Development and Psychopathology (2024), **36**, 1638–1652
doi:10.1017/S0954579423000937

CAMBRIDGE UNIVERSITY PRESS

Regular Article

Biobehavioral mechanisms underlying testosterone and mood relationships in peripubertal female adolescents

Elizabeth Andersen, Julianna Prim, Alana Campbell, Crystal Schiller, Kayla Baresich and Susan Girdler
Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA

Abstract

The pubertal transition is characterized by pronounced sex hormone fluctuation, refinement of affective neural circuitry, and an increased risk of depression in female adolescents. Sex hormones, including testosterone, exert modulatory effects on frontal-limbic brain networks and are associated with emotion dysregulation and depressive symptoms. Weekly changes in hormones predict affective symptoms in peripubertal female adolescents, particularly in the context of stress; however, the biobehavioral mechanisms underlying hormone change and mood relationships during the pubertal transition have yet to be determined and was the objective of the present study. Forty-three peripubertal female adolescents (ages 11–14) collected 8-weekly salivary hormone (estrone, testosterone) samples and mood assessments to evaluate hormone-mood relationships, followed by a biobehavioral testing session with psychosocial stress and EEG. Within-person correlations between weekly hormone changes and corresponding mood were performed to determine individual differences in mood sensitivity to weekly hormone change. Increased frontal theta activity indexing emotion reactivity, reduced cortisol reactivity, and reduced vagal efficiency predicted the strength of the relationship between testosterone and mood. Further, testosterone-sensitivity strength was associated with the enhancement of negative affect following stress testing. Results identify divergent frontal theta and stress responses as potential biobehavioral mechanisms underlying mood sensitivity to peripubertal testosterone fluctuation.

Keywords: peripuberty; stress; EEG; testosterone; negative affect

(Received 3 November 2022; revised 24 June 2023; accepted 24 June 2023; First Published online 2 August 2023)

Introduction

Dramatic changes to the reproductive endocrine environment, physiological stress systems, and brain morphology that occur during the pubertal transition converge to make the pubertal transition a unique window of vulnerability for psychopathology, particularly for female adolescents (Cyranowski et al., 2000; Hankin et al., 2007; Liu et al., 2022; Solomon & Herman, 2009). A differential sensitivity to normal changes (not mean levels) in sex hormones has been shown to precipitate the emergence of affective symptoms across the female reproductive lifespan (Bloch et al., 2000; Gordon et al., 2018; Schiller et al., 2016, 2022), including the pubertal transition (Andersen et al., 2022). Accordingly, a large proportion of peripubertal female adolescents are mood sensitive to changes in estrone and testosterone (Andersen et al., 2022). Rates of depression and suicide attempts are rising faster for female adolescents than other demographics (Mojtabai et al., 2016; Ruch et al., 2019), and earlier onset depression predicts a more debilitating course of illness (Liu et al., 2015). The biobehavioral mechanisms underlying the relationship between hormone changes and affective symptoms have yet to be defined in the pubertal transition, a pivotal developmental window in which mental illness trajectories are established (Blakemore, 2008). The present study investigated the distinct neural, autonomic, and endocrine features of the pubertal transition that may increase mood sensitivity to normal peripubertal hormone fluctuation.

Reproductive endocrine environment and mood during the pubertal transition

As reproductive hormones rise with puberty and begin to fluctuate with the menstrual cycle, there is an increased risk for depression in female adolescents compared to male adolescents (Angold, 1993; SAMHSA, 2020). There is additional risk with reproductive transition events associated with dramatic hormone change (Schiller et al., 2016), including the turbulent hormone fluctuation that occurs during the menopause (Gordon et al., 2016) and pubertal transitions (Andersen et al., 2022). Indeed, 39% of perimenopausal participants exhibited mood sensitivity to changes in E1G, a urinary metabolite of estradiol (Gordon et al. 2020). However, an even larger proportion (>50%) of female adolescents were found to be mood sensitive (i.e., deterioration of mood with greater weekly hormone changes) to estrone and testosterone (Andersen et al., 2022). Testosterone, potentially more than estradiol (Copeland et al., 2019), predicts depressive symptoms in peripubertal female adolescents. To date, most research on testosterone and mood is restricted to diurnal assessments in male participants, along with a few cross-sectional studies reporting a positive relationship between testosterone and aggression (Duke et al., 2014), behavioral impulsivity in females

Corresponding author: Elizabeth Andersen; Email: Elizabeth_Andersen@med.unc.edu

Cite this article: Andersen, E., Prim, J., Campbell, A., Schiller, C., Baresich, K., & Girdler, S. (2024). Biobehavioral mechanisms underlying testosterone and mood relationships in peripubertal female adolescents. *Development and Psychopathology* **36**: 1638–1652, https://doi.org/10.1017/S0954579423000937

(Bjork et al., 2001; Fujisawa et al., 2011), saliency of emotional stimuli (Nielsen et al., 2013) and disinhibition (Hildebrandt et al., 2016). Longitudinal studies, while limited, have shown that increased testosterone over 8 months is associated with greater fluctuations in affect (Klipker et al., 2017). Additionally, a greater change in testosterone over two years predicted increased amygdala activity in response to emotional stimuli in adolescent males (Spielberg et al., 2014).

Stress regulation and frontal-mediated cognitive control as potential biobehavioral mechanisms underlying susceptibility to hormone-induced mood changes

The pubertal transition is accompanied by extensive pruning, myelination, and refinement of frontal neural architecture, making the frontal cortex and associated cognitive processes (e.g., cognitive control) most vulnerable to the deleterious effects of stress (cortisol) exposure (Lupien et al., 2009). Frontal and limbic brain networks that support stress and emotion regulation are densely innervated with estrogen and testosterone receptors (Brann et al., 2007; Hwang et al., 2021), permitting significant hormone-induced neuromodulation of the hypothalamic-pituitary-adrenal (HPA) axis response to stress and frontal cognitive control (Ge et al., 2001; Lupien et al., 2009). The impact of sex hormones on HPA axis regulation may be particularly significant during the pubertal transition, a period of profound reproductive endocrine changes (ter Horst et al., 2012).

Dysregulation of HPA stress activity and frontal-mediated emotional reactivity may increase susceptibility to stress in affective illness (Bos et al., 2018) and contribute to hormone-mood relationships during the pubertal transition (Parker et al., 2003). Following a diathesis-stress model of adolescent psychopathology, exposure to life stress proximal to the pubertal transition may modify vulnerable frontal neural networks responsible for emotion and stress regulation, thus making adolescents more susceptible to experiencing affective impairment in the presence of *normal* peripubertal hormones (i.e., an acute stressor) (Andersen et al., 2023).

Vulnerable stress systems during the pubertal transition

Starting mid-puberty, female adolescents have greater interpersonal stress exposure (Ge et al., 2001), negative affective responses to stress (Ordaz & Luna, 2012), and peripheral physiological stress dysregulation than their male peers (Gunnar et al., 2009). Accordingly, HPA dysregulation (Colich et al., 2015; Gunnar et al., 2009; Hankin et al., 2007; Marcotte et al., 2002; Owens et al., 2018; Rudolph, 2002) and reduced cardiac autonomic function (vagal tone) has been found to predict the emergence of affective illness in adolescents (Mestanikova et al., 2019; Scott & Weems, 2014). Vagal efficiency (VE) is an index of the dynamic "efficiency" of vagal tone (i.e., cardioinhibitory pathways to the heart) in regulating heart rate (Porges, 2022). This reflects the coordination of the parasympathetic and sympathetic autonomic systems in facilitating adaptive responses to environmental challenge and maintaining homeostasis (Porges, 2007b). Functionally, VE provides an estimate of how much heart rate would change with a standardized unit change in the amplitude of parasympathetic influence (respiratory sinus arrhythmia) (Porges, 2022). Low vagal tone is associated with inferior emotion regulation in youth and may indicate sensitivity to stress-related affective illness (Beauchaine, 2001; McLaughlin et al., 2015). Like vagal tone (Appelhans & Luecken, 2006), VE may be used as a marker of self-regulation and has been an indicator in specific conditions (dysautonomia [Dale et al., *under review*], Ehlers-Danlos Syndrome [Kolacz et al., 2021; Porges, 2022]). Dysregulation of endocrine and autonomic stress responses, with deviations in either direction (i.e., hyperreactivity or hyporeactivity "blunted" response profiles), often precedes mental illness onset, and contributes to the risk of psychopathology (Guerry & Hastings, 2011).

Frontal-mediated emotion regulation and cognitive control related to adolescent psychopathology

During puberty, delayed maturation of frontal networks critical for top-down cognitive control, are overshadowed by the rapid development of limbic regions involved with emotion and stress reactivity. This heterogeneous pattern of neural development produces instability between emotion processing and frontal-control systems, contributing to affective dysregulation and greater risk for affective disorders during adolescence (Spear, 2000). Frontal-mediated cognitive and emotion regulation can be indexed by increased oscillations in the theta frequency band (4-–8 Hz) (Ertl et al., 2013; Knyazev, 2007), which are potentially generated in the prefrontal cortex and anterior cingulate cortex and can be modified by sex hormones (Brötzner et al., 2015). Frontal theta activity has been widely studied in patients with affective illness. Patients with major depression show increased theta in the frontal cortex and anterior cingulate cortex (Arns et al., 2015; Auerbach et al., 2015), which may predict a beneficial response to antidepressant medications. This effect, however, is likely specific to the type of antidepressant treatment (Arns et al., 2015; Koo et al., 2017). While most studies examine differences in frontal theta between clinical groups at rest, distinct neurophysiological profiles may be best exposed during emotional challenges (Coan et al., 2006). Additionally, theta oscillations have been proposed to provide a mechanism to support the functional coupling of distributed frontal and limbic neural networks (Lesting et al., 2011; Sperl et al., 2019), implicated in cognitive paradigms like the emotional go/no-go task (Hare et al., 2008).

The current study

A multimodal approach combining weekly salivary hormone and mood collections with a laboratory session involving EEG and stress testing was used to identify distinct neurophysiological, stress, and behavioral profiles that may predict the strength of the relationship between weekly change in sex hormones (testosterone, estrone) and affective symptoms (hormone-sensitivity strength). The primary objective of the present study was to examine frontal brain dynamics and stress reactivity as mechanisms contributing to hormone change-induced affective symptoms during the pubertal transition. Distinct neurophysiological (i.e., increased event-related frontal theta oscillations during an emotional go/no-go paradigm) and stress profiles (i.e., greater HPA cortisol reactivity, reduced RSA, and vagal efficiency to a psychosocial stress manipulation) were expected to predict a stronger relationship between hormone change and affective symptoms in peripubertal female adolescents. Hormone-sensitivity strength, particularly T-sensitivity strength, was expected to be associated with greater depressive symptoms, perceived stress, behavioral inhibition, and a greater affective response to stress testing.

https://doi.org/10.1017/S0954579423000937 Published online by Cambridge University Press

Methods

Participants

Adolescents (11–14) assigned female at birth and pre- or within 1-year post-menarche participated in the present study. Recruitment began in December 2017 and ended abruptly in March 2020 with the COVID-19-related restrictions on human research. 46 participants (out of the 52 total participants) completed Phase 1 – enrollment, Phase 2 – assessment of hormone and mood relationships, and Phase 3 – the biobehavioral testing session, due to the abrupt cessation of in-person human subject research. Participant characteristics and Phases 1 and 2 of the study have been published previously (Andersen et al., 2022, 2023). Briefly, participants were recruited from the local community using flyers, parent online communication from local middle schools, and mass emails to university staff. Based on self- and parental-reported puberty status on the Pubertal Development Scale (Petersen et al., 1988), participants met criteria for mid-puberty (corresponding to Tanner Stages 3 or 4) and were undergoing a typical pubertal transition. Exclusion criteria included using any hormonal supplement or pharmacological intervention affecting hormone or mood (e.g., hormonal contraceptives, antidepressants), active suicidal ideation, or severe mental illness (e.g., psychosis, bipolar disorder) that would prevent compliance with the study protocol. The study was conducted with strict adherence with the ethical standards stated by the Declaration of Helsinki for the protection of human participants. Participants received a $150 Visa Gift Card for full compliance.

Procedure

The study was completed in three phases: 1) enrollment; 2) weekly hormone and mood assessments; and 3) a biobehavioral testing session. The procedure for each phase is described below and illustrated in Figure 1.

Phase 1: Screening and enrollment

After online and phone screening with parents to determine eligibility, an enrollment session was administered at which time parents provided written consent and participants gave assent to participate in the study. At enrollment, participants and parents completed online questionnaires to assess pubertal development, demographics, medical history, and current stress and mood. Height and weight were measured to compute BMI. An abbreviated diagnostic clinical interview (Structured Clinical Interview for DSM-V) assessed suicidality and severe mental illness. Participants and their parents were given instructions and collection vials for the weekly saliva collections, confirmed with research personnel that they understood the weekly assessment protocol, and scheduled the biobehavioral testing session for 8 weeks later.

Enrollment assessments

In addition to the parental report of pubertal development at screening, pubertal maturation was self-reported at enrollment with the *Pubertal Development Scale* (PDS, Petersen et al., 1988) and Tanner staging line drawings, in which participants matched line drawings of breast development and pubic hair growth with their own development (Taylor et al., 2001). Breast development and pubic hair growth were reflected in the average PDS and pictorial score, and were summed with menarche status to compute a category pubertal development score, as described previously (Carskadon & Acebo, 1993). Category scores range from 3-prepubertal to 12-post-pubertal. *Behavioral Inhibition and Behavioral Activation Systems* (BIS/BAS) is comprised of 20 items that assess behavioral activation (Reward Responsiveness, Drive, and Fun Seeking) and behavioral inhibition (anxiety; BIS) (Carver & White, 1994). Reliability scores (Cronbach's alpha) for the present sample were as follows: Reward Responsiveness = .801; Drive = .852; Fun seeking = .679; behavioral inhibition = .838.

Phase 2: Weekly hormone collections and symptom ratings

Salivary hormone collections

Participants used an unstimulated passive drool technique to provide 3 mL of saliva into cryovials at the same time each week for eight consecutive weeks. The timing of saliva collection was consistent among participants; however, 18 participants completed saliva collection visits in the afternoon (approximately 3 PM), whereas the remaining participants collected immediately upon awakening (approximately 7 AM). Saliva samples were immediately frozen, transferred to a −80°C laboratory freezer every 1–3 weeks, and later shipped in batches to ZRT Laboratory (Beaverton, OR) for analysis. Hormone samples were assayed using liquid chromatography–tandem mass spectrometry (LC–MS/MS) to achieve the most sensitive and accurate quantification of salivary hormones. Average inter-assay precision was 7.27% for estrone (E1), and 9.77% for T, with the average intra-assay coefficients of variance of 9.47% for E1 and 4.20% for T. Minimum detection limits were 0.4 pg/mL for E1 and 3.2 pg/mL for T. Measurements that fell below assay sensitivity were assigned a value that was one-half the limit of detection. Weekly compliance checks were completed to assess any changes in activity level, diet, sleep, or medication use prior to the saliva collection. Estrone was selected over estradiol (E2) for the present analyses because estrone rises before E2, and therefore has greater concentrations relative to E2 during the pubertal transition (Biro et al., 2014; Janfaza et al., 2006).

Weekly symptom ratings

Symptom ratings were collected with the saliva collection to assess general dysphoric mood during the previous week. Symptoms were assessed using an abbreviated *Daily Record Severity of Problems* (DRSP; Endicott et al., 2006) for the first 18 participants (sum of 6 items [depression, anxiety, rejection, interpersonal conflict, anhedonia, and anger] were averaged over each week) and *Center for Epidemiologic Studies Depression Scale for Children* (CESD-DC, Radloff, 1977), for the remaining participants. DRSP and CES-DC are widely used and well-validated questionnaires for assessing general dysphoric mood, with items similarly mapping onto depression, low positive affect, and interpersonal symptom constructs. Given that the objective of the present analysis was to determine the relationship between the change in hormone and subsequent general dysphoric mood, not symptom severity, person-standardized mood values were computed for DRSP and CES-DC to examine within-person hormone-induced mood change in a larger sample (Please refer to Andersen et al., 2022).

Strength of hormone-mood relationship

Hormone sensitivity strength was calculated using the method described by Gordon et al. (2020). Two within-person Pearson correlation coefficients were computed in SAS (OnDemand for Academics) to determine the strength of the relationship between hormone change (direction and degree of change) and

https://doi.org/10.1017/S0954579423000937 Published online by Cambridge University Press

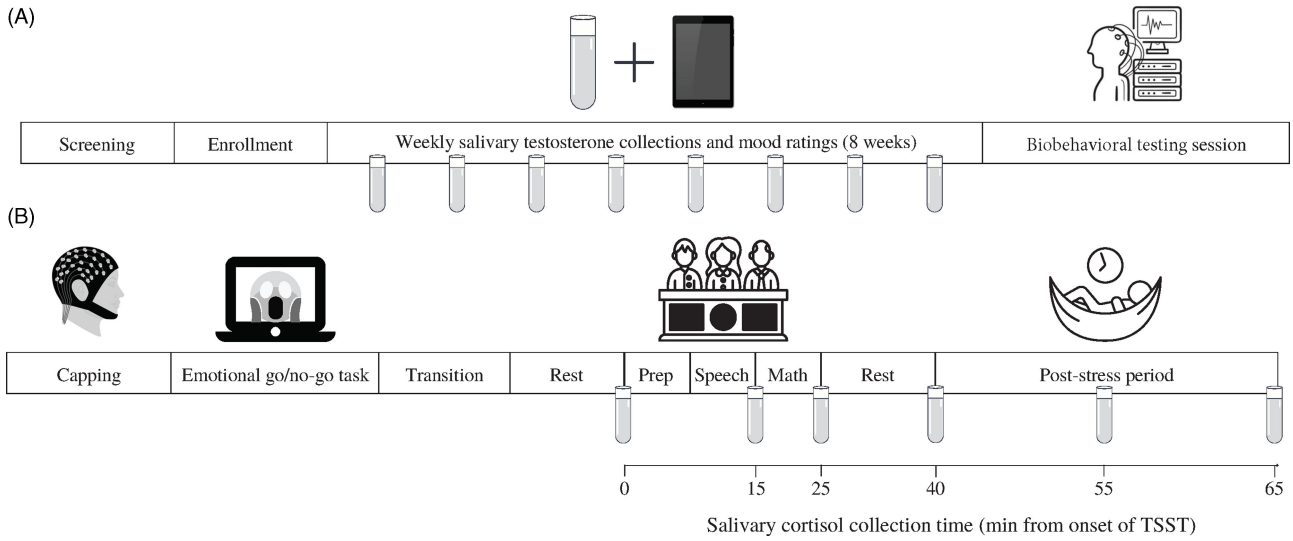

Figure 1. Schematic of A) study protocol and B) biobehavioral testing session. TSST: Trier Social Stress Test (modified for children).

corresponding mood rating, with the correlation largest in magnitude indexing hormone sensitivity strength.

(Direction) hormone-mood correlation (−1 to +1). Within-person correlations were computed between the person-standardized mood score and the weekly hormone change (i.e., the strength of the relationship between increases [positive correlation] or decreases [negative correlation] in estrone and testosterone from the week previously and a within-person elevation in mood).

(Degree) hormone-mood correlation (−1 to +1). Within-person correlations were performed between the person-standardized mood score and the absolute value of hormone change to determine the effect of large changes in hormone in either direction on greater-than-usual mood symptoms.

The absolute value of the correlation coefficient largest in magnitude between the (direction) hormone-mood correlation (positive or negative) and the (degree) hormone-mood correlation (only positive) determines the hormone-sensitivity strength. For example, if a participant has a (direction) hormone-mood correlation of −0.30, and a (degree) hormone-mood correlation of +0.50, their hormone sensitivity strength would be 0.50, suggesting that this participant is more sensitive to large changes in hormone, regardless of the direction of hormone change. Alternatively, a participant with a (direction) hormone-mood correlation of +0.60 and a (degree) hormone-mood correlation of +0.30, would have a sensitivity strength of 0.60, reflecting a mood sensitivity to increases in weekly hormone change. Therefore, hormone sensitivity strength is a summary measure that reflects the relationship between hormone change and mood, and incorporates mood sensitivity to increases, decreases, or large changes in hormone from week-to-week. Because of the limited sample size, hormone sensitivity strength was used as a continuous response variable in the present analysis, except for exploratory or visualization purposes. A hormone sensitivity strength above 0.30 is considered a moderate-to-large correlation (Cohen, 1992) and designated hormone sensitivity group status for illustration purposes, consistent with previous reports (Andersen et al., 2022; Gordon et al., 2020; Lozza-Fiacco et al., 2022).

Two participants did not have acceptable variance in estrone and testosterone (≥6 identical hormone measurements), and one participant missed three mood ratings and was not included in the analyses. All remaining participants ($n = 43$) had five or more hormone-mood pairs.

Phase 3: Biobehavioral testing session

After the 8-week hormone and mood assessments, participants returned to the lab to complete an emotional go/no-go paradigm while EEG was recorded, followed by a modified psychosocial stress test – *Trier Social Stress Test for Children* (TSST-M) (refer to the following description of tasks).

Trier Social Stress Test (TSST-M)

The TSST-M probes a developmentally salient psychosocial stressor and has been shown to elicit a robust cortisol and autonomic stress response in adolescents (Yim et al., 2015). A resting state EEG recording (8 min, not reported in the present analysis) immediately preceded the stress test. The stress task includes a preparation period (3 min), an introductory speech to a pretend new class of 20 students (5 min), and mental arithmetic (5 min) in front of an all-female 2-person committee. For the speech task, participants were instructed that they had 3 min to prepare a 5-min speech using the following prompt: "Imagine that you are in a new class with about 20 other students. Now your teacher asks you to get in front of the class and introduce yourself. In your introduction, please describe your personality, important details about yourself, and why you think you will be liked by the other students in class. You also must tell the committee one good thing and one bad thing about yourself." The prompt of introducing oneself to a new class in school is meant to elicit a psychosocial stress in adolescents that is analogous to the stress response elicited by adults in the common prompt of a job interview in which they must explain why they deserve their dream job. Participants were given a pencil and notepad to outline notes for their speech during the preparation period, but these notes were taken away before their speech. For the mental arithmetic section, participants serially subtracted 7 from 758 unless they continuously made errors and had to start over more than 5 times or were visibly distressed, in which case, they were asked to serially subtract 4 from 1000. After the stress task, participants completed an additional EEG resting state recording

https://doi.org/10.1017/S0954579423000937 Published online by Cambridge University Press

(8 min), completed post-stress questionnaires, and rested quietly while watching a relaxing video until the post-stress period was over (65 min post-stress onset).

Cortisol stress reactivity

Salivary cortisol was collected at pre-defined intervals to capture the well-characterized cortisol response. Participants provided a passive saliva sample before instructions (0 min), after the speech (15 min) and math components (25 min), and 40 min, 55 min, and 65 min following stress onset to capture the HPA cortisol stress response. Salivary cortisol levels were determined using a commercially available high sensitivity (.007 ug/dL, range .012–3 ug/dL) competitive enzyme immunoassay kit from Salimetrics (State College, PA) with inter and intra-assay coefficients of variability at 3.88 and 6.69%, respectively. Cortisol values were natural log normalized to use in analyses. Area under the curve measurements (with respect to ground (AUC_G) and increase (AUC_I)) were calculated according to formulas derived from the trapezoid formula (Pruessner et al., 2003).

Autonomic stress measures

Electrocardiogram was recorded continuously during the bio-behavioral testing session using a Firstbeat Bodyguard 2 device and segmented into seven periods for analysis using 30 second windows: baseline (8-min resting state), preparation (3 min), speech (5 min), math (5 min), resting state post-stress (8 min), post-stress window-1 (10 min), post-stress window-2 (10 min). Heart period (HP), the average time interval between successive heartbeats (milliseconds); and respiratory sinus arrhythmia (RSA), an index of parasympathetic input (Porges, 2007a) associated with respiratory oscillation (Denver et al., 2007) were analyzed from the defined time segments pre- and post-stress manipulation. The Porges-Bohrer method was utilized to calculate RSA with a 51-point moving polynomial filter to extract heart rate variability amplitude in the respiratory frequency associated with spontaneous breathing in adolescents (.12–1.0 Hz) at 250 ms sampling rate with natural log transformation to reduce skewness (Lewis et al., 2012). The mean of 30-s epochs for HP and RSA were calculated for each time segment. Vagal efficiency (VE), a measure of the influence of cardiac vagal tone (RSA) on cardiac output (HP), was calculated from the RSA and HP values during all phases of the TSST (seven time-segments total). VE is defined as the synchronous HP and RSA slope extracted from regression analyses (Kovacic et al., 2020). The resulting single rate value is an individualized index of the myelinated vagus' influence on the dynamic regulation of the heart. VE extends the assessment of vagal tone beyond RSA to quantify the dynamic influence of the vagal 'brake" on the heart (Kovacic et al., 2020). Thus, VE (HP-RSA slope) provides a measure of the efficiency of the vagal brake on the heart in response to acute stressors (i.e., TSST-M) that trigger autonomic reactivity. Tukey's method was used to identify two outliers in VE; thus, VE was winsorized by setting values above the 95th percentile to the 95th percentile to reduce the effect of outliers.

EEG task

A modified emotional go/no-go task (Sackler Institute) was administered to probe neurophysiological correlates of frontal-mediated control of emotion reactivity (Hare et al., 2008). This task has been shown to engage limbic (amygdala) and prefrontal networks and differentiate key domains of cognitive (cognitive control, inhibition) and emotional processing (negative valence) (Colzato et al., 2010; Sundstrom Poromaa & Gingnell, 2014), while distinguishing emotion reactivity between adolescents, children, and adults (Hare et al., 2008). The task was presented using E-Prime coupled with Brain Vision recording software. The emotional go/no-go task required participants to respond as quickly and accurately as possible to emotional faces designated as "go" trials while inhibiting or withholding a response to "no-go" trials. Facial stimuli (18 females, 17 males) were selected from the NimStim stimulus set (Tottenham et al., 2009) depicting happy, fearful, and calm facial expressions and were used in each of the go and no-go combinations for a total of 6 runs (happy-go/calm no-go, happy-go/fear no-go, fear go/calm-no go, fear-go/happy-no go, calm-go/fear-no go, calm-go, happy-no go) presented in a counterbalanced order between participants. Each run had pseudorandomized blocks of go (82, 70%) and no-go (35, 30%) trials across cue types, with a total task duration of 25 min. Stimuli were presented for 500-ms, with a 10% jitter and an average of 1500-ms ISI (pseudorandomized between 1350 and 1650 ms). Proportionate hits and false alarm scores were generated for each participant to calculate *d*-prime. To account for perfect scores (accuracy of 1), 1 was added to false alarm scores and subtracted from hit scores before z-transformation. D-prime was calculated as z (hits) – z (false alarms), where a lower *d*-prime score indicates greater cognitive control.

EEG recording and preprocessing

Recording parameters

Continuous EEG was recorded from 32 electrodes with Fpz electrode as ground and Cz as reference. Data were collected at a sampling rate of 500 Hz. Impedances were maintained below 10 kΩ. A gtec g.LADYbird/Nautilus device with 32 active electrodes was used to record data for the first 27 participants. Because of repeated device and software issues, a Brain Products ActiChamp with a 32-channel actiCAP snap system was used to record the remaining 15 participants. Therefore, EEG analyses were restricted to within-participant analyses.

Preprocessing pipeline

The EEGLAB (version 2021.1) toolbox was used for preprocessing EEG data. Data were downsampled to 250 Hz and high pass filtered at 1 Hz before removing line noise with the EEGLab plugin CleanLine. The clean_rawdata plugin was implemented to correct continuous data and identify bad channels using Artifact Subspace Reconstruction (Chang et al., 2020). Bad channels were interpolated and cleaned data were re-referenced to average. Data were epoched −1 to 2 s surrounding each stimulus type. Epoched data were entered into an EEGLab study design for further processing. A minimum of 80% of trials were available for analysis following the preprocessing procedure. Theta (4–8 Hz) event-related spectral perturbation (ERSP) was extracted from frontal electrodes (Fz, F3, F4) during early (150–300 ms) and late (400–700 ms) windows, time-locked to the onset of fear and happy (paired with calm stimuli) go and no-go trials. The average ERSP recorded from a frontal electrode montage (F3, Fz, F4) was also calculated to use in analyses.

Lab self-report questionnaires

Questionnaires were completed before and after the stress manipulation to track participants' affect. At the beginning of the laboratory session, participants completed the *Mood and*

https://doi.org/10.1017/S0954579423000937 Published online by Cambridge University Press

Feelings Questionnaire (MFQ), a 33-item assessment to examine depressive symptoms over the last two weeks (Cronbach's alpha = 0.922), and the *Perceived Stress Scale* to evaluate perceived distress and ability to cope. *Perceived Stress Scale* is a 10-item survey (NIH Toolbox) that asks about the participant's stress experience over the last month. It can be decomposed into two factors (Hewitt et al., 1992): a positive worded factor that reflects the ability to cope and self-efficacy, and the negative worded factor that evaluates perceived distress. For the current sample, Cronbach's alpha for the positive worded factor (PSS-coping) and negative factor (PSS-distress) were 0.803 and 0.883, respectively. The *Positive and Negative Affective Schedule (PANAS)* assessed *current* positive and negative affect at the beginning of the session and following the stress manipulation to track changes in affect over the study session. Eleven items were used for the positive affect construct (Cronbach's alpha at timepoint 1 = 0.891, Cronbach's alpha at timepoint 2 = 0.907), and 15 items were summed for the negative affect construct (Cronbach's alpha at timepoint 1 = 0.812, Cronbach's alpha at timepoint 2 = 0.925). The items assessing daring, fearless, and alertness were omitted from the positive affect measure, as recommended by Laurent et al., 1999. The positive and negative affect scores for time point 1 were subtracted from timepoint 2 to compute difference scores.

Analytic plan

Predicting the strength of hormone-mood relationship from theta oscillatory activity, cortisol reactivity, and vagal efficiency

PROC MIXED in SAS (OnDemand for Academics) predicted the strength of the hormone-mood relationship (hormone-sensitivity strength) from average frontal theta ERSP in response to fear no-go trials, cortisol reactivity (area under the curve [AUC] with respect to increase) and VE, using a random subject intercept. Degrees of freedom were calculated using an improved Kenward-Roger method.

HPA and autonomic stress reactivity

PROC MIXED predicted cortisol (natural log-transformed, ug/dL) and autonomic stress measures (RSA, HP) from the interaction of hormone-sensitivity strength and time (pre-TSST, [HR only-TSST-prep], TSST-speech, TSST-math, post-TSST-10, post-TSST-20, post-TSST-30), with time as a repeated factor. The model intercept and within-person slope were used as random effects to account for within-person variance between the collection time points.

Stress, behavior, and affective response profiles associated with hormone-sensitivity

Repeated measures (rm) ANOVAs were performed to assess reaction time for fear and happy correct go-trials (embedded in a calm context) and no-go responses (false alarms). To validate the EEG emotional go/no-go paradigm, a Condition (go, no-go) X Emotion (fear and happy paired with calm) X Window (early, late) rm-ANOVA was applied. Subjective affect and response to the testing session were assessed using regression models predicting hormone-sensitivity strength.

Power analysis

Despite not reaching the proposed number of participants ($n = 55$) due to the cessation of research during the COVID-19 pandemic, power analysis performed in G*power confirmed that 80% power was maintained to detect medium-to-large effects of hormone sensitivity on stress and EEG variables.

Results

Demographics

Participant characteristics are presented in Table 1. Participants were predominantly White/Caucasian (79.1%), from highly educated (53.5% with a professional degree), and affluent families (with total household income over $100,000), reflecting the demographics of the local community. Participants were mid-pubertal according to the pubertal development category score, and expressed a varying degree of depressive symptoms, as assessed by the MFQ.

Hormone-sensitivity strength

Testosterone-sensitivity strength

(direction) T-mood correlation ranged from −0.612 to +0.547, with a median of 0.017; (degree) T-mood correlation ranged from −0.914 to +0.644 (median = −0.182); and T-sensitivity strength ranged from 0.017 to 0.644 (median = 0.358).

Estrone sensitivity strength

(direction) E1-mood correlation ranged from −0.576 to 0.839, with a median of 0.014; (degree) E1-mood correlation ranged from −0.818 to +0.783 (median = −0.063), and E1-sensitivity strength ranged from 0.016 to 0.839 (median = 0.355). Illustrations of E1 and T hormone sensitivity strength distributions are included in Appendix 1.

Predicting T-mood sensitivity from frontal theta ERSP and stress variables

Combined model predicting hormone-sensitivity strength

With cortisol-AUC, VE, and frontal theta ERSP in the model, T-sensitivity strength was predicted by greater theta ERSP at the average frontal montage (F3, Fz, F4) for fear-no-go trials ($F(1,34) = 5.21$, $p = .029$). However, removing VE from the model improved model fit, and implicated reduced cortisol AUC_I ($F(1,36) = 5.07$, $p = .031$) and increased frontal theta ($F(1,36) = 6.73$, $p = 0.014$; Figure 2A) as predictors of a stronger relationship between testosterone change and mood (greater T-sensitivity strength).[1] AUC_G did not predict T-sensitivity strength and was omitted from further analyses. E1-sensitivity strength was not predicted by theta ERSP ($F = .20$, $p = .65$), cortisol AUC_I ($F = 0.03$, $p = 0.85$), or VE ($F = 0.05$, $p = 0.83$).

Cortisol stress reactivity

Cortisol changed significantly over time, as indicated by a main effect of Time ($F(5,190) = 2.85$, $p = 0.017$). An interaction of T-sensitivity strength and Time indicated that the change in cortisol level in response to the stress test differed by T-sensitivity strength ($F(5,190) = 2.45$, $p = 0.035$; Figure 3A). The interaction of E1-sensitivity strength and Time was not significant ($p > 0.5$).

[1]Using a modified CES-DC score (i.e., without three items pertaining to appetite loss, fatigue, and sleep disturbances) did not significantly change results of the combined model predicting testosterone-sensitivity strength: Cortisol AUC_I ($F(1,36) = 5.10$, $p = 0.03$); frontal theta ($F(1,36) = 6.01$, $p = 0.02$).

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Table 1. Participant characteristics

Phase 1 – Enrollment			*Mean ± s.d. or %*
Age (years)			12.54 ± 0.97
Race (%)			
White/Caucasian			79.1
Black/African American			0
Asian American			0
American Indian or Alaska Native			2.3
More than one race			18.6
Ethnicity (% Hispanic or Latino)			16.3
Identify as LGBTQ+ (%)			
Yes			7.0
No			81.4
No response			11.6
Parental Education (%)[a]			
Ph.D., Law or Medical degree			16.3
Master's degree			37.2
Some post-graduate			4.7
Bachelor's degree			30.2
Associate degree			7.0
Some college			4.7
High school or GED			0
Total Household Income (%)			
Over $100,000			69.8
$75,000–$99,999			25.6
$50,000–$74,999			2.3
$35,000–$49,999			0
$20,000–$34,999			2.3
Pubertal Development Scale[b]			8.56 ± 2.14
BMI (z-score)			0.12 ± 0.78
Behavioral Approach System (BAS)			31.72 ± 6.84
Behavioral Inhibition System (BIS)			19.67 ± 4.88
Mood & Feelings Questionnaire (MFQ)			13.16 ± 10.97
Phase 2 – Weekly Hormone and Mood		r_s t-sensitivity strength[e]	r_s e1-sensitivity strength[e]
Estrone (E1) mean	1.15 ± 0.45	−0.167	−0.318*
Estrone (E1) s.d.	0.55 ± 0.48	−0.031	−0.088
Testosterone (T) mean	6.30 ± 3.06	−0.191	−0.239
Testosterone (T) s.d.	2.12 ± 1.66	−0.082	−0.261
Mood (z-score)[c] mean	−0.001 ± 0.93	0.025	0.071
Mood s.d.	0.43 ± 0.30	0.024	0.199
Phase 3 – Biobehavioral Testing		r_s t-sensitivity strength[e]	r_s e1-sensitivity strength[e]
Cortisol (AUC_G)	−144.38 ± 45.32	−0.220	0.108
Cortisol (AUC_I)	7.39 ± 28.20	−0.358*	−0.041
Vagal Efficiency (HP-RSA slope)[d]	56.74 ± 78.23	−0.374*	0.048
Reaction Time (fear-go)	407.93 ± 46.06	−0.081	−0.155
Reaction Time (happy-go)	391.66 ± 44.11	−0.003	−0.145
False Alarms (fear no-go)	18.56 ± 6.67	0.226	0.124

(*Continued*)

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Table 1. (*Continued*)

Phase 3 – Biobehavioral Testing		r_s t-sensitivity strength[e]	r_s e1-sensitivity strength[e]
False Alarms (happy no-go)	17.54 ± 7.39	0.143	−0.098
Mood & Feelings Questionnaire (*at lab*)	11.63 ± 9.50	−0.095	−0.060
PANAS-negative affect (difference)	2.07 ± 7.91	0.351*	0.257
PANAS-positive affect (difference)	−5.63 ± 7.46	0.261	−0.091
PSS-coping	6.05 ± 3.05	0.152	0.113
PSS-distress	8.72 ± 4.78	0.249	0.018

*Notes. Means are presented ± standard deviation (s.d.). * p < 0.05.* LGBTQIA+: lesbian, gay, bisexual, transgender, queer, intersex, asexual and more; BMI: body mass index; AUC: area under the curve with respect to increase (I) or ground (G); PANAS: Positive and Negative Affect Schedule; PSS: Perceived Stress Scale.
[a]Primary parent completed education level
[b]PDS: Pubertal Development Scale average category score (averaged PDS and tanner line staging score for breast development and pubic hair growth).
[c]Standardized z-scores based on within-person mean and standard deviation for DRSP (Daily Record Severity of Problems) and CES-DC (Center for Epidemiological Studies Depression Scale for Children)
[d]Vagal efficiency is the synchronous heart period (HP) and respiratory sinus arrythmia (RSA) slope extracted from regression analyses. Winsorized mean.
[e]Spearman correlation between hormone-sensitivity strength and variable.

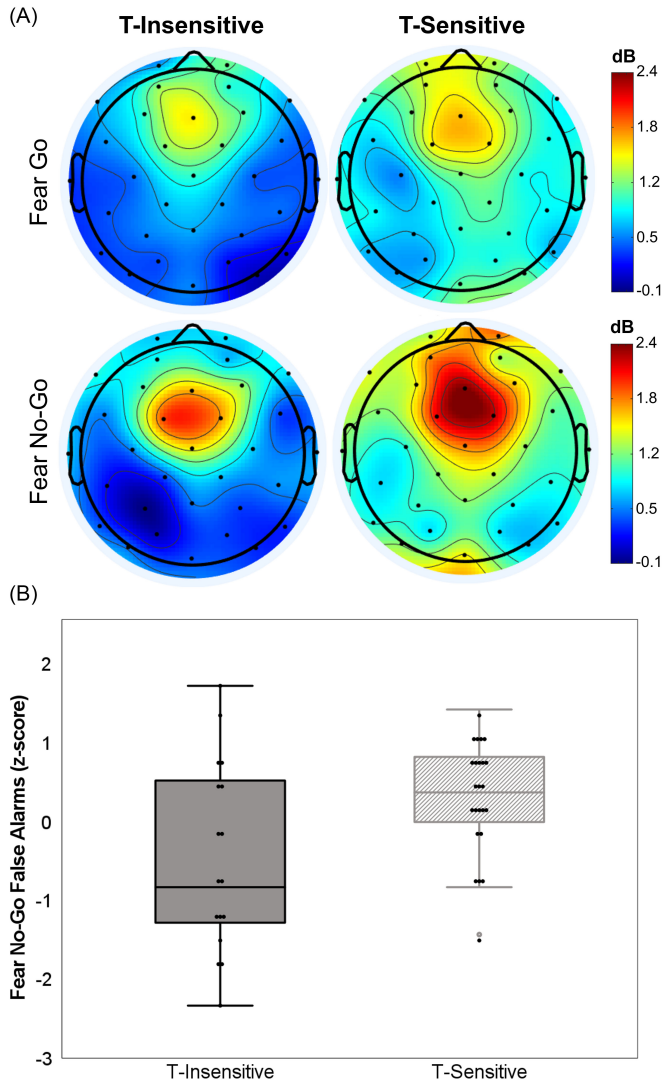

Figure 2. EEG and behavioral responses during the emotional go/no-go task. A) Topographic plots of theta (4–8 Hz) event-related spectral perturbations (dB) evoked 400–800 ms after the presentation of fearful stimuli during go and no-go trials. B) False alarm (z-score) for fear no-go trials for T-sensitive and T-insensitive participants. *Participants with T-sensitivity strength over r = 0.30 were considered "T-sensitive" for exploratory and illustration purposes only.*

Autonomic stress reactivity

Mixed models revealed an effect of Time for both RSA (Time: $F(6,232) = 4.43$, $p = .0003$, Figure 3C) and HP (Time: $F(6,232) = 15.66$, $p < .0001$, Figure 3D). Greater E1-sensitivity strength was associated with reduced HP ($F(1,39) = 5.04$, $p = 0.03$) and marginally reduced RSA ($F(1,39) = 3.23$, $p = 0.07$), as evidenced by main effects of E1-sensitivity strength, although no significant interaction effects were found. Additionally, reduced VE (i.e., HP-RSA slope) predicted greater T-sensitivity strength ($F(1,39) = 6.86$, $p = 0.013$; Figure 3B), but not E1-sensitivity strength ($p = 0.85$).

Validation of the emotional go/no-go task

Increased frontal theta ERSP for fear and happy no-go distractor trials confirmed task validity, indicated by main effects of Condition ($F(1,41) = 12.831$, $p = .001$, $\eta_p^2 = .238$), particularly during the late window ($F(1,41) = 6.713$, $p = .013$, $\eta_p^2 = .141$). Condition discrimination (i.e., greater response for no-go vs. go) was only found during the late window, as evident by a Condition X Window interaction ($F(1,41) = 20.579$ $p < .0001$, $\eta_p^2 = .334$). Planned pairwise comparisons showed greater theta ERSP for no-go trials for both fear ($F(1,41) = 5.577$, $p = 0.023$, $\eta_p^2 = .12$) and happy ($F(1,41) = 21.397$, $p < .0001$, $\eta_p^2 = .343$) (paired with calm) emotional stimuli.

Behavior during the emotional go/no-go task

Faster correct responses were made for happy-go trials (paired with calm) compared with fear-go trials, indicated by a main effect of Emotion ($F(1,39) = 11.59$, $p = .002$, $\eta_p^2 = .23$). Exploratory analyses revealed greater disinhibition (no-go errors, false alarms) for fear no-go trials ($F(1,39) = 6.579$, $p = 0.014$, $\eta_p^2 = .14$, Figure 2B), and lower *d*-prime scores for fear responses ($F(1,39) = 7.303$, $p = 0.010$, $\eta_p^2 = .16$) in participants with greater T-sensitivity strength. No additional effects were significant.

Self-report affect measures

A greater enhancement of negative affect (PANAS) between pre- and post-stress tasks was associated with greater T-sensitivity strength ($r_s = 0.351$, $p = .021$). Depressive symptoms (MFQ), and behavioral activation and inhibition (BIS/BAS) were not associated with T- or E1-sensitivity strength.

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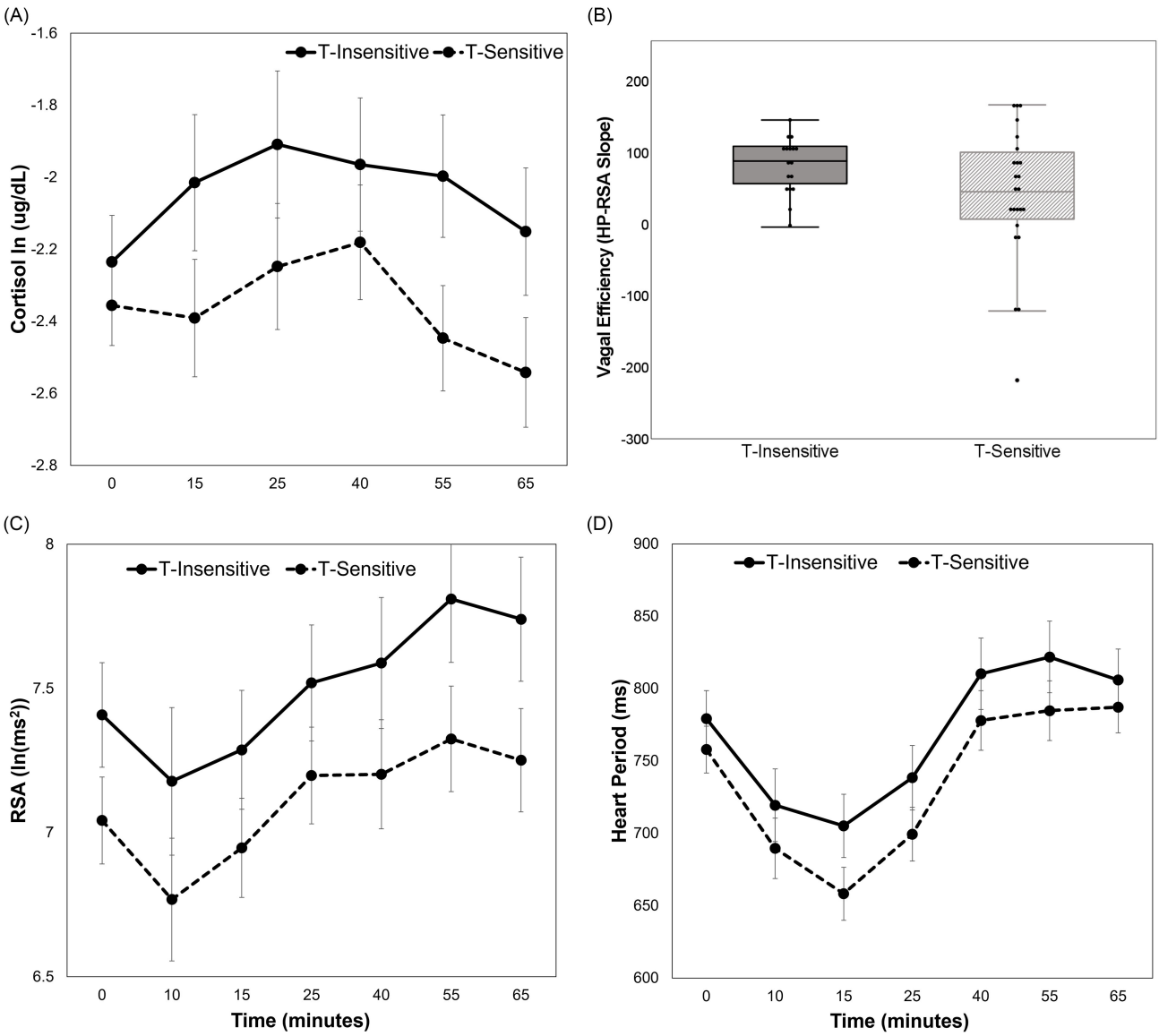

Figure 3. Cortisol and autonomic stress reactivity profiles predict T-sensitivity strength. A) Unlike T-insensitive participants, T-sensitive participants demonstrated a blunted stress response, indicated by no significant increase in cortisol during stress exposure ($p > .05$). B) Vagal efficiency (HP-RSA slope) was reduced for T-sensitive participants relative to T-insensitive participants. C) Respiratory sinus arrhythmia (RSA) (ln(ms^2)) and D) heart period (ms) during the TSST did not differ by T-sensitivity group status. *X*-axis represents the time (minutes) since the onset of the Trier Social Stress Test. *Participants with T-sensitivity strength over r = 0.30 were considered "T-sensitive" for exploratory and illustration purposes only.*

Discussion

Building off our previous results demonstrating that a high proportion of adolescent females are mood sensitive to sex hormone changes, including testosterone and estrone (over 50% using the current method), the objective of the present study was to examine frontal-mediated cognitive control and stress reactivity as potential mechanisms underlying the hormone-mood relationship during the pubertal transition. Frontal-mediated cognitive control (indexed by frontal theta oscillatory activity) and disruptions in stress regulation emerged as potential biobehavioral mechanisms underlying the relationship between hormone change, specifically testosterone change, and mood symptoms during the pubertal transition. Using a multimodal approach, we found that decreased HPA cortisol reactivity and increased event-related frontal theta oscillations associated with cognitive control predicted a stronger testosterone-mood relationship. Further, T-sensitivity strength was associated with reduced VE and increased impulsive behavioral tendencies, which is consistent with a disinhibited, impulsive neurophysiological profile.

Blunted stress reactivity predicted testosterone-sensitivity

Given the important role of adaptive stress regulation in optimal social and emotional functioning, a dysregulated stress response may make individuals more susceptible to the mood effects of peripubertal testosterone changes. Contrary to our prediction, T-sensitivity was associated with a reduced or blunted cortisol response to the psychosocial stress test. While enhanced cortisol release more often predicts affective symptoms (Gunnar et al., 2009), depression (Hankin et al., 2010; Rao et al., 2008), and

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familial risk for depression (Gotlib et al., 2015; Klimes-Dougan et al., 2022), hypo-cortisol "blunted" response patterns have been found for youth with trauma histories (Pfeffer et al., 2007) and impulse control disorders (Lovallo, 2013). Indeed, a blunted cortisol response is consistent with what has been found in adults (Melhem et al., 2016; O'Connor et al., 2017) and adolescents (Eisenlohr-Moul et al., 2018) with suicide behaviors. Specifically, in prior research, heightened peer stress predicted suicide attempts in adolescent females with a blunted cortisol stress response to the TSST (Eisenlohr-Moul et al., 2018), indicating a distinct role of interpersonal stressors in the HPA-mediated pathway to psychopathology in female adolescents. Further, blunted cortisol reactivity is associated with increased risk-taking in male adolescents (Daughters et al., 2013) and in youth with attention-deficit/hyperactivity disorder (ADHD) with the combined inattentive and impulsive subtype (van West et al., 2009).

Menarche is associated with a normative shift toward greater HPA reactivity (Stroud et al., 2009); however, this developmental transition event may make adolescents more vulnerable to dysregulation of the HPA axis, and in turn, psychopathology. Despite the positive effects of the HPA cortisol response on enhancing memory consolidation (Wolf, 2009) and beneficially modifying executive functions (Oei et al., 2009), a blunted stress (cortisol) response has been found to disrupt cognitive and emotional processing and may make key frontal and limbic regulatory regions more sensitive to developmentally salient stress events (Lupien et al., 2009; Ordaz & Luna, 2012). Further, subjective and physiological stress responses are not consistently aligned, as a reduced cortisol response has been associated with increased negative affective responses to stress (Het et al., 2012; Ordaz & Luna, 2012; Villada et al., 2016). As such, peripubertal females with HPA dysfunction may experience greater mood disturbances in the presence of normal peripubertal hormone fluctuation.

In addition to a blunted cortisol response, greater T-sensitivity strength was associated with reduced VE, a potential marker of poor self-regulation and stress sensitivity (Porges et al., 2019). Individuals with low VE have more difficulty adjusting to stressors (Kovacic et al., 2020), with prolonged physiological activation and slower emotional and physiological recovery from stress exposure (McLaughlin et al., 2015). Interventions that increase vagal tone (e.g., meditation, mindfulness-based stress reduction) may beneficially modify physiological and emotional recovery from stress, and thus, improve stress sensitivity and reduce risk of psychopathology (Ditto et al., 2006). Together with the present results, these findings suggest that stress dysregulation manifested as a blunted cortisol response and reduced VE, may contribute to dysregulated emotional and behavioral responses in the context of normal peripubertal hormone flux.

Enhanced frontal theta predicted testosterone-sensitivity

Results from the present study suggest that disrupted frontal-mediated cognitive control (indexed by theta activity), may increase susceptibility to T-induced mood dysregulation. The present study employed an emotional go/no-go task to probe maturing frontal-mediated cognitive control and examine neurophysiological correlates of inhibition and emotion regulation. Enhanced frontal theta activity for fear no-go trials predicted a stronger relationship between testosterone change and mood symptoms, suggesting that disruptions in frontal-mediated cognitive control may enhance susceptibility to experiencing mood symptoms with normal hormone fluctuation.

Testosterone differentially impacts gray matter volume in the anterior cingulate based on sex (Koolschijn et al., 2014), which is one of the primary regions involved in attributing salience (Hickey et al., 2010) and the generation of frontal theta oscillations (Brötzner et al., 2015). Theta oscillations generated in the anterior cingulate have proposed associations with affective processing (Christie & Tata, 2009) and psychopathology (Arns et al., 2015; Auerbach et al., 2015; Koo et al., 2017). Further, stronger connectivity between the dorsal medial prefrontal cortex and the amygdala during negative emotion processing was associated with increased testosterone levels (Lungu et al., 2015). Testosterone's effect on hippocampal volume during development also mediates the translation of early life stress into emotion dysregulation and depression (Barch et al., 2020).

Testosterone has been shown to increase slow (i.e., theta, 4–8 Hz) relative to fast (i.e., beta, 13–30 Hz) oscillatory activity, which was associated with approach-driven behaviors and reduced risk aversion (Schutter & Van Honk, 2005). Accordingly, increased theta may indicate deficient frontal control over greater subcortical engagement, and consequently, dysregulated emotional control (Grotegerd et al., 2013). Testosterone may act on already vulnerable frontal-limbic circuitry via receptors located in key regulatory limbic regions (i.e., amygdala, hypothalamus)(Cooke, 2006; Sarkey et al., 2008) to modify frontal-mediated emotion regulation, and thereby, increase affective symptoms during periods of substantial reproductive endocrine instability (Spielberg et al., 2014).

Deviations in frontal theta are a shared feature exhibited across psychopathology, including unipolar and bipolar depression (Koller-Schlaud et al., 2020) and schizophrenia spectrum disorders (Andersen et al., 2018). While predominantly examined during rest, increased theta is found in patients with anorexia nervosa (Hestad et al., 2016) and ADHD (Bink et al., 2015). Further, increased theta and increased theta relative to fast oscillations (e.g., beta) are proposed to underlie deficient frontal regulation of enhanced limbic activity and associated disruptions in cognitive and emotion regulation (Knyazev, 2007; Schutter & Van Honk, 2005), which are observed in youth with ADHD (Bink et al., 2015; Hermens et al., 2005) and adolescents at risk of suicidal behaviors (Lee et al., 2017).

Negative affect and behavioral impulsivity in testosterone-sensitive participants

Dysregulation of affective and stress systems may increase susceptibility to the behavioral and affective effects of testosterone flux. As such, participants sensitive to testosterone fluctuation demonstrated a higher frequency of impulsive errors (i.e., responses to no-go trials) and greater sensitivity (*d*-prime) for negative stimuli. These behavioral results suggest that T-sensitive participants have facilitated attention towards threat and difficulty disengaging and inhibiting behavior from salient emotional stimuli – a behavioral response pattern that is also observed in patients with ADHD (Wodka et al., 2007), anorexia-nervosa (Hildebrandt et al., 2016), and obsessive-compulsive disorder (Bannon et al., 2002). It may also support a psychophysiological model of a hormone-related enhancement of motivational salience for the preparation of emotional and behavioral responses (Nielsen et al., 2013; Radke et al., 2015). Consistent with this proposed model, an emotion-

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processing bias (possibly via enhanced sensitivity to testosterone) may increase susceptibility to rejection and interpersonal stress in peripubertal females due to a misinterpretation of salient emotional events (Yoon et al., 2009), thus making them more susceptible to psychopathology (Slavich et al., 2010). Female adolescents experience a heightened sensitivity to interpersonal rejection, which is a strong predictor of depression (Slavich et al., 2010) and represents a developmentally relevant psychological construct of female adolescent depression (Kupferberg et al., 2016; Slavich et al., 2010). T-sensitivity strength was associated with a greater increase in negative affect following neurophysiological testing. Consistent with testosterone's role in motivated salience, it is possible that these participants had a more difficult time disengaging from negative experiences, reflected in the increased change in negative affect. Converging biobehavioral results from the present study suggest that neurophysiological and behavioral profiles subserving the cognitive elaboration of emotional stimuli, enhanced salience, dysregulated cognitive and emotional control, and behavioral impulsivity are associated with testosterone sensitivity. Participants in the present study who were mood sensitive to testosterone did not exhibit greater depressive symptoms, but rather reported greater negative affect, which included items assessing anger, a loss of control, or feeling overwhelmed. Further investigation is warranted to determine the relationship between testosterone sensitivity and heightened attention to negative affect during the pubertal transition and its predictive value in identifying psychopathology risk.

Limitations

To our knowledge, this is the first study to examine potential biobehavioral correlates of the testosterone-mood relationship in peripubertal female adolescents. However, results should be considered in light of the following limitations. Importantly, using two different EEG collection systems restricted the scope of our analyses to exploratory within-subject regression models. Further, "mood" was not assessed consistently across all participants; however, using person-standardized mood scores permitted the examination of within-person hormone change and mood relationships. Despite these limitations, the present analyses provide a promising pathway for future research, examining frontal theta oscillations in mediating the relationship between peripubertal hormone variability and mood dysregulation. Additionally, university-mandated COVID-19-related restrictions on in-person human research prevented the study from completing data collection for 10 participants, resulting in a relatively small sample size. The present study investigated biobehavioral mechanisms predicting the strength of hormone and mood relationships, without differentiating between mood sensitivity to increases, decreases, or substantial changes in hormone level from week to week. Previous research has examined the role of sex-hormone variability, along with abrupt increases or decreases in hormones, in the emergence of affective symptoms during reproductive transition events (Gordon et al., 2016, 2020). Therefore, future research with larger samples could examine whether there are distinct biobehavioral profiles that distinguish between testosterone withdrawal, increase, or change-sensitive participants. Further, the sample was comprised predominately of white female adolescents from high-income families, which may limit the generalizability of the results. Future research would benefit from including a more demographically diverse sample. Recruitment was restricted to female adolescents between the ages of 11 and 14 to examine neurophysiological factors that may contribute to the increased prevalence of affective illness in females starting at puberty. However, testosterone-mood relationships are undoubtedly relevant to peripubertal male adolescents, and it will be important to examine sex-specific neural and endocrine features of the pubertal transition that may mediate the translation of sex hormone fluctuation into affective symptoms. While this study provided a foundation for studying the neurophysiological basis of hormone-mood relationships in a non-clinical sample, the future inclusion of participants with clinically significant affective symptoms and who are at risk for suicide would strengthen our understanding of hormone-induced mood symptoms and adolescent psychopathology.

Conclusion

The present study expanded previous findings demonstrating that hormone fluctuation precipitates mood symptoms in peripubertal female adolescents and identified distinct profiles in neurocognitive and behavioral tendencies that are associated with mood sensitivity to testosterone change. Consistent with a novel diathesis-stress model, stress-related modifications of frontal and limbic circuitry may make the brain more vulnerable to abrupt changes in peripubertal hormones. While speculative, a differential sensitivity to testosterone fluctuation during the pubertal transition may promote greater salience for emotional stimuli and behavioral disinhibition and contribute to the emergence of affective illness. Ultimately, this research will be critical for identifying early risk factors and potential treatment targets for adolescent psychopathology during a pivotal window for intervention efforts.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579423000937.

Acknowledgments and funding sources. This study was supported by the National Institute of Mental Health Grant K01MH121575 (to EA), the National Institute of Health T32 postdoctoral fellowship MH093315 (to EA), the NIH Clinical Translational Science Award pilot grant UL1TR002489 (to EA), and a Foundation of Hope for Research and Treatment of Mental Illness grant (to EA).

Competing interests. The authors have no conflicts of interest to disclose.

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