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The Association Between Early Life Stress and Prefrontal Cortex Activation During Implicit Emotion Regulation is Moderated by Sex in Early Adolescence

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Abstract

Early life stress (ELS) is a significant risk factor for the emergence of internalizing problems in adolescence. Beginning in adolescence, females are twice as likely as males to experience internalizing disorders. The present study was designed to examine sex differences in the association between ELS and internalizing problems in early pubertal adolescents, and whether and how corticolimbic function and connectivity may underlie these associations. Fifty-nine early-pubertal males and 78 early-pubertal females, ages 9–13 years (all Tanner Stage 3 or below) underwent fMRI as they performed an emotion label task that robustly interrogates corticolimbic function. Participants were also interviewed about their experience of ELS. Females exhibited a positive association between ELS and internalizing problems, whereas males exhibited no such association. Whole-brain and amygdala region-of-interest analyses indicated that whereas females exhibited a positive association between ELS and ventrolateral prefrontal cortex (vlPFC) during implicit emotion regulation, males showed no such association. Activation in these regions was positively associated with internalizing problems in females but not males; however, activation in these regions did not mediate the association between ELS and internalizing problems. Finally, both boys and girls exhibited an association between ELS and increased negative connectivity between right vlPFC and bilateral amygdala. Using a carefully characterized sample of early pubertal adolescents, the current study highlights important sex differences in the development of corticolimbic circuitry during a critical period of brain development. These sex differences may play a significant role in subsequent risk for internalizing problems.

Keywords

Internalizing problems; sex differences; puberty; amygdala; ventrolateral prefrontal cortex

Introduction

The experience of early life stress (ELS) is associated with mental health difficulties such as depression and anxiety (Andersen & Teicher, 2008; Heim & Nemeroff, 2001; Lupien, McEwen, Gunnar, & Heim, 2009; Teicher & Samson, 2016). In fact, exposure to ELS accounts for nearly one-third of all mood and anxiety disorders in the United States, underscoring the critical role of ELS as a risk factor for the onset of internalizing psychopathology (Green et al., 2010; McLaughlin et al., 2012). ELS has been theorized to confer risk for the emergence of psychopathology through several stress-related neurobiological pathways. Specifically, ELS may affect functioning of the hypothalamus-pituitary-adrenal (HPA) axis and consequently influence the development of neural structures with high densities of corticotropin-releasing factor (CRF) neurons, including portions of the prefrontal cortex (PFC) and amygdala (Heim et al., 2002; Lupien et al., 2009; Malter Cohen, Tottenham, & Casey, 2013; Nemeroff, 2004). ELS-induced alterations in the development of neural regions involved in this corticolimbic stress regulatory system may contribute to risk for psychopathology (for a review see Heim & Binder, 2012 and Lupien et al., 2009).

For instance, researchers have found that adults with a history of ELS exhibit both heightened amygdala response and positive functional connectivity, or temporal correlation, between right ventrolateral PFC (right vIPFC) and amygdala while labeling threatening (i.e., fearful and angry) faces, compared to adults without histories of adversity (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006). Negative functional connectivity between PFC and amygdala during the processing of threat-related stimuli is typically found in adults and is posited to reflect adaptive emotion regulation by the PFC (Gee, Humphreys, et al., 2013). In contrast, the positive functional connectivity of PFC and amygdala in adults with ELS suggests that stress leads to atypical emotion regulation, presumably through ineffective PFC regulation of amygdala responses (Taylor et al., 2006). It is important to note, however, that most of the studies that have found altered corticolimbic function following exposure to ELS have been conducted with adult samples and have used retrospective reports of ELS obtained many years after exposure to stress (Burghy et al., 2012; Dannlowski et al., 2012; Fan et al., 2014; Heim & Binder, 2012; Herringa et al., 2013; Herringa et al., 2016; Taylor et al., 2006; van Harmelen et al., 2013, 2014). Thus, it is difficult to assess whether these neurobiological changes are a direct consequence of having experienced adversity early in development or, alternatively, are a signature of adult-onset psychopathologies.

Given the significant consequences of exposure to ELS, combined with the growing recognition that many of these effects are not observed until adolescence (Gee & Casey, 2015; Kessler et al., 2005; Lee et al., 2014), researchers have begun to focus on elucidating the psychological and neurobiological consequences of ELS during this developmental period (see Tottenham & Galván [2016] for a review). Investigators have posited that exposure to ELS alters the development of neural structures and connections that underlie emotion processing and regulation, including the PFC and amygdala, that, in turn, increases adolescents' risk for developing internalizing disorders (Burghy et al., 2012; Eiland & Romeo, 2013; Maughan & Cicchetti, 2002; Pechtel & Pizzagalli, 2011; Tottenham et al.,

2010). This is particularly salient in adolescence when these neural systems are undergoing dramatic reorganization (Casey, Jones, & Hare, 2008). Supporting this formulation, researchers have found that children and adolescents who have experienced high levels of ELS exhibit heightened activation to emotionally evocative faces and images in brain regions that are involved in processing salient stimuli (i.e., amygdala, anterior insula, dorsal anterior cingulate cortex (Garrett et al., 2012; Gee, Gabard-Durnam, et al., 2013; Marusak, Martin, Etkin, & Thomason, 2014; McCrory et al., 2013; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015; Suzuki et al., 2014; Tottenham, Hare, Millner, et al., 2011). Fewer investigators have examined how ELS may affect PFC regulation of the processing of emotional stimuli.

The PFC may be particularly sensitive to exposure to ELS given its high density of glucocorticoid receptors and its protracted development into adulthood (Giedd, 2004; McEwen & Morrison, 2013; Pechtel & Pizzagalli, 2011; Sanchez, Young, Plotsky, & Insel, 2000; Teicher et al., 2003). For example, McLaughlin et al. (2015) used a cognitive reappraisal task to examine fMRI responses of 13- to 19-year-old participants as they attempted to explicitly regulate their affective responses to emotionally salient images. Although previously maltreated adolescents showed the typical increased response in regions involved in processing salient stimuli to viewing negative images, they also showed increased activation in superior frontal gyrus and frontal pole when downregulating their negative affect to a negative image, relative to nonmaltreated adolescents. Similarly, Marusak et al. (2014) found that adolescents exposed to childhood trauma exhibited elevated dorsolateral PFC (dlPFC) activation when performing an emotional conflict task, suggesting early adverse experiences may have important consequences on the development of the PFC in adolescence.

In addition to the effects of ELS on activation to salient stimuli in the amygdala and the PFC, researchers have documented that ELS affects the functional connectivity between these two structures (Burghy et al., 2012; Gee, Gabard-Durnam, et al., 2013; Marusak et al., 2014; Wolf & Herringa, 2016). Using task-based connectivity analyses, researchers have found that adolescents exposed to ELS show stronger negative amygdala–PFC connectivity—a more mature, adult-like pattern of connectivity—while viewing negative stimuli (Gee, Gabard-Durnam, et al., 2013; Wolf & Herringa, 2016). These findings may reflect adaptive functioning in the face of adversity – children exposed to ELS may develop more adult-like patterns of connectivity at an earlier age in order to deal more effectively with environmental adversity. In fact, Gee et al. (2013) showed that among previously institutionalized children and adolescents, having a negative pattern of amygdala–medial PFC connectivity was associated with lower separation anxiety, indicating that this adult-like pattern may be protective following experiences of early adversity. However this pattern may also represent a premature end to a sensitive period for the development of this circuit. The long-term consequences of this earlier maturation are unclear, as are the developmental trajectories of the effects of ELS on this circuitry from childhood to adulthood.

Although researchers have now demonstrated that ELS affects the development of corticolimbic circuitry in childhood and adolescence, they have not examined possible sex differences in this association. ELS has, among females, been found to be a particularly

important risk factor in the development of Major Depressive Disorder (MDD; Ge, Conger, & Elder, 2001; Ge, Lorenz, Conger, Elder, & Simons, 1994; Rudolph & Flynn, 2007; Weiss, Longhurt, & Mazure, 1999). Females also differ from males in their perceptions of stressful life events (Raffaelli et al., 2016), in their biological response to both acute and chronic stressors, and in their neural responses to negative stimuli (Bourke, Harrell, & Neigh, 2012; Kajantie & Phillips, 2006; for reviews see (Bangasser & Valentino, 2014; Novais, Monteiro, Roque, Correia-Neves, & Sousa, 2016; Ordaz & Luna, 2012; Stevens & Hamann, 2012). Given striking sex differences in the incidence of internalizing disorders—including evidence that females are twice as likely as males to develop MDD in adolescence and adulthood (Hankin & Abramson, 1999)—there may be sex-specific mechanisms, including sex-specific effects on corticolimbic circuitry, through which ELS contributes to vulnerability for internalizing problems in adolescence (Teicher et al., 2003).

In this context, the age at which sex differences in internalizing disorders become most pronounced corresponds to the complex developmental period of puberty; moreover, there is evidence that pubertal status is a stronger predictor of the onset of depression than is chronological age (Angold, Costello, & Worthman, 1998; Hayward, Gotlib, Schraedley, & Litt, 1999; Oldehinkel, Verhulst, & Ormel, 2011). Thus, puberty is a critically important period to study in order to understand neurobiological differences between males and females that may underlie sex differences in internalizing problems. It is important to note, however, that males and females differ significantly in pubertal timing; females typically experience the onset of puberty 1.5 years earlier than do males (Negriff & Susman, 2011). These sex differences in pubertal timing mean that age-matched samples of adolescent males and females are almost certain to be confounded by sex differences in pubertal stage. Similarly, given the difficulties inherent in recruiting and studying high-risk samples such as adolescents who have been exposed to maltreatment or who have experienced institutional care, many studies are simply not sufficiently powered to detect sex differences in the neurobiological effects of ELS during the narrow developmental window of early puberty during which sex differences in internalizing problems begin to emerge. Significant puberty-related changes occur in corticolimbic circuitry in adolescence (Peters, Jolles, Duijvenvoorde, Crone, & Peper, 2015; Spielberg, Forbes, et al., 2014; Spielberg, Olino, Forbes, & Dahl, 2014). Therefore, it is critical that we examine sex differences in corticolimbic development in carefully characterized samples of adolescent males and females, matched for pubertal development.

The present study was designed to address these issues by examining how ELS differentially affects male and female corticolimbic activation and connectivity during early puberty, a period in which sex differences in rates of internalizing problems begin to emerge. We also examined how corticolimbic circuitry is associated with internalizing disorders in adolescence. Given significant differences between males and females in pubertal timing (Negriff & Susman, 2011) and the documented impact of pubertal stage on corticolimbic circuitry (Peters et al., 2015; Spielberg, Forbes, et al., 2014; Spielberg, Olino, et al., 2014), in this study we used a puberty-matched sample of early adolescent boys and girls. We examined fMRI activation as boys and girls labeled emotion faces compared to matching emotion faces. Previous findings using this task suggest that labeling versus matching emotional face stimuli recruits implicit emotion regulation processes and elicits strong

activation in the PFC, particularly in the ventrolateral PFC (Gee et al., 2012; Lieberman et al., 2007; Taylor et al., 2006). This design allows us to examine emerging differences in the effects of ELS on corticolimbic circuitry during a period of development in which sex differences in internalizing problems are beginning to emerge. Based on evidence of sex differences in rates of internalizing symptoms in this age group, we hypothesized that early-pubertal females will show a stronger association between exposure to ELS and internalizing problems than will their male counterparts. We predicted further that the association between ELS and internalizing problems in females would be mediated by increased amygdala activation and PFC activation during implicit emotion regulation. Finally, we expected to find greater negative connectivity between amygdala and PFC in individuals who were exposed to more severe ELS and, further, that this negative connectivity would mediate the association between ELS and internalizing problems. We also explored sex differences in patterns of PFC-amygdala connectivity, but made no directional hypotheses.

Methods

Participants and Procedure

A total of 137 participants met criteria for inclusion in this study and analyses: 59 early-pubertal males and 78 early-pubertal females, ages 9–13 years ($M=11.42$, $SD=1.08$). An additional thirty-nine participants were excluded from the analyses due to excessive motion ($n=35$) or incomplete scans ($n=4$). The participants were part of a larger study examining the effects of ELS on brain structure and function across early adolescence. After completing a brief phone interview to determine eligibility, participants were invited to the laboratory to complete parental consent and child assent forms. In this session, parents and children also completed interviews and questionnaires assessing their experience of ELS and measures of their cognitive and emotional functioning. Males and females were matched on pubertal development based on self-report Tanner Stage and exposure to ELS (see Table 1 for descriptive statistics by child sex). Participants were recruited from the San Francisco Bay area through a combination of print and online advertisements. Exclusion criteria included: 1) self-reported Tanner pubertal stage greater than 3 and the experience of menarche in female participants; 2) nonfluent English speakers; 3) contraindications to scan (e.g., metal implants, braces, etc.); 4) history of major neurological disorder or illness; and 5) intellectual delay or learning difficulties. Upon confirming eligibility, participants were invited to return within one month to complete the fMRI portion of the study. This study was approved by the Stanford University Institutional Review Board and all participants were compensated for their participation in the study.

Measures

Early Life Stress—We assessed levels of ELS severity and the impact of early life stressors using a modified version of Traumatic Events Screening Inventory for Children (TESI-C; (Ribbe, 1996)). In this interview we assessed 30+ types of stressful life experiences. For each type of ELS endorsed, interviewers followed up with general and specific probes in order to gather detailed information about the severity of the experience and the child's perceived severity of the stressor (e.g., relationship of persons involved, duration of experience, consequences of experience). A panel of three coders, blind to the

child's subjective severity ratings and reactions and behaviors during the interview, rated the objective severity of each type of stressor based on a modified version of the UCLA Life Stress Interview coding system (Rudolph et al., 2000; Rudolph & Hammen, 1999). Coders made objective severity ratings on a 5-point scale (0 = *non-event or no impact* [e.g., witnessed debris from car crash]; 4 = *extremely severe impact* [e.g., experienced sexual abuse]; ICC=0.99). For each child, objective ratings for each type of ELS endorsed were summed to create an index of the cumulative severity of ELS.

Pubertal Status—Pubertal stage was determined using self-reported Tanner staging (Marshall & Tanner, 1969, 1970). Using schematic drawings of two secondary sex characteristics (pubic hair and breast/testes development), each participant reported on his/her developmental stage on a scale of 1–5. A Tanner staging of 1 signifies that no pubertal development has begun, and a staging of 5 signifies that adult levels of pubertal maturation have been achieved. To be included in this study, all participants rated themselves at stage 3 or below on measures of both pubic hair and breast/testes development. Tanner staging scores have been found to correlate with physicians' physical examinations of pubertal development (Coleman & Coleman, 2002; Slora et al., 2009, see also Shirtcliff, Dahl, & Pollak, 2009).

Internalizing Problems—Participants completed the Youth Self Report (YSR; (Achenbach, 1991; Achenbach & Rescorla, 2001) measure, which assesses a broad array of behavioral problems in children and adolescents. For this study we examined total scores on the Internalizing Problems subscale of the YSR. One male participant did not complete this questionnaire.

Magnetic Resonance Imaging

Implicit Emotion Regulation fMRI Task—We used a modified emotion label task to examine the neural correlates of implicit emotion regulation (see (Hariri, Bookheimer, & Mazziotta, 2000; Lieberman et al., 2007). This task was designed based on the formulation that linguistic processing of an emotional expression (e.g., labeling an emotional face) requires greater downregulation of regions responsible for processing salient information than does perceptual processing of the same emotional expression (e.g., matching emotional faces), potentially serving as a marker of the neural correlates of implicit emotion regulation (Lieberman et al., 2007). This task requires participants to identify, or label, a target emotional expression (emotion label) or to match a target emotional expression to two other emotional expressions (emotion match). We also included a sensorimotor control condition in which participants were required to match a target shape to two other shapes (shape match). For the label conditions, participants were instructed to make a button press to indicate whether the appropriate label for the target figure was located on the bottom left or the bottom right of the screen. For all match conditions, participants were instructed to make a button press to indicate whether the target figure at the top of the screen was more similar to the figure below it on the left or on the right. Each face/label set was presented on the screen for 5000 ms, and each block of stimuli consisted of 10 trials. All task blocks were interspersed with rest blocks (lasting 15000 ms) in which participants were instructed to focus on a fixation cross in the middle of the screen. Each run consisted of one block of each

task condition (Positive Label, Positive Match, Negative Label, Negative Match, Shape Match) as well as interspersed rest blocks. Presentation of conditions was randomized across participants, and all participants completed two complete runs of the task.

The task was presented using E-Prime software Version 2.0. A total of 50 trials were divided across two emotion conditions (positive, negative) and two response conditions (match and label) in addition to the control shape match condition. The positive and negative emotional expressions were facial displays from the NimStim picture set (Tottenham et al., 2009). Ten actors (5 female, 5 male) were displayed showing positive or negative emotional expressions. Positive emotional expression blocks included both high and low arousal positive displays including happy, excited, surprised, and calm facial expressions. Negative emotional expression blocks included both high and low arousal negative displays including sad, angry, and fearful facial expressions. To optimize power in testing our hypotheses, our analyses focused on the contrast of all emotion label relative to all emotion match conditions.

fMRI acquisition—Participants who met eligibility criteria completed an fMRI scan. All scans were conducted on a 3 Tesla GE whole-body scanner (GE Healthcare Systems, Milwaukee, Wisconsin). Foam padding was used to minimize head movement. Two T2*-sensitive gradient echo-planar pulse sequences were used for functional imaging (TR = 2000 ms, TE = 30 ms, flip angle = 77°, matrix size = 70×70, 43 axial slices, FOV = 22.4 cm, 3 mm thick), each run lasting 5 minutes and 54 seconds. An automated high-order shimming procedure was used to reduce B₀ inhomogeneity. Additional high-resolution structural images were acquired with an axial 3D FSPGR sequence with T1 contrast (TR = 6.0 ms, TE = 2 ms, flip angle = 12°, matrix size = 256×256, 186 axial slices, FOV = 23 cm, 0.9 mm) for spatial registration.

fMRI data analysis—Analyses were conducted in FSL Version 6.0.0 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl), using FEAT (FMRI Expert Analysis Tool). The first four volumes of each participant's functional scan were discarded to allow for stabilization of longitudinal magnetization. The remaining images were preprocessed using standardized procedures, including motion correction to the mean image using MCFLIRT (Motion Correction FMRIB's Linear Image Registration Tool) (Jenkinson, Bannister, Brady, & Smith, 2002), slice-timing correction using Fourier-space time-series phase shifting, spatial smoothing using a Gaussian kernel of FWHM 5mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and high pass temporal filtering (Gaussian-weighted least squares straight line fitting, with sigma=50.0s). Functional data were linearly registered to a common stereotaxic space by first registering the in-plane T2 image to the T1-weighted structural image (6 degrees of freedom), transforming the T1-weighted structural image to the MNI152 T1 brain, and then applying that deformation matrix and resampling to 2 mm resolution onto the functional images using FLIRT (12 degrees of freedom; FMRIB's Linear Image Registration Tool; Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001). All fMRI analyses were therefore performed in MNI space at 2 mm³ resolution.

Time series statistical analysis was conducted using FILM with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). The voxel-wise general linear model (GLM) included regressors for each block condition (positive/match, positive/label, negative/match, negative/label, and shape match) as well as their temporal derivatives. Twelve motion correction parameters, as well as an indicator function to identify volumes as having excessive motion according to framewise displacement of 0.9mm, were included as covariates of non-interest. Participants with absolute motion > 3mm or > 20% of volumes with framewise displacement > 0.9mm were excluded from the analyses (n=35). Both within-subject runs were combined in a fixed-effects model for each participant, which averaged the contrast estimates over runs within participant by setting the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). All participants were then combined in a higher-level mixed effects model to investigate within and between-group differences. Prior to thresholding, we used a binarized gray matter mask (obtained from https://canlabweb.colorado.edu/wiki/doku.php/help/core/brain_masks). Higher-level group analyses were conducted using FLAME (FMRIB's Local Analysis of Mixed Effects State) stage 1 (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Given significant age differences between males and females, we included age as a covariate in all analyses.

Whole-Brain Analyses: Effects of Sex and ELS—We examined the effects of sex and ELS severity on BOLD response during contrasts of interest in whole-brain analyses. Statistical images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $\alpha = .05$ (Worsley, 2001).

Region of Interest Analysis of Amygdala—We also examined amygdala activation during implicit emotion regulation using a region-of-interest (ROI) analysis. A bilateral amygdala ROI was created using the Harvard-Oxford subcortical Atlas in FSL (25% threshold).

Psychophysiological Interaction (PPI) Analyses to Assess PFC-Amygdala Functional Connectivity—We used psychophysiological interaction (PPI) analyses to examine functional connectivity during implicit emotion regulation between the bilateral amygdala ROI and the two PFC regions that showed a significant interaction of ELS and sex (Friston et al., 1997; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). This analysis identifies regions in the brain that are correlated most strongly with the significant prefrontal ROIs during emotion label relative to emotion match conditions. For each PFC ROI, the GLM analysis was conducted in FSL and included regressors for each task condition, the ROI timeseries, and the interaction of the task contrast (emotion label vs. emotion match) and the ROI timeseries. Again, both within-subject runs were combined in a fixed-effects model for each participant, which averaged the contrast estimates over runs within participant by focusing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects; Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). All participants were then combined in a higher-level mixed effects model to investigate connectivity patterns across both groups. Higher-level group analyses were

conducted using FLAME (FMRIB's Local Analysis of Mixed Effects State) stage 1 (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $\alpha = 0.05$ (Worsley, 2001). We then extracted parameter estimates from the bilateral amygdala ROI (as defined above) and used linear regression in SPSS (version 23) to examine the effect of sex, ELS, and the interaction between sex and ELS on connectivity patterns between bilateral amygdala and the two PFC regions that showed a significant interaction effect with sex and ELS severity, after covarying for chronological age. We used simple slope analyses to probe significant interactions (Aiken & West, 1991).

Demographics and Behavioral Analyses

All statistical analyses reported below were conducted with SPSS (version 23) using two-tailed tests ($\alpha = .05$). Independent samples t-tests or chi-squared tests were used to compare males and females on demographic variables, exposure to ELS severity, and scores on the YSR Internalizing Problems subscale. We conducted analyses of covariance (ANCOVAs) to compare task performance between males and females, after covarying for chronological age. Finally, we conducted correlational analyses to test whether ELS severity was associated with task performance.

Mediation Analyses

Based on our findings (described below), we tested whether BOLD responses to emotion label relative to match in regions that showed a significant interaction between ELS severity and sex mediated the association between ELS severity and YSR Internalizing scores in females. To do this, we used a single-step nonparametric resampling procedure (1,000 samples with replacement) for testing indirect effects (Hayes, 2013). Mediation is supported when the indirect effect is statistically significant. To assess the indirect effect, we calculated 95% confidence intervals (CIs) for coefficients; if the CI does not include zero, the indirect effect is considered to be statistically significant.

Results

Demographic and Clinical Characteristics

Participant demographic and clinical characteristics are presented in Table 1. As shown in this Table, boys and girls did not differ significantly in Tanner stage, medication use, handedness, race/ethnicity, or family income. As expected, however, given that we matched boys and girls on pubertal status, the two sexes did differ in chronological age ($t(135) = 5.115, p < .001$).

Sex Differences in the Effects of ELS on Internalizing Problems

There were no significant sex differences in ELS severity or in internalizing problems in our sample (see Table 1). In examining the contributions of sex and ELS severity to self-reported internalizing problems after controlling for chronological age, a linear regression indicated that sex moderated the association between ELS severity and internalizing problems ($B = .903, SE = .306, t(131) = 2.953, p = .004$). Post-hoc simple slopes analyses within each sex

controlling for age indicated that ELS was significantly associated with internalizing problems in females ($r(75)=.476, p<.001$), but not in males ($r(55)=-.079, p=.559$).

fMRI Task Behavioral Performance

We conducted analyses of covariance (ANCOVAs) to compare task performance between males and females, controlling for age. Males and females did not differ on task accuracy or response time (RT; Table 2). ELS severity was associated with longer RT to match emotions ($r(134) = .174, p=.042$). ELS severity was not associated with RT to label emotions ($r(134) = .069, p=.425$) or with task accuracy ($|rs|<.048, ps>.576$).

Whole-Brain Analysis: Main Effect of ELS

We conducted whole-brain correlational analyses to examine the effect of ELS severity, controlling for the effects of chronological age, on brain regions involved in implicit emotion regulation (i.e., labeling emotion faces versus matching emotion faces). These analyses yielded a significant cluster that was negatively correlated with ELS severity: right lateral occipital cortex/precuneus cortex ($k=1088$; peak voxel: $x=18, y=-72, z=42$; $Z=3.95$).

We also conducted a linear regression to examine the effect of ELS severity, controlling for the effects of chronological age, on activation in a bilateral amygdala ROI during implicit emotion regulation. There was no association between ELS severity and bilateral amygdala activation ($r(134)=-.049, p=.575$).

Whole-Brain Analysis: Main Effect of Sex

We conducted whole-brain t-tests to examine sex differences, controlling for the effects of chronological age, in regions involved in labeling emotion faces versus matching emotion faces. Direct comparisons between males and females yielded one significant cluster in left lingual gyrus in which males showed significantly greater activation than did females ($k=580$; peak voxel: $x=-12, y=-70, z=-6$; $Z=3.38$). There were no clusters in which females showed greater activation than did males.

We also conducted an analysis of covariance to examine sex differences in activation in a bilateral amygdala ROI, controlling for the effects of chronological age. There were no significant differences between males and females in amygdala activation when labeling emotion faces relative to matching emotion faces ($F(1,134)=.034, p=.855$).

Whole Brain Analysis: Interaction of ELS and Sex

Finally, we conducted a whole brain interaction model to examine whether the linear association between ELS severity and brain regions involved in labeling emotion faces versus matching emotion faces differed by sex, controlling for the effects of chronological age. This interaction model yielded three significant clusters (Figure 1). Compared with males, females showed a significantly greater association between ELS and activation in left vIPFC ($k=606$; peak voxel: $x=-36, y=48, z=-4$; $Z=3.8$), right dIPFC/vIPFC ($k=784$; peak voxel: $x=44, y=44, z=26$; $Z=4.1$) and bilateral intracalcarine cortex ($k=1999$; peak voxel: $x=-18, y=-72, z=12$; $Z=4.18$).

ROI Analysis of Amygdala: Interaction of ELS and Sex

We also conducted a linear regression to examine the interaction between ELS severity and sex in predicting bilateral amygdala ROI response to labeling emotion faces relative to matching emotion faces. This interaction was not significant ($B=.488$, $SE=1.147$, $t(132)=-.426$, $p=.671$).

Associations between Brain Regions and Internalizing Symptoms

We next examined the association between self-reported internalizing problems and parameter estimates extracted from the ROIs defined by the interaction of ELS and sex, including left vIPFC, right dIPFC/vIPFC, and bilateral intracalcarine cortex, separately for males and females (Figure 1). Females showed a positive association between all three ROIs and YSR Internalizing Problems total score, such that greater activation in left vIPFC, right dIPFC/vIPFC, and intracalcarine cortex was associated with greater internalizing problems (left vIPFC: $r(78)=.237$, $p=.037$; right dIPFC/vIPFC: $r(78)=.232$, $p=.041$; intracalcarine cortex: $r(78)=.260$, $p=.021$). In contrast, males showed a positive association between internalizing problems and activation only in intracalcarine cortex (intracalcarine cortex: $r(58)=.320$, $p=.014$); there was no significant relation in males between internalizing problems and activation in left vIPFC or in right dIPFC/vIPFC (left vIPFC: $r(58)=-.070$, $p=.601$; right dIPFC/vIPFC: $r(58)=.141$, $p=.293$).

Mediation Analysis: Testing whether Brain Activation Mediates the Association between ELS Severity and Internalizing Symptoms in Females

Because there was a significant positive association between activation during implicit emotion regulation in left vIPFC, right dIPFC/vIPFC, and intracalcarine cortex and internalizing symptoms in females only, we tested whether activation in these regions mediated ELS severity and internalizing symptoms. Activation during implicit emotion regulation in these three regions did not mediate the association between ELS and internalizing problems in females; that is, the indirect effect did not differ significantly from zero (left vIPFC: point estimate=.010 [.018], 95% CI [-.011, .070]; right dIPFC/vIPFC: point estimate=.025 [.034], 95% CI [-.023, .117]; intracalcarine cortex: point estimate=.076 [.081], 95% CI [-.057, .270]).

PPI Analysis to Assess PFC-Amygdala Functional Connectivity

We also conducted PPI analyses to examine task-dependent functional connectivity between the two prefrontal regions that showed a significant interaction of ELS severity and sex and the bilateral amygdala ROI. We tested the main effects of ELS severity and sex and their interaction on the strength of these connections during emotion label relative to emotion match conditions. The main effects of ELS and sex, and the interaction of ELS and sex, on the strength of connectivity between left vIPFC and bilateral amygdala were not significant. There was a significant main effect of ELS severity on the strength of connectivity between right dIPFC/vIPFC and bilateral amygdala ($B=-.002$, $SE=.001$, $t(132)=-2.352$, $p=.020$), such that greater ELS severity is associated with more negative amygdala-PFC connectivity for emotion label relative to emotion match conditions (Figure 2).

Associations between PFC-Amygdala Functional Connectivity and Internalizing Symptoms

Functional connectivity between bilateral amygdala and left vIPFC and right dIPFC/vIPFC was not associated with internalizing symptoms across all participants (left vIPFC: $r(133)=-.138$, $p=.110$; right dIPFC/vIPFC: $r(133)=-.084$, $p=.334$) or in each sex separately (males: left vIPFC: $r(58)$, $p=.776$, right dIPFC/vIPFC: $r(58)=.162$, $p=.225$; females: left vIPFC: $r(78)=-.181$, $p=.112$, right dIPFC/vIPFC: $r(78)=-.210$, $p=.065$). Given null associations between functional connectivity and internalizing symptoms, we did not conduct follow-up mediation analyses.

Discussion

In a sample of puberty-matched early adolescent males and females, we documented differential associations between ELS severity and internalizing problems. Among girls, there was a significant association between ELS severity and internalizing problems, whereas among boys there was no such association. In attempting to understand the neurobiological bases of emerging sex differences in the effects of ELS on internalizing problems, we conducted whole-brain and *a priori* ROI analyses of brain activation while participants were performing an emotion label task designed to measure implicit emotion regulation. We found a significant interaction of ELS severity and sex in left vIPFC, right dIPFC/vIPFC, and bilateral intracalcarine cortex. Among girls, there was a positive association between ELS severity and activation in these regions during implicit emotion regulation, and as above, among boys there was no association between ELS severity and activation in these regions. Moreover, greater activation in these three regions was associated with higher levels of internalizing problems in girls. Nonetheless, this activation did not statistically mediate the association between ELS severity and internalizing problems. We also found a significant effect of ELS severity on right lateral occipital/precuneus cortex and a significant main effect of sex in left lingual gyrus during emotion label relative to emotion match conditions. Contrary to our hypothesis, ROI analyses yielded no significant main effects or interactions of ELS severity and sex on amygdala response during emotion label relative to emotion match conditions. When we examined patterns of PFC-amygdala functional connectivity, we found greater negative association between ELS severity and connectivity in both sexes combined between right dIPFC/vIPFC and bilateral amygdala during implicit emotion regulation; this did not mediate the relation between ELS and internalizing symptoms.

The vIPFC is largely involved in cognitive responses to negative emotions, including cognitive reappraisal and emotion regulation (Ochsner, Silvers, & Buhle, 2012) and thus plays a significant role in modulating negative affect (Forbes, Phillips, Silk, Ryan, & Dahl, 2011; Phan et al., 2005). Although there are no known direct anatomical connections between vIPFC and the amygdala, vIPFC is posited to modulate amygdala response through activation in the medial PFC (Pessoa, 2010; Pessoa, Kastner, & Ungerleider, 2002; Silvers et al., 2016). Cognitive reappraisal has been associated with a negative correlation between vIPFC and amygdala activation (Silvers et al., 2016). The vIPFC does, however, share direct anatomical connections with the dIPFC; research suggests that both these regions support executive function and inhibitory processes (Pessoa, 2010; Pessoa et al., 2002). Given our

finding that greater vIPFC activation is associated with higher levels of ELS severity in early pubertal females, several possible interpretations can be generated. For example, heightened PFC activation in response to affective stimuli has been interpreted as reflecting immaturities in regulating an affective response (see Pfeifer & Blakemore (2012) for a review of this literature in adolescence). In this context, it is plausible that early pubertal females require additional neural engagement to label the facial emotion and, in turn, to downregulate amygdala response. Given the nonsignificant results of our mediation analyses, however, it is not clear how increased activation in these brain regions during this implicit emotion regulation task gives rise to heightened internalizing symptoms in early pubertal females. It is possible that increased neural recruitment at this point in early puberty contributes to maladaptive cognitive processes and risk for disorder in the future (i.e., late puberty when first depressive episodes commonly occur and sex differences in depressive symptoms peak); it is important that this possibility be examined longitudinally in future research.

One additional theoretical explanation for our finding that greater exposure to ELS is associated with greater recruitment of PFC in early pubertal females is the stress acceleration hypothesis. Integrating evidence from both animal and human studies of exposure to early adversity, the stress acceleration hypothesis posits that experiencing ELS leads to a faster maturation of neural circuits involved in emotional functioning, primarily the corticolimbic circuit. Callaghan and Tottenham (2016) argue that in the face of high levels of stress, accelerated development of neural circuitry involved in emotion functioning is adaptive in the short-term, as it facilitates earlier independence from a potentially unstable or harmful environment. Indeed, Gee et al. (2013) found a more mature pattern of amygdala–mPFC functional connectivity (i.e. more negative connectivity) in previously institutionalized children and adolescents relative to never-institutionalized children and adolescents, which was in turn associated with reduced separation anxiety in the previously institutionalized group only. However, this accelerated development could have later consequences and researchers have yet to explore this possibility longitudinally. Increasing age in adolescence has been associated with greater vIPFC activation both in an emotion regulation context and during passive viewing of fearful faces (McRae et al., 2012; Yurgelun-Todd & Killgore, 2006; see also Forbes, Phillips, Silk, Ryan, & Dahl, 2011). Given typical developmental increases in the recruitment of dorsal and lateral PFC (Cohen-Gilbert & Thomas, 2013; Somerville, Hare, & Casey, 2011; Tottenham, Hare, & Casey, 2011) in support of emotion regulation, the increased recruitment of left vIPFC and right dIPFC/vIPFC that we found in our sample of early adolescent females who were exposed to high levels of ELS may represent a more developmentally mature pattern of neural function. Indeed Gee et al. (2013) found heightened activation in the amygdala and in prefrontal and superior temporal gyrus when viewing fear faces in a sample of previously institutionalized children and adolescents, but no difference in mPFC activation between children with and without a history of adversity. When we examined functional connectivity of prefrontal ROIs that exhibited significant interactions of sex and ELS severity, we also found that ELS severity was associated with greater negative connectivity of right dIPFC/vIPFC and bilateral amygdala for emotion label relative to emotion match conditions. Although sex did not

moderate this association, we believe that this is nonetheless an important demonstration of the stress acceleration hypothesis.

Contrary to our hypothesis, we did not find significant effects of stress, sex, or their interaction on amygdala activation during implicit emotion regulation. Activation in the amygdala increases in response to salient (both positive and negative) stimuli in the environment; amygdala activation is posited to serve as a motivating signal to guide learning and memory for emotional material. Our nonsignificant findings for the effect of ELS on amygdala activation during implicit emotion regulation stand in contrast to a large body of work suggesting that individuals exposed to ELS show heightened amygdala reactivity to emotion face stimuli (including angry, happy, fearful, sad and neutral faces; Garrett et al., 2012; Gee et al., 2013; Tottenham et al., 2011; Marusak et al., 2014; McCrory et al., 2013; Suzuki et al., 2014), as well as to negative images (McLaughlin et al., 2015). In understanding these discrepant findings, it is instructive to note that because of the block design of this task, we combined a range of emotional face stimuli, including happy, surprised, sad, angry, and fearful faces. The block design of the task prevents us from being able to assess reliably amygdala activation to each emotion. It is possible that the effects of ELS on amygdala activation are selective to fearful or angry faces or specific to task demands (i.e., passively attending to facial stimuli or performing a cognitive task involving emotional face stimuli). Future research should investigate the specificity of this effect across a range of emotional faces and task conditions.

Similarly, the majority of existing work examining the effects of ELS on amygdala activation to threat-related stimuli in adolescence uses an extreme-group approach to examine brain function in individuals exposed to severe and homogenous forms of ELS, including early institutional care and severe maltreatment, relative to healthy controls (McLaughlin et al., 2015; Mueller et al., 2010; Tottenham, Hare, Millner, et al., 2011). Less work has focused on the neurobiological consequences of more commonly experienced forms of ELS such as those reported by the young participants in this study, including witnessing an injury or an accident and moving homes. It is possible that heightened amygdala reactivity as a consequence of ELS occurs only after exposure to extreme forms of early adversity or to specific types of ELS, such as exposure to severe threat or harmful input from caregivers early in development (Humphreys & Zeanah, 2015; McLaughlin, Sheridan, & Lambert, 2014; Teicher & Samson, 2016). The measure of ELS severity that we used in this study includes both more severe forms of ELS such as physical and sexual abuse, as well as less severe stressors. Thus, heightened amygdala reactivity may occur only after exposure to specific types of extreme ELS, a possibility that should be examined more explicitly in future research.

In summary, this is the first study to carefully assess sex differences in corticolimbic activation and connectivity during implicit emotion regulation in a unique sample of early pubertal youth as a function of exposure to ELS severity. In addition to the strengths of this investigation, there are three important limitations of this investigation. First, although we used careful coding systems to evaluate the cumulative effects of objectively rated ELS severity on corticolimbic development, we use the term ELS broadly to include multiple forms of adverse childhood experiences, ranging from maltreatment and neglect to

residential moves and exposure to marital disagreements. As we noted above, researchers have suggested that different forms of early adverse experiences have different psychobiological consequences (Humphreys & Zeanah, 2015; McLaughlin & Sheridan, 2016; Teicher & Samson, 2016; Teicher, Samson, Anderson, & Ohashi, 2016). Future research should examine the differential effects of types of stress exposure, including exposure to threat and neglect, on neural functioning. Second, we did not examine effects of the timing of ELS severity or its chronicity in this study. Researchers have developed coding systems to describe more fully experiences of maltreatment; one notable example of this is the Maltreatment Classification System (MCS; Barnett, Manly & Cicchetti, 1993). Given our use of child-reported stressors and objectively-rated severity of stressors (as opposed to obtaining both child and parent reports, or reports from Child Protective Services for more severe stressors), we did not have sufficient details in our stress assessment to explore specific and differential effects of onset, chronicity, or developmental timing. It will be important in future research to elucidate how exposure to ELS at different points in development, as well as chronicity of adverse experiences, differentially affect corticolimbic circuitry, given that this system is still maturing through adulthood. In the present study, we defined ELS as any adverse experience prior to participating in the study, when adolescents were in early pubertal development. There is evidence in both human and rodent models, however, to suggest that the effects of adverse experiences on different neural systems depends on the individual's developmental stage at the time of exposure (Andersen et al., 2008; Andersen & Teicher, 2008; Lupien et al., 2009; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). Finally, it is important to mention the limitations of cross-sectional investigations such as the present study, which precludes our ability to draw causal inferences. It will be important in future research to understand how corticolimbic development across puberty differs in males and females, particularly with respect to its temporal relation to ELS and risk for internalizing problems. Elucidating deviations from normative neural development in individuals who are exposed to ELS will lead to a better understanding of the etiology of internalizing problems and will highlight potential ways to intervene in the association between ELS and internalizing problems.

Despite these limitations, this study documents the effects of a wide range of ELS exposure on corticolimbic function in early puberty, and elucidates how sex moderates the effects of ELS on corticolimbic function. These results are important in refining models describing the impact of ELS on development, and highlight the need to study homogenous samples of well-characterized individuals at specific points in development. Understanding how ELS affects psychobiological development over time will facilitate the generation of a model describing the emergence of internalizing disorders, and will help to identify specific points or sensitive periods at which intervention may be most effective.

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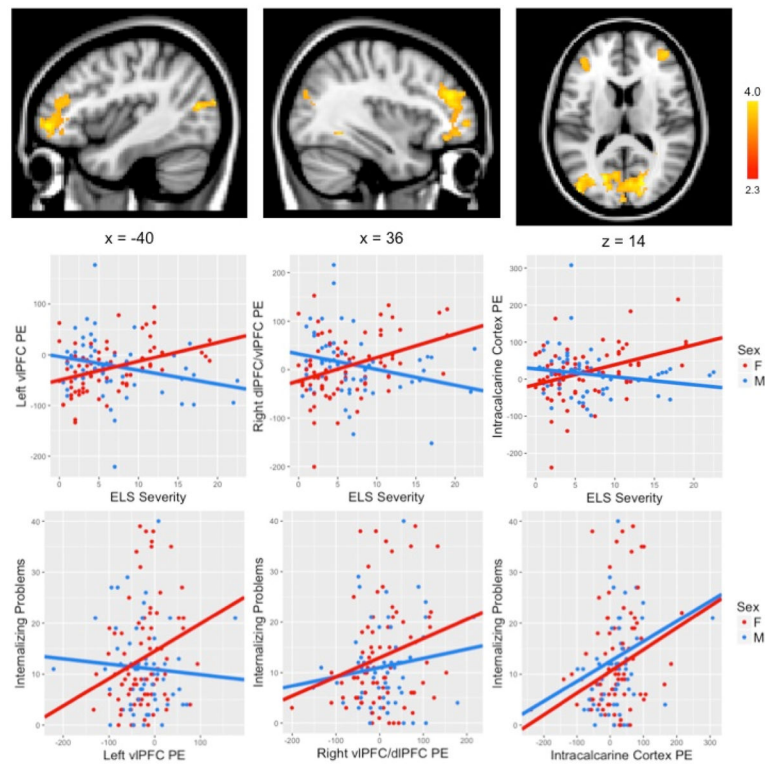


Figure 1.

A whole brain interaction model examining whether the linear association between ELS severity and brain regions involved in labeling emotion faces versus matching emotion faces differed by sex yielded three significant clusters in left vIPFC, right dIPFC/vIPFC and bilateral intracalcarine cortex. Activation maps are thresholded at $Z > 2.3$ and corrected for multiple comparisons using a cluster-based $p < .05$. MNI coordinates are indicated for slice distance (in mm). Parameter estimates (showing the amount of signal change measured in arbitrary units) of BOLD signal response were extracted from each significant cluster and plotted in the bar graph. Parameter estimates were also related to internalizing problems in males and females separately. vIPFC = ventrolateral prefrontal cortex; dIPFC = dorsolateral prefrontal cortex.

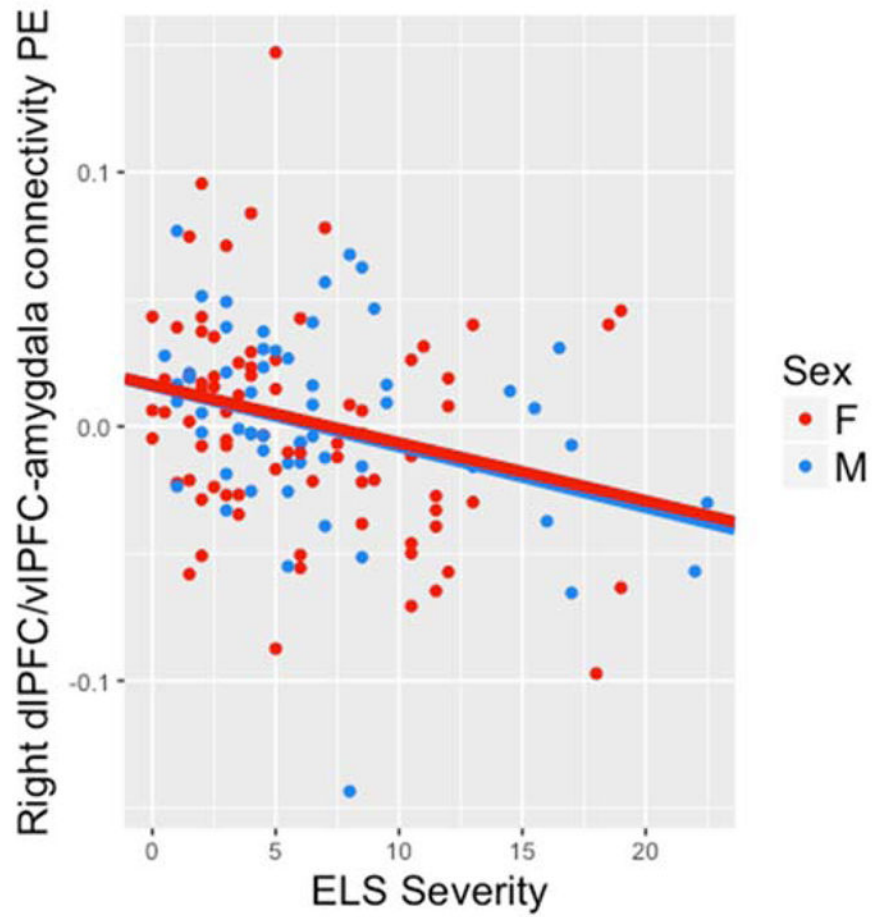


Figure 2. Strength of connectivity between right dIPFC/vIPFC and bilateral amygdala was negatively associated with ELS severity across males and females. vIPFC = ventrolateral prefrontal cortex; dIPFC = dorsolateral prefrontal cortex.

Table 1

Descriptive Statistics for Males and Females

	Males	Females	<i>t</i> or χ^2	df	<i>p</i>
Age	12.018 (0.925)	11.146 (1.033)	5.115	135	<.001
Tanner Hair Development	1.881 (0.672)	1.872 (0.795)	0.074	135	0.941
Tanner Breast Development	2.000 (0.615)	2.083 (0.787)	-0.672	135	0.503
Medication Use	17%	13%	0.532	1	0.627
Handedness (% R Dominant)	88%	81%	0.865	1	0.510
Race/Ethnicity			3.859	1	0.570
White/Caucasian	44%	40%			
African American	9%	9%			
Hispanic	13%	9%			
Asian	12%	11%			
Native American	2%	0%			
Pacific Islander	0%	0%			
Other	18%	31%			
No response	2%	0%			
Family Income			9.787	1	0.550
<\$5000	0%	1%			
\$5001–10,000	0%	3%			
\$10,001–15,000	0%	1%			
\$15,001–25,000	3%	4%			
\$25,001–35,000	3%	1%			
\$35,001–50,000	5%	3%			
\$50,001–75,000	9%	8%			
\$75,001–100,000	12%	11%			
\$100,001–150,000	24%	26%			
\$150,001+	34%	33%			
No response	10%	9%			
ELS Severity	6.864 (5.265)	5.987 (4.768)	1.019	135	0.310
YSR Internalizing Problems	11.220 (8.413)	13.150 (10.276)	-1.168	134	0.245

M (SD) or %, ELS= early life stress.

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Table 2

Task Performance

	Males	Females	
Response Time (RT)			
Emotion Label	1847.172 (276.215)	1857.447 (260.699)	$F(1,134)=.092, p=.762$
Emotion Match	1950.548 (315.084)	2001.075 (295.768)	$F(1,134)=.174, p=.678$
Accuracy (% Correct)			
Emotion Label Accuracy	72.966 (15.246)	72.308 (12.714)	$F(1,134)=.102, p=.750$
Emotion Match Accuracy	83.517 (14.74)	83.75 (14.83)	$F(1,134)=.576, p=.449$

Standard deviations are presented in parentheses.

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