Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Subjects

All of the participants were post-menarche at the time of scanning (age of menarche 12.33±1.32 years; 6.80±2.52 years before the MRI scan). Although this study was not designed to assess the relation of puberty to the onset of psychopathology, we did collect Tanner staging data at study entry (although not longitudinally), and we also subsequently recorded age of menarche. Parenthetically, Tanner staging ranged from 1 to 4.5 (3.20±1.10; average of breast and hair rating) at study entry, an average of six years before the neuroimaging scans.

20 low-risk CTL participants were excluded for meeting DSM criteria for MDD or another Axis I disorder (n=8), or subthreshold criteria for an Axis I disorder (defined as the minimum number of symptoms minus 1; n=12). Two participants (1 CTL and 1 CVT) were excluded because they obtained scores >13 on the Children's Depression Inventory (CDI) on the day of the scan, and another five participants (2 CVT, and 3 CTL) were excluded because of unusable fMRI data (e.g., excessive motion or incomplete coverage).

eAppendix 2. fMRI and Resting-State fMRI Data Preprocessing

Resting-state fMRI scans were conducted at T2 (M=6.28 ± 1.96 years after entry to the study). All fMRI data were acquired using a 3T MR750 Discovery scanner (GE Medical Systems, Milwaukee, WI) with a 32-channel head coil (Nova Medical). T1-weighted whole-brain anatomical images were acquired using a 5-minute GE 3D BRAVO sequence, with an IR-prep fast spoiled gradient (SPGR) sequence with 0.9mm^3 voxel resolution (186 slices, FOV=230mm, TR=6.2ms, TE=2.3ms, TI=450ms, flip angle=12 degrees, 256 x 256mm matrix, sagittal acquisition). Following the anatomical scan, participants underwent a 6-minute resting-state fMRI scan during which they were instructed to keep their eyes closed but remain awake. The resting-state fMRI data were acquired with a T2*-weighted interleaved echo planar imaging sequence designed to measure whole brain BOLD contrast with 3.2mm^3 voxel resolution (37 slices, FOV=224mm, TR=2000ms, TE=30ms, flip angle=77 degrees, 180 volumes, axial acquisition with right-to-left frequency direction).

Functional MRI data were first preprocessed in SPM12 (Wellcome Trust Center for Neuroimaging, University College London, United Kingdom). The first six volumes were trimmed prior to fMRI data preprocessing to account for magnetization equilibration. Data were slice-time and motion corrected, realigned, normalized in Montreal Neurological Institute (MNI) space, and smoothed with a 6-mm full width at half maximum (FWHM) Gaussian kernel. The anatomical image for each participant was normalized to MNI space and segmented into white matter (WM), gray matter, and cerebrospinal fluid (CSF) masks to be used as regressors for artifacts (see below). The residual BOLD time-series was bandpass filtered over a low-frequency (0.009Hz-0.08Hz) window of interest.

eAppendix 3. Artifact and Motion Correction

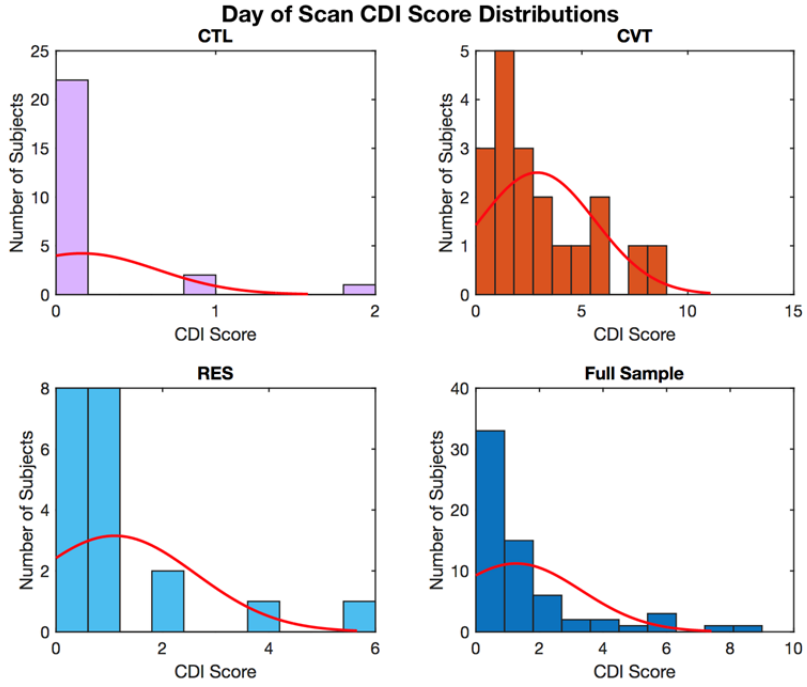
To address the spurious correlations in resting-state networks caused by head motion and artifact, and allow for valid identification of correlated networks,[1] we used quality assurance software Artifact Detection Tools (http://www.nitrc.org/projects/artifact_detect) to identify problematic time points during the scan. Artifact/outlier scans, defined as average intensity deviating more than 3 standard deviations from the mean intensity in the session or if composite head movement exceeded 0.5 mm from the previous image, were regressed out simultaneously with the WM and CSF signals and prior to bandpass filtering. Specifically, a single regressor for each outlier image was included in the first-level general linear model along with 6 motion parameters and their first order derivatives. Participants who had more than 20% of their volumes identified as motion outliers were excluded from our final analyses (2 participants, one

from each HR group, were excluded for this reason). Physiological and other spurious sources of noise were estimated and regressed using the anatomical CompCor method (aCompCor),[2] given the controversy over the use of global signal regression.[3-5]. Signals from the eroded WM and CSF masks were extracted from the unsmoothed functional volumes to avoid the risk of contaminating WM and CSF signals with gray matter signals and were included in our first-level general linear models as regressors of non-interest.

As we note in Table 1 of the paper, the three groups did not differ with respect to head displacement across the resting-state scan for either number of volume outliers, frame-to-frame transitions, or frame-to-frame rotations (all *p*s>0.25).

eAppendix 4. No Main Effects of CDI or WAIS on Group Differences in Functional Connectivity.

We investigated potential contributions of day of scan CDI scores and maternal WAIS scores on amygdala-OFC FC by performing two multivariate analyses of covariance (MANCOVA; model: connectivity ~ Intercept + group + CDI [or WAIS] + group*CDI [or WAIS]). We found no significant main effect of the CDI or WAIS term, nor a significant CDI*group or WAIS*group effect. It is important to note, however, that the CDI scores were largely skewed with most subjects reporting a score of zero (see figure below) and is thus not a suitable distribution for generalizing to potential contributions of current depressed mood on functional connectivity of these regions. The multivariate effects and pairwise comparisons for each MANCOVA are reported in the tables below.



Multivariate Tests (CDI MANCOVA)

Model Term	F Statistic	Sig.
Intercept	31.26	<0.001
Group	7.65	<0.001
CDI	1.46	0.18
Group * CDI	0.83	0.69

Group Pairwise Comparisons with CDI as a Covariate							
		Comparison P-Value					
		CTL		CVT		RES	
Seed	Cluster	CVT	RES	CTL	RES	CTL	CVT
Left Amygdala	Left fusiform	0.18	1.00	0.18	<0.001	1.00	<0.001
	Right OFC	1.00	0.01	1.00	<0.001	0.01	<0.001
Right Amygdala	Left OFC	0.05	0.57	0.05	<0.001	0.57	<0.001
	Left ITG	0.19	1.00	0.19	0.003	1.00	0.003
	Right fusiform	0.19	1.00	0.19	<0.001	1.00	<0.001
Left Anterior Insula	Right anterior insula	0.01	0.97	0.01	0.001	0.97	0.001
	Right thalamus	0.01	0.14	0.01	0.16	0.14	0.16
	Right ITG	0.29	0.03	0.29	<0.001	0.03	<0.001
	Left ITG	0.31	0.16	0.31	<0.001	0.16	<0.001
	Right SFG	0.01	1.00	0.01	<0.001	1.00	<0.001
Left Dorsolateral Prefrontal Cortex	Left VLPFC	0.84	0.55	0.84	0.001	0.55	0.001
Right Dorsolateral Prefrontal Cortex	Right STG	0.18	1.00	0.18	0.001	1.00	0.001

Multivariate Tests (WAIS MANCOVA)		
Model Term	F Statistic	Sig.
Intercept	1.08	0.40
Group	1.27	0.21
WAIS	0.62	0.81
Group * WAIS	1.07	0.40

Group Pairwise Comparisons with WAIS as a Covariate							
		Comparison P-Value					
		CTL		CVT		RES	
Seed	Cluster	CVT	RES	CTL	RES	CTL	CVT
Left Amygdala	Left fusiform	0.84	0.01	0.84	0.001	0.01	0.001
	Right OFC	0.58	0.01	0.58	<0.001	0.01	<0.001
Right Amygdala	Left OFC	<0.001	0.31	<0.001	<0.001	0.31	<0.001
	Left ITG	0.02	0.73	0.02	0.001	0.73	0.001
	Right fusiform	0.01	0.15	0.01	<0.001	0.15	<0.001
Left Anterior Insula	Right anterior insula	<0.001	0.003	<0.001	0.001	0.003	0.001
	Right thalamus	<0.001	0.29	<0.001	0.04	0.29	0.04
	Right ITG	0.01	0.02	0.01	<0.001	0.02	<0.001
	Left ITG	0.87	0.001	0.87	<0.001	0.001	<0.001
	Right SFG	0.02	0.07	0.02	<0.001	0.07	<0.001
Left Dorsolateral Prefrontal Cortex	Left VLPFC	0.07	0.01	0.07	<0.001	0.01	<0.001
Right Dorsolateral Prefrontal Cortex	Right STG	0.68	0.04	0.68	0.002	0.04	0.002

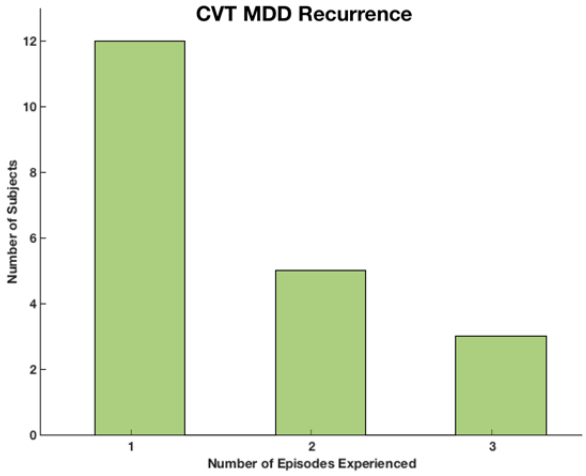
eAppendix 5. Additional Study Limitations, Alternative Explanations, and Future Directions

Given our sample size, we were unable to examine group differences in specific life events experienced across all groups. Future studies are needed to examine not only how life experiences contribute to neural mechanisms of resilience to depression, but also, and perhaps more importantly, how differences in interpretation of these experiences, may predict resilience or the onset of depression in adolescence. While there was no significant difference in reported number (p=0.77) or impact (p=0.19) of significant negative life events between the three groups, it is possible that with a larger sample the number and impact of negative life events would be statistically significant between at-risk resilient and depressed adolescents. It would however, be difficult to disentangle this from negative bias found both in in adolescents with depression.[6,7] An additional limitation is that the present study was designed to evaluate life experiences over the course of adolescence, and did not evaluate early life experiences which we know to be an important risk factor for adolescent depression.[8] Future studies examining the impact of early life stress, familial risk, and adolescent life events are needed to elucidate the contribution of adolescent experience to developing depression.

One particularly intriguing finding in our data was that maternal IQ scores (as measured by WAIS) was higher in the RES than in the CVT group. Although including maternal WAIS scores as a covariate did not change connectivity findings (see S4), they suggest that having a mother with higher IQ is a potential buffering factor of risk or a contributor to resilience. This possibility warrants further investigation.

It is also important to note that the emotion regulatory neural networks we investigated in the present study are changing over the course of development.[9-11] Further, given the well documented differences in these intrinsic networks between adolescents with and without history of MDD,[12] and that MDD-related effects on connectivity are associated with age of depression onset,[13] it is likely that MDD also affects the development of these neural networks in adolescents. Therefore, if the RES and CVT adolescents were at different neurodevelopmental stages, this could have influenced our findings. Future studies are needed to investigate the effects of MDD, as well as of antidepressant treatments, on neurodevelopmental changes over the course of adolescence.

Studies have implicated amygdala-OFC connectivity in course of illness such that recurrence of MDD correlates to decreased connectivity of these regions.[14] This may contribute to the reduced connectivity found in the CVT group. It is important to note, however, that our participants experienced relatively few discrete episodes of MDD (see figure below).



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