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

Supplementary Information

Temporal Sequencing of IDAS-II, SLES and MRI

If the IDAS-II was administered both at Wave 2 and at imaging (n=81), the imaging day IDAS-II Dysphoria was utilized (correlation between the two IDAS-II Dysphoria scores was robust: $r=0.74$, $p<0.001$). The median duration between MRI and SLES was 24 days (mean=37.1±36.6 days, range=2-228) and the median duration between MRI and IDAS-II was 10 days (mean=12.9±22.3 days, range=10-228). Within 14 days of imaging, 24.6% and 66.8% of participants had been assessed with the SLES and IDAS-II, respectively. Within 30 days of imaging, 59.5% and 95.3% of participants had been assessed with the SLES and IDAS-II, respectively.

As noted in the footnote in manuscript Table 2, SBM analyses between brain and stress (controlling for age) were repeated additionally covarying for the duration between the MRI and SLES assessments. The results were unchanged.

Supplementary Analysis 1: Surface-based morphometry analyses with IDAS-II Wave 1 and Wave 2 scores as covariates

SLES was significantly associated with prior and concurrent IDAS-II scores (see main manuscript results). Thus, to investigate whether prior or cross-sectional dysphoric mood accounted for the SBM results, the analyses were repeated while covarying for age and (1a) IDAS-II scores at Wave 1 (9 months prior to imaging) or (1b) IDAS-II scores at Wave 2 (at the time of imaging).

The results of these supplemental analyses were largely similar to those in the main text of the manuscript. Three of the four clusters (left precuneus thickness, left superior frontal volume, and right inferior parietal thickness) remained significant when controlling for Wave 1 IDAS-II Dysphoria (p=0.03, 0.004, 0.004, respectively). The left superior frontal and right inferior parietal volume clusters remained associated with stress while controlling for Wave 2 IDAS-II Dysphoria (p=0.03 and p=0.0006, respectively). No additional clusters emerged after inclusion of these covariates.

We take these findings to mean that the right inferior parietal and left superior frontal clusters were associated with recent stress in a manner that is independent of past or current dysphoria. By the end of the period in which the recent life stress was assessed (Wave 2), left precuneus thickness may capture some effect of concurrent, but not remote, dysphoria symptoms. The left post-central volume was sensitive to remote and current dysphoria symptoms.

Supplementary Analysis 2: Surface-based morphometry analyses with lifetime presence of an anxiety disorder

Next, we conducted analyses to determine to what extent prior history of DSM-IV Anxiety Disorders at Wave 1 (9 months prior to imaging), a potent predictor of future depression, explained our results. For these analyses, the imaging sample (N=232) was split into those with any DSM-IV Anxiety Disorder diagnosis at Wave 1 (n=54; 23.3% of sample) and those without a DSM-IV Anxiety Disorder diagnosis (n=178; 76.7% of sample) at Wave 1. The any DSM-IV Anxiety Disorder group included 88.5% (54/61) of all girls rated as meeting lifetime criteria for a DSM-IV diagnosis at Wave 1.

First, we examined whether the two groups differed in total burden of recent stressful life events at Wave 2. This association was not statistically significant (t=0.19, CI=[-2.12, 2.57], p=0.850). The association was also not statistically significant by category of stressful life event: (SLES Education: t=0.85, CI=[-0.34, 0.86], p=0.40; SLES Work: t=-0.77, CI=[-0.47, 0.21],

p=0.44; SLES Money: t=1.73, CI=[-0.02, 0.25], p=0.08; SLES Housing: t=0.71, CI=[-0.09, 0.19], p=0.48; SLES Crime: t=-0.27, CI=[-0.45, 0.34], p=0.79; SLES Health: t=-1.38, CI=[-2.16, 0.39], p=0.17; SLES Death: t=-0.31, CI=[-0.78, 0.57], p=0.76; SLES Romantic Relationships: t=1.05, CI=[-0.25, 0.81], p=0.30; SLES Other Relationships: t=1.40, CI=[-0.30, 1.72], p=0.17).

We also conducted Anxiety Disorder analyses using whole-brain surface-based morphometry. After controlling for age and multiple comparisons correction, two very small clusters (<30 mm^2; compared to the 173-339 mm^2 stress-linked clusters) in the right pre-central and right middle temporal cortices were found to be thicker/larger in the any DSM-IV Anxiety Disorder group relative to the non-Anxiety disorder group (Figure S1). Importantly, these anxiety-linked regions did not overlap with the stress-linked regions.

In summary, prior history of any DSM-IV Anxiety Disorders at Wave 1 does not appear to account for SLES score at Wave 2, the key independent variable in the main SBM analysis. It was also largely unrelated to the dependent variable in the main SBM analysis (brain structure). Thus, Anxiety Disorders were not further considered.

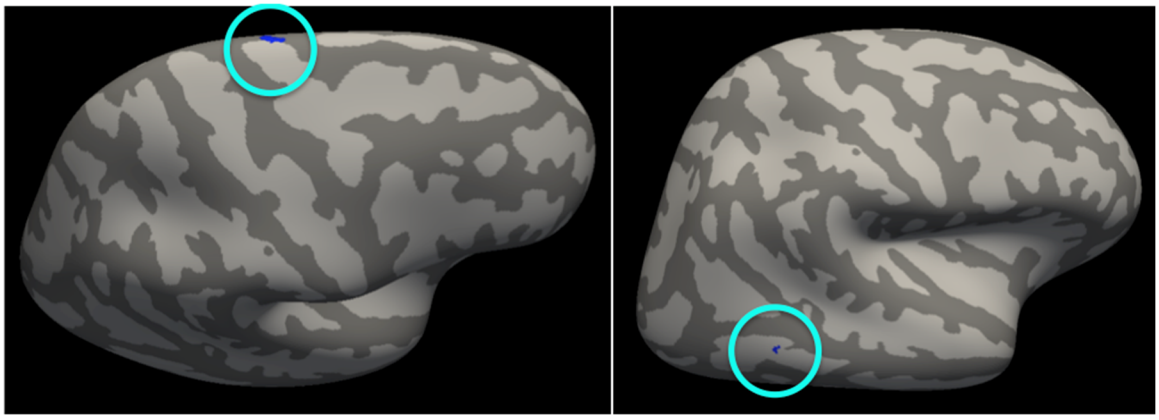

Figure S1: Surface-based morphometry results surviving multiple comparisons correction for the binary lifetime anxiety diagnosis analysis (covarying for age; cluster-wise p<0.05). Circles highlight the two clusters found. LEFT: Thicker right pre-central cortical thickness found in the Anxiety Diagnosis group relative to the No Anxiety Diagnosis group. RIGHT: Thicker right middle temporal volume found in the Anxiety Diagnosis group relative to the No Anxiety Diagnosis group.

Supplementary Analysis 3: Bivariate correlations between extracted stress-linked morphology estimates and SLES total load

Supplementary Figure S2 shows the relationship between the unadjusted mean value in each of the 4 significant clusters and SLES total load (age as a covariate). The non-parametric relationship between SLES and the extracted average value in each of the 4 clusters as assessed with the Spearman correlation were rho=-0.25 for left precuneus CT, rho=-0.27 for left post-central CT, rho=-0.22 for left superior frontal volume, and rho=-0.32 for right inferior parietal volume, where all relationships are significant ($p<0.05$). These non-parametric correlations were similar to Pearson's correlations (r=-0.27 to -0.44).

These bivariate associations were not included in the main manuscript because the extracted mean value in each cluster is somewhat biased as a correlate of SLES score. This is because a vertex-wise general linear model between cortical thickness volume/surface area and SLES (adjusted for age) was used to identify and extract the clusters in FreeSurfer. As Kriegeskorte et al. 2009 explains, using the same data set for selection and selective analyses gives distorted descriptive statistics if the statistics are not independent of the selection criteria (1). Yet, the bivariate associations may be informative to review.

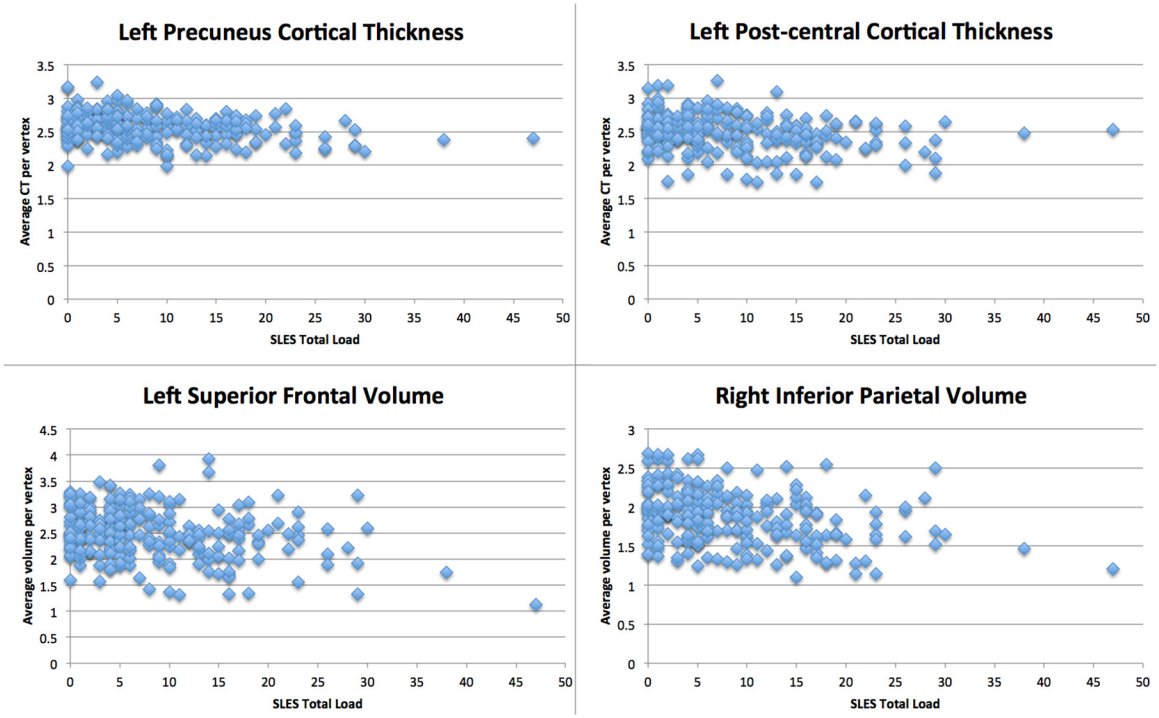

Figure S2: Average volume or cortical thickness values extracted for each subject from the clusters found to significantly correlate with SLES total load in surface-based morphometry analysis (age was a covariate in the analysis). Estimates are unadjusted (i.e. not adjusted for age as a result of model fitting). Average subject-wise value is plotted against SLES Total Load.

Supplementary Analysis 4: Individual IDAS-II Dysphoria trajectories over the course of the study (Waves 1-5)

Supplementary Figure S3 shows the person-centered trajectories of IDAS-II Dysphoria scores and means across each wave of data collection (Waves 1-5). As shown, there were many different patterns across participants, including some increasing, some decreasing, and some who remained stable. Of note, in the linear mixed model aimed at predicting IDAS-II scores throughout waves 3-5 from precuneus cortical thickness (see main text results), the main fixed effects of wave and wave^2 were both non-significant ($p=0.68$ and 0.66). Participant ID was included in these models as a random effect to account for inter-individual differences in IDAS-II scores over time.

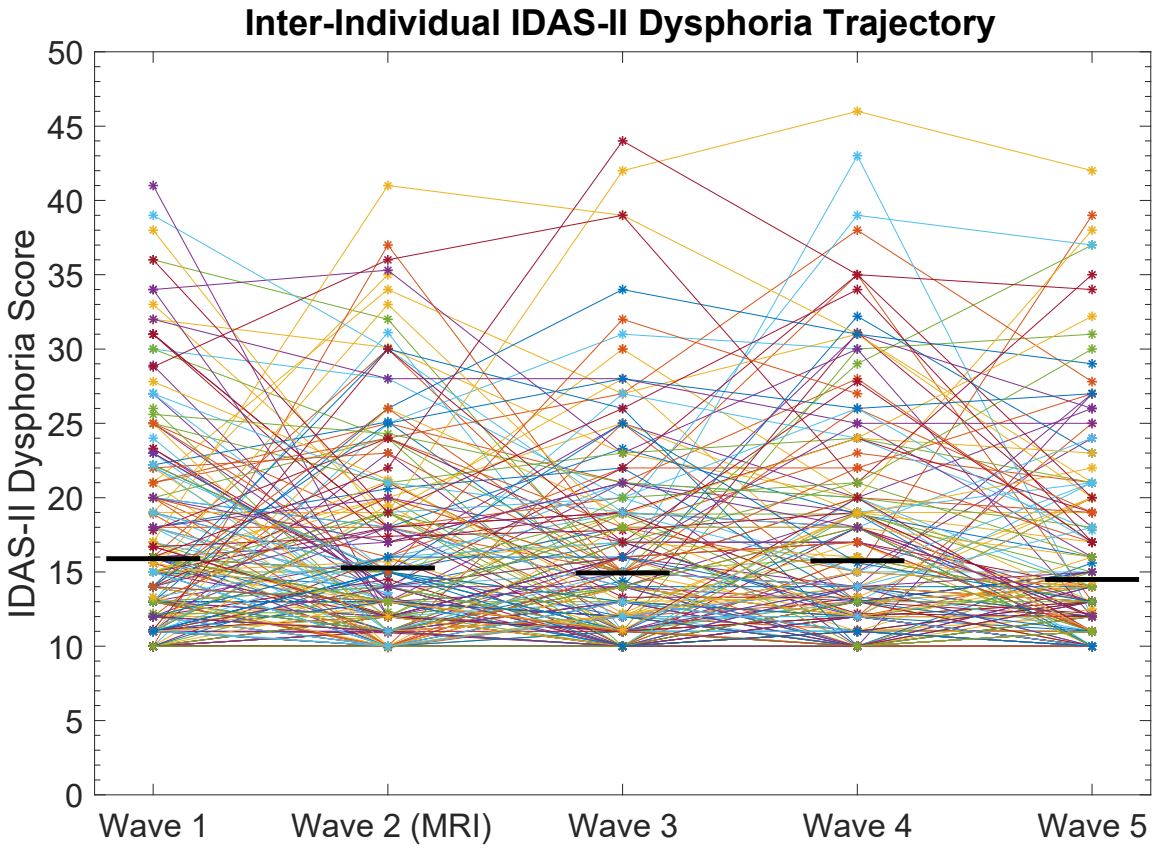

Figure S3: Trajectories of IDAS-II Dysphoria scores across the 5 waves of data collection for each participant (N=232). Means are shown with black horizontal bars. The Y-axis shows the IDAS-II Dysphoria score, while the x-axis shows each Wave, with Wave 2 denoted as the Wave with the MRI acquisition.

Supplementary Analysis 5: Exploratory analyses using the stress-linked left precuneus cortical thickness to predict other symptom dimensions

Although our *a priori* hypothesis pertained to IDAS-II Dysphoria, the other 17 mood and anxiety symptom dimensions that comprise the full IDAS-II battery were examined for specificity. Thus, we repeated the hierarchical linear regression analysis as described in the main analysis for each of the other 17 IDAS-II symptom dimensions. The predictors in the model were stress-linked left precuneus cortical thickness and covariates (age, Wave, and Wave^2). The dependent variable was a symptom dimension assessed up to three time points (Waves 3, 4, and 5) across 27-months. The results are summarized in Supplementary Table S1, sorted in ascending

order by p-value (uncorrected for multiple comparisons) for convenience. Briefly, in addition to predicting dysphoric mood (p=0.0004), stress-linked precuneus thickness also predicted higher levels of Lassitude, Mania, Social Anxiety, and Ill Temperament symptom dimensions (p<0.01). Using a weaker threshold of p<0.05, stress-linked precuneus thickness also predicted Panic, Appetite Gain, Traumatic Intrusions, and Suicidality symptom dimensions. On the other hand, Well-being, Cleaning, Insomnia, Appetite Loss, Claustrophobia, Checking, Euphoria, Traumatic Avoidance, and Ordering were not predicted by stress-linked precuneus thickness. Thus, stress-linked precuneus thickness was associated with higher levels of mood and anxiety symptoms across several IDAS-II scales, albeit Dysphoria was the strongest association.

Table S1: Exploratory Analyses using Precuneus Thickness to Predict IDAS-II Scales

	Estimate	Standard Error	DF	t-value	p-value
IDAS-II Dysphoria	-0.169	0.047	207	-3.620	0.0004
IDAS-II Lassitude	-0.151	0.052	208	-2.910	0.0041
IDAS-II Mania	-0.160	0.057	208	-2.820	0.0053
IDAS-II Social Anxiety	-0.119	0.044	208	-2.690	0.0077
IDAS-II Ill Temper	-0.131	0.049	209	-2.690	0.0078
IDAS-II Panic	-0.107	0.043	209	-2.500	0.0130
IDAS-II Appetite Gain	-0.131	0.052	208	-2.500	0.0131
IDAS-II Traumatic Intrusions	-0.103	0.044	208	-2.360	0.0191
IDAS-II Suicidality	-0.068	0.032	204	-2.130	0.0345
IDAS-II Low Well-being	-0.101	0.053	207	-1.910	0.0576
IDAS-II Cleaning	-0.098	0.052	209	-1.890	0.0599
IDAS-II Insomnia	-0.089	0.048	209	-1.840	0.0669
IDAS-II Appetite Loss	-0.072	0.045	206	-1.610	0.1087
IDAS-II Claustrophobia	-0.067	0.043	208	-1.540	0.1239
IDAS-II Checking	-0.062	0.050	207	-1.230	0.2202
IDAS-II Euphoria	-0.051	0.051	208	-0.990	0.3232
IDAS-II Traumatic Avoidance	-0.042	0.046	205	-0.920	0.3608
IDAS-II Ordering	-0.021	0.054	206	-0.380	0.7017

Note: A line is drawn to separate scales with p-value < 0.01. Abbreviations: IDAS: Inventory of Depression and Anxiety Symptoms II, DF: degrees of freedom. Well-being was reversed-coded for interpretability.

Supplementary Analysis 6: Exploratory analyses using the stress-linked left precuneus cortical thickness to predict binary onset of depression

First onset of a Depressive Disorder (MDD or Dysthymia) in Waves 3-5 was observed in a small set of participants (n=25; 11.36%), whereas 195 participants were never rated as meeting full criteria for a Depressive Disorder by the Wave 5 assessment (88.64%). Of the 25 participants, n=10 had a first onset at Wave 3, the next diagnostic interview after imaging (i.e. 9 months after imaging). First onset of a Depressive Disorder at Wave 3 (n=10, total SLES burden = 12.90±9.76) was associated with higher SLES burden at Wave 2 than the never-depressed comparison group (n=195, total SLES burden = 8.02±7.67; t=-1.94, df=203, p=0.05, Cohen's d = 0.63). The effect weakened when considering the full group of first onsets through Wave 5 (n=25, total SLES burden = 10.96±8.52) against the comparison group (total SLES burden = 8.02±7.67) and was no longer statistically significant (t=-1.782, df=218, p=0.08, Cohen's d = 0.38). For reference, the 10 participants with first-onset of a Depressive Disorder at Wave 3 reported higher levels of IDAS-II Dysphoria at Wave 3 (n=10, Dysphoria score = 24.50±8.22) than the never-depressed comparison group at Wave 3 (n=192, Dysphoria score = 13.97±5.09; t=-6.16, df=200, p<0.01, Cohen's d=2.00).

Next, we examined if stress-linked left precuneus thickness predicted onset of Depressive Disorders at Waves 3-5 using logistic regression. Unlike with IDAS-II Dysphoria, precuneus thickness did not predict first onset of MDD (age and precuneus thickness as fixed factors): Odds Ratio: 0.97, 95% CI: 0.63-1.47, p=0.87. Therefore, stress-linked precuneus thickness may be associated with increases in subthreshold symptoms of Dysphoria considered continuously for 27 months after imaging, but not first-onset of a Depressive Disorder considered categorically. This analysis is limited by small sample size, as only 25 participants met criteria for Depressive Disorders. In addition, first onset was only tracked for 27 months following MRI. The cohort is not yet through the highest periods of risk for first onset of Depressive Disorders and longer longitudinal follow-up is required to record onsets.

Supplemental Reference

1. Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI (2009): Circular analysis in systems neuroscience: the dangers of double dipping. *Nat Neurosci*. 12:535-540.