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Individual differences in frontal alpha asymmetry moderate the relationship between acute stress responsivity and state and trait anxiety in adolescents

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Abstract

Stress is a risk factor in the development and maintenance of psychopathology, particularly anxiety. Despite theory suggesting differences in stress responsivity may explain heterogeneity in anxiety, findings remain contradictory. This may be due to failure to account for individuals' neurobiological states and outdated methodologic analyses which confound conceptually and biologically distinct stress response pathways. In 145 adolescents, this study examined whether individual differences in neural activation underlying motivational states, indexed by resting frontal alpha asymmetry (FAA) before and after the Trier Social Stress Test (TSST), moderate the relationship between stress responsivity (measured by cortisol) and anxiety. Adolescents with rightward FAA activation (indexed by changes in resting FAA pre-to-post TSST) and high trait anxiety showed blunted cortisol reactivities while those with leftward FAA activation and high state anxiety showed prolonged cortisol recoveries. Our work reveals individual differences in vulnerability to psychosocial stressors and is the first study to show that FAA activation moderates the relationships between anxiety and distinct phases of the stress response in adolescents.

Keywords

Individual differences; Anxiety; Stress; Electrophysiology; Cortisol; Frontal asymmetry; Adolescence; HPA axis

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2022.108357.

1. Introduction

Stress is a risk factor in the development, maintenance, and exacerbation of psychopathology, particularly in anxiety and mood-related disorders (Roberts & Lopez-Duran, 2019). Individual differences in stress responsivity are theorized to explain heterogeneity in anxiety symptomatology, manifestation, and long-term health outcomes (Dunn & Berridge, 1990; Shackman et al. 2013). Furthermore, neurobiological systems governing acute stress responses undergo critical maturational changes during adolescence which may contribute to the onset and exacerbation of anxiety (Grant et al. 2003). Yet, findings are contradictory as to whether hyper or hypo-responsiveness—two documented patterns of stress dysregulation—to acute psychosocial stressors relate to anxiety (Duval, Javanbakht, & Liberzon, 2015; Juruena, Eror, Cleare, & Young, 2020; Tafet & Nemeroff, 2020). Conflicting evidence may be due to (1) failure to account for individuals' neurobiological states which underlie these relationships (Myers, Scheimann, Franco-Villanueva, & Herman, 2017; Reznik & Allen, 2018) and (2) outdated methodologic analyses which confound conceptually and biologically distinct stress response pathways (reactivity and recovery) (Galatzer-Levy, Bonanno, Bush, & Ledoux, 2013; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Using newer growth curve modeling with landmark registration for neuroendocrine analysis (Lopez-Duran, Mayer, & Abelson, 2014), this study aims to examine how individual differences in neurobiological states moderate the relationship between stress responsivity and anxiety across the Trier Social Stress Test for Children (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993) in adolescents.

Asymmetric frontal activation represents a key neurophysiologic marker of emotional processing and approach-avoidance motivation (Smith, Reznik, Stewart, & Allen, 2017), and an important contributor to processes governing emotion regulation and stress responsivity, all recognized as key contributors to dimensions of anxiety (Page & Coutellier, 2019; Shin & Liberzon, 2010). The frontal cortex is a key neuro-regulator of the hypothalamic-pituitary-adrenal (HPA) axis response to an acute stressor (de Kloet, 2019). Appraisal of stress relies on frontal processes which activate the HPA axis to release cortisol, an acute stress hormone (Russell & Lightman, 2019). There is strong biologic evidence pointing to asymmetric control of stress regulation via differential expression of cortisol receptors in the frontal cortex (Joëls, 2018). Yet, little is known about the dynamic interplay between these pathways and their role in hyper and hypo-responsiveness to stressors and related individual differences in anxiety (Kaldewaij et al. 2019). Adolescence is a critical time of maturation in frontal and HPA axis circuits which contributes to heightened acute-stress reactivity (Foulkes & Blakemore, 2018; Ji, Negriff, Kim, & Susman, 2016; White, 2009) and may be associated with the emergence of anxiety symptoms that are predictive of future onset and severity of psychopathology (Dieleman, Huizink, Tulen, Utens, & Tiemeier, 2016; Grant et al., 2003; Oldehinkel et al., 2011). This is the first study in adolescents to simultaneously examine the interplay between asymmetric frontal activity, biological stress responsivity, and anxiety in a developmentally sensitive period. While previous findings support the importance of these neurobiological mechanisms in anxiety (Duval et al., 2015; Smit, Posthuma, Boomsma, & De Geus, 2007), they fail to examine the heterogeneity in these domains and their interactive influences across individuals; this may help reveal

the underlying mechanisms of the complex relationships between neurobiology, stress, and anxiety.

Neuronal oscillations in the alpha frequency band (8–13 Hz) inversely relate to cortical activity, indicating that the difference in frontal hemispheric alpha may reliably index asymmetric cortical activity (Herrmann, Struber, Helfrich, & Engel, 2016). Frontal alpha asymmetry (FAA) is associated with measures of motivational states, stress biomarkers, and mood and stress-related disorders (Adolph & Margraf, 2017; Demerdzieva & Pop-Jordanova, 2015; Harrewijn, Van der Molen, & Westenberg, 2016a; Harrewijn, Van der Molen, & Westenberg, 2016b; Hewig et al. 2008; Moran et al., 2017). Left FAA is defined as left greater than right frontal activation and vice versa for right FAA. Left FAA is associated with better emotional regulation and approach related-affect while right FAA indexes behavioral inhibition and withdrawal related-affect (Cacioppo, 2004; Rodrigues, Müller, Mühlberger, & Hewig, 2018). The approach system controls goal directed behaviors and attainment of rewards whereas the withdrawal system governs avoidance behaviors and inhibition (Ellis, Salgari, Miklowitz, & Loo, 2018a; Ellis, Salgari, Miklowitz, & Loo, 2018b). Both left and right FAA have been linked to anxiety disorders (Demerdzieva & Pop-Jordanova, 2015; Harmon-Jones & Allen, 1997; Harrewijn et al. 2016a, 2016b) and to biologic measures of hyper and hypo-responsiveness to stress (Düsing, Tops, Radtke, Kuhl, & Quirin, 2016; Quaedflieg, Meyer, Smulders, & Smeets, 2015; Zhang et al. 2018a, Zhang et al. 2018b). In adolescents, right FAA has been associated with exaggerated biologic stress responses and higher anxiety symptoms (Hannesdottir, Doxie, Bell, Ollendick, & Wolfe, 2010). Facets of anxiety (momentary versus trait anxiety) have been associated with differential activation of frontal regions. For instance, greater trait anxiety has been linked to right FAA (Adolph & Margraf, 2017; Demerdzieva & Pop-Jordanova, 2015) in children and adolescents, while state anxiety, worry, and rumination have been related to left FAA (Smith, Zambrano-Vazquez, & Allen, 2016).

Inconsistent findings indicate that higher total cortisol release (indexing HPA stress responsivity) is related to right FAA (Zhang et al., 2018a, Zhang et al., 2018b) and lower total cortisol is linked to left FAA (Quaedflieg et al., 2015). Other studies suggest that left FAA relates to higher total cortisol (Düsing et al., 2016). However, no studies explicitly evaluate the association between distinct phases of the stress response (reactivity and recovery), which likely contributed to the inconsistent evidence. The reactivity (immediate increase in cortisol in response to stress) indexes an individual's sensitivity to a stressor (Ji et al., 2016) while the recovery (the decline or persistence in cortisol over time) indicates an individual's tolerance to withstand stressors or perceived ability to cope (Linden, Earle, Gerin, & Christenfeld, 1997; Meuwly et al. 2012). Thus, FAA may reflect an underlying neural process linking components of an individual's stress response to anxiety. This is the first study to examine how FAA may differentially moderate the relationship between anxiety and distinct phases of HPA responsivity in adolescents. Examining these relationships is important, as neurobiological evidence in human and animal studies suggest these pathways are key in the development and treatment of anxiety (Peeters, Ronner, Bodar, van Os, & Lousberg, 2014).

Examining the literature related to anxiety in adolescents, authors found significant and non-significant relationships between FAA and anxiety measures (Demerdzieva & Pop-Jordanova, 2015; Ellis et al. 2018a, 2018b; Goldstein et al., 2019; Harrewijn et al. 2016a, 2016b; Moran et al., 2017; Nusslock et al. 2018; Smith et al., 2016). However, many of these key studies examined FAA activity (measured at a single time during rest) as opposed to FAA activation (change in frontal asymmetry in response to environmental stimuli or a task); activation is thought to more reliably index an individual's motivational state and emotional arousal than a single measure of activity in the absence of preceding environmental perturbations (Reznik & Allen, 2018; Stewart, Coan, Towers, & Allen, 2014). Theory supports the role of frontal activation (change in FAA after a stimulus or task) over frontal activity (FAA measured at a single point in time in the absence of any provocation) in moderating the relationship between neural processes governing motivational states, emotional regulation, and acute stress reactivity (J. A. Coan & Allen, 2004; Reznik & Allen, 2018). Thus, FAA activation may underlie withdrawal-motivational tendencies as these processes are closely tied to environmental context compared to stable, trait-like characteristics of FAA activity (James A Coan, Allen, & Harmon-Jones, 2001; Deng, Jiang, Li, & Zhou, 2019; Goodman, 2013; Schöne, Schomberg, Gruber, & Quirin, 2016; Zhang et al., 2018a, Zhang et al., 2018b). As FAA activation may substantially account for more of the variance in acute emotional and stress regulation than FAA activity, this study explored the role of FAA activation (change in resting FAA before and after a stressor) in moderating acute HPA responses and anxiety to fill this crucial gap in frontal asymmetry literature.

Adolescence may be a particularly stress-vulnerable time as it is marked by significant shifts in frontal activation and heightened HPA axis responsivity (Grant et al., 2003; Ji et al., 2016; Stroud, Papandonatos, Williamson, & Dahl, 2004; Sturman & Moghaddam, 2011), both of which have been separately associated with adolescent anxiety (David, Predatu, & Maffei, 2021; Ellis et al. 2018a, 2018b; Kentgen et al. 2000; Mennella, Patron, & Palomba, 2017). Left and right FAA are associated with increased anxiety and worry in children and adolescents (Demerdzieva & Pop-Jordanova, 2015; Harrewijn et al. 2016a, 2016b; Heffer & Willoughby, 2020; Mathersul, Williams, Hopkinson, & Kemp, 2008; Thibodeau, Jorgensen, & Kim, 2006). Furthermore, adolescents with anxiety disorders and more severe symptoms demonstrate a blunted or attenuated cortisol compared to age-matched controls (Ayer et al., 2013; Fiksdal et al., 2019; Oskis, Loveday, Hucklebridge, Thorn, & Clow, 2011; Oskis, Smyth, Flynn, & Clow, 2019; Schiefelbein & Susman, 2006). However, it is unclear how these motivational states may moderate the relation between HPA responsivity and anxiety in this critical developmental period.

This study examines the relationship between FAA activation (change in resting FAA before and after stress) and adolescent stress responses (indexed by cortisol) and anxiety (state and trait) over the course of an acute psychosocial stressor (TSST). Specifically, we propose that FAA is a key moderator of the adolescent stress response, informing our mechanistic understanding of how individual differences in stress responses across a range of symptom severity may be explained by underlying neurobiological motivational states. Given findings from prior studies in adolescents examining single constructs, we hypothesized that left FAA activation would predict a steep increase (reactivity) and decrease (recovery) in cortisol, following a typical adolescent cortisol trajectory across the TSST and potentially

reflecting adaptive coping and emotion regulation. We postulated that individuals with high levels of trait and state anxiety would show steeper reactivity and peak cortisol, but delayed recovery as these individuals are more likely to be stress sensitive, needing more cortisol for prolonged periods. Extrapolating from prior bivariate relations, we anticipated right FAA activation, indexing withdrawal motivation following stress, would moderate the relationships between cortisol response and anxiety; individuals with right FAA activation (avoidance motivation) would tend to have prolonged cortisol recoveries and more severe anxiety.

2. Methods

2.1. Participants

A total of 147 children and adolescents from North Carolina aged 9–16 (mean age 12.5, 63 females) participated in this study, but only 145 had usable salivary cortisol data. As a part of a larger ongoing study (Corr et al. 2021) and in line with the aims of the National Institute of Mental Health, the parent study utilized the Research Domain Criteria (RDoC) to recruit participants in order to maximize variability in cognitive and anxiety symptom domains (Casey, Oliveri, & Insel, 2014). Study information containing inclusion criteria was disseminated through websites, emails, and informational flyers. Parents of potential participants completed a virtual pre-screening instrument which assessed family history of psychiatric disorders, the adolescent's psychiatric and medication history, and asked parents to subjectively qualify relative severity of their child's psychopathology. Participants with a family history of a psychiatric disorder and who passed exclusionary criteria were preferentially recruited. In these ways, the larger parent study targeted a clinically heterogenous population. Exclusionary criteria included chronic medical conditions, recent illnesses (e. g. flu), medication use known to disrupt the HPA axis (e.g. steroids, contraceptives), substance use and dependence, history of a current psychotic disorder, mood disorders, post-traumatic stress disorder, traumatic brain injury, and an IQ < 70 (assessed via Wechsler Abbreviated Intelligence Scale).

Demographic information can be found in Table 1. Of 145 subjects, 64 had a diagnosis of either ADHD, OCD, generalized anxiety disorder, social anxiety disorder, or adjustment disorder. 53 individuals were on medication (ADHD stimulants and non-stimulants, antidepressants, 4 instances of an antipsychotic and 2 instances of an anti-convulsant). 69% of adolescents identified as white, 2% Native American, 17% African American, 10% mixed race, and 2% declined to answer. Of these individuals, 8.2% identified as Hispanic. 87% of participant fathers had a GED or higher (13% provided no response) and 90% of all mothers had a GED or higher (10% provided no response).

2.2. Current study

This study was conducted at the University of North Carolina at Chapel Hill and approved by the Institutional Review Board (IRB). Following parental consent and child assent, parents and children completed several self-report surveys. Participants then underwent the Structured Clinical Interview for DSM-IV (SCID-I) to screen for the presence of DSM-IV Axis I disorders with a trained clinician. After the clinical interview, adolescents

completed neurocognitive testing as part of a larger ongoing study, followed by the electroencephalography (EEG) stressor protocol (Fig. 1). As part of a larger study, this included resting state and working memory tasks before and after a psychosocial stressor. Brain activity was recorded continuously during all tasks via EEG while self-reports and saliva were collected at 5 pre-determined intervals.

During the resting state tasks, participants were instructed to sit comfortably for two 3-minute resting state conditions, eyes open (EO) and eyes closed (EC) (6 mins total), which occurred at the start and immediately following the stressor (Fig. 1). In the EO condition, participants were instructed to relax and focus on a fixation cross in order to minimize eye movements. In the EC condition, participants were instructed to close their eyes and relax, but to stay awake and alert during the recording. EEG recordings took place in a light, sound and temperature-controlled room. Subjects were continuously monitored to detect drowsiness or sleep.

To induce a stressor response, this study implemented the validated acute psychosocial stressor manipulation, the Trier Social Stress Test for Children (TSST) (Kirschbaum et al., 1993), which has been used in diverse populations of adolescents to elicit a reliable cortisol stress response (Narvaez Linares, Charron, Ouimet, Labelle, & Plamondon, 2020). We conducted the TSST similar to prior published protocols. In brief, participants performed a public speaking task in front of a panel of “behavioral specialists” (participant told prior that “specialists” were excellent at reading nonverbal signs of discomfort) who were instructed not to provide any verbal or non-verbal feedback; participants had 5 min to prepare, 5 min to perform a story, followed by a 5-minute serial subtraction task. Math difficulty was adjusted based on age. Adolescents had to serially subtract 7 from 758 (9–11 years) or 13 from 1023 (12–16 years). With each mistake, the panelist interfered to say “Stop, please start again.” TSST story prompt details are described fully in Supplementary Section 4.

2.3. Data acquisition

2.3.1. State and trait anxiety—Participants completed subjective self-reports of their state anxiety at each saliva collection time point (Fig. 1). Specifically, individuals were asked to rate how “stressed, worried, or nervous” they felt at that moment on a scale of 1–5 (not at all to very much). This scale has been used reliably in other studies to indicate momentary, transient anxiety levels (Vedhara et al., 2003). Trait anxiety (stable measure) was assessed using the validated Spielberg’s State-Trait Anxiety Inventory questionnaire for Children (STAI-C) prior to the EEG session (Marteau & Bekker, 1992). The STAI-C comprises a 20-item self-report scale to measure the severity of anxiety and a generalized propensity to be anxious. We utilized the trait scale which quantifies a stable tendency to experience anxiety.

2.3.2. Asymmetric frontal cortical activity—EEG was utilized to measure brain activity at rest. Recordings were made with a BioSemi Active2 system (BioSemi B.V., Amsterdam, Netherlands) with a 64-channel cap (10–20 international system). All scalp electrode impedances were below 5κΩ and all homologous electrodes were kept within 1κΩ. Horizontal electro-oculogram (VEOG, HEOG) recordings were collected (later used to

correct eye artifacts), sampled at 1024 Hz, and bandpass filtered online between 0.1 and 100 Hz. In order to prepare recordings to extract frontal activity, first raw data were preprocessed offline within Matlab software (2019b) using the EEGLab toolbox and custom MATLAB scripts. Similar to published protocols, continuous raw data were down sampled to 256 Hz, high pass filtered at 1 Hz to remove baseline drift with a basic finite impulse response (FIR) filter, and re-referenced to mastoid electrodes; then 60 Hz electrical line noise and muscle and movement artifacts were removed from data using automatic subspace reconstruction (Chang, Hsu, Pion-Tonachini, & Jung, 2018). Data were subjected to channel interpolation and Independent Component Analysis applied to determine eye-blink components. EEGLab *icablinkmetrics* was used to remove eye-blink artifacts from continuous data. Dummy 4 s epochs (50% overlapping) were extracted through a Hamming window and trials were rejected if values exceeded + /− 75μV in any channel. After preprocessing, participants with fewer than 20 artifact-free epochs were excluded from further asymmetry analysis. A total of 131 subjects had sufficiently clean EEG data.

Preprocessed data were then analyzed to extract FAA which is a reliable index of asymmetric frontal cortical activity (Smith et al., 2017). We performed a Fast Fourier Transformation in 1 Hz frequency steps to extract spectral power (μV^2) in the alpha-band (8–13 Hz) to obtain average absolute power across artifact-free epochs. We focused our analysis on the EC condition given the effect of alpha blocking during EO (Barry, Clarke, Johnstone, Magee, & Rushby, 2007). Drawing from prior findings (see Supplementary Section 5), we evaluated alpha power in electrode pairs F7-F8 (frontolateral) and F3-F4 (frontomedial) which are the homologous right and left sided lateral frontal electrodes respectively. Primary analyses focused on frontolateral sites as recent findings cite higher reliability of FAA in children and adolescents compared to frontomedial sites (Koller-Schlaud, Querbach, Behr, Ströhle, & Rentzsch, 2020). To keep accordance with FAA literature, tables with full estimates from frontomedial sites are presented in Supplementary Section 6.

A laterality coefficient (LC) indexing relative right versus left sided alpha power was computed as follows: LC = ((R − L) / (R + L)) x 100 (Coan & Allen, 2004). The LC index of FAA is almost perfectly correlated with the log difference estimate and the LC, as an untransformed variable, has a more straightforward interpretation (Allen, Coan, & Nazarian, 2004a). Given estimation, positive LC values indicate a higher alpha power in the right relative to the left hemisphere. As alpha power and cortical activity are inversely related, a positive LC reflects higher left frontal cortical activity or left FAA (Thompson & Patterson, 1974). FAA values were extracted from resting state conditions before and after the TSST. In line with Coan and colleagues' conceptualization of relative shifts in frontal asymmetry, we extracted the post-stress LC which was weighted by the relative change from baseline or pre-stress value (J. A. Coan & Allen, 2004). This represents FAA activation (change in resting EEG asymmetry before and after a stimulus) which allows inference of motivational state in response to the stressor (see Supplementary Section 8). The sign (+/−) of the LC indicated relative hemispheric activation—positive values indexed left hemispheric activation (left FAA), negative values indexed right activation (right FAA), and values close to zero indicated no lateralization in frontal activation. The magnitude of the continuous LC score captured the overall relative change in FAA from baseline (pre-stress).

Thus, larger and positively weighted post-stress LC scores signify greater leftward FAA activation in response to stress. Conversely, larger and negatively weighted values signify greater rightward FAA activation following stress (Allen et al. 2004a; Reznik & Allen, 2018). For consistency, we will use this same terminology (left vs right FAA activation) throughout this paper to indicate state-related changes in frontal cortical activation both before and after the TSST.

2.3.3. Salivary cortisol—A total of 5 salivary cortisol samples were collected over the course of the EEG session (Fig. 1). Prior to arrival, participants were given instructions not to eat or drink 30 min beforehand to minimize confounding factors. The first sample was collected 30 min prior to the TSST, the second at the start of the TSST (t = 0), and the third, fourth, and fifth samples were collected around 21, 35, and 60 min following the TSST. Time of day was recorded at each sample collection. Saliva was stored at − 80 °C until batch analysis. Salivary cortisol levels were determined using a commercially available competitive enzyme immunoassay (EIA) kit and protocol available from Salimetrics, State College, PA. The sensitivity of the cortisol assay is < 0.007 ug/dL with a standard range of.007 to 1.8 ug/dL. The intra- and inter- assay variation is 3.88% and 6.69%, respectively.

2.3.4. Pubertal status—To assess pubertal status, participants completed the Pubertal Development Scale (PDS). The PDS is a self-report questionnaire which evaluates gonadal, adrenal, and neuroendocrine pubertal stages. The PDS scale faithfully approximates gonadal and adrenal hormone concentrations as well as bone age during pubertal maturation (Hibberd, Hackney, Lane, & Myers, 2015; Schmitz et al., 2004; Shirtcliff, Dahl, & Poliak, 2009). Point values are averaged to give a possible range of scores from 1 to 12 and indicate relative progression through pubertal stages. Scores were used in final analyses to control for pubertal status.

2.4. Statistical analysis

Data preparation steps are detailed in Supplementary Section 2. Statistical analyses were conducted in R 3.5.2 using *lme4* package. Student's *t*-tests were used to test for significant differences on primary measures between groups (sex, medication, diagnosis). We utilized a single growth curve model with landmark registration (GCM-LR) for neuroendocrine data (Lopez-Duran et al., 2014) to test our primary hypothesis that FAA activation moderates the relationship between acute stress response (cortisol) and trait and state anxiety. In short, this newer method captures the biologically distinct phases of the HPA response (the peak, reactivity, and recovery) and outperforms traditional methods (area under the curve or ANOVAs) which confound these distinct phases. Supplementary section 3 describes the process of landmark registration in detail. Briefly, cortisol time of collection is transformed to center each person's peak on time = 0 and produce two newly coded variables: time before peak (TBP) and time after peak (TAP) which are predictors in the GCM-LR. The cortisol concentrations are the dependent variable. Thus, the TBP and TAP estimate the linear change in cortisol from baseline to peak and peak to final recovery respectively. This allows for examination of cortisol peak, reactivity and recovery respectively while controlling for time of day (diurnal confounds) in a piecewise growth function.

Fixed effect time varying predictors included TBP, TAP, state anxiety, and FAA activation, while time invariant predictors included baseline cortisol (30-min pre-TSST), age, sex, medications, and clinical status. Continuous predictors were mean centered due to differing scales and interpretability of interaction (moderation) effects. Random effects structure allowed random slopes and intercepts for each participant. We used the *RePsychLing* package with PCA to test for overfitting in the random effects structure (Ivanova, Molenberghs, & Verbeke, 2016). Variance inflation factors (VIF) were examined to diagnose any problematic multicollinearity. Robust maximum likelihood estimation was employed which allows for missing data (Porter, Gruber, van der Laan, & Sekhon, 2011). P values were estimated using the Satterthwaite approximations to degrees of freedom, and heteroscedasticity consistent (HC3) robust standard errors were reported. Standardized regression coefficients were reported to allow for comparison of effect sizes. As sex, medication, and clinical status covariates were non-significant and parameter estimates did not significantly change in their absence, they were excluded from the final model (see Supplementary Section 7 for these analyses repeated in with medicated individuals excluded). Age and pubertal score were included as covariates in all models.

3. Results

FAA results from frontomedial sites (F3-F4 pair) can be found in Supplementary Section 6. FAA results described below refer to frontolateral sites (F7-F8 pair) unless otherwise specified. The overall cortisol response rate for this study was 70% (30% non-responders) which is in line with other rates found in studies using the TSST (Narvaez Linares et al., 2020). Average cortisol and perceived stress followed a typical trajectory, increasing across stress then declining (Fig. 2). While a Wilcoxon Signed-Ranks Test indicated there was no mean difference in FAA before and after stress ($W = 915$, $p = 0.26$), visual examination of individuals' FAA both pre-and-post stress suggested a high amount of individual variability (Fig. 3). Descriptive measures (Table 2) revealed a wide distribution in FAA activation (computed LC indexing changes in resting asymmetry before and after stress). Table 2 presents the unadjusted correlations for age, pubertal status, baseline cortisol, FAA activation, and trait and state anxiety (note: these are raw, non-mean centered measures). There were no significant correlations between baseline cortisol (indexing acclimation to a lab environment) and FAA activation, state anxiety, trait anxiety, nor pubertal status. Age was weakly correlated with baseline cortisol ($r = 0.193$, $p = 0.021$) indicating older individuals tend to have higher baseline cortisol and is in line with findings that show cortisol increases with age (Miller et al., 2016).

The estimates from our primary model can be found in Table 3. Results show that FAA activation significantly affected cortisol reactivity ($\beta = -0.065$, SE = 0.025, $p = 0.01$) and recovery ($\beta = 0.063$, SE = 0.027, $p = 0.021$) slopes, but not cortisol peak. Contrary to our initial hypothesis, left FAA activation (indexing leftward asymmetry pre-and-post stress) was associated with flatter cortisol reactivity and recovery slopes. The magnitudes of these estimates suggest that FAA activation plays an important role in both phases given the similar effect size on blunting reactivity and recovery slopes. Interestingly, trait and state anxiety did not significantly relate to cortisol peak, reactivity, or recovery ($p > 0.05$).

FAA activation moderated the relationship between trait anxiety and reactivity slope (β = 0.058, SE = 0.027, $p = 0.034$) such that individuals with right FAA activation differed in their cortisol reactivity depending on their trait anxiety (Fig. 4)—those with high trait anxiety had blunted cortisol reactivity, while those with low trait anxiety had steeper reactivity slopes (closely resembling a typical cortisol trajectory). Contrary to our hypothesis, there was no moderation effect on the relationship between trait anxiety and cortisol peak or recovery. There were no significant moderation effects of left FAA activation on the relation between cortisol and trait anxiety.

Conversely, left FAA activation significantly moderated the relationship between state anxiety and cortisol recovery (β = 0.099, SE = 0.032, $p = 0.002$). Individuals with leftward resting FAA activation changes before and after the TSST differed in their recovery slopes depending on their state anxiety (Fig. 5); in adolescents showing this pattern of frontal activation, those with higher levels of state anxiety had flatter, more prolonged recovery slopes. Examining the magnitude of the standardized estimates, FAA activation had a stronger moderating effect on the relation between state anxiety and cortisol recovery than trait anxiety and cortisol reactivity. Most model estimates remained significant for FAA in electrode pair F3-F4 except we failed to find a significant effect ($p > 0.05$) of FAA activation in F3-F4 electrodes on the relationship between trait anxiety and cortisol reactivity. Nevertheless, the associations at F3-F4 are in the same direction as those at F7-F8 (Supplementary Table 1).

4. Discussion

This is the first study in adolescents to illustrate that individual variability in lateralization of frontal cortical activation (indexed by FAA) before and after the TSST significantly moderates the relationship between the HPA stress response and trait and state anxiety (Fig. 6). FAA activation had stronger effects on state anxiety and recovery than on the relationship between trait anxiety and reactivity. This suggests that when controlling for trait or stable characteristics of underlying anxiety, an individual's momentary neural motivational state (indexed by FAA activation) strongly interacts with concurrent feelings of anxiety to significantly predict a prolonged recovery slope. Given newer technologies and therapeutics targeting asymmetric frontal activation, our findings illuminate the potential clinical relevance of underlying neurobiological mechanisms governing stress regulation and anxiety, and elucidate potential targets for intervention.

4.1. The need to examine state-dependent changes in FAA as a moderator

While FAA activation is a reliable index of an approach/withdrawal motivational state (J. A. Coan & Allen, 2003), its role in psychopathology research has recently come under debate (Reznik & Allen, 2018), particularly because FAA is often collected tonically at single point in time (reflecting activity) without examining state related changes in response to or following a perturbation (reflecting activation). In the few studies utilizing FAA activation, analyses primarily consider associations with trait-like or stable characteristics (Meyer et al., 2015; Yu et al., 2020), which contradicts our findings showing stronger relations to state or momentary changes in mood.

Additionally, studies examining FAA activation as a moderator are rare, and thus insights to its true function are lacking. Therefore, contributory neurobiological mechanisms underlying heightened stress sensitivity and anxiety during adolescence remain unclear. The current study reveals that FAA activation plays a more relevant role in state or momentary changes in mood and stress regulation when controlling for differences in trait anxiety and stress reactivity—conceptualized as an individual's sensitivity to stressors (a more stable indication of stress tolerance). These findings indicate that an individual's FAA activation (their state-dependent changes favoring a certain motivational state in response to environmental triggers) plays an integral role in stress and emotional regulation processes.

4.2. Stress regulation: motivational states reveal stress vulnerability

Perhaps most relevant to understanding our results of leftward FAA activation across stress predicting prolonged recovery, Düsing et al. found that higher total cortisol release over stress was related to left FAA activity, but only in individuals with low-action orientation (tendency to ruminate, perseverative cognition, and remain in an approach-motivated state without decisive action) (Düsing et al., 2016). This is in line with our findings that left FAA activation only prolonged cortisol recovery in individuals who endorsed high state anxiety. As perseverative cognition and worry are thought to engage more verbal or language-related processes which are differentially supported by the left prefrontal cortex, individuals in our study who reported higher levels of "stress, worry, or nervousness" (state anxiety) and had leftward FAA activation may have actively engaged in these processes more than their peers who felt similar levels of anxiety across the TSST but had rightward FAA activation. This disconnect between perception and neural processing is important; individuals with left FAA activation showed a more prolonged or flatter cortisol recovery which is known to be associated with a host of downstream mental and physical health consequences due to sustained cortisol effects on neural structure, metabolic regulation, immune response, and autonomic functioning (McEwen, 2017). Thus, individuals favoring leftward FAA activation following an acute psychosocial stressor may represent a vulnerability or mechanism of heightened stress sensitivity, regardless of an individual's subjective momentary anxiety.

However, our analysis partly contradicts previous reports of findings between FAA and stress. Quaedflieg et al. found that baseline right FAA activity prior to a stressor task predicted higher total cortisol release, but not post-stress FAA activation, and that left FAA was positively correlated with behavioral activation (Quaedflieg et al., 2015). They concluded that FAA represented a trait characteristic that could predict individual differences in stress response. Our findings partly contradict this, as we found that individuals with left FAA activation had flatter reactivities but more prolonged recoveries. Their analysis confounds HPA response phases, and their interpretations may align more with our findings; the observed increase in cortisol (measured by area under a curve) could be driven by a longer recovery period and those individuals who had right FAA activity at baseline subsequently changed to left FAA activation following the stressor. Thus, it may be the individual's relative change from their baseline FAA activity driving these changes in cortisol response. This lack of clarity and merging of cortisol dynamics into a single measure emphasizes the need to measure stress-related FAA activation, cortisol reactivity, and recovery.

Trait anxiety may impact an individual's set point for reactivity to a psychosocial stressor (Souza et al., 2015) and reflect an adolescent's baseline susceptibility or propensity to abnormally respond to external threats (Villada, Hidalgo, Almela, & Salvador, 2016). How prone a child is to become anxious across any circumstance is known to affect stress responses, but limited literature exists examining how it may differentially affect reactivity and recovery phases. Our results show that right FAA activation moderated the relationship between cortisol reactivity and trait anxiety in adolescents; this suggests the propensity to be anxious only significantly differentiated cortisol reactivity to psychosocial stress in those with a rightward FAA activation (indexing resting asymmetry changes pre-to-post stress). Given trait anxiety's known role in heightening stress sensitivity and decreasing an individual's capacity to withstand stressors (Maeda, Sato, Shimada, & Tsumura, 2017), it is surprising that trait anxiety only affected stressor reactivity but not recovery in individuals with right FAA activation. In line with FAA moderation theory (J. A. Coan & Allen, 2003), individuals high in trait anxiety (greater propensity to negatively react to stress) who additionally have the tendency to lateralize activation to the right frontal cortex (indicating withdrawal motivation associated with fear, disengagement, avoidance) may be the most sensitive to reacting negatively to social stressors; thus, we observed an aberrant, blunted cortisol reactivity in these individuals. This aligns with the distinct conceptualization of neuroendocrine reactivity and recovery—trait anxiety may be more closely associated with biological processes governing stress reactivity and more distantly affect recovery processes through a number of regulatory mechanisms. This helps explain why several studies have contradictorily found blunted and heightened total cortisol in individuals with anxiety. While it is imperative to investigate the phases separately, neuroendocrine responses depend not only on intensity of overall anxiety but state flexibility in FAA activation.

Frontal activation significantly moderated the relationship between state anxiety and cortisol recovery at both the F3-F4 and F7-F8 sites. While there was no significant moderation effect of frontal activation at the F3-F4 sites on trait anxiety and cortisol reactivity, the effect was trending in the same direction. Prior literature has typically examined both electrode pairs and studies have found convergent associations (Allen, Urry, Hitt, & Coan, 2004b; Coan & Allen, 2003) with behavioral and psychological variables while others have found differential relations (Minnix & Kline, 2004; Steiner & Coan, 2011). Furthermore, a meta-analysis found minimal overlap between F3-F4 and F7-F8 FAA in individuals with anxiety and mood disorders (Thibodeau et al., 2006). Future work is needed to clarify whether there is a dissociation between frontolateral and frontomedial sites in moderating anxiety and HPA stress responses.

4.3. Limitations and future directions

A few limitations of the present study should be noted. This study was performed in clinically heterogeneous adolescents as part of a larger study investigating mechanisms and shared characteristics underlying a continuous spectrum of cognitive domains and anxiety outside of diagnostic group constraints; while it is possible there were confounding factors, diagnostic grouping in analyses revealed no effect. As mood disorders were part of the exclusion criteria, the results described in this study may not generalize to those with depression or comorbid mood disorders. Further work examining these relationships

is needed in these populations. Medications such as psychotropics and stimulants have been shown in prior studies to associate with EEG power across several frequency bands, including alpha (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002). When excluding individuals on medication, the relationship between FAA (at both electrode pairs), state anxiety, and HPA stress responses remained significant ($p < 0.05$, Supplementary Section 7). Only the relationship with trait anxiety became nonsignificant, although it was trending (p = 0.08). These analyses need to be repeated in a larger, medication naïve sample.

Results are mixed as to whether there are pubertal effects and sex differences in FAA and acute cortisol responses (Liu et al. 2017). While we did not find any effect of pubertal status nor sex in our model, it could be that our examination into the individual differences in FAA and cortisol change across stress are similar across developmental stages and sex—the direction of change is similar—but the magnitudes or starting points may vary. However, we did not find any effect of pubertal score or sex on peak or baseline cortisol. One major limitation of this study is the design. While we measure FAA directly after the completion of the stressor, as part of a larger ongoing study, all participants complete a working memory task following this (Fig. 1). While there are no indications that the task itself is a stressor, engagement of working memory processes may serve as a distractor from the stressful experience and may interrupt normal cortisol recovery (Shull et al. 2016). Thus, it is possible this task influenced observed cortisol responses, particularly the recovery dynamics.

4.4. Conclusions

An individual's change in resting FAA activation before and after stress, indexing neurobiological substrates of motivation and emotional regulation, may reveal an individual's ability to adapt or govern the cascade of neuroendocrine and subjective perceptions over the course of a stressful experience and recovery from it. While trait anxiety may influence an individual's propensity to strongly react to a stressor, their underlying neural state may tip the balance from achieving homeostasis to dysregulated reactivity. Furthermore, their change in neural state (asymmetric frontal activation) following stress may reflect individual coping processes which interact with momentary anxiety levels to heighten vulnerability to prolonged effects of cortisol in the recovery phase.

4.5. Future directions

Further research should evaluate if FAA activation moderates or mediates the relationships between stable or momentary constructs and psychopathology. Longitudinal studies are needed to address whether individual changes in stress-related FAA activation are consistent over time. This may reveal patterns in emotional regulation and motivational states that increase vulnerability to psychopathology. As we begin to understand how lateralization of frontal activation may influence stress responses, tools like neurofeedback may be employed as an intervention to alter neural activation and mitigate effects of a dysregulated stress response (Peeters et al., 2014).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

EEG	electroencephalography
HPA	hypothalamic-pituitary-adrenal axis
FAA	frontal alpha asymmetry
TSST	Trier Social Stress Test
GCM-LR	growth curve modeling with landmark registration

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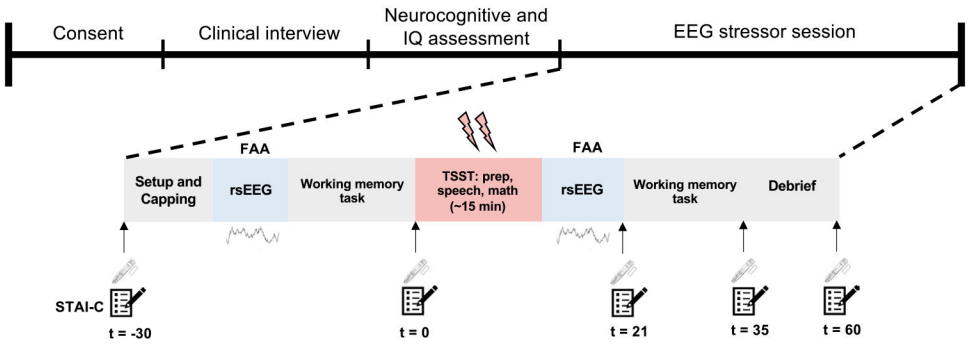

Fig. 1.

Study timeline and experimental paradigm. EEG session design: breakdown of cortisol and state anxiety sampling timepoints, STAI (trait anxiety), and frontal alpha asymmetry (FAA) collection during resting state EEG (rsEEG).

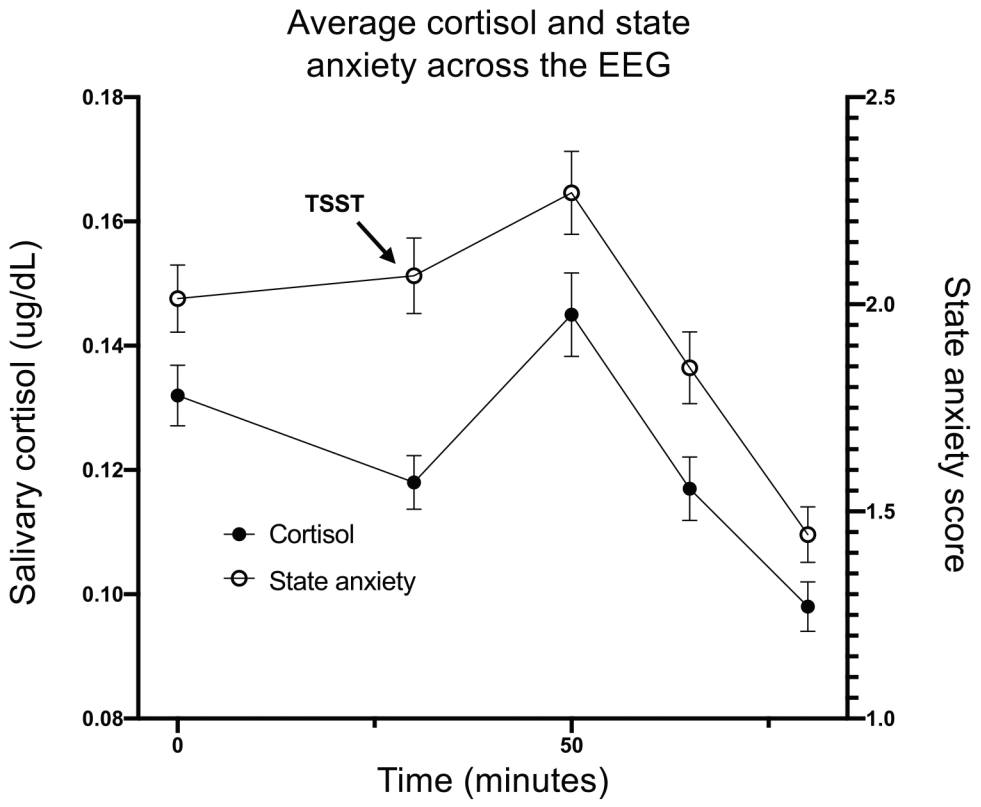

Fig. 2.

Average trajectory of cortisol and perceived “stress, worry, and nervousness” (state anxiety) across the EEG session. X axis indicates raw cortisol concentrations. Y axis indicates state anxiety scores. Means and standard errors are shown in the graph. A sharp increase in both measures is seen following onset of the TSST with sharp declines after reaching their peak.

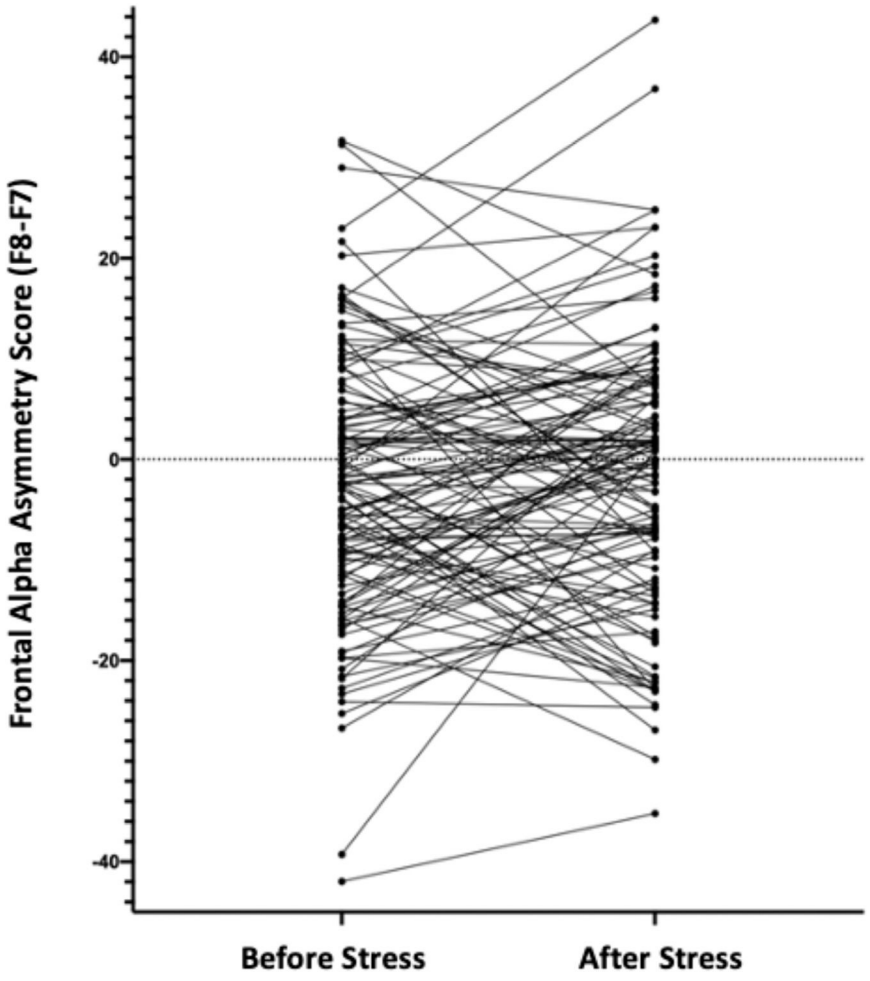

Fig. 3.

Individual change in FAA plotted before and after stress. Lines connect data from a single individual. Though no mean difference in group, there is individual variability in the slop (change) across stress.

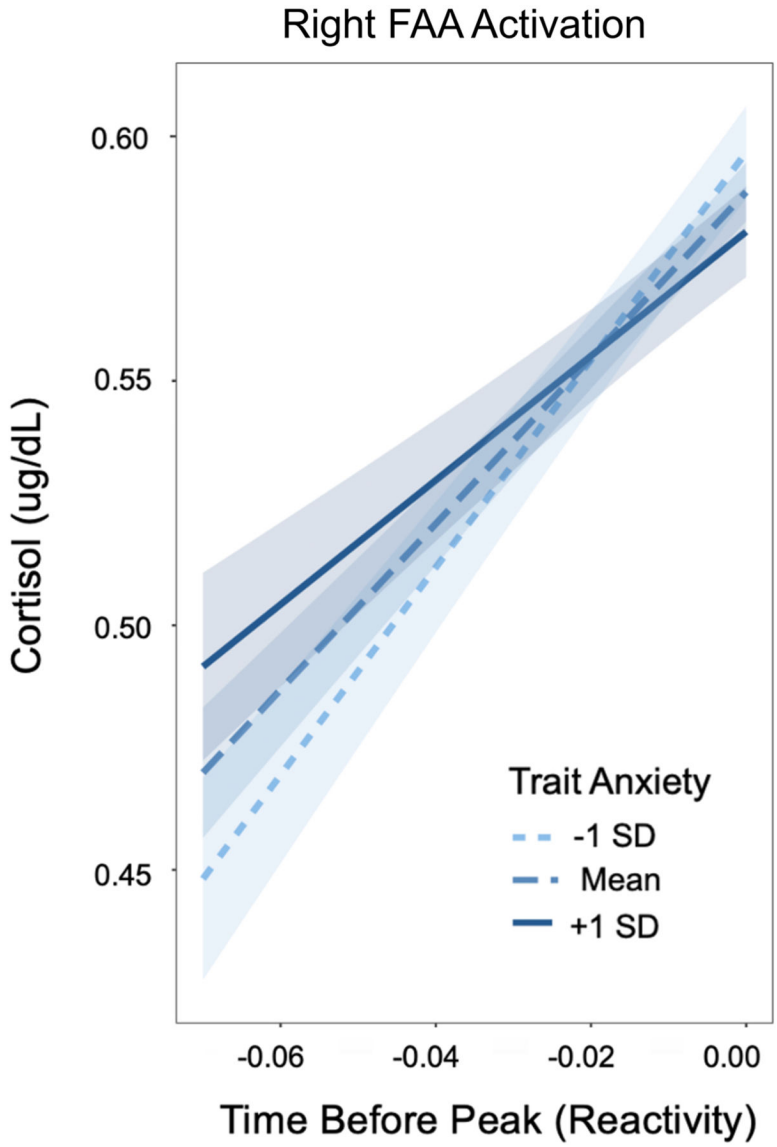

Fig. 4.

Linear mixed effects plot: rightward frontal alpha asymmetry (FAA) activation across the TSST moderates the relationship between trait anxiety and cortisol reactivity. X axis shows time before peak (TBP) and Y axis depicts the transformed cortisol concentration; thus, the slope of the line (cortisol / TBP) represents the reactivity slope. Line color indicates scaled trait anxiety score (lighter colors had lower scores and darker had higher scores) and shaded areas depict 90% confidence interval for slope of line. Individuals who had rightward FAA activation across stress with high trait anxiety had blunted reactivity slopes.

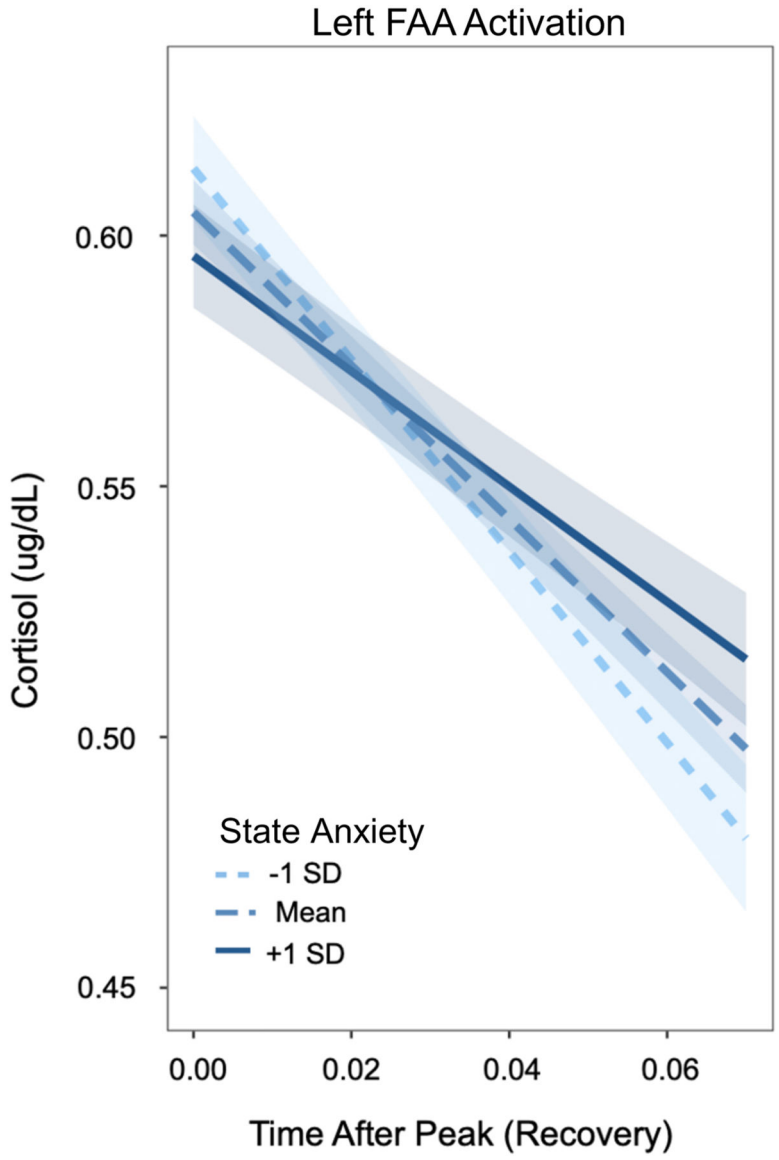

Fig. 5.

Linear mixed effects plot: leftward frontal alpha asymmetry (FAA) activation across stress moderates the relationship between state anxiety and cortisol reactivity. X axis shows time after peak (TAP) and Y axis depicts the transformed cortisol concentration; thus, the slope of the line (cortisol / TAP) represents the recovery slope. Line color is based on scaled state anxiety score (lighter colors had lower scores and darker had higher scores) and shaded areas depict 90% confidence interval for slope of line. Individuals with left FAA activation across stress and high state anxiety had blunted recovery slopes.

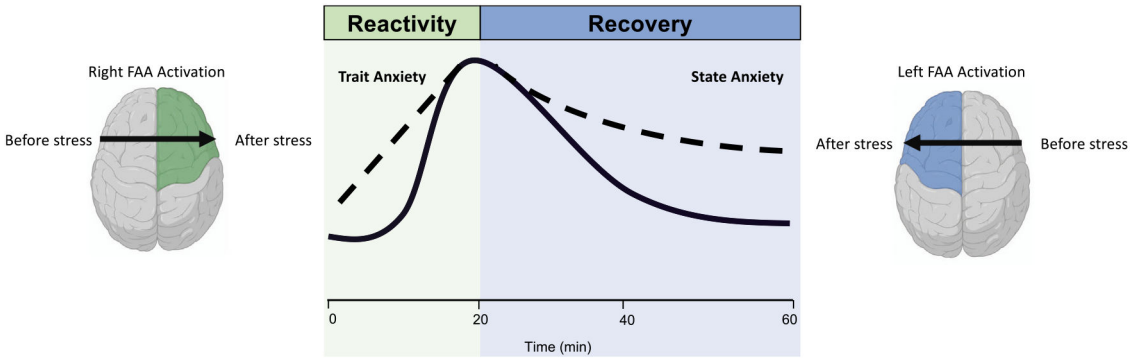

Fig. 6.

Time 0 indicates the start of the TSST. Solid line illustrates typical cortisol trajectory following stress. Green shading reflects HPA reactivity phase (left), and blue shading indicates HPA recovery phase (right). Dashed lines illustrate moderated effects of frontal alpha asymmetry (FAA) activation across stress on the relationship between anxiety and cortisol reactivity (left) and recovery (right). Illustrated peak was placed at 20 min post-stress as it was the mode peak time in study sample. Rightward FAA activation indicates individuals who had higher right lateralized frontal activation (right FAA) across stress and vice versa for leftward FAA activation. Those with rightward FAA activation and high trait anxiety had blunted cortisol reactivity slopes. Those with leftward FAA activation and high state anxiety had prolonged recovery slopes. There were no significant moderation effects on cortisol peak.

Table 1

Descriptive statistics for key study variables.

	Sample Size	Mean (SD) or Frequency (%)
Biologic Sex	145	56.5%
Males	82	43.5%
Females	63	
Race/Ethnicity	145	17%
Black or African American, non-Hispanic	25	69%
Hispanic	100	2%
White or Caucasian, non-Hispanic	3	10%
Native American	14	2%
Mixed Race	3	
No Response		
Mother's Education Status	145	90%
High School Graduate or more	131	10%
No response	14	
Father's Education Status	145	87%
High School Graduate or more	126	13%
No response	19	
Age in years	145	12.5 (2.31)
Pubertal Status (PDS score)	145	7.95 (2.96)
Clinical Status (SCID screen)	145	44.1%
Presented with disorder	64	55.9%
No disorder	81	
Medication Status	145	36.6%
On medication	53	63.4%
Medication free	92	

Adolescent sex coded male = 0, female = 1. TSST = Trier Social Stress Test. Disorders included: ADHD, OCD, generalized anxiety disorder, social anxiety disorder, or adjustment disorder (see Methods Section 2.1). Medications included: ADHD stimulants and non-stimulants, antidepressants, 4 instances of an antipsychotic and 2 instances of an anti-convulsant.

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Table 2

Descriptive statistics and unadjusted spearman correlations for variables of interest.

Variable	N	M (SD)	Range	1	2	3	4	5	6	7
1. Baseline Cortisol (μg/dL)	145	0.13 (0.06)	0.02 – 0.28							
2. Age (years)	145	12.5 (2.30)	9–16	0.19*						
3. Trait Anxiety	126	32.5 (6.97)	20–49	−0.07	0.10					
4. State Anxiety	143	2.15 (1.0)	1–5	0.00	0.22**	0.47***				
5. $FAA_{F8/F7}$ Before Stress	125	−2.89 (13.2)	−42.0 – 31.7	−0.09	−0.19*	−0.13	−0.15			
6. $FAA_{F8/F7}$ After Stress	126	−1.82 (13.6)	−35.2 – 43.7	−0.06	−0.29**	−0.07	−0.16	0.49***		
7. $FAA_{F8/F7}$ change across TSST	123	1.40 (13.2)	−35.2 – 40.2	0.001	−0.07	0.04	−0.02	−0.43***	0.51***	
8. Pubertal Score	145	7.95 (2.96)	3–12	−0.07	0.61***	0.19	0.20*	−0.15	−0.20*	−0.037

Variables shown here in their raw, untransformed scores and values.

* Notep< 0.05

** p < 0.01

*** p < 0.001.

Table 3

Estimates for growth curve model with landmark registration of the cortisol response to psychosocial stress predicted by frontal alpha asymmetry (FAA) in F7-F8 sites and anxiety.

	β	SE	*t*-value
Time Before Peak	0.28	0.024	**11.28** ***
Time After Peak	−0.54	0.026	**−20.48** ***
Trait Anxiety	−0.016	0.056	−0.29
State Anxiety	−0.021	0.058	−0.36
FAA	−0.019	0.048	−0.39
Age	0.188	0.076	**3.3** **
Pubertal Score	0.066	−0.045	1.16
Trait anxiety x FAA	0.049	0.060	0.81
State anxiety x FAA	0.009	0.058	0.16
Time Before Peak x Trait Anxiety	−0.027	0.028	−0.96
Time After Peak x Trait Anxiety	0.015	0.031	0.48
Time Before Peak x State Anxiety	0.001	0.028	0.001
Time After Peak x State Anxiety	0.020	0.032	0.61
Time Before Peak x FAA	−0.065	0.025	**−2.60** **
Time After Peak x FAA	0.063	0.027	**2.31** *
Time Before Peak x Trait Anxiety x FAA	0.058	0.027	**2.13** *
Time After Peak x Trait Anxiety x FAA	−0.064	0.039	−1.65
Time Before Peak x State Anxiety x FAA	−0.050	0.031	−1.58
Time After Peak x State Anxiety x FAA	0.099	0.032	**3.09** **

Dependent variable is the repeated cortisol concentration (n = 580). Time before peak indexes cortisol reactivity slope (x = time, y = cortisol concentration), time after peak reflects cortisol recovery slope. Model controls for baseline cortisol, medication status, pubertal score, and age in years.

* Note.p < 0.05

** p < 0.01

*** p < 0.001.