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The roles of early life adversity and rumination in neural response to emotional faces amongst anxious and depressed adults

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Abstract

Background: Early life adversity (ELA) is a risk factor for internalizing psychopathology (IP). ELA is also linked to alterations in neural phenotypes of emotion processing and maladaptive emotion regulatory strategies, such as ruminative brooding, in adulthood. We therefore expected that ELA would predict cortical brain activation to emotional faces in trans-diagnostic IP and in turn, mediate the extent of rumination among patients with IPs and ELA (IP+ELA).

Method: 132 individuals, including 102 treatment-seeking adults with heterogeneous IPs and 30 healthy controls (HCs) performed an emotional face-matching task during fMRI. Whole brain analyses compared HC (n=30), IP (n=52), and IP+ELA (n=50) neural responses to emotional (angry, fearful, happy, and sad) faces versus shapes, controlling for depression and anxiety symptoms. Parameter estimates of activation were extracted for significant between-group differences and tested as a mediator of ruminative brooding in IP+ELA.

Results: IP+ELA demonstrated increased activation in the superior frontal gyrus and anterior cingulate cortex (fear), superior parietal lobule, precuneus, posterior cingulate, and inferior temporal gyrus (fear only), and cuneus (fear and angry). These regions were preferentially correlated with ruminative brooding in IP+ELA, many of which mediated the link between IP+ELA and ruminative brooding.

Conclusions: Results provide evidence that ELA history among IP patients augments engagement of brain regions involved in emotion processing, above and beyond what is accounted for by current symptoms. Though longitudinal designs are needed, alterations in the neural correlates of maladaptive processing of socio-emotional information may be a common pathway by which ELA poses risk for psychopathology.

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Conflict of Interest

None.

Keywords

early childhood adversity; emotion processing; functional neuroimaging; rumination; anxiety; depression

Introduction

Childhood maltreatment is a damaging form of early life adversity (ELA) and stress broadly defined as the intentional or unintentional commission of acts (e.g. verbal, physical, or sexual abuse) or withholding of resources (emotional or physical neglect) by caregivers that adversely influence the emotional and physical health, growth, or adaptation of a child (Egeland, 2009). ELA is a particularly potent risk factor for many internalizing psychopathologies (IPs) in adulthood, such as depression, posttraumatic stress disorder (PTSD), and other anxiety disorders (Gilbert *et al.*, 2009, Widom *et al.*, 2007). Moreover, IP patients with a history of ELA demonstrate a particularly chronic course of illness and treatment resistance (Arnow, 2004, Wegman and Stetler, 2009). Developing a better understanding of the mechanisms by which ELA may foster a predisposition to poor long-term mental outcomes is paramount for improving targeted prevention and intervention for this vulnerable population.

From a theoretical standpoint, ELA may increase vulnerability to IPs via altered brain function underlying processing and modulation of emotion (McCrory *et al.*, 2017, Teicher *et al.*, 2016). Specifically, this latent vulnerability theory postulates that ELA is thought to enhance neurobiological sensitivity to sources of potential threat or negative valence (Heany *et al.*, 2017, McCrory *et al.*, 2017). In a childhood environment saturated with constant threats to wellbeing, heightened responsiveness to social signals of possible adverse experiences may evolve as an adaptive coping mechanism, initially facilitating early identification and avoidance of potentially harmful interactions with a caregiver (McCrory and Viding, 2015). However, if increased stress susceptibility is instantiated during a malleable period of brain development and endures over time, the success of this compensatory mechanism may break down or become maladaptive with repeated overuse (McCrory and Viding, 2015). It is this chronic “wear and tear” to regulatory and compensatory emotional processes that is suspected to increase vulnerability to emotional dysregulation and mental health problems later in life (Danese and Baldwin, 2017, Dannlowski *et al.*, 2012).

In initial support of this hypothesis, there is an extant literature documenting structural alterations in frontal and limbic brain regions involved in the experience and regulation of emotion, such as the anterior cingulate cortex, medial and dorsolateral prefrontal cortex (Lim *et al.*, 2014, Paquola *et al.*, 2016), hippocampus (Riem *et al.*, 2015), and amygdala (Ahmed-Leitao *et al.*, 2016). Building on these structural findings, task-based functional magnetic resonance imaging (fMRI) has allowed for more direct inferences regarding the neural correlates of emotion processing via the use of socio-affective cues deliberately designed to signal threat, stimulate mentalizing, or elicit negative/positive affective states. One recent meta-analysis summarizing these studies revealed that, in whole brain analyses,

adults exposed to childhood maltreatment consistently demonstrated altered activation in the superior frontal gyrus, middle temporal gyrus, hippocampus, and superior parietal lobule across a variety of socio-affective stimuli (Heany *et al.*, 2017). Additionally, in region of interest analyses, amygdala and anterior cingulate hyper-responsivity to socioaffective cues were replicated, but marked by more heterogeneity across studies and sampling design (Heany *et al.*, 2017). These results converge with another meta-analysis of neural response during emotional faces tasks, where across all emotions, the right but not left parahippocampal gyrus and amygdala activation was a correlate of maltreatment in whole brain-studies (Hein and Monk, 2017).

Understanding the clinical significance of these functional brain changes in ELA is limited by the fact that many existing studies are undertaken in healthy individuals or small disease-based case control samples designed around one primary diagnosis of interest (Heany *et al.*, 2017, Hein and Monk, 2017). This approach lays the foundation for possible candidate mechanisms, but reduces explanatory power and fragments conclusions that may cut across psychological disorders, which commonly co-occur (Cuthbert, 2014). An additional caveat to the interpretation is that adults with IPs (Buff *et al.*, 2016, Feldker *et al.*, 2017), as well as those exposed to ELA (Heany *et al.*, 2017, Hein and Monk, 2017), both display alterations of distributed affective corticolimbic networks in response to stimuli conveying threat or negative emotionality. Particularly, there is an extensive literature assessing the neural correlates of facial emotion processing in IPs (Etkin and Wager, 2007, Gentili *et al.*, 2016, Hamilton *et al.*, 2012). Illustratively, our group has previously demonstrated that both depression and anxiety symptoms are linked with activation in paralimbic, cingulate, and lateral prefrontal regions in response to negative facial expressions (MacNamara *et al.*, 2017a). Given this overlap, it is prudent to identify whether internalizing symptoms or ELA are the primary driver of neural alterations associated with emotion processing. If a neural signature specific to individuals with IPs and ELA is identified, this level of precision could promote the early identification of individuals with ELA at highest risk for psychopathology or offer novel intervention targets for this subgroup of patients.

Seeing as ELA constitutes risk for a number of IPs (Gilbert *et al.*, 2009, Widom *et al.*, 2007) and in alignment with the Research Domain Criteria initiative to understand how biologically based constructs explain the core, shared features of diagnostic categories (Cuthbert, 2015), linking neural phenotypes of ELA to patterns of thought or behavior common to IPs is also of substantial clinical utility (Insel, 2014, Sharp *et al.*, 2016). One shared feature of IPs is rumination (Nolen-Hoeksema and Watkins, 2011), a maladaptive cognitive style, defined as the tendency to constantly focus on a negative thought, problem, or mood state and on the possible causes and implications of negative feelings (Smith and Alloy, 2009). As childhood adversity is not often easily discussed and is suppressed (Levy and Anderson, 2008), internal extortion and re-production of ELA events may further increase rumination amongst individuals with IPs (Grierson *et al.*, 2016). In fact, in a non-clinical sample, rumination was associated with depression and anxiety symptoms in individuals with ELA, (Kim *et al.*, 2017) implicating a possible role of rumination in the maintenance of IPs. More specifically, brooding is the component of rumination most strongly associated with IP (Aldao *et al.*, 2010, McLaughlin and Nolen-Hoeksema, 2011, Nolen-Hoeksema *et al.*, 2008) and also involved in the maintenance of symptoms in

individuals exposed to ELA and other types of adversity, such as interpersonal trauma (Allbaugh *et al.*, 2016, Raes and Hermans, 2008). At the neural level, it is noteworthy that there is substantial overlap between the functional correlates of ruminative thought patterns and emotion processing in ELA, including in the amygdala, anterior and posterior cingulate, medial and dorsolateral prefrontal cortex, (para-) hippocampus, medial and inferior temporal gyri, and inferior parietal lobule (Burkhouse *et al.*, 2017, Cooney *et al.*, 2010). Additionally, rumination has been linked to activation in visual and somatosensory brain regions, such as the insula, precuneus, and cuneus, which are involved in visual cortical facial emotion processing (Burkhouse *et al.*, 2017). Put together, ELA may heighten cortico-limbic sensitivity to negative emotional cues, in turn, promoting increased attention to symptoms and possible causes of one's own distress. However, the integration of ELA, neural emotion processing, and rumination has yet to be examined in a clinical sample.

To address these gaps in the literature, we sought to examine the neural correlates of facial emotion processing in a large, heterogeneous, and clinically diverse population of patients with multiple and comorbid IPs, with and without exposure to ELA (IP+ELA), and healthy controls (HC). As ELA shares similar proclivity for depression, mixed anxiety disorders, and PTSD, this approach was intentionally designed to maximize generalizability. We hypothesized that IP+ELA would demonstrate the most pronounced activation in the superior frontal gyrus, lateral temporal gyri, medial temporal lobe, anterior/posterior cingulate cortex, and inferior parietal lobule. We also expected that IP+ELA patients would report a higher degree of ruminative brooding and that enhanced brain activation in these regions would account for (mediate) brooding in IP+ELA.

Method

Participants and Procedures

The current study was designed in-line with, and funded by, the NIMH RDoC initiative (RFA-MH-13-080). The aims of the larger study sought the enrollment of a clinically representative patient population, with a full range of internalizing psychopathology and symptoms, that consented to begin treatment with pharmacotherapy (selective serotonin reuptake inhibitors) or cognitive behavioral therapy. All data used in the current study were collected prior to treatment. Eligibility criteria included: 1) age 18–65; 2) current full threshold DSM-5 depression or anxiety disorder; and 3) total score of ≥ 23 on the Depression, Anxiety, and Stress Scale [DASS-21; (Lovibond and Lovibond, 1995)], and ≤ 60 on the Global Assessment of Functioning [GAF; (Jones *et al.*, 1995)]. Exclusion criteria included: 1) inability to provide consent and read and write in English; 2) active medical or neurological problem; 3) history of mania or psychosis; current obsessive compulsive disorder; 4) current substance dependence; 5) intellectual disability; 6) contraindication to SSRIs; 7) ongoing treatment with psychiatric medications or psychotherapy; 8) medication use (psychiatric and other), besides oral contraceptive, within the past four months; 9) history of traumatic brain injury with loss of consciousness; and 10) being pregnant. The University of Illinois at Chicago Institutional Review Board approved this study and informed consent was obtained from all participants.

Participant clinical demographic characteristics are reported in Table 1. Diagnoses were made according to the Structured Clinical Interview for DSM-5 Disorders [SCID-5; (First *et al.*, 2015)] by trained research staff. In-line with the strategy encouraged by RDoC (Kozak and Cuthbert, 2016), individuals were not excluded for comorbid disorders, but instead classified by their clinician-determined principal diagnosis, as determined by the most severe and impairing symptoms (Table 1). Current symptom severity of depression and anxiety based on clinician-administered interviews was evaluated by trained raters using the Hamilton Depression Rating Scale [HAM-D; (Hamilton, 1960)] and Hamilton Anxiety Rating Scale [HAM-A; (Hamilton, 1959)].

Assessment of Early Life Adversity

The Childhood Trauma Questionnaire (CTQ) is a 28-item self-report measure that provides brief, reliable, and valid screening for histories of abuse and neglect (Bernstein *et al.*, 1997). It inquires about five subscales of maltreatment - emotional, physical, and sexual abuse, and emotional and physical neglect. The total score of each sub-scale ranges from 5 to 25, thus the total score of CTQ fluctuates from 25 to 125. Although the total score of the CTQ is intended to represent the cumulative severity of childhood adversity exposure, the distribution of the measure is often skewed by the base-rate of childhood adversity (proportion of respondents reporting little to no childhood adversity experiences). In the current sample, the skewness value was 1.52. To adjust for the degree of skewness, existence of childhood adversity exposure can be determined by a cut-off score of each CTQ subscale. Participants who score higher than the threshold of any one subscale are treated as a positive case of ELA. Consistent with previous studies (Bernstein *et al.*, 1997, Bernstein *et al.*, 2003, Bevilacqua *et al.*, 2012, Gibb *et al.*, 2009, Johnson *et al.*, 2011, Kudinova *et al.*, 2015, Lu *et al.*, 2013, Walker *et al.*, 1999), the cutoffs of each subscale for moderate exposure which best differentiate clinically-significant adversity exposure were used: 1) emotional abuse 13, 2) emotional neglect 15, 3) sexual abuse 8, 4) physical abuse 10, and 5) physical neglect 10. In this sample, emotional abuse $\alpha = .83$, physical abuse $\alpha = .67$, sexual abuse $\alpha = .95$, emotional neglect $\alpha = .91$, and physical neglect $\alpha = .63$. Relatively low Chronbach's alpha for physical abuse and neglect is likely influenced by particularly high skewness values for these subscales (Sheng and Sheng, 2012).

Within the patient sample, 50 participants (49.0%) had a positive history of ELA based on the cut-off scores, forming a sub-group of IPs with significant early life adversity (IP+ELA). Importantly, we also verified none of the healthy control participants reported significant ELA based on these criteria. The convergent validity of these cut-off scores was also evaluated using an exploratory cluster analysis of the study sample. This was performed with CTQ raw subscale scores as input using Wards method of minimum variance with a squared Euclidean distance measure. Ward's method is distinct from other methods because it uses an analysis of variance approach to evaluate the distances between clusters. The cluster solution was determined from inspection of the dendrogram. The cases in the resulting cluster solution identified the same three groups, with the subset of $n = 50$ IP+ELA patients as most similar to each other.

Assessment of Rumination

Self-reported rumination was evaluated with the Ruminative Response Scale [RRS; (Treyner *et al.*, 2003)], which contains subscales representing brooding and reflective pondering components of rumination. As noted earlier, brooding is the component of rumination most strongly associated with IP (Aldao *et al.*, 2010, McLaughlin and Nolen-Hoeksema, 2011, Nolen-Hoeksema *et al.*, 2008) and particularly relevant to the development of IP symptoms in trauma exposed individuals (Raes and Hermans, 2008). The brooding subscale consists of five Likert-type items ranging from 1 (almost never) to 4 (almost always). The measure has demonstrated good internal consistency and 1-year retest reliability (Treyner *et al.*, 2003). In this study, brooding $\alpha = 0.87$.

Task

Participants completed a version of the Emotional Face-Matching Task (Hariri *et al.*, 2002) previously validated for use with fMRI of blood-oxygen-level dependent (BOLD) signal (Gorka *et al.*, 2015, Hariri *et al.*, 2002, MacNamara *et al.*, 2017b, Phan *et al.*, 2013). Angry, fearful, happy, and sad faces were selected from the Gur emotional faces set (Gur *et al.*, 2002). There were three angry, three fearful, three happy, and three sad blocks of trials, interspersed with shape-matching blocks. Each block lasted 20s and consisted of four back-to-back 5-s trials. Shapes were used as control stimuli instead of neutral faces because they may provide a more truly neutral baseline for comparison, particularly when patients are involved (Filkowski and Haas, 2017).

fMRI Data Acquisition and Processing

fMRI based on BOLD contrast was performed on a three 3T GE (General Electric Healthcare, Waukesha, WI) MR750 scanner at the University of Illinois at Chicago (UIC). Scanning was performed using an eight-channel phased-array radio frequency head coil, using either a gradient-echo echo planar imaging sequence, with the following parameters: repetition time 2s, echo time 25 ms, flip angle 90°, field of view 22 cm, acquisition matrix 64 × 64, 3 mm slices with no gap, 44 axial slices per volume.

All data met our criteria for image quality with minimal motion correction (movements < 3 mm in any direction across the run). The first four volumes were discarded to allow for the magnetization to reach equilibrium. Statistical Parametric Mapping (SPM8) software (Wellcome Trust Centre for Neuroimaging, London, www.fil.ion.ucl.ac.uk/spm) was used to perform conventional image pre-processing steps. In brief, slice-time correction was performed to account for temporal differences between slice collection order and images were spatially realigned to the first image of the run, normalized to a Montreal Neurological Institute (MNI) template using the EPI template, resampled to 2 mm³ voxels, and smoothed with an 8-mm isotropic Gaussian kernel.

The time series data were subjected to a general linear model, convolved with the canonical hemodynamic response function, and filtered with a 128-s high-pass filter. Because of the heterogeneous IP sample and that we did not have any particular predictions about specific emotional expressions, Angry, Fearful, Happy, Sad, and Shapes conditions were modeled separately, with effects estimated for each voxel for each participant. Individual motion

parameters were entered in the model as covariates of no interest. Angry>Shapes, Fearful>Shapes, Sad>Shapes and Happy>Shapes, contrasts, created separately for each participant, were included as random effects for the second level analysis. Each emotion contrast was modeled as a separate dependent variable due to violations of generalized linear model assumptions that occur in repeated measures fMRI designs, particularly when covariates of non-interest are included. Therefore, this approach allowed us to maximize explanatory power by covarying for brain activation related to symptoms of depression and anxiety.

Data Analytic Approach

Clinical Analyses: Clinical and demographic measures comparing IP+ELA, IP, and HC participants were inspected for normal distribution and analyzed using analysis of variance and chi-square tests, as appropriate.

fMRI Analyses.—Whole-brain group (IP+ELA, IP, and HC) differences were modeled using a one-way ANOVA in SPM8, with follow-up *t*-contrasts for all possible pairwise differences. Symptoms of depression (HAM-D scores) and anxiety (HAM-A scores) were included in the model as covariates of no interest. To threshold results, we used a whole-brain mask encompassing all gray matter regions excluding cerebellum owing to limited coverage [created with MARINA; (Walter *et al.*, 2003)]. Clusters of activation were identified using an uncorrected voxel threshold of $p < .001$ and then subjected to correction for multiple comparisons via simulation using 3dClustSim utility (December 16, 2015, updated release; 10,000 iterations; http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). Given the smoothness estimates of the data, family-wise error (FWE) correction at $\alpha < .05$ was achieved using a voxel threshold of $p < .001$, with minimum cluster sizes of 93 (angry>shapes), 91 (fearful>shapes), 76 (sad>shapes), and 92 (happy>shapes) voxels. To clarify the direction of significant between-group differences, we extracted parameter estimates of BOLD signal responses (beta-weights, in arbitrary units of activation) averaged across voxels within a 5-mm radius sphere surrounding each peak maxima.

Mediation Analyses: After identifying foci of between-group differences in brain activation, a series of mediation analyses tested whether brain activation to emotions versus shapes (extracted using the 5mm-radius sphere surrounding each peak maxima from group contrasts) was, in turn, associated with ruminative brooding in IP+ELA (relative to HC and IP). A separate mediation model was run for each cluster of between group differences in brain activation. Mediation analyses were conducted using the SPSS macro PROCESS (Hayes, 2012), including covariates of no interest for depression (HAM-D) and anxiety (HAM-A) symptoms, age, and sex. Multiple parallel tests were controlled using a false-discovery rate adjusted alpha threshold of $p < .036$ (Benjamini and Hochberg, 1995). Tests of mediation employed a bootstrapping approach with $N = 5,000$ bootstrap resamples and a 95% confidence interval to assess indirect effects using PROCESS (Preacher and Hayes, 2004). Bootstrapping is a nonparametric resampling procedure that generates an approximation of the sampling distribution of a statistic from the available data. Sampling distributions of indirect effects are generated by taking a sample (with replacement) of size

N from the full data set and calculating the indirect effects (i.e. conducting mediation analyses) in each of the resamples. Thus, the 95% confidence interval represents that of each of those 5,000 resample analyses, 95% of the generated indirect effects fall between the given two estimates.

Results

Demographic and Clinical Characteristics

IP+ELA, ($n=50$), IP ($n=52$), and healthy controls (HC, $n=30$) were equivalent in terms of age, education, and distribution of race/ethnicity (Table 1). IP+ELA, IP, and HC groups did differ in sex distribution, with a greater proportion of females in the IP+ELA group relative to both IP and HC (Table 1). HAM-A scores were higher in IP+ELA ($t = -19.38$, $p < .001$) and IP ($t = -18.88$, $p < .001$) relative to HC, but IP+ELA and IP did not differ ($t = .79$, $p = .433$). HAM-D scores were higher in IP+ELA ($t = -18.78$, $p < .001$) and IP ($t = -18.67$, $p < .001$) relative to HC, but IP+ELA and IP did not differ ($t = -.64$, $p = .522$). IP+ELA reported higher levels of ruminative brooding than IP ($t = -3.46$, $p = .001$) and HC participants ($t = -21.56$, $p < .001$). Ruminative brooding was also higher in IP relative to HC ($t = -13.20$, $p < .001$).

ELA and Brain Activation to Emotional Faces—Overall activation for each emotion condition is presented in Supplemental Figure 1. There were no differences in brain activation between IP and HC groups for any of the emotion contrasts. All findings below pertain to increased activation in IP+ELA relative to IP and HC; there were no significant foci of decreased activation in IP+ELA.

Angry>Shapes: IP+ELA demonstrated greater activation (Figure 1c, Table 2) in the right cuneus [BA 19]).

Fearful>Shapes: IP+ELA demonstrated greater activation (Figure 1a, Table 2) in the right superior frontal gyrus (encompassing aspects of the dorsolateral and dorsomedial prefrontal cortex; [BA 6, 8, 9]), bilateral anterior/mid cingulate [BA 24], and right posterior cingulate [BA 23]. Greater activation was also observed in the left temporal lobe [BA 20, 36, 37], including the inferior temporal, fusiform, and parahippocampal gyri, right precuneus [BA 7], right superior parietal lobule [BA 7], and right cuneus/lingual gyrus [BA 17, 18, 19).

Sad>Shapes: No significant findings.

Happy>Shapes: No significant findings.

A post-hoc multivariate general linear model of extracted peak BOLD signal indicated there were no significant main effects of sex [$F(11, 132) = .14$, $p = .999$] or sex by group interactions [$F(22, 132) = .978$, $p = .494$] in relation to BOLD activation of any of these clusters. Findings were also maintained when including sex as a covariate of non-interest in the SPM8 analysis.

Brain Activation to Emotional Faces as a Mediator of Rumination in IP+ELA

Table 3 reports BOLD response to emotional faces in relation to ruminative brooding

(Path B: Illustratively, Figure 2) and tests of brain activation to emotional faces as a mediator of ruminative brooding in IP+ELA participants (Path C: For a conceptual model, Figure 3). Eight separate mediation models were conducted (1 for angry > shapes, 7 for fearful > shapes).

Angry>Shapes: The indirect pathway (test of mediation) was significant in IP+ELA for the right cuneus; the total direct effect also remained significant indicating partial mediation.

Fearful>Shapes: Indirect pathways were significant in IP+ELA for the right superior frontal gyrus, right precuneus, right superior parietal lobule, and right cuneus. Tests of mediation for the bilateral anterior cingulate, right posterior cingulate, and left inferior temporal gyrus did not yield significant indirect pathways in IP+ELA; the total direct effects also remained significant indicating partial mediation.

Discussion

Recent initiatives underscore the importance of examining neurobiological signatures that span diagnostic boundaries (Cuthbert, 2014, 2015), particularly those that might be amenable to early detection and prevention (Garvey *et al.*, 2016), yet few studies have comprehensively accomplished this task. In this study, we utilized functional neural activation patterns to facial emotions across a large, heterogeneous, and clinically diverse sample of IP diagnoses with and without exposure to ELA and HCs, in effort to understand whether ELA is a correlate of aberrant neural activity relevant to behavioral constructs involved in internalizing psychopathology. Specifically, we tested the hypothesis that enhanced neural activity in response to negative facial emotions would characterize IP+ELA and that these patterns of brain activity would in turn, relate to brooding in IP+ELA. The present findings, which were most pronounced for fearful faces, implicate hyper-activation of superior frontal gyrus, cingulate cortex, inferior temporal gyrus, and the inferior and superior aspects of the parietal and occipital lobes, respectively, as a correlate of ELA in IPs. We speculate that ELA is candidate etiological mechanism of these neural alterations such that the observed brain changes may be due to the effects of ELA exposure on the brain. Moreover, no group differences were observed between HC and IP only, further implicating ELA exposure as a possible driver of cortico-limbic hyperactivity to negative emotions; however, future studies are needed to demonstrate this among an ELA-exposed control group. Interestingly, the aforementioned brain regions were also consistently correlated with brooding rumination, and many of these neural regions mediated the link between IP+ELA and brooding. Taken together, these findings provide preliminary evidence that greater cortico-limbic reactivity to negative affective stimuli may explain the relationship between ELA and rumination in IPs.

On the whole, we observed cortico-limbic responsivity to especially fearful facial expressions, with some key regions that warrant attention. Namely, fearful faces elicited activation of the right middle anterior cingulate and superior frontal gyrus amongst IP+ELA.

These findings are broadly in accordance with existing emotional regulatory theories implicating the anterior cingulate in the recognition, experience, and appraisal of emotional and the dorsolateral and medial prefrontal cortex in regulating emotional reactivity (Etkin *et al.*, 2011). However, as there are some opposing findings regarding activation directionality in anxiety versus depression (MacNamara *et al.*, 2017a), our design offers some confidence that enhanced anterior cingulate and dorsolateral prefrontal engagement may transcend internalizing diagnoses and symptoms when ELA is present. Additionally, and consistent with recent meta-analytic work (Heany *et al.*, 2017), we observed increased activation in the left inferior temporal gyrus, including the fusiform gyrus and extending to the parahippocampal gyrus in IP+ELA. This cluster of regions is typically activated by a broad array of social cognitive tasks requiring abstract reasoning and perspective taking (Schurz *et al.*, 2014), implicating their involvement with an excessive focus on negative social judgment. Collectively, these results underscore convergent neurobiological alterations among IP+ELA related to emotion perception and social reasoning, particularly to fearful stimuli.

Processing of fearful faces was also associated with activation in the posterior cingulate, aspects of the medial prefrontal cortex, and superior parietal lobule amongst IP+ELA. Although these regions have not been extensively reported in relation to ELA amongst healthy samples (Dannlowski *et al.*, 2012, Holz *et al.*, 2015), they are linked to rumination (Burkhouse *et al.*, 2017, Cooney *et al.*, 2010) in IPs. The observed correlations with rumination may suggest that individuals with ELA who develop IPs are particularly prone to engage in affect-congruent self-focus when faced with external cues of fear (Waters and Craske, 2016). It is also noteworthy that ELA patients demonstrated greater activation in visual processing and somatosensory areas during fear (and to a lesser extent anger) processing, such as the cuneus and precuneus. Since IP+ELA were more likely to engage in ruminative brooding relative to IPs and HCs, rumination may also be a more elaborate process for these individuals, particularly when confronted with social signals of threat (Burkhouse *et al.*, 2017). That is, IP+ELA may be more likely to ruminate on social signals of threat more extensively and vividly, as supported by superior occipital and inferior parietal recruitment (Vuilleumier and Pourtois, 2007). Indeed, these regions, in addition to the superior frontal gyrus, superior parietal lobule, partially mediated the extent of rumination present amongst IP+ELA patients. Notably, the observed patterns of brain activation accounted for 13–18% of the variance in rumination, consistent with a moderate to large effect size, suggesting that targeting this neurocircuitry among IP+ELA could have measureable effects on maladaptive coping styles known to increase proneness to or persistence of internalizing mental health problems (Kim *et al.*, 2017). Of particular interest, in light of the emotional faces eliciting the neural response is to evaluate whether cognitive therapy emphasizing appraisals of other's emotional responses and interpretation bias, would have effects on these brain alterations. Additionally, another possibility would be to target regulatory neural circuits (e.g. cognitive control network) with brain stimulation (e.g. trans-cranial magnetic stimulation) as a top-down approach to reduce the observed cortico-limbic reactivity to negative affective stimuli.

There are aspects of the present findings that were inconsistent with our hypotheses. Namely, in contrast to the expectation that IP+ELA would exhibit similar neural alterations

to all negative facial emotions, the overwhelming pattern of results showed dominance for fearful faces; ELA-specific neural correlates were surprisingly sparse for angry faces. One possible reason for this discrepancy relates prior work implicating neural sensitivity to angry faces as a mediator of aggressive behavior (Shackman and Pollak, 2014), of which base rates in this internalizing psychopathology sample were very low. It may be the case that maltreated children who tend to respond to threat with reactive aggression are more likely to develop forms of externalizing psychopathology (Lee and Hoaken, 2007) and hyper-vigilance to facial expressions of anger is therefore more relevant in that context. Equally, sensitivity to angry faces is particularly pronounced in victims of physical, as opposed to other forms of abuse (Pollak *et al.*, 2000, Pollak and Tolley-Schell, 2003). Although we were not powered to undertake within- and between-group comparisons of specific types of abuse and neglect, higher levels of emotional than physical maltreatment characterized the current sample and the emotion-specificity of our findings may reflect this variability. On the other hand, we must also consider that cortico-limbic hyper-responsivity to angry faces has nevertheless been reported in both depression and anxiety disorders (MacNamara *et al.*, 2017a); this may be a broader marker of psychological distress that simply is not a specific etiological pathway related to ELA.

Additionally, it was also somewhat surprising that activation in the amygdala was not enhanced in ELA. Amygdala hyperactivity has been reported in association with ELA (McCrary *et al.*, 2012, Teicher *et al.*, 2002) and in the pathophysiology of IPs (Heller, 2016, Shin and Liberzon, 2010); nonetheless, many of these studies are small, single disorder case control designs (Heany *et al.*, 2017, Hein and Monk, 2017). In fact, whole-brain evidence in support of amygdala hyperactivity is actually somewhat inconsistent, identified in certain meta-analyses (Hein and Monk, 2017), but not others (Heany *et al.*, 2017, Hein and Monk, 2017). Both recent meta-analyses identified increased amygdala activation using a region of analysis (ROI) approach, lending credence to the need for small volume correction of this small anatomical region. However, an ROI-driven approach to threshold results can also increase the likelihood of identifying significant areas of activation; thus, amygdala activation may be preferentially present in experiments that opt to report ROI versus whole brain analyses. Alternatively, as there is great heterogeneity in social-affective stimuli and tasks reporting amygdala hyperactivation in ELA and IPs (Etkin and Wager, 2007, Gentili *et al.*, 2016, Hamilton *et al.*, 2012, Heany *et al.*, 2017), we also consider the possibility that faces are less evocative, depersonalized elicitors of emotion for some patients. For instance, facial expressions of others are likely to have less emotional significance compared to a personal narrative of adversity experiences (MacNamara *et al.*, 2017a). Particularly in the case of ELA-exposed IPs, recruitment of the amygdala for emotional learning of facial expressions could be superseded by the salience of ongoing personal fear memories (Clark and Mackay, 2015).

We are also cautious not to over interpret null findings for the amygdala, as amygdala activation in response to the emotional stimuli in this task *was* present, but across all participants and not specific to the IP or IP+ELA groups (Supplemental Figure 1). Likewise, it is also noteworthy that IP and HC groups did not demonstrate other differences in brain activation. One explanation relates to the fact that most case-control designs have compared single disorders to controls rather than a heterogeneous group of different internalizing

diagnoses. Accordingly, the lack of group differences identified could simply represent there are not *shared* neural alterations across different anxiety disorders and depression *diagnoses* relative to controls. Alternatively, as demonstrated in our prior work (MacNamara *et al.*, 2017a) and in line with the RDoC initiative, trans-diagnostic neural alterations may be more likely to co-vary with depression and anxiety symptoms dimensionally, rather than discrete diagnostic categories.

There were several limitations to the current study. First, ELA assessment was retrospective by means of a self-report measure. This kind of reporting could be subject to inaccuracies or mood congruent recall, which might be particularly relevant in IP+ELA (Gaddy and Ingram, 2014, Ono *et al.*, 2016, Schonfeld and Ehlers, 2017). Second, while the present analysis benefited from an HC comparison and IP reference group without ELA equivalent in anxiety and depression symptoms, this design could be further strengthened by inclusion of an ELA-exposed HC group. That is, although ELA substantially increases the risk for IPs, not all individuals exposed to ELA develop IPs and this kind of comparison could elucidate key determinants of adaptive coping and resilience (Bowes and Jaffee, 2013, Kim-Cohen and Turkewitz, 2012). Moreover, there may also be unique markers involved the propensity for ELA to develop into other forms of psychopathology, such as substance use (Puetz and McCrory, 2015) or externalizing disorders (Busso *et al.*, 2017), that were not the emphasis of the current study. A third limitation is that our IP sample, and particularly the IP+ELA group, constituted a greater proportion of female participants relative to controls. Although this is reflective of the sex differences that characterizes sensitivity to stress and prevalence of internalizing disorders (Bekhhbat and Neigh, 2018), these group differences called for careful post-hoc analysis to ensure sex effects did not drive our significant findings (footnote, Table 2). The null results of such post-hoc analyses notwithstanding, additional confidence in these findings would be procured in a design matched on sex across groups. Additionally, the patients in this study were seeking treatment and we do not know if these findings are generalizable to what might be observed in naturalistic, community settings. Last, the present study was cross-sectional; therefore the results are correlational in nature and we are unable to draw definitive conclusions regarding causal effects of ELA on brain function or how any such effects may influence susceptibility to rumination. Although the analytic approach of the current study was informed by theory and prior evidence (Hart and Rubia, 2012, Heany *et al.*, 2017), they are hypothesis generating and future longitudinal designs are needed to establish temporal precedence of these constructs.

To close, this study provides evidence supporting a neural mechanism (i.e., cortico-limbic hyper-responsivity) linking ELA to rumination among adults with current IPs. Findings may suggest that for individuals experiencing childhood adversity, enhanced cortico-limbic reactivity to negative socio-emotional stimuli may enhance vulnerability to psychological characteristics involved in the maintenance of internalizing symptoms, such as rumination. Therefore, targeting aberrant emotion neurocircuitry in IP+ELA, possibly throughout psychological interventions, could be a novel target for modifying ruminative habits known to increase persistence of internalizing mental health problems. These results also help to close the gap between the segregated sampling designs of earlier studies (Hart and Rubia, 2012, Heany *et al.*, 2017), affirming that ELA is associated with trans-diagnostic alterations to cortico-limbic emotional processing, above and beyond what can be accounted for by

current internalizing symptoms. This is an important step towards identifying a common pathway to prevalent and co-occurring forms of internalizing psychopathology in adulthood. We hope that the work herein will provide further impetus for the assessment of longitudinal, developmental trajectories of risk and resilience to adversity within systems neuroscience models; it is these models that are most likely to bring the field closer to early detection of etiological factors involved in IP across the lifespan.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

a) Foci of increased neural response for Fearful Faces > Shapes (**cyan**) and Angry Faces > Shapes (**yellow**). Areas of anatomical overlap between Fear > Shapes and Angry > Shapes (**green**). IP+ELA, IP, and HC extracted parameter estimates of activation (beta-weights) for b) Fearful > Shapes, c) Sad > Shapes, and d) Angry > Shapes. SFG = Superior Frontal Gyrus; ACC = Anterior Cingulate Cortex; PCC = Posterior Cingulate Cortex; Prec = Precuneus; SPL = Superior Parietal Lobule; ITG = Inferior Temporal Gyrus

Figure 2.

Scatterplot of association between fear-related brain activation in the right superior frontal gyrus and ruminative brooding (as unstandardized residuals after controlling for covariates).

HC = Healthy Control; IP = Internalizing Psychopathology Patients; IP+ELA = Internalizing Psychopathology Patients with Early Life Adversity history.

Figure 3. Conceptual mediation model evaluating enhanced brain activation to emotional faces as a mediator of increased ruminative brooding in IP+ELA. IP+ELA = Internalizing Psychopathology Patients with Early Life Adversity history.

Table 1.

Sample Characteristics

	HC (n = 30)		IP (n = 52)		IP + ELA (n = 50)		Omnibus Test	
	M	SD	M	SD	M	SD	F	p-value
Age	25.00	9.98	26.73	8.89	25.94	8.34	.36	.698
Education	15.33	2.50	15.98	3.35	15.60	2.62	.32	.733
HAM-D ^{a,b}	.50	.78	12.31	4.44	12.88	4.55	107.38	<.001
HAM-A ^{a,b}	.77	.89	18.42	6.64	17.44	5.97	110.10	<.001
CTQ Total ^{a,b,c}	27.30	1.91	32.15	5.50	50.38	12.31	91.55	<.001
Sexual Abuse ^{a,b}	5.00	.00	5.00	.00	7.30	5.18	8.08	<.001
Physical Abuse ^{b,c}	5.33	.71	5.67	1.10	7.44	2.87	15.15	<.001
Emotional Abuse ^{a,b,c}	5.47	.73	7.27	2.20	12.60	4.51	60.33	<.001
Physical Neglect ^{a,b,c}	5.10	.31	5.98	1.42	8.52	2.91	33.37	<.001
Emotional Neglect ^{a,b,c}	6.40	1.61	8.23	2.76	14.52	4.00	80.98	<.001
RRS Brooding ^{a,b,c}	5.97	.93	13.08	3.69	15.32	2.82	98.29	<.001
# Comorbid Diagnoses	--	--	2.56	1.53	2.08	1.27	2.91	.088
	N	%	N	%	N	%	χ²	p-value
Sex (% Female) ^{a,b,c}	15	50.0	35	67.3	40	80.0	7.81	.020
Ethnicity								
Hispanic	2	6.7	10	19.2	10	20.0	2.81	.246
Non-Hispanic	28	93.3	42	80.8	40	80.0	2.81	
Race								
Caucasian	12	40.0	36	69.2	28	56.0	17.66	.061
African American	6	20.0	5	9.6	11	22.0		
Asian	11	36.7	6	11.5	6	12.0		
American Indian/Alaskan	0	0.0	1	1.9	2	4.0		
Other/Unknown	1	3.3	4	7.7	3	6.0		
Primary Diagnosis								
Major Depression	--	--	11	21.2	15	30.0	3.68	.597
Dysthymia	--	--	0	0.0	2	4.0		
Generalized Anxiety	--	--	21	40.4	18	36.0		
Social Anxiety	--	--	14	26.9	10	20.0		
Panic Disorder	--	--	3	5.8	3	6.0		
Post Traumatic Stress	--	--	3	5.8	2	4.0		

HC = Healthy Control; IP = Internalizing Psychopathology Patients; IP+ELA = Internalizing Psychopathology Patients with Early life adversity; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; CTQ = Childhood Trauma Questionnaire; RRS = Rumination Response Scale

^aSignificant ($p < .05$) post-hoc pairwise comparison, IP vs. HC

^bSignificant ($p < .05$) post-hoc pairwise comparison, IP+ELA vs. HC

^cSignificant ($p < .05$) post-hoc pairwise comparison, IP vs. IP+ELA

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Table 2.

Whole brain activation during facial emotion processing in IP+ELA relative to IP and HC

MNI Coordinates						
Contrast/Region [^] *	BA	cluster k	z-score	x	y	z
Angry > Shapes						
R Cuneus	19	269	4.86	30	−90	24
			3.59	26	−90	38
Fearful > Shapes						
R Superior Frontal	6/8/9	448	4.17	28	48	40
			3.90	10	48	46
			3.18	12	56	32
R-L Anterior/mid cingulate	24	150	3.79	2	−4	36
R Superior Parietal	7	678	4.01	22	−48	60
			3.82	38	−48	60
			3.81	18	−62	52
R Precuneus	7	194	3.66	28	−74	40
			3.32	22	−90	38
R Posterior Cingulate	23	104	3.54	4	−32	22
			3.23	6	−24	24
L Inferior Temporal	20/36/37	219	3.69	−42	−34	−20
			3.48	−48	−22	−22
R Cuneus	17/18/19	576	4.73	28	−90	24
			3.82	12	−84	6
			3.45	16	−88	16
Happy > Shapes						
No significant findings						
Sad > Shapes						
No significant findings						

MNI = Montreal Neurological Institute; BA = Brodmann's area; k = number of contiguous voxels; L= Left; R = Right;

[^] Results are unchanged when re-performed without HAM-D and HAM-A as covariates. Results are also maintained when including sex as a covariate of non-interest in the SPM8 analysis.

Table 3.

Mediation analyses evaluating brain activation to fearful and angry faces as a mechanism of increased rumination in IP+ELA

Path B ^{a,b,c,d} Relative Direct Effects of Brain Activation on Ruminative Brooding											Path C ^{a,e} Brain Activation as a Mediator of Ruminative Brooding			
Contrast	β	SE	p	LLCI	ULCI	R ²		Effect	SE (boot)	LLCI	ULCI			
Angry > Shapes														
	R Cuneus						R Cuneus							
1) Cuneus	.87	.36	.018	0.15	1.58	.17	Full Sample	.08	.06	0.009	0.27			
2) Cuneus x IP+ELA	2.06	.59	<.001	0.88	3.23		IP+ELA	.46	.25	0.08	1.09			
Fearful > Shapes														
	R SpFrnt						R SpFrnt							
1) SpFrnt	.72	.40	.076	-0.08	1.51	.15	Full Sample	.06	.05	0.003	0.19			
2) SpFrnt x IP+ELA	2.12	.59	<.001	1.03	3.37		IP+ELA	.31	.18	0.03	0.74			
R-L ACC														
1) ACC	.96	.71	.176	-0.44	2.35	.14	Full Sample	.04	.07	-0.01	0.28			
2) ACC x IP+ELA	2.32	.58	<.001	1.16	3.48		IP+ELA	.20	.17	-0.04	0.64			
R PCC														
1) PCC	1.32	.75	.081	-0.16	2.80	.15	Full Sample	.02	.04	-0.01	0.16			
2) PCC x IP+ELA	2.36	.57	<.001	1.23	3.49		IP+ELA	.15	.12	-0.01	0.16			
R Prec														
1) Prec	1.07	.43	.014	0.22	1.91	.17	Full Sample	.08	.06	0.01	0.23			
2) Prec x IP+ELA	2.12	.58	<.001	0.95	3.26		IP+ELA	.41	.19	0.12	0.87			
R SPL														
1) SPL	1.79	.65	.006	0.51	3.07	.18	Full Sample	.12	.08	0.01	0.35			
2) SPL x IP+ELA	2.09	.58	<.001	0.94	3.23		IP+ELA	.47	.24	0.12	1.12			
R Cuneus														
1) Cuneus	.76	.39	.058	-0.03	1.55	.17	Full Sample	.06	.05	-0.001	0.21			
2) Cuneus x IP+ELA	2.74	.75	<.001	1.25	4.24		IP+ELA	.43	.20	0.13	0.93			

Contrast	Path B ^{a,b,c,d} Relative Direct Effects of Brain Activation on Ruminative Brooding					Path C ^{a,e} Brain Activation as a Mediator of Ruminative Brooding		
	β	SE	p	LLCI	ULCI	R ²	Effect	SE (boot)
L ITG								
1) ITG	1.72	1.02	.094	-0.29	3.73	.15	.12	.11
2) ITG x IP+ELA	2.24	.59	<.001	1.08	3.41		.27	.20
L ITG								
1) ITG								
2) ITG x IP+ELA								

^aCovariates: age, sex, HAM-D, HAM-A

^bEstimates 1) association between extracted parameter estimates of brain activation and brooding across the entire sample and 2) association between extracted brain activation and brooding in IP+ELA, with HC+IP as a combined reference group. There are no significant associations between brain activation and brooding in IP alone with HC as the reference group.

^cAll correlations between extracted parameter estimates of brain activation and brooding are non-significant in HC.

^dExploratory, post-hoc analyses also evaluated whether brain activation to fearful and angry faces was significantly related to the other component of rumination, self-reflection; there were no significant associations.

^eEstimates 1) mediation in the full sample and 2) mediation in IP+ELA relative to HC+IP. There are no significant tests of mediation in IP alone with HC as the reference group.

SE = Standard Error; LLCI = Lower Limit Confidence Interval; ULCI = Upper Limit Confidence Interval; R = Right; L = Left; SpFmrt = Superior Frontal Gyrus; ACC = Anterior Cingulate Cortex; PCC = Posterior Cingulate Cortex; Prec = Precuneus; SPL = Superior Parietal Lobule; ITG = Inferior Temporal Gyrus;