Biological Psychiatry: Celebrating 50 Years

Depression Severity Over 27 Months in Adolescent Girls Is Predicted by Stress-Linked Cortical Morphology

Elizabeth A. Bartlett, Daniel N. Klein, Kaiqiao Li, Christine DeLorenzo, Roman Kotov, and Greg Perlman

ABSTRACT

BACKGROUND: Evidence supports the notion that early-life stress and trauma impact cortical development and increase vulnerability to depression. However, it remains unclear whether common stressful life events in community-dwelling adolescents have similar consequences for cortical development.

METHODS: A total of 232 adolescent girls (mean age 15.29 ± 0.65 years) were assessed with the Stressful Life Events Schedule (a semistructured interview of stressors in the previous 9 months) and underwent a magnetic resonance imaging scan. FreeSurfer 5.3.0 was used to perform whole-brain surface-based morphometry. Dysphoria was assessed at the time of imaging and prospectively at three 9-month follow-up appointments using the Inventory of Depression and Anxiety Symptoms II.

RESULTS: At least one stressful life event was reported in 90% of the adolescent participants during the 9 months preceding imaging. Greater burden of recent life stress was associated with less left precuneus and left postcentral cortical thickness and smaller left superior frontal and right inferior parietal volume (all $p < .05$ after multiple comparisons correction). Left precuneus thickness in the stress-associated cluster significantly predicted dysphoria for 27 months after imaging controlling for prior dysphoria ($\beta = -.11$, $p = .004$). Left precuneus cortical thickness accounted for 17.0% of the association between stress and dysphoric mood for 27 months after imaging ($\beta = .04$, $p = .05$).

CONCLUSIONS: Consistent with evidence from imaging studies of trauma-exposed youths and preclinical stress models, a heavy burden of recent common life stress in community-dwelling adolescent girls was associated with altered frontal/parietal cortical morphology. Stress-linked precuneus cortical thickness represents a candidate prospective biomarker of adolescent depression.

Keywords: Adolescent development, Cortical thickness, Depression, Dysphoric mood, Life stress, Volume

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Stress-induced changes in cognitive and biological processes are central to leading paradigms of depression (1) [e.g., diathesis-stress, stress generation, and learned helplessness (2–4)]. In such models, stress exposure is internalized within the central nervous system, shaping development deleteriously, thereby increasing risk for and maintenance of depressive symptoms. The phenotypic link between stress and adolescent depression is well supported; life stress potently predicts depressive symptoms, such as dysphoria and onset of depressive disorders (DDs) (5). However, progress in identifying the neurobiological mechanisms linking stress exposure to the course of adolescent depression has been slow, likely hindering the development of targeted prevention and treatment programs. Identifying and understanding the neurobiological vectors along which stress increases vulnerability for depression represents a key target for the next generation of translational research.

Two prominent hypotheses have been proposed to account for stress-induced neurodevelopmental adaptations. First, the neurotoxicity hypothesis (6), also known as the glucocorticoid cascade hypothesis (7), is based largely on preclinical investigations that used severe, chronic stress models to track inhibition of dendritic arborization and glucocorticoid-induced synaptic loss and atrophy (8,9). This has been reported in the hippocampus, as well as in the amygdala and prefrontal cortex (6,8,9). Second, the stress acceleration hypothesis (10) posits that stress-related gray matter (GM) loss represents accelerated maturation, especially in circuits implicated in emotion processing (10,11). Neural sensitivity to stress then varies as a function of the linear and nonlinear negative trajectories in GM volume, thickness, and surface area across the cerebral cortex during development, which may reflect, for example, experience-based synaptic pruning and expansion of cerebral white matter owing to axonal myelination (12–16).

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Such hypotheses were largely developed from preclinical studies, which benefit from experimentally controlled models of stress exposure. In humans, laboratory stress experiments are necessarily brief [e.g., public speaking evaluation (17)]. Such stress inductions in humans have been shown to increase cortisol production, which helps bridge human studies with preclinical stress models (18,19). However, laboratory studies have limited utility for investigating long-term consequences of stress exposure on neural development in humans. An alternative approach is to combine neuroimaging with careful phenotyping of naturally occurring stressors (20). In adults, several studies link reduced GM volume in frontal and temporal lobes and the hippocampus with early life stress, chronic life stress, and recent stressful life events (21–23). In youths, imaging studies report that exposure to severe or extreme life events, such as trauma, neglect, or onset of posttraumatic stress disorder (PTSD), is associated with reduced GM volume, particularly in frontal and temporal lobes (24–30). One study in children found that cumulative early life stress occurring more than 1 year before imaging was associated with smaller prefrontal, temporal, and precuneus volumes (31). Altogether, exposure to extreme and/or distal stressors, such as trauma or higher burden of cumulative early life stress, appears to be sufficient to alter GM maturation, particularly in cognitive-affective substrates necessary for healthy adaptation (24,31).

Middle-to-late adolescence is notable for increased autonomy and exposure to common stressful life events relative to earlier in childhood (e.g., dissolution of relationships, financial struggles, and health problems) (32). Most structural imaging studies in youths have focused on extreme or traumatic stressors, which limits generalizability to the general population of adolescents, many of whom are exposed to common stressors. Thus, a critical gap in the literature is whether common stressful life events are sufficient to alter ongoing neuromaturation. This developmental period is also associated with increases in depressive symptoms, especially in girls, in whom the rate of DDs reaches 2:1 relative to boys (33). Imaging studies have reported several GM correlates of depression in adults and adolescents, especially in the superior frontal and parietal cortices and hippocampus (34–37). Of note, these imaging studies did not assess the mediative role of stress exposure on cortical structure. One study in adolescent girls linked early life stress to accelerated pituitary gland development, but this was unrelated to depressive symptoms (38). Thus, a second critical gap in the literature is lack of integration of stress-linked alterations in cortical morphology with depression in youths.

The first aim of this study was to assess the relationship between recent stressful life events and cortical structure in a community-dwelling sample of 232 girls with the Stressful Life Events Schedule (SLES) and surface-based morphometry. The second aim was to test the link between stress-sensitive cortical markers and dysphoric mood for up to 27 months after imaging. We then characterized the mediative role of stress-linked regions in accounting for the depressogenic effects of stress.

METHODS AND MATERIALS

Participants

Participants were a subset of the multiwave Adolescent Development of Emotions and Personality Traits study at Stony Brook University. Exclusion criteria at wave 1 included intellectual disability, inability to complete questionnaires, lack of English fluency, lack of consent of a biological parent, and a lifetime history of DDs (e.g., major depressive disorder [MDD] or dysthymia). The aim of the Adolescent Development of Emotions and Personality Traits project was to identify predictors and consequences of first-onset DDs. Other psychopathologies are well-known predictors of first-onset DDs (39–41) and thus were not excluded. Absence of lifetime DDs was confirmed first by phone screen [depression module of the Patient Health Questionnaire (42)] and then in person [Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (43)]. Adolescents provided written assent, and biological parents provided written permission. The study was approved by Stony Brook University's Committee on Research Involving Human Subjects.

The Adolescent Development of Emotions and Personality Traits study enrolled 550 girls (13.5–15.5 years old) and included five assessment waves at 9-month intervals (Figure 1). Additional funding was received that allowed for a single magnetic resonance imaging (MRI) scan proximal to wave 2. All participants were invited to undergo imaging, yielding a sample of 261 (reduction in sample was due to refusal, attrition, and contraindications, e.g., braces, claustrophobia).

Clinical Measures

The SLES, a semistructured interview designed for adolescents (44), was administered at wave 2. Trained interviewers asked about exposure to 77 stressful events "since we last saw you," which spanned from wave 1 to wave 2 (Figure 1). Descriptions of endorsed events, dates of onset and offset, real-life impact, and exposure frequency were recorded using uniform SLES-provided probes. A consensus team of trained interviewers reviewed each endorsed event and assigned an objective threat rating from 1 (little to no effect) to 4 (great effect), per SLES-provided anchors, to ensure uniformity and generalizability (44). Each objective threat rating was squared to provide larger weight to more impactful/severe events and then summed into a total SLES score (45). This procedure shows excellent test-retest reliability [intraclass correlation coefficient = .93 in the range of 5 to 15 days apart (44)].

The 99-item, self-report Inventory of Depression and Anxiety Symptoms II (IDAS-II) (46), which contains 18 factor-analytically derived scales, was completed at waves 1–5 (Figure 1). Analysis focused on IDAS-II Dysphoria given a priori interest in the core emotional and cognitive symptoms of depression. This 10-item scale comprises items such as "I felt depressed" and "I blamed myself for things" that are rated from 1 (not at all) to 5 (extremely) based on how the participant "felt or experienced things during the past 2 weeks, including today" and then summed (46,47). Ipsative mean imputation was used if nine or more items were endorsed. The IDAS-II displays excellent 1-week test-retest reliability [r = .75–.84 (48)].

During MRI quality control [details included in Image Acquisition and Processing (49)], 29 girls were excluded, yielding 232 participants for analysis. Retention at waves 3–5 was excellent (n = 228, n = 218, n = 221). Details on temporal sequencing of IDAS-II, SLES, and MRI at wave 2 is provided in the Supplement.

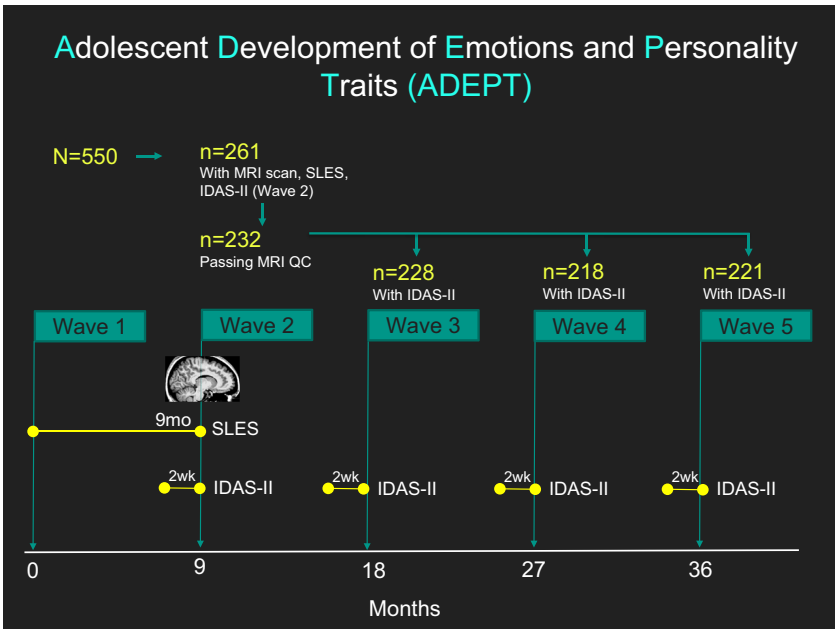

Figure 1. Timeline for the Adolescent Development of Emotions and Personality Traits (ADEPT) study as relevant to the present analysis. IDAS-II, Inventory of Depression and Anxiety Symptoms II; MRI, magnetic resonance imaging; QC, quality control; SLES, Stressful Life Events Schedule.

Image Acquisition and Processing

T1-weighted structural magnetization-prepared rapid acquisition gradient-echo images were obtained at Stony Brook University on a 3T Siemens MAGNETOM Trio MRI scanner (Siemens Healthcare, Erlangen, Germany) with the following parameters: repetition time = 1900 ms, echo time = 2.53 ms, field of view = 350 × 263 × 350 mm, integrated parallel acquisition technique factor 2, flip angle = 9°, slice oversampling = 18.2%, voxel resolution = 1 mm^3 isotropic, and duration = 4 minutes 30 seconds. As noted above, a validated manual inspection quality control procedure (49) excluded 29 participants owing to poor FreeSurfer segmentation (N = 232 approved MRI scans). In brief, the standard, automated cortical reconstruction pipeline in FreeSurfer 5.3.0 (http://surfer.nmr.mgh.harvard.edu/) was used to generate surface models on a Linux-based computing cluster. The surface models were inflated and registered to a spherical surface atlas (50) and underwent quality control (49). The pial and white matter surface models, overlaid on the T1-weighted image, were inspected for fidelity to visible tissue class boundaries. Cases in which inaccurate tissue delineation persisted for six or more consecutive coronal and axial slices were deemed inaccurate and disapproved. All technicians were blinded. This validated quality control procedure was shown to significantly boost reliability of structural metrics (intraclass correlation coefficient = .81 with approved scans relative to intraclass correlation coefficient = .75 with the whole sample) and thus boosts statistical power (49).

Statistics

Relationship Between Brain Structure and Stress. Surface-based morphometry analyses were performed in FreeSurfer. Cortical thickness, volume, and surface area maps were registered to a common spherical atlas and smoothed with a 10-mm Gaussian kernel (50). General linear models were used to examine the vertexwise correlations with total SLES, controlling for age. Right and left hemispheres were examined separately. Monte Carlo null-z simulation cluster analyses with 10,000 iterations and cluster-forming threshold of $p < .001$ were used to correct for multiple comparisons (mri_glmfit-sim) (51,52). In short, the familywise error significance threshold was set at $p < .05$, and through a combination of probability and cluster-size thresholding, clusterwise p values were obtained for resulting clusters (53). The FreeSurfer flag "–2spaces" was additionally used to account for left and right hemispheres. Clusters remaining significant after multiple comparisons correction were defined per the Desikan-Killiany atlas (54). Average volume, cortical thickness, or surface area cluster values were extracted if the cluster survived multiple comparisons correction.

Regionwise subcortical volumes were examined separately from the FreeSurfer automatic subcortical segmentation (55). Nine unilateral regions were tested: accumbens area, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, cerebellar white matter, and cerebellar cortex. Linear regressions were fit for each region entered separately with the predictors SLES total load and age.

Relationships Between Stress-Linked Morphology and Depressive Symptoms. Linear mixed effects regression models were fit for each stress-linked cluster with IDAS-II Dysphoria at waves 3–5 as the model outcome (SAS 9.1.3; SAS Institute Inc., Cary, NC). Participant was modeled as a random effect, and the stress-linked structural metric, age at imaging, wave, and $wave^2$ were time-invariant covariates. If a stress-linked cluster was significantly associated with IDAS-II

Dysphoria (waves 3–5), we reran analysis with wave 2 dysphoria (concurrent to imaging) as an additional covariate to determine if the effect was over and above current symptoms. All models used robust regression (Huber sandwich estimator) to correct model standard errors in the case of outliers (56), and β estimates were standardized. The IDAS-II Dysphoria scale was of a priori interest, but specificity was examined in exploratory analyses using the remaining 17 IDAS-II scales (see Supplementary Analysis 5).

Mediation Analysis. Stress-linked clusters found to significantly predict IDAS-II Dysphoria (waves 3–5) in the linear mixed models were retained for mediation analysis (independent variable = SLES total load, mediator = cluster extracted from FreeSurfer, dependent variable = mean IDAS-II Dysphoria from waves 3–5) (57) [Mplus 7.11 with bootstrapping for confidence intervals (58)]. The proportion of variance explained by the mediator was computed as previously described (59).

RESULTS

Participants

Table 1 summarizes demographic characteristics. The 232 girls had a mean age of 15.29 ± 0.65 years (range = 14.10–15.37 years) at the time of imaging and were largely Caucasian (87.9%), reflecting the catchment area around Stony Brook, New York. The 9-month burden of stressful life events varied considerably (mean total SLES = 8.54 ± 7.84, median = 6, range = 0–47, interquartile range = 3–15). The MRI sample (N = 232) did not differ from the nonimaged sample in total SLES (t_{256} = 0.55, p = .58). Table 2 shows the total and categorywise number of distinct stressful events (3.59 ± 2.59 total events); 90.1% of participants reported experiencing one or more stressful events. Health and other (nonromantic) relationships were common categories for events. Anxiety disorders were the most common type of DSM-IV diagnosis (23.28%) (Table 1). The presence of an anxiety disorder was not associated with total or categorywise stressful life event burden (see Supplementary Analysis 2). Thus, lifetime history of DSM-IV anxiety disorders was unlikely to complicate interpretation of results and was not further considered.

Cortical Morphology Correlates With Life Stress

When controlling for age and after multiple comparisons correction, four clusters significantly correlated with SLES total load (Figure 2A). Higher SLES total load was associated with thinner clusters in left precuneus (p = .037) and left postcentral (p = .035) cortices. Higher SLES total load was also associated with smaller volumetric clusters in left superior frontal (p = .006) and right inferior parietal (p = .001) cortices (Tables 3 and 4; Figure 2A). SLES total load was not significantly associated with surface area or subcortical volume ($p > .05$). Supplementary Analysis 3 presents the association between the four extracted clusters and SLES.

Stress-Associated Morphology Predicts Dysphoric Mood

IDAS-II Dysphoria showed modest stability across 9-month follow-up appointments (r = .41–.64; scores = 15.26 ± 6.35 [wave 2], 14.98 ± 6.31 [wave 3], 15.74 ± 7.14 [wave 4], 14.54 ± 6.44 [wave 5]) (trajectories of IDAS-II Dysphoria across waves are shown in Supplementary Analysis 4). During post-imaging follow-up (waves 3–5), first onset of MDD or dysthymia was observed in 11.36% of participants (25 of 220; 12 participants with incomplete data). Wave 2 SLES total load was significantly correlated with IDAS-II dysphoria (wave 1: r = .16, p = .015; wave 2: r = .24, $p < .001$; wave 3: r = .25, $p < .001$; wave 4: p = .14, p = .035; wave 5: r = .18, p = .007).

We examined whether dysphoria levels assessed before imaging could underlie the association between wave 2 SLES and the four clusters identified with surface-based morphometry. Thus, surface-based morphometry analyses were repeated with wave 1 IDAS-II Dysphoria (assessed 9 months before imaging and before the start of the SLES assessment window) and wave 2 IDAS-II Dysphoria (assessed concurrent to imaging and at the end of the SLES assessment window), respectively, as additional covariates (see Supplementary Analysis 1). In summary, left superior frontal and right inferior parietal volume clusters remained associated with SLES when controlling for remote and current dysphoria, whereas left precuneus thickness remained associated with SLES when controlling for remote, but not current, dysphoria. The postcentral thickness cluster was no longer associated with SLES in both analyses.

We next examined whether these clusters predicted future IDAS-II Dysphoria (waves 3–5). The covariates (wave, wave^2, and age) were not significantly related to IDAS-II Dysphoria ($p > .05$). The stress-linked left precuneus cortical thickness cluster prospectively predicted IDAS-II Dysphoria (β = −.169, t_{207} = −3.620, p = .0004). This effect remained significant when controlling for wave 2 IDAS-II Dysphoria (β = −.110, t_{206} = −2.930, p = .004) (Figure 2B), indicating that prediction of 27-month increases in dysphoria is over and above the level

Table 1. Sample Characteristics

Characteristic	*n* (%)
Demographics	
Hispanic	25 (10.80)
Caucasian	204 (87.90)
Lifetime Psychopathology	
Any diagnosis	61 (26.29)
Any anxiety disorder	54 (23.28)
Generalized anxiety disorder	5 (2.16)
Specific phobia	30 (12.93)
Social phobia	24 (10.34)
Separation anxiety	5 (2.16)
Panic disorder	3 (1.29)
Obsessive-compulsive disorder	2 (0.86)
Posttraumatic stress disorder	0 (0.00)
Any behavioral disorder	11 (4.74)
Conduct disorder	0 (0.00)
Oppositional defiant disorder	5 (2.16)
Attention-deficit disorder	6 (2.59)
Bulimia nervosa/anorexia nervosa	0 (0)
Eating disorder not otherwise specified	5 (2.16)
Any substance use disorder	0 (0)

Table 2. Stressful Life Events

Stressful Life Events Category	Mean (SD)	Median (Range)	Frequency of Events						
			0	1	2	3	4	5	>5
SLES Total	3.59 (2.59)	3 (0–12)	23	33	36	33	29	26	52
Education	0.41 (0.66)	0 (0–3)	158	57	14	3	0	0	0
Work	0.23 (0.53)	0 (0–3)	189	33	9	1	0	0	0
Money	0.12 (0.32)	0 (0–1)	205	27	0	0	0	0	0
Housing	0.12 (0.36)	0 (0–2)	208	21	3	0	0	0	0
Crime	0.07 (0.31)	0 (0–2)	218	11	3	0	0	0	0
Health	1.03 (1)	1 (0–5)	82	85	48	12	4	1	0
Death	0.32 (0.52)	0 (0–2)	163	63	6	0	0	0	0
Romantic Relationships	0.29 (0.6)	0 (0–3)	180	40	9	3	0	0	0
Other Relationships	1.01 (1.07)	1 (0–5)	92	75	43	15	6	1	0

SLES, Stressful Life Events Schedule.

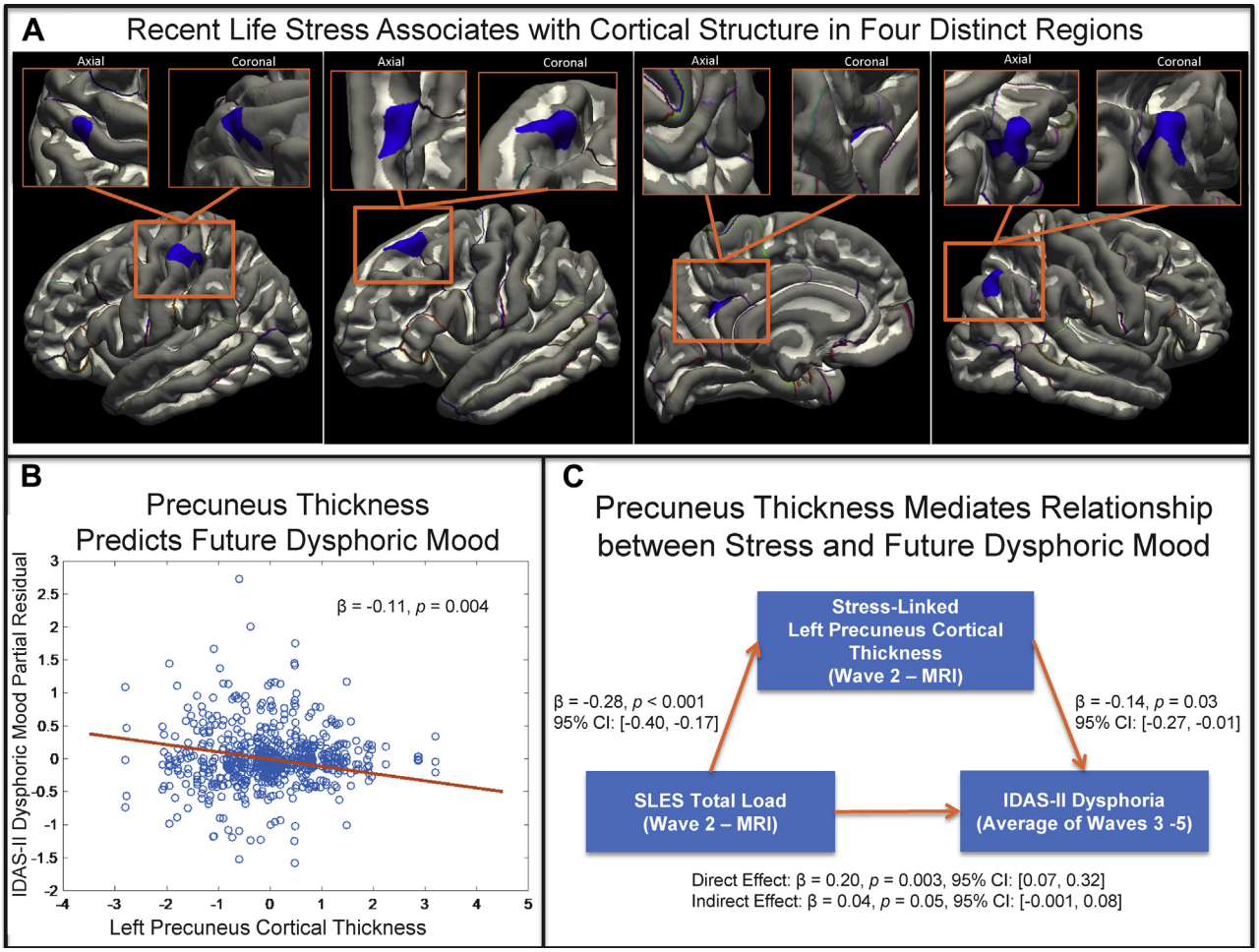

Figure 2. **(A)** Surface-based morphometry results surviving multiple comparisons correction for the stress analysis (clusterwise $p_{corrected} < .05$). Thinner left postcentral associated with more stress (left region). Smaller left superior frontal associated with more stress (left-center region). Thinner left precuneus associated with more stress (right-center region). Smaller right inferior parietal associated with more stress (right region). **(B)** Partial residual for Inventory of Depression and Anxiety Symptoms II (IDAS-II) Dysphoria scores across waves 3–5 as estimated from the linear mixed model accounting for age, wave, wave^2, IDAS-II dysphoria score at the time of imaging (wave 2), and the stress-linked left precuneus cortical thickness estimate. Resulting model standardized β for the fixed effect of precuneus cortical thickness shown and resulting *p* value. **(C)** Mediation results shown for x = Stressful Life Events Schedule (SLES) total load, M = stress-linked left precuneus cortical thickness, and y = IDAS-II dysphoria score over waves 3–5. Standardized model β, *p* values, and 95% confidence intervals (CIs) shown. MRI, magnetic resonance imaging.

Table 3. Surface-Based Morphometry Stress Association Results

Region	Measure	Clusterwise Probability	Size (mm^2)	MNI Coordinates (x, y, z)	Direction of Effect
Left Precuneus Cortex	Cortical thickness	.037	173.12	−13.2, −53.1, 34.8	More stress, thinner
Left Postcentral Cortex	Cortical thickness	.035	174.12	−50.0, −22.6, 54.2	More stress, thinner
Left Superior Frontal Cortex	Volume	.006	283.24	−18.5, 30.4, 50.1	More stress, smaller volume
Right Inferior Parietal Cortex	Volume	.001	339.09	40.4, −65.3, 46.4	More stress, smaller volume

Surface-based morphometry analyses were repeated covarying for duration between magnetic resonance imaging and Stressful Life Events Schedule assessments, and the results were unchanged.

MNI, Montreal Neurological Institute.

of dysphoria at time of imaging. The other three clusters were not significant predictors of IDAS-II Dysphoria. Specificity analyses (Supplementary Analysis 5) revealed that stress-linked precuneus thickness predicted increased levels of other mood and anxiety symptom dimensions at waves 3–5, including lassitude, mania, social anxiety, and ill temperament ($p < .01$) and additionally panic, appetite gain, traumatic intrusions, and suicidality ($p < .05$).

Mediation Analysis

In mediation analysis, left precuneus cortical thickness accounted for approximately 17.0% of the association between SLES total load and mean IDAS-II Dysphoria ($\beta = .040$, $p = .053$) (Figure 2C). Controlling for wave 2 IDAS-II Dysphoria yielded a minor reduction of the mediative effect of the precuneus ($\beta = .030$, $p = .084$) but increased the variance accounted for to 24.2%.

DISCUSSION

Despite the prominent role of depressogenic stress in translational models, evidence connecting stress-sensitive cortical markers to depression in human adolescents has been elusive (1,5). In this project, we examined stress-sensitive cortical markers in a typically developing cohort of adolescent girls during a developmental period notable for neural maturation, exposure to stress, and increased rates of depression (33). Then we tested prognostic value using longitudinal follow-up of depression symptoms over 27 months.

Our first finding was that portions of the frontal and parietal lobes (precuneus, postcentral, inferior parietal, and superior frontal cortices) were associated with 9-month exposure to stressful life events. Similar results (smaller/thinner prefrontal and precuneus cortices) have been reported in relation to remote events in 12-year-old children (31), youths exposed to stimulus deprivation (60), childhood sexual abuse (61), temporally distal traumatic life events (31), and diagnosis of PTSD (28). Our second main finding was that left precuneus thickness predicted subthreshold increases in dysphoric mood, the cardinal symptom of DDs, for up to 27 months after imaging. Furthermore, precuneus thickness mediated a modest amount of the depressogenic effects of stress.

Importantly, this identifies stress-linked precuneus thickness as a viable candidate biomarker for the depressogenic effects of stress. Ultimately, longitudinal, multimodal neuroimaging is needed to pinpoint the molecular mechanisms through which recent life stress alters cortical structure in vulnerable regions, especially using tools such as positron emission tomography to target levels of neuroinflammation following stress exposure. Such information is critical for translating these findings to the clinic, where articulated mechanisms can drive the development of effective interventions.

One intriguing aspect of these results is that the community-dwelling cohort was not recruited based on risk status (e.g., not recruited based on trauma or neglect) and was rated at, or near, normative levels of stress exposure and dysphoria. For instance, mean SLES scores (8.5 ± 7.8) were comparable to adolescent control subjects (44), and mean wave 2 IDAS-II Dysphoria scores (15.3 ± 6.4) placed the sample slightly above the 47th percentile of norms (62). Given the characteristics of the present cohort, these results suggest a model by which high concentrations of recent life stress impact similar regions as implicated with severe stressors, neglect, and trauma.

A corollary of the stress acceleration hypothesis is that ongoing neural development dynamically shapes regional sensitivities to stress. Thus, these regions may be sensitive to recent life stress during midadolescence in particular, whereas a comparable study in an older cohort might detect effects in prefrontal and cingulate regions (12–16). Indeed, parietal and frontal lobe thickness peak at 10 and 11 years old, respectively, whereas temporal lobe thickness peaks at 17 years of age in girls (12). The medial prefrontal and cingulate cortices, which are implicated in stress and depression literature (63–66), are the last to develop and appear to follow a complex cubic trajectory (16). The age of the sample may also account for the absence of effects in subcortical regions, such as the hippocampus, which appears volumetrically stable during this period of adolescence (15,67). Previous studies have identified subcortical regions, especially the hippocampus, as sensitive

Table 4. Bivariate Pearson Correlations Among Extracted Stress-Linked Clusters

	2	3	4	5	Mean (SD)
1. Left Precuneus Cortical Thickness	.26[c]	.25[c]	.20[b]	−.05	2.57 (0.21)
2. Left Postcentral Cortical Thickness	—	.23[c]	.12	−.04	2.50 (0.27)
3. Left Superior Frontal Volume		—	.27[c]	−.05	2.50 (0.49)
4. Right Inferior Parietal Volume			—	−.16[a]	1.87 (0.35)
5. Age				—	15.29 (0.65)

[a] $p < .05$.
[b] $p < .01$.
[c] $p < .001$.

to stress (8,64,66). This includes studies of perceived stress in adolescents and recent life stress in adults (21,68) as well as youths with posttraumatic stress symptoms (69). However, null results have also been reported in youths with distal life stress (31) and in a meta-analysis that concluded hippocampal volume was reduced in adults, but not in youths with childhood PTSD (67). Thus, hippocampal volume may be sensitive to trauma, but not stressful life events, or the effects do not emerge until adulthood.

A second corollary of the stress acceleration hypothesis is that programmed developmentally sensitive periods are necessary for healthy adaptation. Premature activation by stress may alter developmental programming and increase vulnerability to develop psychopathology (10). The four stress-linked regions share physical connection via the occipitofrontal fasciculus (70), implicating maturation of this particular fiber pathway in vulnerability to stress (more so than other tracts for this cohort). In addition, these regions are part of functional connectivity networks that increase after trauma (71) and during recovery from experimentally induced social stress (72). Thus, altered maturation of these regions, stemming from repeated stress exposure, may affect reactivity to and recovery from later stress exposure. In addition, mistiming of precuneus maturation may alter structural connections with limbic structures and areas of the frontal cortex (71) or alter functional connectivity in circuitry involved in emotional learning, reactivity, and self-referential processes (10,64,73,74). Cognitive functions of the precuneus include first-person perspective taking and an experience of agency (73,74) as well as complex cognitive functions (e.g., coping styles and self-regulation [10]). Interestingly, in adults with MDD, hypogyrification in the precuneus cortex was associated with default mode network hyperconnectivity (75).

Dysphoria was not predicted by the other three stress-linked regions, but other consequences are plausible given their varied behavioral, cognitive, and affective functions. The inferior parietal cortex (posterior section of the inferior parietal lobule; angular gyrus) has been implicated in semantic and number processing, memory retrieval, attention, and social cognition (76) as well as propensity for self-referential thoughts (77). Interestingly, depressed individuals exposed to experimentally induced stress show hyperconnectivity between the inferior parietal and prefrontal cortex relative to nondepressed individuals (78). Furthermore, the prefrontal cortex may have top-down control over emotional responses through modulation of limbic activity. Therefore, disrupted maturation of this region could eventually impact emotional processing (79). The superior frontal gyrus is a key component of working memory networks (80) and, through connections with middle and inferior frontal gyri (81), is thought to support high-level executive functions (80). The identified portion of the postcentral gyrus (mid-to-superior portion) selectively encodes fear/anger emotions over happiness/surprise (i.e., emotion-predictive patterns) (82). Thus, altered maturation in the postcentral gyrus could have an impact on emotion encoding and prediction.

These findings support the hypothesis that reduced cortical GM could serve as a viable biomarker for depression, especially in high-risk youths (35,83,84). Case-control studies of adolescents with depression have reported reduced superior frontal morphologic properties (35), and adolescents with accelerated frontal and parietal lobe thinning exhibit higher depression severity (37). Thinning in the superior frontal and inferior parietal gyri was also correlated with genetic risk for depression (83). Our results contribute to this literature by suggesting that recent life stress may have underappreciated and similar impacts on cortical structure in subthreshold symptoms, as observed for DDs and familial risk for depression.

Strengths of this study include a semistructured stress interview and consensus team–derived objective-stress ratings. This rigorous approach prevents same-reporter bias from creating spurious correlations between stress and dysphoria. The study also repeatedly assessed dysphoria up to 27 months after imaging. Additionally, MRI data were closely screened using a validated quality-control procedure.

However, there were also limitations. First, our study examined female participants of a narrow age range. The parent project aimed to minimize heterogeneity, focusing on a population at great risk of first depression onset. Diverse samples are needed to replicate these results in different age groups and explore gender differences. Importantly, whether these results generalize to clinical populations of adolescents is unclear. In addition, the clinical significance of precuneus thickness is unclear because it did not predict first onset of DSM-IV MDD or dysthymia (n = 25) (see Supplementary Analysis 6). Increases in subthreshold symptoms are a robust predictor of risk for first-onset depression (85). Thus, longer follow-up may be necessary to capture associations between stress-linked precuneus thickness and transition from subthreshold symptoms to disorder onset. Indeed, the cohort is not yet through the period of highest risk for onset, and relatively few participants have converted. Second, participants were assessed for stress and depression ecologically and completed one assessment of MRI. Thus, the causal link between stress and cortical structure requires further investigation using longitudinal neuroimaging.

Third, it is unclear why effects vary by GM parameter on a region-by-region basis. Preclinical studies suggest that inter-individual variability in cortical volume is more closely related to surface area and mostly independent of cortical thickness (86–88). Twin studies suggest that the genetic and environmental factors are distinct for surface area and cortical thickness (89). Furthermore, regional GM properties may be sensitive to distinct pathophysiological processes, as they each mature along distinct developmental trajectories (15). A comprehensive model of the neurodevelopmental mechanisms underlying individual differences in each aspect of GM is needed to reconcile this phenomenon.

Fourth, the study was not well suited to identify consequences of early adversity, trauma, or neglect on cortical morphology. Exclusion of lifetime history of DSM-IV MDD or dysthymia at wave 1 may have led to enrollment of few, if any, high-risk youths. Indeed, no participants met criteria for DSM-IV PTSD at wave 1. In addition, stressful life events were first assessed at wave 2 and covered the period since wave 1. This prevented direct comparison of effects of earlier stressful life events with effects of more recent stressful life events. That cortical effects of stress at wave 2 were largely independent of wave 1 dysphoria (except in the postcentral gyrus) may be informative, given that wave 1 dysphoria should be elevated in participants who experienced a high burden of early stressful

life events. Future studies would benefit from direct comparison of community-dwelling youths exposed to normative stressful life events and youths selected for significant early adversity.

In this study, recent life stress was associated with subtle differences in GM morphology in adolescent girls. This is novel evidence that common stressful life events may affect adolescent development and contrasts with the notion that only particularly harsh, traumatic exposures alter neurodevelopment. The stressogenic effects on precuneus thickness represent a novel biomarker for understanding the depressogenic effects of stress. Imaging modalities such as positron emission tomography are necessary to investigate the molecular mechanisms of stress-induced deviations from normative neurodevelopment. Such studies could eventually make it feasible to ameliorate or block stress-induced neurodevelopmental structural changes via targeted therapies and early intervention strategies.

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ARTICLE INFORMATION

From the Departments of Biomedical Engineering (EAB, CD), Psychology (DNK), Applied Mathematics and Statistics (KL), and Psychiatry (CD, RK, GP), Stony Brook University, Stony Brook, New York.

Address correspondence to Elizabeth A. Bartlett, Ph.D., Department of Biomedical Engineering, Health Sciences Center T-10-041O, Stony Brook, NY 11794; E-mail: Elizabeth.Bartlett@stonybrook.edu.

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