, Shirtcliff, Lemery-Chalfant, & Goldsmith, 2012; Burghy et al., 2016). To reduce cost, testosterone and DHEA were assayed for the first two days of sample collection at the morning collection period because a) morning samples are generally considered to represent “basal” sex hormones when levels are at their peak, and b) sex hormones are relatively stable across consecutive days (Liening, Stanton, Saini, & Schultheiss, 2010). Average intra-assay coefficient of variances were 5.2% for cortisol, 4.6% for testosterone, and 5.6% for DHEA. Inter-assay coefficient of variances were 5.7% for cortisol, 8.3% for testosterone, and 8.2% for DHEA.

Analytic Strategy

Of the total 444 twin pairs included in data analyses, random missingness of data were treated as pairwise deletions within statistical analysis programs (e.g., HLM, Mplus). Pairwise deletions were performed within analysis programs due to systematic missing hormones, family measures, and puberty data. In other words, cases with a few missing data were still included in data analysis, but the cases with missing all hormone and puberty data were treated as listwise deletions during analysis within statistics programs. Data included for analyses are listed in Table A1 and A2 of the supplement section.

Morning Hormone Levels.—Morning hormone level across two days for cortisol, DHEA, and testosterone were included in the analyses. All hormone data were screened for outliers, and all outliers were winsorized to +/− 3 SDs. Hormone data were then log-transformed to reduce skewness prior to standardizing; hormone data were standardized within sex. Since 10% of the hormone data were assayed using a different manufacturer than the rest of the sample, hormone data were standardized within manufacturers. Using the standardized log-transformed hormone data, a null model was fit separately to cortisol, DHEA, and testosterone using Hierarchical Linear Modeling (HLM v7.0; Raudenbush & Bryk, 2002). Intraclass correlations demonstrating total variance broken down by nested level effects for each null model are as follows: cortisol (46.73% between-families, 0.19% between-twin pairs, 53.08% between-sample); testosterone (49.89% between-families, 25.34% between-twin pairs, 24.77% between-hormone sample); and DHEA (52.58% between-families, 18.76% between-twin pairs, 28.66% between-hormone sample). Z-scored, log-transformed hormone data were used for primary analysis.

Hormone Coupling and Puberty.—To examine hormone coupling associations, we fit Hierarchical Linear models to test the direction (negative or positive) and magnitude (unit change in hormone levels) of coupling using standardized log-transformed hormone data as

predictor and as outcome (see equations 1-3 below). All HLM models included control variables of no interest (twin age and SES) and covariates (gender, puberty). Correlations among control variables, covariates, and hormones are shown in Table 3. We selected 'stress hormones' as the outcome variable as stress hormones typically display more variance than 'sex hormones;' also, high correlations between interchanging hormones as outcome indicated the bivariate associations were very similar (see Table A3 in supplement section). Only significant associations with control variables and covariates in each hormone coupling HLM model are reported.

$$ZLNCORTij = \beta 0j + \beta 1j^{*}(ZLNTESTOij) + rij \quad (1)$$

$$ZLNCORTij = \beta 0j + \beta 1j^{*}(ZLNDHEAij) + rij \quad (2)$$

$$ZLNDHEAij = \beta 0j + \beta 1j^{*}(ZLNTESTOij) + rij \quad (3)$$

Using equations 1-3, we extracted empirical Bayes (EB) estimates using HLM to capture the overall average hormone level associations and the individual's average hormone levels associations relative to the grand mean. Empirical Bayes estimates are estimators that reflect data points regressed to the grand mean (Efron, 2012, pp. 20-25). Empirical Bayes estimates for the three HLM hormone coupling models were then used as the outcome measures in analyses examining the effect of family stress and psychopathology on hormone coupling.

Family Antecedents, Puberty, and Hormone Coupling.—We used Structural Equation Modeling (SEM) in Mplus v8.3 (Muthen & Muthen, 2017) to test the hypotheses that family antecedents have both distal and concurrent effects on puberty and morning hormone levels and their coupling. A multiple group SEM was conducted separately for females and males. Two models were fit. Both models examined 1) the associations between T1 and T2 family psychopathology and stress variables, 2) the effects of these family antecedents on puberty and hormone outcomes, and 3) puberty's effect on hormone outcomes. The first model tested these variables' effects on average morning hormone levels (standardized log transformed hormone data for cortisol, testosterone, and DHEA). The second model substituted hormone coupling associations as the outcomes (EB estimates for coupling between cortisol and DHEA, coupling between cortisol and testosterone, and coupling between DHEA and testosterone, deriving from the three HLM equations above).

Biometric Modeling.—The biometric twin model, a multiple group SEM, relies on the assumption that individual differences (i.e. phenotypic variation) in an observed trait can be attributed to variation in unmeasured latent additive genetic influences (A), shared environmental influences (C) that vary between families, and non-shared environmental influences (E) that vary within families (including measurement error). Correlations within monozygotic (MZ) twin pairs are expected to be higher than dizygotic (DZ) twin pairs for heritable traits because MZ twins share effectively 100% of their genes, and DZ twins share on average 50% of their genes. In standard twin models, the additive genetic effect is

modeled with a correlation of 1.0 in MZ twin pairs and 0.5 in DZ twin pairs. Because members of both MZ and DZ twin pairs raised together are expected to be influenced by the shared environment to the same degree, the shared environmental effect is modeled with a correlation of 1.0 regardless of zygosity. Non-shared environmental effects, or those environmental factors that serve to make twins different, are modeled as uncorrelated within both MZ and DZ pairs. Standardized estimates for A, C, and E reflect the proportion of the total phenotypic variance that is accounted for by additive genetic variation or heritability (a^2), shared environmental variation (c^2), and non-shared environmental variation (e^2). These three variance components sum to 1.0.

The biometric model can incorporate multiple observed traits and potential sex differences in the magnitude of genetic and environmental influences on the variation of each trait and their covariation (Neale & Cardon, 2013). The bivariate Cholesky model provides estimates of A, C, and E influences on one trait that also influence a second trait, thus composing their phenotypic covariance, as well as estimates of residual A, C, and E influences that are unique to the second trait. Thus, variance in the second trait in the model may be due wholly to factors that also influence the former trait, variance specific to the latter trait only, or some combination thereof. References to bivariate models throughout the remainder of the paper specify the ordering of the phenotypic variables in the model. Sex differences are estimated by grouping twin pairs by sex and zygosity so that opposite-sex twin pairs are included as a separate twin pair type. In this model, opposite-sex twins are assumed to have a genetic correlation of 0.5, as same-sex DZ twin pairs do, but the parameters for A, C, and E are allowed to vary by sex. Following the HLM models, we fit bivariate Cholesky-sex differences models to cortisol-DHEA, cortisol-testosterone, and DHEA-testosterone coupling measures. All models were fit using Mplus v8.3 (Muthen & Muthen, 2017).

Results

Is There Positive Coupling and Do Puberty and Gender Moderate Hormone Coupling?

To examine stability or change in hormone coupling when considering covariates (e.g., family antecedents), we first need to establish direction of hormone coupling and the degree of coupling associations across axes while controlling for age, gender, puberty, and SES. Table 3 presents intercorrelations of all variables included in preliminary analyses. More details on other control variables that did not have significant effects on hormone levels can be found in our previous study (Van Hulle et al., 2015).

Cortisol and Testosterone Coupling.—Cortisol and testosterone were positively coupled (Model equation 1; B = 0.12, SE = 0.03, t-ratio = 3.604, df = 405, $p < 0.001$). Males and females showed similar Cortisol-Testosterone coupling (B = 0.071, SE = 0.08, t-ratio = 0.934, df = 382, p = 0.351).

Controlling for age, puberty moderated the effect on Cortisol-Testosterone coupling such that older youth with earlier pubertal stage showed stronger positive cross-axis coupling (B = 0.114, SE = 0.05, t-ratio = 2.525, df = 37, p = 0.016), but younger youth with later pubertal stage showed diminished coupling (B = −0.097, SE = 0.05, t-ratio = −2.099, df = 344, p = 0.037). The control variable socioeconomic status (SES, with a main effect, B =

−0.094, SE = 0.05, t-ratio = −2.007, df = 343, p = 0.046) reduced the effect of puberty to a trend (B = −0.097, SE = 0.046, t-ratio = −2.099, df = 344, p = 0.037 vs. B = −0.082, SE = 0.046, t-ratio = −1.778, df = 343, p = 0.076). For lower SES youth, later pubertal stage moderately had less positive Cortisol-Testosterone coupling; however, for higher SES youth, earlier pubertal stage significantly predicted less coupling between cortisol and testosterone.

Cortisol and DHEA Coupling.—We found positive coupling between cortisol and DHEA (Model equation 2; B = 0.248, SE = 0.04, t-ratio = 5.763, df = 344, p < 0.001). Females showed tighter coupling of cortisol and DHEA than males, but only at a trend level of significance (B = 0.142, SE = 0.08, t-ratio = 1.778, df = 41, p = 0.083). There were no puberty, age, and SES effects on cortisol and DHEA (ps > 0.507).

DHEA and Testosterone Coupling.—DHEA and testosterone were positively coupled (Model equation 3; B = 0.248, SE = 0.04, t-ratio = 5.762, df = 41, p < 0.001). Females showed tighter coupling of DHEA and testosterone than males (B = 0.176, SE = 0.07, t-ratio = 2.414, df = 148, p = 0.017). Youth with later pubertal status had, at a trend level, less coupling of DHEA and testosterone (B = −0.064, SE = 0.04, t-ratio = −1.835, df = 147, p = 0.069). We observed no age or SES effects on DHEA and testosterone coupling (ps > 0.163). Pearson correlations between hormone coupling and pubertal status by gender are displayed in Figures 2a and 2b.

Do Distal and Concurrent Family Antecedents Impact Puberty, Morning Hormone Levels, and Their Coupling, and Are There Gender Differences?

Given that an overall positive hormone coupling was found in preliminary models, we examined stability or change in coupling associations and the degree to which these changes were affected by family antecedents. First, we examined family antecedent effects on pubertal status and morning hormone levels using multiple group analysis (SEM model 1; N = 2 groups: males and females). All parameter estimates were set as free. Fit indices indicated that the model adequately fit the data (RMSEA = 0.013, CFI = 1.000, TLI = 0.996). We then conducted an SEM with the same family antecedent effects on pubertal status and on hormone coupling (SEM model 2; RMSEA = 0.019, CFI = 0.999, TLI = 0.984). Below, we report the results separated by males and females, starting first with SEM model 1 (average morning hormone levels) and then SEM model 2 (hormone coupling).

Males.—Time 1 (T1) Family Psychopathology positively predicted Time 2 (T2) Family Psychopathology. We found a similar pattern for Family Stress. Family Psychopathology at T1 and Family Stress at T2 were correlated. Family Psychopathology at T1 predicted a negative association with Family Stress at T2 indicating that higher family psychopathology at age 8 years that did not persist at age 13 years had less concurrent family stress. Family Psychopathology and Family Stress did not predict pubertal status (Puberty), although higher Family Stress at T2 predicted elevated morning cortisol. Youth with advanced stages of puberty showed elevated morning DHEA and Testosterone levels (see SEM model 1 results in Figure 3).

Family Psychopathology at T1 predicted tighter coupling between cortisol and DHEA; however, Family Psychopathology at T2 predicted less Cortisol-DHEA coupling, indicating a decoupling of the HPA-HPG axes as a result of higher family psychopathology symptoms. As expected from the HLM models, males who were more developed in puberty had less coupling of DHEA and Testosterone (see SEM model 2 results in Figure 4).

The present study focused on family stress and family psychopathology as family ecological effects on pubertal development and hormones, but we also included in the supplement section distal and concurrent effects of parental depression and child psychopathology (separately) on pubertal development and hormone coupling for males (Figures A1 and A3) and for females (Figures A2 and A4).

Females.—As was shown for males, higher Family Psychopathology at T1 predicted Family Psychopathology at T2, suggesting high stability in family psychopathology over time. We observed similar levels of stability for Family Stress. Beyond this high level of stability, families with greater psychopathology exposure in T1 (that did not persist to T2) showed less family stress by T2. Family Psychopathology and Family Stress at T1 were highly correlated. Females who had higher Family Stress at T1 had less pubertal maturation by age 13 years than females with lower family stress, though it is only a trend-level effect. However, higher concurrent Family Stress at T2 predicted more advanced puberty in girls. Females who were advanced in puberty (Tanner stages 4-5) had higher morning levels across all three hormones. Distal Family Stress at T1 affected morning testosterone and DHEA showing elevated levels (see SEM model 1 results in Figure 5). These family antecedent findings indicate that females are affected differently than males by type of family factors and the timing of the stressor.

For Cortisol-DHEA coupling, higher concurrent Family Psychopathology at T2 was associated with tighter coupling between Cortisol and DHEA. Higher distal Family Stress at T1 was associated with less coupling (at trend level) of Cortisol-DHEA.

For Cortisol-Testosterone coupling, Family Psychopathology at T1 predicted tighter positive coupling between cortisol and testosterone; however, Family Psychopathology at T2 predicted less Cortisol-Testosterone coupling (at trend level) indicating a decoupling of the two hormones.

A similar pattern of findings emerged for DHEA-Testosterone coupling such that Family Stress at T1 predicted less coupling between DHEA-Testosterone at T2. Family Psychopathology at T1 was associated with tighter positive DHEA-Testosterone coupling (trend level). These findings suggest there may be different levels of impact of family antecedents on females' hormone coupling during adolescence.

Finally, females who were more advanced in puberty (later pubertal stage) showed tighter positive coupling between Cortisol-DHEA but less positive coupling between Cortisol-Testosterone and DHEA-Testosterone, which suggests that during pubertal maturation, decoupling is occurring and that testosterone has a unique effect on the HPA axis in females compared with males (see SEM model 2 results in Figure 6).

What Are the Genetic and Environmental Contributions to Hormone Coupling and Does Gender Moderate these Contributions?

We examined the genetic and environmental influences on coupling between DHEA and cortisol, testosterone and cortisol, and DHEA and testosterone in males and females using bivariate Cholesky decomposition models (Neale & Cardon, 2013). Although gender differences in the genetic and environmental influences on coupling between DHEA and testosterone are reported from this same project in Van Hulle et al. (2015), we repeated these analyses with the larger sample available here. All models fit the data well (Cortisol-DHEA: RMSEA = 0.073, CFI = 0.926, TLI = 0.957; Cortisol-Testosterone: RMSEA = 0.065, CFI = 0.940, TLI = 0.965; DHEA-Testosterone: RMSEA = 0.050, CFI = 0.985, TLI = 0.991). For each hormone pairing, we tested a model that specified no sex differences in the magnitude of genetic and environmental influences. For Cortisol-DHEA, the no sex differences model fit the data equally well ($\Delta\chi^2 = 11.6$ with 9 df, $p = 0.240$) as the model that allowed sex differences. For Cortisol-Testosterone and DHEA-testosterone, a model that allowed no sex differences model failed to describe the data as well as the sex differences model (Cortisol-Testosterone: $\Delta\chi^2 = 46.6$, 9 df, $p < 0.001$; DHEA-testosterone: $\Delta\chi^2 = 63.6$, 9 df, $p < 0.001$). The unstandardized parameters estimates are shown in Table 4. The first additive genetic factor (A1) represents heritable effects that influence both phenotypes (i.e., cortisol and DHEA). The second factor (A2) represents residual heritable effects that only influence the second phenotype in the model (i.e., cortisol). Analogous shared and non-shared environmental parameters are shown in Tables 5. For example, the amount of shared environmental variation in cortisol due to factors shared with DHEA is $0.31^2 = 0.096$ and the amount of shared environmental variation specific to cortisol is $0.60^2 = 0.360$.

Standardized estimates that reflect the proportion of total variation accounted for by each factor can be obtained by squaring the parameters estimates for the variance components influencing each trait and dividing by the total estimated variance (see Table 5). The proportion of covariance due to genetic and environmental factors that influence both traits is calculated in a similar manner.

Coupling between cortisol and DHEA was due primarily to shared and non-shared environmental factors; 63% of the covariance was due to shared environment; and 37% was due to non-shared environment. There was little evidence for heritable influences on cortisol but substantial, though distinct, additive genetic influences on DHEA.

For Cortisol-Testosterone coupling, shared and non-shared environmental factors also contributed to tighter coupling in both females and males (Females: 64% of covariance is due to shared environment and 15% to non-shared environment; Males: 49% is due to shared environment and 14% due to non-shared environment). We see some evidence that genetic factors contribute to weaker Cortisol-Testosterone coupling, but the parameter estimates only reached significance for males.

Shared and non-shared environmental factors contributed to the coupling between DHEA and testosterone in females and males (74% and 24% respectively in females, and 70% and 10% respectively in males), with further coupling due to genetic factors in males (20%). In females, we find evidence for DHEA specific genetic, shared environment, and non-shared

environmental effects. In males, we find evidence for DHEA specific genetic and non-shared environmental effects but no DHEA specific shared environmental effects.

Discussion

For our adolescent sample, we generally observed positive coupling of hormonal outputs from the HPA and HPG axes, including all hormone pairs (i.e., cortisol-testosterone, cortisol-DHEA, DHEA-testosterone). Through different methodology, our SEM analyses also revealed positive links as well as decoupling across measures of different hormones within this adolescent twin sample. This finding was expected, given our prior work on this topic (Shirtcliff et al., 2015) and our systematic literature review, which found over 40 replications of positive coupling (Zakreski et al., 2018). Although we acknowledge that positive coupling runs counter to a traditional view of these endocrine inter-relationships (Viau, 2002; Viau & Meaney, 1996), a recent systematic review of the dual-hormone hypothesis uncovered little empirical evidence for suppression or inhibition of HPA-HPG axis functioning and instead found evidence for a “file drawer” problem in this literature (Grebe et al., 2019).

Puberty appears to impact coupling.

Against a backdrop of robust positive HPA-HPG axis coupling, variations in these hormonal associations emerged when examining individual and contextual factors. We found that youth with later pubertal status had elevated testosterone and lower cortisol (less positive cortisol-testosterone coupling), suggesting that testosterone was downregulating (or less strongly upregulating) cortisol during the later stages of pubertal maturation. The HLM results showed that older youth with earlier pubertal status continued to show tighter positive cortisol-testosterone coupling – a finding resembling pre-pubertal hormone coupling patterns, while younger youth with later puberty showed less positive cortisol-testosterone coupling. The pattern of findings suggests that a developmental transition toward less positive coupling may be more related to puberty rather than age. This suggestion fits with prior studies showing that positive coupling diminishes for adolescents nearing the end of pubertal maturation (Black et al., 2018; Marceau, Ruttle, Shirtcliff, Essex, & Susman, 2015; Ruttle et al., 2015). During puberty, testosterone and DHEA are largely responsible for activating secondary sexual characteristic changes; these hormones rise dramatically during the mid-late pubertal stages (Braams, van Duijvenvoorde, Peper, & Crone, 2015). While the rise in basal testosterone decreases as individuals age, basal DHEA levels continue to rise into young adulthood (Guazzo, Kirkpatrick, Goodyer, Shiers, & Herbert, 1996; Majewska, 1995; Rendina, Ryff, & Coe, 2017). Within the individual as was found in the present study, a decoupling between DHEA-testosterone may gradually occur as youth transition to a consistent adult-like status.

Gender appears to impact coupling.

Females showed tighter coupling of the hormonal outputs from the HPA axis (cortisol and DHEA) compared with males. Females also had tighter positive coupling between putative outputs of the HPG axis (DHEA and testosterone) in comparison with males. This gender difference fits with the results of prior studies conducted on adolescents (Simmons et al.,

2015), as well as the observation that many sex hormones may be of adrenal origin in females (Byrne et al., 2017). Thus, the differentiation between stress and sex hormones for females may be less distinct than for males. We also note below that the genetic analyses suggest that DHEA was functioning similarly to testosterone due to genetic influences within females.

Gender and stress effects.

We used SEM to incorporate longitudinal and cross-sectional family antecedent effects on puberty and hormonal outcomes. First, gender differences were apparent such that, for males, concurrent family stress predicted elevated morning cortisol level; however, no family antecedent effect was found on pubertal development. Distal family psychopathology symptoms showed stronger positive coupling between cortisol and DHEA in males, but concurrent family psychopathology symptoms had a different effect showing decoupling of these two hormones indicating that timing of stressor played a role in hormone coupling. The impact on hormone coupling in females in our study were more complex than in males and was based on the stressor, timing of the stressor, and the hormones in the coupling association. For the cross-axes hormone coupling, family psychopathology symptoms appeared to affect cortisol-testosterone coupling in females regardless of timing but not family stress. For the DHEA and testosterone coupling association, distal family stressors (both psychopathology and stress) influenced coupling but not concurrent stressors. This finding is consistent with the life history view as theorized by Ellis (2004) that the pubertal processes in females are more sensitive to stress effects earlier on, and the current study showed that developmental timing may further explain the process of environmental influence on hormonal regulation.

Surprisingly, family psychopathology and family stress when youth were around age 8 years predicted delayed pubertal status when females were age 13 years, which appears to run counter to the expectation that stress exposure advances puberty (Ellis, 2004). It is possible that puberty, independent of its hormonal corollaries, may display unique associations with stress exposure. Perhaps stress exposure at age 8 years, during a period of neuroendocrine quiescence and neural plasticity (Guyer, Pérez-Edgar, & Crone, 2018), may not be potent enough to exert an impact on psychophysiology (Fuhrmann et al., 2015). Alternatively, a more severe level of stress exposure may be needed to reveal positive associations between puberty and stress than we observed in this community-sample. A more susceptible, sensitive developmental period would typically be much earlier during infancy or even prenatally (Hines, Constantinescu, & Spencer, 2015; Charmandari, Kino, Souvatzoglou, & Chrousos, 2003; Glover, 2015). Future studies need to distinguish when (and whether) the effects of stress on development and later mental health risk are mediated by physical development, which carries its own psychosocial implications (Siegel, Yancey, Aneshensel, & Schuler, 1999; Mendle, Turkheimer, & Emery, 2007) or when biopsychosocial stress mechanisms are implicated via hormonal measures (Dismukes et al., 2016; Drury et al., 2014).

Complex developmental associations of family stress, psychopathology, and hormone coupling.

When we examined within-HPA axis associations with family psychopathology and family stress, we found that females with greater concurrent family psychopathology had tighter cortisol-DHEA coupling of these two "stress hormones." Distal stress exposure showed elevated morning testosterone levels as well as elevated morning DHEA levels. This could mean that DHEA's co-regulatory mechanisms are activated in a stressful context alongside pubertal maturation in which DHEA is demonstrating both its stress responsiveness and sexual maturation processes in adolescents, particularly for females. Prior research has conceptualized DHEA as a flexible hormone that functions as both a stress and sex hormone, and during times of stress, may serve as a sort of "reservoir" for the HPA axis (Marceau et al., 2015; Ruttle et al., 2015; Dismukes et al., 2016). Early versus concurrent stress exposure is thought to impact the HPA axis differently (Essex et al., 2011; Ruttle et al., 2011), and such divergence may extend to within-HPA axis coupling between DHEA and cortisol.

Once the HPG axis is included in cross-axes communication, however, prior studies suggest that the developmental significance of the HPG axis may become more prominent (Shirtcliff et al., 2015). In coupling associations that paired with testosterone, testosterone downregulated both cortisol and DHEA during puberty. Consistent with the inhibitory effect theory, the HPG axis inhibits the HPA axis enabling secondary sexual characteristic maturation in high stress contexts. The downregulatory mechanism of testosterone may also indicate a quiescent developmental phenomenon in which the adolescent brain and the HPG axis become malleable in stressful contexts, and that mechanism is genetically identified (Wingfield & Sapolsky, 2003). In other words, adolescents exposed to high stress contexts as they experience pubertal maturation can adapt to the simultaneous influence of their context and the physiological changes due to puberty (Wingfield & Sapolsky, 2003).

Genetic and environmental influences.

Given the complexity of the stress findings in this study and in prior studies, we also sought to understand the nature and magnitude of shared, nonshared environmental and genetic influences on these hormones and their coupling. Few studies examined hormone heritability. Cortisol heritability estimates range up to 72% using hair cortisol concentration levels (Rietschel et al., 2017) in both males and females; in these studies, hair concentration reflect basal hormone levels spanning approximately 1 month (Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013). Bartels and colleagues (2003) reviewed early twin studies, which often have limitations, that generally estimated moderate-to-high heritability of cortisol levels. Later, we reported lower heritability estimates for cortisol in prior waves of this sample using a parent-offspring design when twins were age 8 years (Schreiber et al., 2006). This prior report used saliva samples from morning to afternoon, which highly correlate with plasma and serum levels of free cortisol (Gallagher, Leitch, Massey, McAllister-Williams, & Young, 2006; Gozansky, Lynn, Laudenslager, & Kohrt, 2005), and has an approximate half-life of 0.44 nM/sec per 2.2 minutes (Dorin, Qiao, Qualls, & Urban, 2012). The difference in basal hormone concentration by sample type (hair, saliva) as well as timing of samples could contribute to inconsistent findings across studies.

In the current analyses, bivariate biometric Cholesky decompositions revealed robust shared and non-shared environmental influences on coupling for males and females. The presence of these abstract environmental variance components fits with our other analyses that revealed effects of family stress on coupling parameters, under the assumption that family stress acts mainly as an environmental variable. More specifically, for males, both genetic and non-shared environmental influences but not so much their shared environmental context (27% of the phenotypic variance from Table 5) explained DHEA level output. However, for females, shared environmental factors contributed 51% of the variance in DHEA level. This sex difference in variance accounted for by the shared environment is consistent with family stressors having larger impacts on females than males.

Males showed stronger additive genetic influences on elevated morning testosterone levels than females. In twin adolescents, Grotzinger et al. (2018) compared males' and females' hair concentrations of testosterone and DHEA and found that in males, these hormones were largely influenced by genetic factors whereas environmental influences were stronger in females. Previous studies have found high heritability of testosterone in male adolescents, up to 60% of the total variance, and up to 40% of the total variance in female adolescents (Harris, Vernon, & Boomsma, 1998). Our results, with biometric analyses of three hormones, measured individually and in terms of coupling, provide the beginnings of a foundation for better understanding of developmentally sensitive hormone associations by integrating a different level of analysis — genetics — to the investigation of hormones and behavior.

Limitations and Future Directions

Some study limitations should be considered. This was a normative sample of children and adolescents, and therefore, only a subset of family members and twins had high stress and psychopathology symptoms. In this community sample, self-reports of severe stress (indirectly indexed by low parent education and low SES) only accounted for approximately 22% of the variance, and severe psychopathology symptoms accounted for about 30% of the variance.

A strength of the study is the longitudinal sampling of the same twins and their families at age 8 years and then at age 13 years, which allowed us to examine distal and concurrent family measures of stress and psychopathology symptoms. One weakness of the study is that we did not have puberty at the T1 sampling to compare physical status pre-puberty to during puberty and hormone levels and coupling across two time points.

Our study adds to a small literature studying waking hormone levels and coupling, prior to stressful events of the day (King, Colich, & Gotlib, 2019; Ruttle et al., 2015; Black et al., 2018). Studies that have relied on waking hormone levels also typically reveal strong developmental effects on HPA-HPG axis coupling, as we did here. That being said, examining only morning hormone levels and coupling has limitations. Unique patterns of hormone coupling have been revealed when hormones are collected across the day to reveal a diurnal rhythm (Marceau et al., 2015; Matchock et al., 2007); these studies find that stressful moments within the day impact the strength of coupling. Observing morning

hormone levels controls for other day-to-day confounders as youth have not yet experienced stress outside of waking up. Examining hormone level and coupling in the evening times may provide useful information on regulatory patterns of the HPA-HPG axes throughout an adolescent's day.

Regarding genetic considerations, our study focused on basic research questions on gender differences in additive genetic, shared and non-shared environmental influences on hormone coupling. Future work is needed to examine moderators of coupling and the genetic and environmental influences on hormone coupling. For example, puberty has genetic and environmentally mediated influences on coupling (Van Hulle et al., 2015). Adding on stress load (or allostatic load) to biometric models would be informative. Future research should also incorporate samples than are enriched for youth who have earlier vs. delayed puberty relative to their peers. While this future work is needed to better understand the mechanisms of cross-axes coupling, a consistent take-away message from our study as well as (Van Hulle et al., 2015) is that these hormonal parameters and their coupling, despite being physiological biomarkers, are highly influenced by the youth's environment including their overall family ecology, which is shared across family members. Parenting behaviors or styles can also influence hormone coupling and is worth examining in the family context.

Lastly, youth's own psychopathology symptoms were not examined in the present study; these symptoms can arise, in part, from early life stress (McEwen, 2003; Hodes & Epperson, 2019). Testing the link between youth's psychopathology symptoms and hormone coupling as a result of family antecedents is a likely next step.

Conclusion

The goal of this paper was to advance the study of stress, early experiences, and development through relatively novel approaches. We approach the study of stress psychobiology by extending beyond cortisol as the sole hormonal end-product of the HPA axis and consider HPA-HPG axis coupling in depth. Within a large twin sample, we replicated positive coupling in adolescents and further demonstrated modulation of HPA-HPG axis coupling by concurrent family stress (especially in females), as well as by stress exposure 5 years earlier. These SEM analyses were complemented by bivariate biometric Cholesky models, which consistently demonstrated large shared and non-shared environmental effects on HPA-HPG axis coupling. These genetically informed models point to the profound impact of the environmental milieu and family ecology for shaping psychobiological processes through puberty (Morris, Silk, Steinberg, Myers, & Robinson, 2007; Steinberg, 2000)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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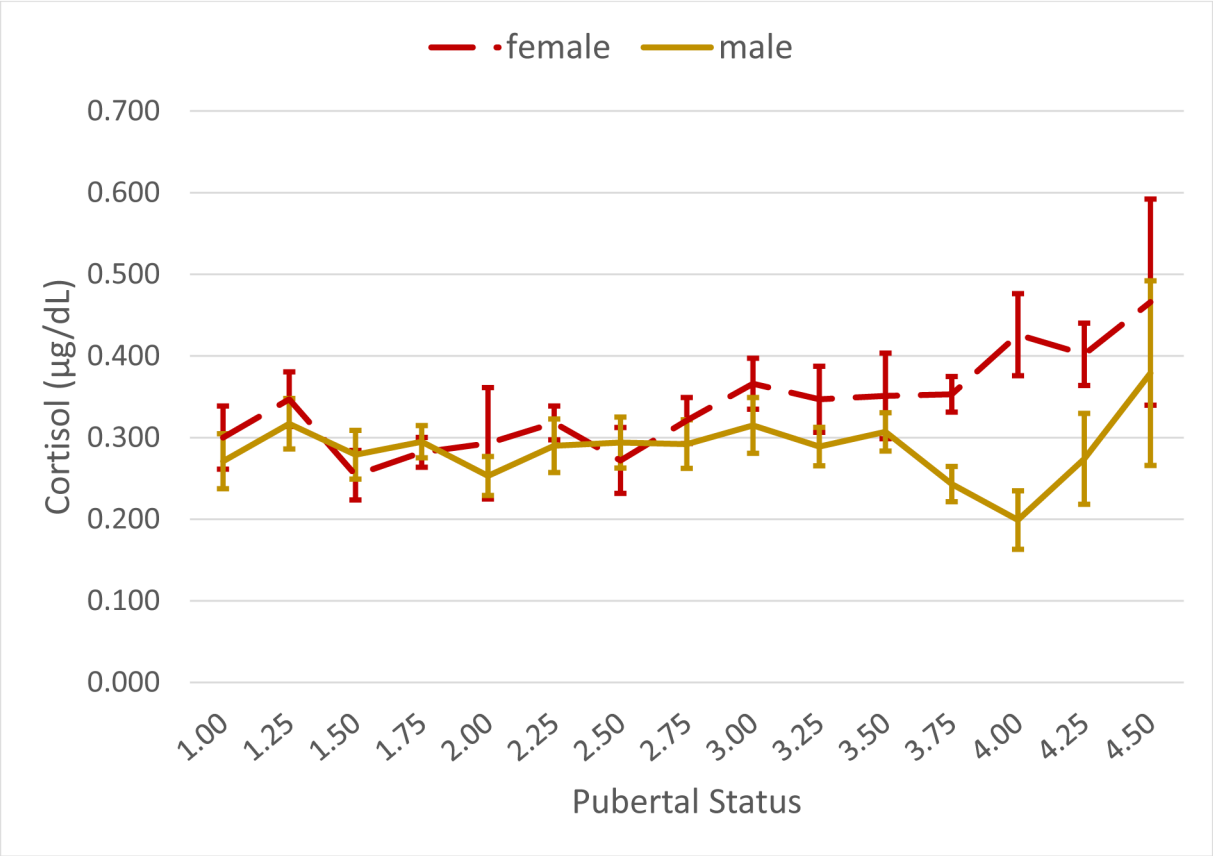

Figure 1a.

Gender differences in average morning cortisol level by pubertal status

Note: Approximately 10% adolescents were excluded due to manufacturer differences in hormone metrics. Pubertal status, derived from Shirtcliff et al., 2009, is a semi-continuous measure, that maps onto Tanner stages. See Table A1 in the supplement section for total number of adolescents by pubertal status.

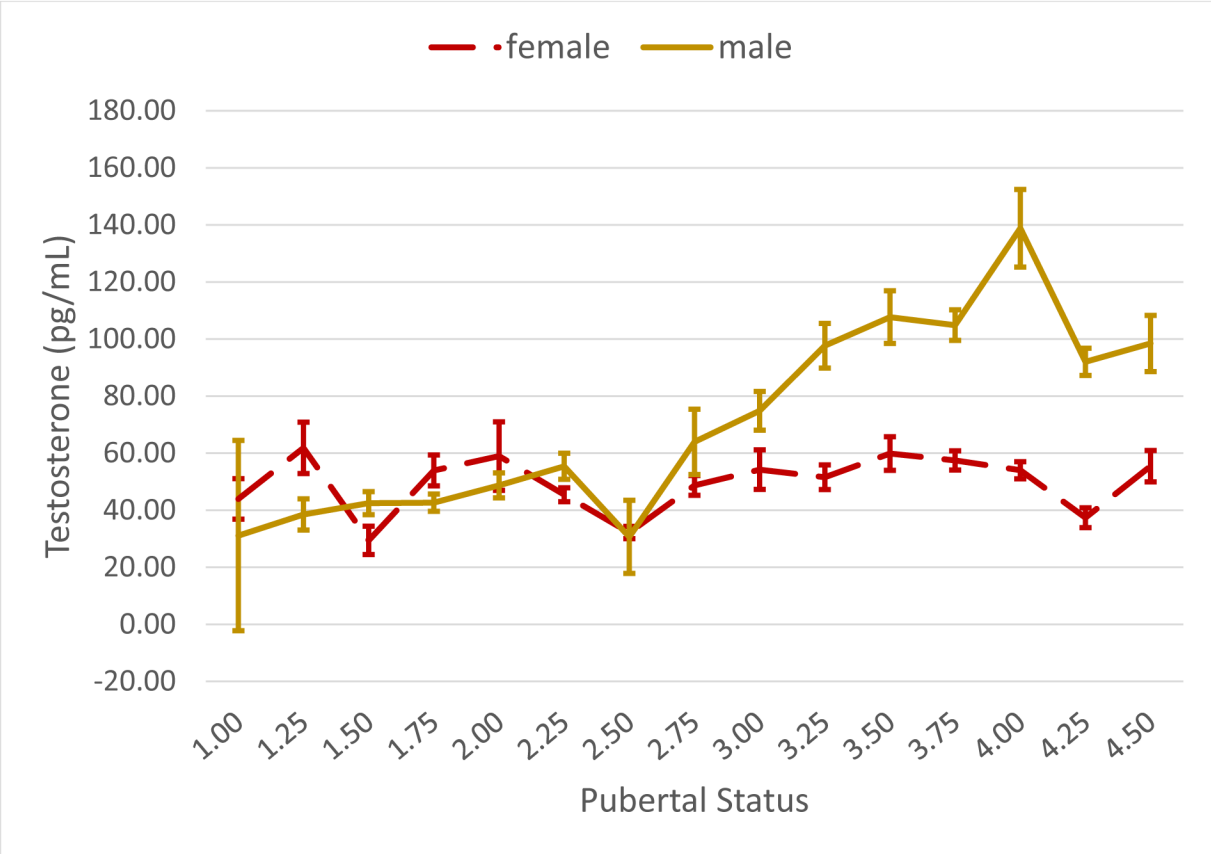

Figure 1b.
Gender differences in average morning testosterone level by pubertal status
Note: See Table A1 in supplement section.

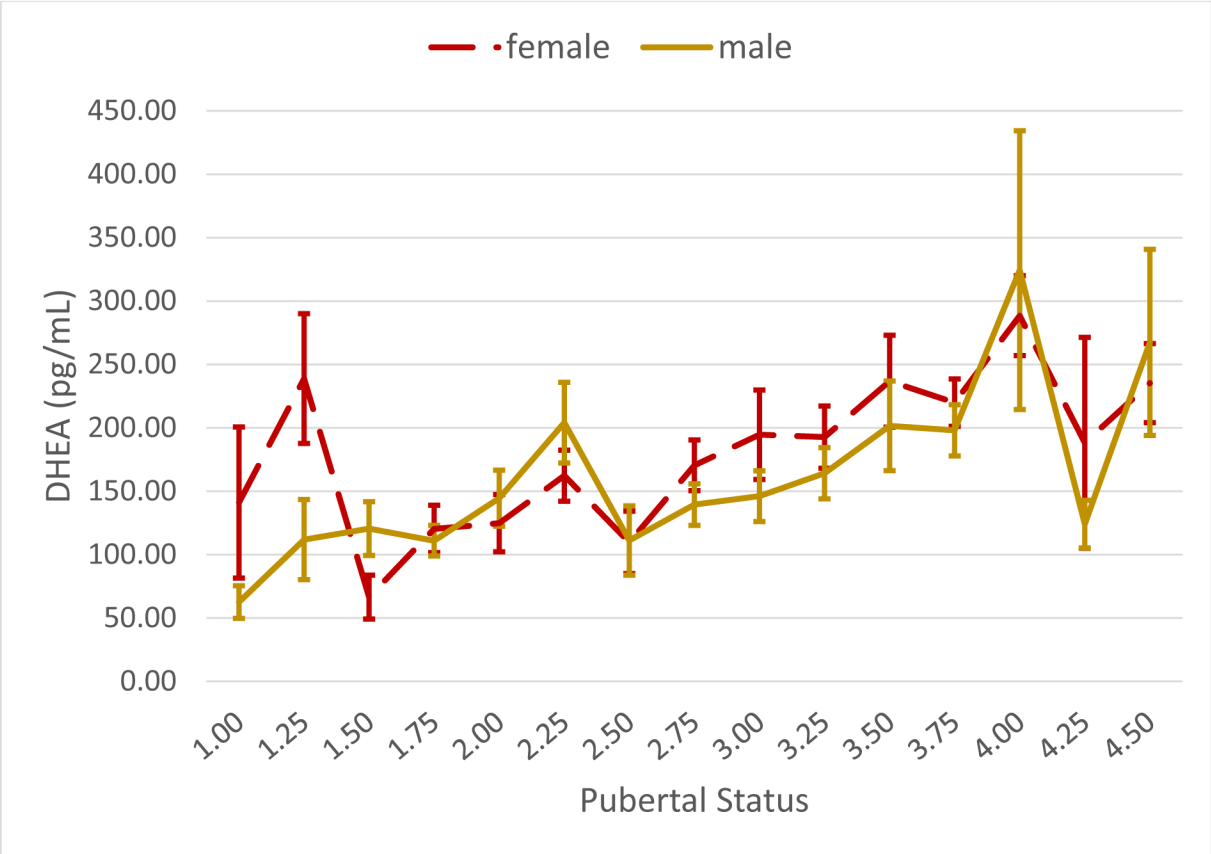

Figure 1c.
Gender differences in average morning DHEA level by pubertal status
Note: See Table A1 in supplement section.

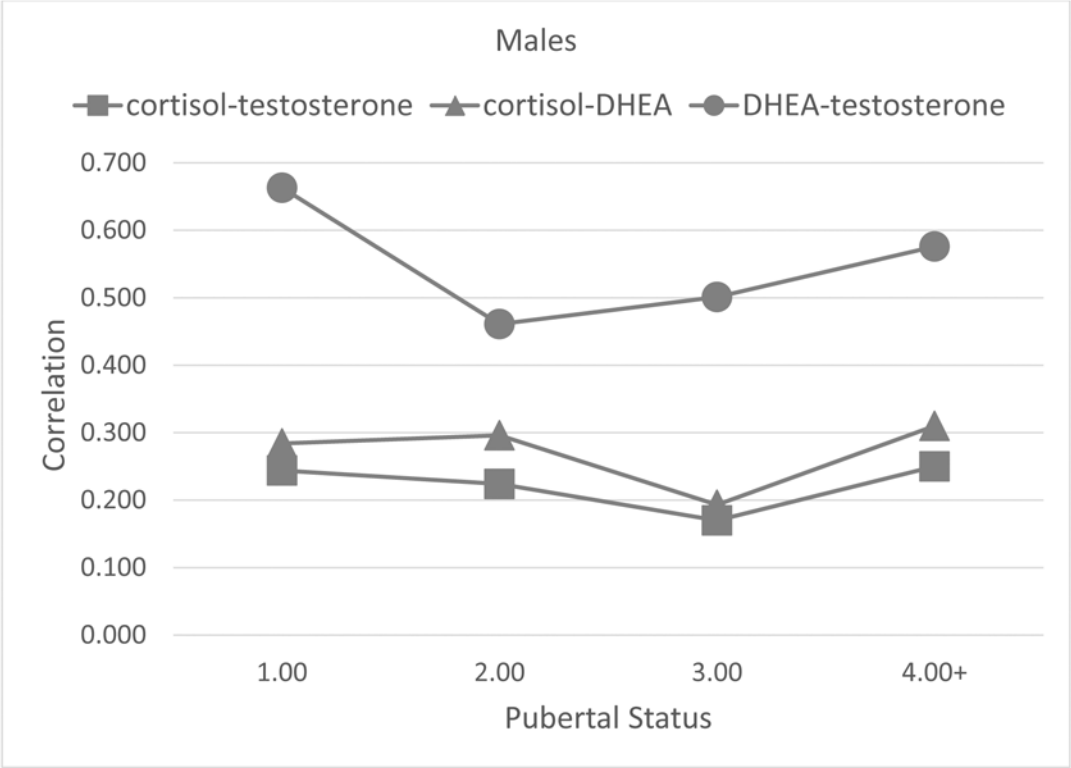

Figure 2a.

Pearson correlations of log transformed hormone coupling at each pubertal stage in males

Note: Pubertal status is a categorical variable deriving from Shirtcliff et al., 2009. Fractional pubertal stage was recoded into whole numbers, and due to only N = 3 adolescents were in Tanner stage 5, it was then combined with stage 4.

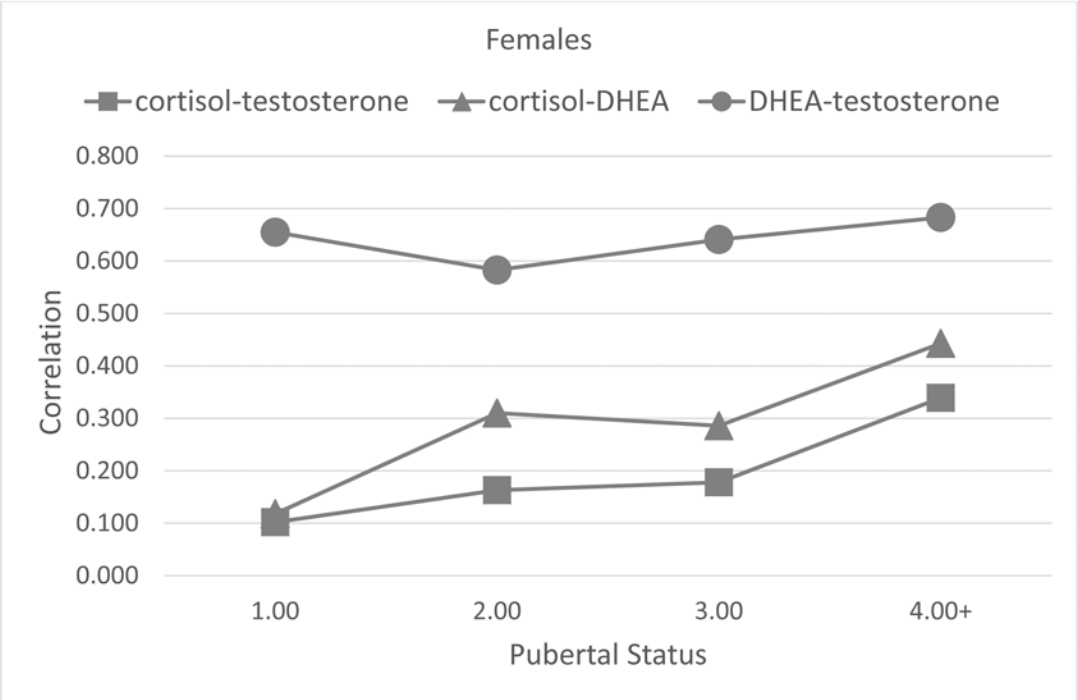

Figure 2b.
Pearson correlations of log transformed hormone coupling at each pubertal stage in females

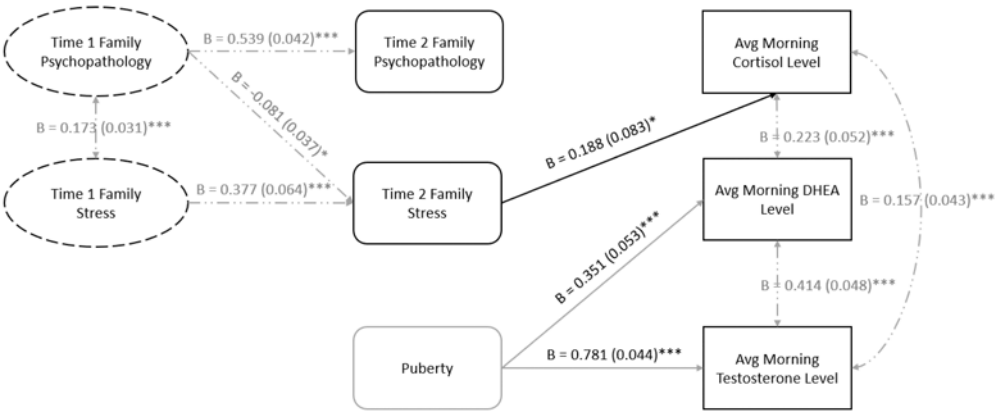

Figure 3.

SEM of distal and concurrent family factors examining effects on average morning hormone levels in males.

Note: Unstandardized beta coefficients included first and standard error of the mean in parentheses. All variables standardized prior to analysis. Only paths that were significant at $p < 0.05$ (or trend level) shown. Time 1 = 8 years of age. Time 2 = 13 years of age. Puberty = pubertal stage. B = unstandardized beta coefficient. Avg = average.

$p < 0.10+$, $p < 0.05*$, $p < 0.01**$, $p < 0.001***$

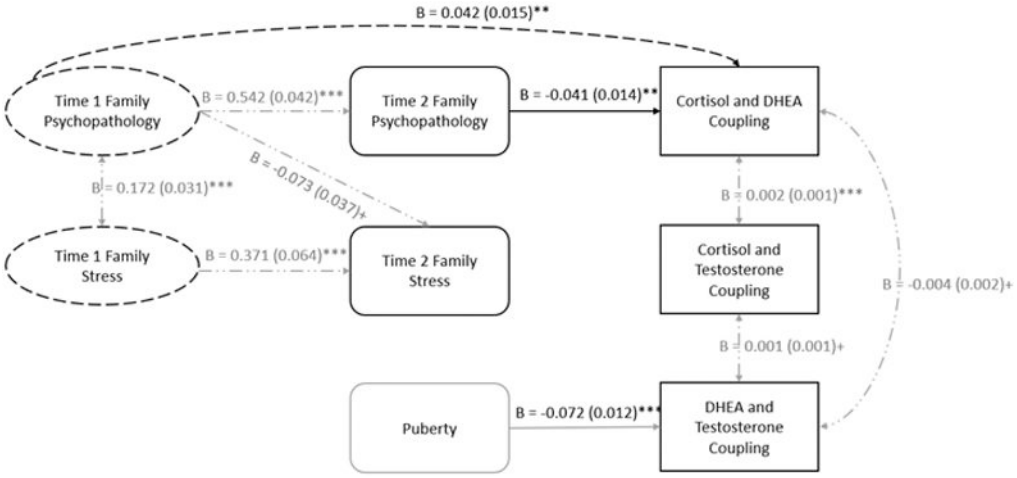

Figure 4.

SEM of distal and concurrent family factors examining effects on hormone coupling in males

Note: Hormone coupling variables are the empirical Bayes estimates extracted from the Hiearchical Linear Model equations 1 to 3. The first listed hormone in each box is the outcome hormone, and the second listed hormone is the predictor hormone.

$p < 0.10+$, $p < 0.05*$, $p < 0.01**$, $p < 0.001***$

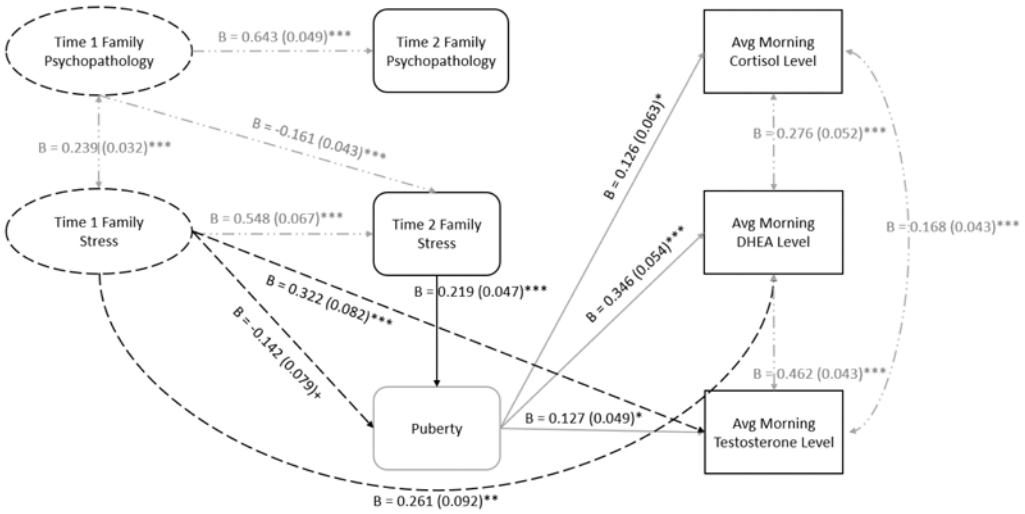

Figure 5.

SEM of distal and concurrent family factors examining effects on average morning hormone levels in females

p < 0.10+, p < 0.05*, p < 0.01**, p < 0.001***

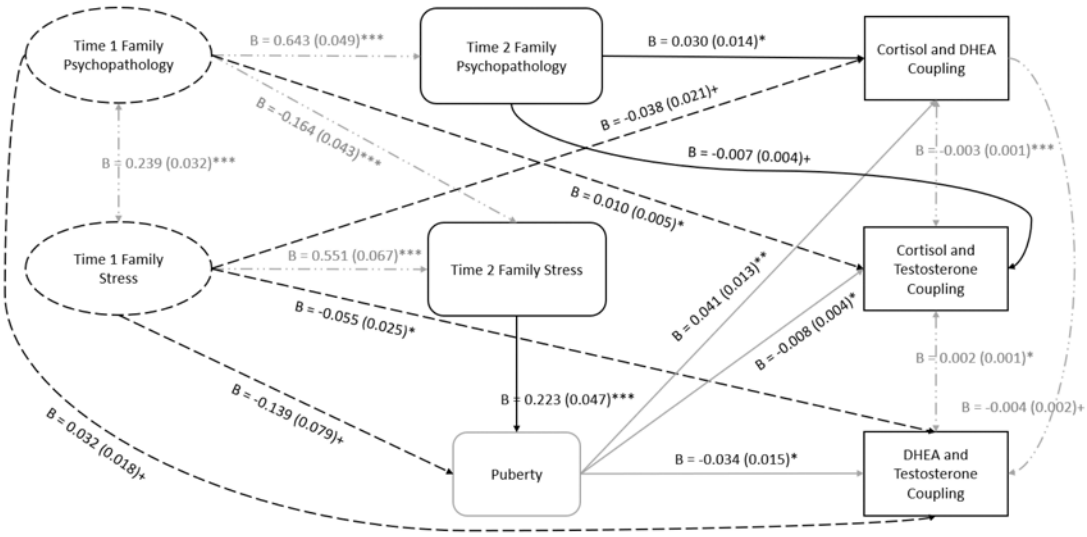

Figure 6.

SEM of distal and concurrent family factors examining effects on hormone coupling in females

$p < 0.10+$, $p < 0.05*$, $p < 0.01**$, $p < 0.001***$

Table 1

Descriptive Statistics of Family Psychopathology and Family Stress Measures across Time

Psych Symptoms, Stress	Reported	N		Means (SD)		Range	
		T1	T2	T1	T2	T1	T2
BDI	Mother	700	726	6.52 (6.59)	5.75 (5.74)	0-35	0-30
	Father	614	580	7.48 (4.66)	4.72 (5.14)	0-25	0-27
HBQ	Mother						
Internalizing		580	831	0.374 (0.28)	0.229 (0.26)	0-1.41	0-1.73
Externalizing		580	831	0.340 (0.30)	0.162 (0.22)	0-1.72	0-1.39
FCS	Mother	699	676	21.88 (5.89)	22.53 (6.10)	6-46	10-46
SIPA	Mother	-	445	-	49.50 (3.89)	-	34-59
	Father	-	366	-	48.37 (4.26)	-	28-62
PSI	Mother	722	62	3.84 (0.64)	3.49 (0.84)	6.18-2772.81	5.94-216.59

Note. T1 = time 1. T2 = time 2. Psych = Psychopathology. BDI = Beck Depression Inventory (mother- and father-reported for self). HBQ = Health & Behavior Questionnaire (mother-reported for children). FCS = Family Conflict Scale (mother-reported). SIPA = Stress Index for Parents of Adolescents (mother- and father-reported). PSI = Parenting Stress Index - short form (mother-reported).

Table 2

Means and Standard Deviations of Twin Pairs' Age and Tanner Stage at Time 2

Zygosity and sex	Age		Tanner Stage	
	M	SD	M	SD
monozygotic female	13.39	1.50	3.19	0.87
monozygotic male	13.59	1.57	2.87	1.05
dizygotic same-sex female	12.85	1.20	2.92	0.92
dizygotic same-sex male	13.16	1.32	2.57	1.00
dizygotic opposite-sex female	12.92	1.29	3.06	0.85
dizygotic opposite-sex male	12.92	1.29	2.58	0.95

Note. Means and standard deviations are based on twin long-file format (i.e., each twin is a case).

Table 3

Correlation among Age, Pubertal Status, Gender, SES, and Hormone Level Variables at Time 2

		1	2	3	4	5	6
1	Gender						
2	Age	0.062					
3	SES	0.045	−0.114 *				
4	Pubertal Status	−0.185 **	0.607 **	0.054			
5	Cortisol	−0.158 **	0.028	0.048	0.117 *		
6	Testosterone	0.219 **	0.312 **	0.018	0.346 **	0.145 **	
7	DHEA	−0.178 **	0.251 **	−0.045	0.323 **	0.309 **	0.485 **

Note. In this table, the pubertal status variable is the factor score that combined the derived score from Shirtcliff et al., 2009 and Tanner staging (see Methods). Cortisol, testosterone, and DHEA were log-transformed, z-scored variables. SES was a z-score of family income and mom and dad education levels. Gender was coded 1 = female, 2 = male.

p<0.10+

* p<0.05

** p<0.01

*** p<0.001

Table 4

Unstandardized Parameters Estimates from Biometric Models

	A1	A2	C1	C2	E1	E2	Total Variance
Cortisol-DHEA bivariate Cholesky							
Females/Males							
DHEA	.66 (.09)		.49 (.11)*		.55 (.03)*		0.98
Cortisol	−.01 (14)	.00 (.39)	.31 (.14)*	.60 (.08)*	.24 (.04)*	.67 (.03)*	0.97
Cortisol-Testosterone bivariate Cholesky							
Females							
Testosterone	.31 (.11)*		.56 (.07)*		.52 (.03)*		0.67
Cortisol	−.17 (.14)	.00 (.39)	.30 (.09)*	.64 (.08)*	.14 (.06)*	.70 (.04)*	1.03
Males							
Testosterone	.67 (.11)*		.78 (.11)*		.45 (.04)*		1.26
Cortisol	−.31 (.11)*	.00 (.43)	.35 (.09)*	.49 (.10)*	.19 (.07)*	.64 (.05)*	0.91
DHEA-Testosterone bivariate Cholesky							
Females							
Testosterone	.30 (.13)*		.58 (.07)*		.52 (.03)*		0.69
DHEA	−.06 (.17)	.40 (.16)*	.56 (.07)*	.40 (.16)*)	.32 (.04)*	.43 (.03)*	0.92
Males							
Testosterone	.68 (.12)*		.76 (.11)*		.45 (.05)*		1.25
DHEA	.47 (.29)*	.64 (.05)*	.54 (.10)*	.02 (.19)	.21 (.06)*	.50 (.04)*	1.08

Note: Total variance is the model estimated phenotypic variance. Standard errors are shown in parentheses. A1 = additive genetic effect on first hormone level. A2 = residual additive genetic effect on second hormone level; C1 = shared genetic effect on first hormone level. C2 = residual shared environmental effect on second hormone level. E = non-shared environmental effect on first hormone. E2 = residual non-shared environmental effect on second hormone level.

* $p < 0.05$

Table 5

Proportion of Phenotypic Variation Accounted for by Each Factor

	A1	A2	C1	C2	E1	E2
Cortisol-DHEA bivariate Cholesky						
Females/Males						
DHEA	45%		25%		30%	
Cortisol	0%	0%	10%	37%	6%	47%
Cortisol-Testosterone bivariate Cholesky						
Females						
Testosterone	14%		46%		39%	
Cortisol	3%	0%	8%	40%	2%	47%
Males						
Testosterone	36%		48%		16%	
Cortisol	10%	0%	13%	27%	4%	46%
DHEA-Testosterone bivariate Cholesky						
Females						
Testosterone	13%		48%		39%	
DHEA	0%	17%	34%	17%	11%	20%
Males						
Testosterone	37%		46%		16%	
DHEA	8%	38%	27%	0%	4%	23%

Note: Standardized estimates for A, C and E, reflect the proportion of the total phenotypic variance that is accounted for by additive genetic variation or heritability, shared environmental variation, and non-shared environmental variation. Values in each row sum to 1.0 (minus rounding errors).