

1 Running Title: STRESS FEATURES, BRAIN NETWORKS, AND YOUTH MOOD SYMPTOMS

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4 **Shared and unique lifetime stressor characteristics and brain networks predict**
5 **adolescent anxiety and depression**

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27 prediction, anxiety, depression, adolescence

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Abstract

Background

Exposure to major life stressors and aberrant brain functioning have been linked to anxiety and depression, especially during periods of heightened functional brain plasticity, such as adolescence. However, it remains unclear if specific characteristics of major life stressors and functional network disruptions differentially predict anxiety and depression symptoms over time and, if so, whether they act independently or jointly.

Methods

We collected baseline lifetime stressor exposure data and resting-state functional magnetic resonance imaging data in a longitudinal sample of 107 adolescents enriched for anxiety and depressive disorders. We examined five stressor characteristics: physical danger, interpersonal loss, humiliation, entrapment, and role change/disruption. Anxiety and depression symptoms were assessed at baseline, 6-month and 12-month follow-ups. Linear mixed effect models tested if these stressor characteristics, functional connectivity within and between frontoparietal, default, and ventral attention networks, and their interactions differentially predicted anxiety and depression symptoms at 6-month and 12-month follow-ups.

Results

Greater lifetime severity of physical danger and humiliation prospectively predicted increased anxiety symptoms at both follow-ups, whereas greater lifetime entrapment severity prospectively predicted higher anxiety and depression symptoms. Only the effects of lifetime entrapment severity were robust to including within- and between-network functional connectivity metrics and other significantly predictive stressor characteristics. Lifetime entrapment severity more strongly predicted anxiety symptoms in youth with higher default network connectivity. Greater functional connectivity between frontoparietal and default networks prospectively predicted increased depression symptoms.

Conclusions

Taken together, these results underscore the critical importance of using stressor characteristics and functional connectivity jointly to study predictors for adolescent anxiety and depression.

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Introduction

Exposure to major life stressors is a strong risk factor for the onset and subsequent recurrence of affective disorders (1–5), especially in adolescence when there is increased brain plasticity and heightened vulnerability to the emergence of psychopathology (6–10). However, stressors come in many different forms and are diverse with respect to both their characteristics and associations with clinical symptoms (11,12). Results from large-scale, prospective cohort studies have suggested that certain characteristics of major life stressors may preferentially increase risk for specific clinical outcomes. For instance, stressors that involve devaluation of the self, such as interpersonal loss and humiliation, are theorized to preferentially heighten risk for depression (13–17). In contrast, stressors marked by a threat to one’s physical integrity, such as danger, are theorized to be stronger predictors of anxiety (13,15,16,18). Stressors characterized by feelings of failure without any means of escape, such as entrapment, predict both anxiety and depression (13,19). These patterns may be explained by the cognitive content-specificity hypothesis of anxiety and depression which posits that anxiety and depression can be discriminated by distinct forms of negative beliefs (20) and which has been partially supported (21,22). However, the potential neural mechanisms linking distinct stressor characteristics with adolescent anxiety and depression remain unknown.

Major life stressors can induce long-lasting effects on neurobiological functioning (23–27), particularly when they occur during childhood and adolescence (24,25,28–30). Prior neuroimaging studies have associated changes in brain functioning during monetary reward and emotional face tasks with exposure to life stressors (31–34). Altered brain functioning is also evident when considering resting-state functional connectivity (RSFC) patterns within and between the frontoparietal (35), default (36,37), and salience/ventral attention (38) networks among people who were exposed to early-life stress and trauma (28,39–42). Because altered connectivity within the frontoparietal, default and ventral attention networks are theorized to underlie dysfunctional cognitive (43–45), self-referential (44–46) and salience processing (44,47) respectively in anxiety and depression, it is possible that disruptions within and between these functional networks moderate the process of stress exposure leading to psychopathology. Although prior research has examined the extent to which intrinsic patterns of functional connectivity predict adolescent anxiety and depression following general stress exposure (48,49), these studies have not considered the interactions between neurobiological factors and life experience in differentiating anxiety and depression. Longitudinal associations linking distinct dimensions of life stressor exposure, network connectivity, and clinical symptoms thus remain to be established.

93 **Present Study**

94 To address these gaps in knowledge, we first conducted hypothesis-driven analyses
95 investigating if distinct characteristics of major life stressors occurring over the entire life course
96 differentially predicted anxiety and depression symptoms at 6-month and 12-month follow-ups.
97 We then explored if total lifetime severity of any stressor characteristics, RSFC metrics within
98 and between the frontoparietal, default, and ventral attention networks, and their interactions
99 predicted anxiety and depression symptoms at both follow-ups. These analyses were conducted
100 in a longitudinal sample of adolescents recruited from school-based and hospital-based child
101 treatment programs (50). Most participants had a current diagnosis of at least one anxiety or
102 depressive disorder at the time of baseline assessment. Based on the prior research
103 summarized above, we tested three hypotheses using linear mixed-effects (LME) models: (a)
104 greater lifetime severity of physical danger at baseline would differentially predict higher anxiety
105 symptoms at both follow-ups; (b) greater lifetime severity of interpersonal loss and humiliation at
106 baseline would differentially predict higher depression symptoms at both follow-ups; (c) greater
107 lifetime severity of entrapment at baseline would predict higher levels of both depression and
108 anxiety symptoms at both follow-ups. In further exploratory analyses, we assessed whether any
109 stressor characteristics and RSFC metrics within and between the three large-scale networks
110 predict anxiety/depression symptoms at two 6-month follow-ups, and whether these RSFC
111 metrics would moderate the strengths of prospective associations between stressor
112 characteristics and anxiety/depression symptoms.

113

Methods and Materials

114 **Participants**

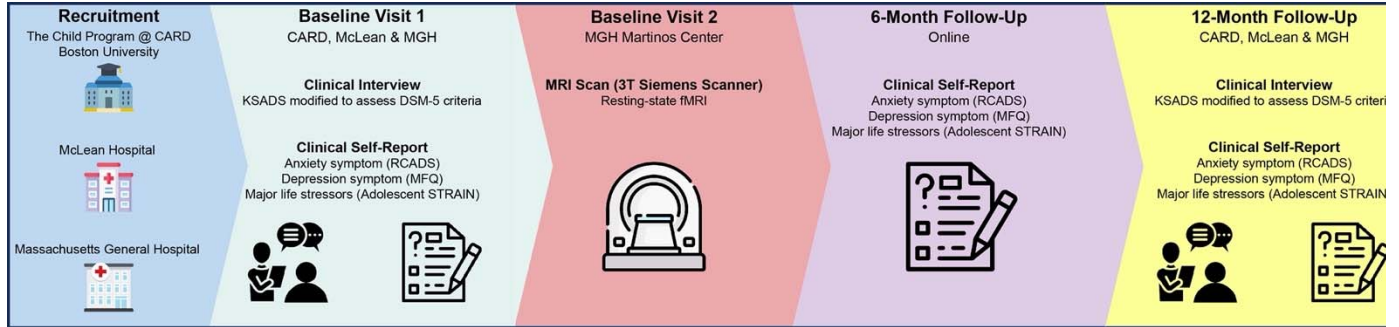
115 Data were collected from 215 adolescents ($M_{\text{age}} = 15.44$, range = 14-17 years old)
116 enrolled in the Boston Adolescent Neuroimaging of Depression and Anxiety (BANDA) study (50)
117 and assessed at 6-month intervals after the initial visit for up to 12 months. The present
118 analyses were restricted to data from the baseline, 6-month follow-up and 12-month follow-up
119 assessments. Resting-state functional magnetic resonance imaging (rsfMRI) data was available
120 for 203 participants at baseline (50). Out of these 203 adolescents, 107 had available self-
121 reported anxiety and depression symptoms at baseline, 6- and 12- month follow-up
122 assessments and were included in the final analytical sample (**Table 1; Figure 1**). Of these 107
123 participants, 62% ($n = 66$) had a current diagnosis of at least one anxiety or depressive disorder.
124 These diagnoses were given by a blinded, licensed clinical psychologist based on the
125 Diagnostic and Statistical Manual of Mental Health Disorders, 5th Edition (DSM-5; 51) and
126 reached moderate to substantial inter-rater agreement (50).

127 **Table 1.** Demographic characteristics for the final analytical sample ($n = 107$)

Baseline		
	<i>M/n</i>	<i>SD/%</i>
Demographics		
Age, mean \pm SD	15.42	0.87
Sex, (% female)	66	61.68
Diagnostic group	<i>n</i>	%
Anxiety ^a	38	35.51
Control	41	38.32
Depression ^b	28	26.17
Race/ethnicity	<i>n</i>	%
African American	2	1.87
Asian	2	1.87
Hawaiian	1	0.93
White	102	95.33
Lifetime severity of stressor characteristics ^c	<i>M</i>	<i>SD</i>
Entrapment	11.21	10.30
Humiliation	7.60	7.18
Interpersonal loss	10.59	8.48
Physical danger	4.50	5.50
Role change/disruption	5.82	5.44
Clinical symptoms	<i>M</i>	<i>SD</i>
Anxiety symptoms ^d	24.36	17.86
Depression symptoms ^e	15.74	14.82
Six-month follow-up		
Clinical symptoms	<i>M</i>	<i>SD</i>
Anxiety symptoms ^d	23.81	17.71
Depression symptoms ^e	16.84	15.43
Twelve-month follow-up		
Clinical symptoms	<i>M</i>	<i>SD</i>
Anxiety symptoms ^d	21.35	15.61
Depression symptoms ^e	14.62	14.13

128 Note: ^a Anxiety = having a current diagnosis of at least one anxiety disorder and no depressive
 129 disorder based on DSM-5. ^b Depression = having a current diagnosis of at least one depressive
 130 disorder based on DSM-5. ^c The total lifetime severity for each social-psychological stressor

131 characteristic based on self-reported acute and chronic stressors from the Stress and Adversity
132 Inventory for Adolescents (STRAIN). Entrapment: 0-26. Humiliation: 0-35. Interpersonal loss: 0-
133 50. Physical danger: 0-65. Role change/disruption: 0-70^d Anxiety symptoms was computed by
134 summing the four anxiety subscales (Separation Anxiety Disorder, Social Phobia, Generalized
135 Anxiety and Panic Disorder) from the Revised Children's Anxiety and Depression Scale
136 (RCADS), ranging from 0 to 93. ^e Depression symptoms was computed by the total Mood and
137 Feelings Questionnaire (MFQ) score ranging from 0 to 66.



138

139 **Figure 1.** Schematic representation of the Boston Adolescent Neuroimaging of Depression and
140 Anxiety (BANDA) study. Participants were recruited across three sites and underwent four study
141 sessions, including in-person clinician evaluations, self-report measures, neuroimaging, and
142 online and in-person follow-up assessments. The two clinical and imaging baseline visits
143 occurred within two weeks from each other. Participants completed an online batter of self-
144 report questionnaires 6 months after their second baseline visit. Finally, they went through on-
145 site clinical evaluations and completed an additional batter of self-report questionnaires 12
146 months after their second baseline visit. Picture icons were downloaded from www.freepik.com.

147 **Measures of social-psychological characteristics of life stressors**

148 Exposure to acute and chronic stressors occurring over the entire life course was
149 assessed using the Stress and Adversity Inventory for Adolescents (STRAIN) (52). The STRAIN
150 measured the total lifetime severity for each social-psychological stressor characteristic,
151 including physical danger, interpersonal loss, humiliation, entrapment, and role
152 change/disruption, for each participant based on their self-reported acute and chronic stressors
153 (see <https://www.strainsetup.com>). Examples of stressors linked to each of these five
154 characteristics have been described elsewhere (52). Total lifetime severity scores for these five
155 characteristics were used to predict the levels of anxiety and depression symptoms at two six-
156 month follow-up assessments. Brief definitions for these stressor characteristics are as follows
157 (13,16,53,54):

158 **Physical danger.** The degree of potential future threat to one's physical safety that
159 might occur as a result of the stressor.

160 **Interpersonal loss.** Diminution of a sense of connectedness or well-being as a result of
161 a real or realistically imagined loss of a person by death or by separation.

162 **Humiliation.** The likelihood of a stressor rendering a person devalued in relation to
163 others or self, usually due to rejection or a sense of core failure.

164 **Entrapment.** Ongoing circumstances of marked difficulty of at least 6 months' duration
165 that the individual can reasonably expect to persist or get worse, with little or no possibility that a
166 resolution can be achieved as a result of anything that might reasonably be done.

167 **Role change/disruption.** Life transitions that involve addition, subtraction or change of
168 social roles.

169 The STRAIN has demonstrated excellent test-retest reliability, good concurrent and
170 discriminant validity, as well as predictive utility in relation to various clinical outcomes including
171 anxiety and depression (52,55).

172

173 **Measures of anxiety and depression symptoms**

174 Self-reported anxiety symptoms in this study were assessed by the Revised Children's
175 Anxiety and Depression Scale (RCADS) (56). The RCADS has exhibited excellent internal
176 consistency, test-retest reliability, convergent and discriminant validity (56). The RCADS have
177 six subscales: separation anxiety disorder, social phobia, generalized anxiety, panic disorder,
178 obsessive-compulsive disorder and low mood. Total anxiety symptoms for each participant were
179 computed by summing the four anxiety subscales (Separation Anxiety Disorder, Social Phobia,
180 Generalized Anxiety and Panic Disorder).

181 Self-reported depression symptoms were assessed by the Mood and Feelings
182 Questionnaire (MFQ) (57,58). Prior studies have found the MFQ to be a reliable and valid
183 measure of adolescent depression in both clinical and non-clinical samples across different
184 populations (59–62). We used the total MFQ score as the measure of depression symptoms for
185 each participant.

186

187 **Neuroimaging**

188 *Data acquisition and processing*

189 Functional and anatomical neuroimaging data were acquired at baseline assessment
190 using a 3-Tesla Siemens Prisma scanner with a 2D multi-band gradient-recalled echo-planar
191 imaging (EPI) sequence. Each participant underwent four 5.8-minute resting-state functional
192 MRI (rsfMRI) runs, consisting of two runs with opposite phase encoding directions (AP/PA).
193 Each rsfMRI scan was acquired using 2mm isotropic resolution and a TR of 800ms. Full details
194 of the acquisition protocol can be found elsewhere (63).

195 The acquired rsfMRI data then went through the previously established Human
196 Connectome Project (HCP) minimal preprocessing pipelines (64). Minimally preprocessed T1w
197 images (64) went through bias- and distortion- correction using the *PreFreeSurfer* pipeline and
198 registered to MNI space. Cortical surface reconstruction was conducted using FreeSurfer v5.2
199 using recon-all adapted for high-resolution images. The reconstructed surface meshes were then
200 registered to the Conte69 surface template (65). During preprocessing, the fMRI data were first
201 corrected for gradient-nonlinearity-induced distortions. The fMRI time series in each frame were
202 then realigned to the single-band reference image to correct for subject motion using rigid body
203 transformation (66,67) with FSL. The resulting single-band image underwent spline interpolation
204 to correct for distortions and was then registered to the T1w image (68). The registered fMRI
205 volumes then went through nonlinear registration to the Conte69 surface template (65) and
206 mapped to the standard CIFTI grayordinate coordinate space. Further details about the HCP
207 minimal preprocessing pipelines of structural and functional images can be found elsewhere (64).
208 The minimally preprocessed fMRI data for each run were then denoised using ICA+FIX (69,70)
209 pre-trained using HCP_hp2000.RData and aligned across participants using MSMAll multi-modal
210 surface registration (71,72).

211

212 *Resting-state functional connectivity*

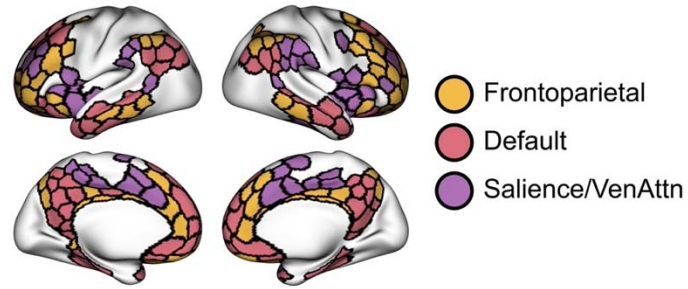
213 We defined 400 cortical regions of interest (ROIs) using a previously validated atlas (73).
214 Resting-state functional connectivity (RSFC) was measured by Pearson's r correlations

215 between the mean time series of each pair of ROIs. The average FC matrix across all runs in
216 each participant was computed after applying Fisher Z-transformation and used for subsequent
217 analyses.

218 Specifically, this study focused on RSFC within and between the frontoparietal, default,
219 and ventral attention networks (**Figure 2**) according to the 17-network solution (74) as
220 predictors of anxiety and depression symptoms levels at two 6-month follow-ups. Within-
221 network connectivity was assessed by averaging the pairwise RSFC of all regions assigned to
222 that network, resulting in three within-network connectivity values per individual. “Between”
223 network connectivity was assessed by computing the pair-wise correlations of each ROI in one
224 network (e.g., frontoparietal) to each ROI in the other network (e.g., default) and averaging
225 across them, resulting in three between network connectivity values per individual.

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228

229 **Figure 2.** The functional network organization of the human cerebral cortex revealed through
230 intrinsic functional connectivity. Colors reflect regions estimated to be within the same network.
231 Cortical regions-of-interest (ROIs) defined by Schaefer's parcellation (73) and assigned to
232 frontoparietal (yellow), default (red), and salience/ventral attention (purple) networks (74).

233 **Covariates**

234 The following covariates were dummy coded, converted to factors and entered into each
235 LME model: participant's race (White: Yes=1, No=0; African American: Yes=1, No=0; Asian:
236 Yes=1, No=0; Hawaiian: Yes=1, No=0), ethnicity (Hispanic: Yes=1, No=0), sex (female=0,
237 male=1), participant's current diagnostic group (Depression [having a current diagnosis of at
238 least one depressive disorder]: Yes=1, No=0; Anxiety [having a current diagnosis of at least one
239 anxiety disorder and no depressive disorder]: Yes=1, No=0; Control [having no current or
240 lifetime diagnosis of any psychiatric disorder]: Yes=1, No=0). We included current diagnosis of
241 depressive and anxiety disorders as covariates because there were significant differences in
242 depression and anxiety symptoms severity as well as total lifetime severity of stressor
243 characteristics across the three diagnostic groups (**Supplemental Result 1**). Participant's age
244 at scan was entered as a continuous covariate in each LME model. We additionally included
245 baseline depression symptoms in each LME model predicting anxiety symptoms and baseline
246 anxiety symptoms in each LME model predicting depression symptoms as covariates to parse
247 out unique predictors of each symptom (i.e., anxiety, depression) over time.

248

249 **Statistical analyses**

250 We constructed linear mixed-effect (LME) models using the *lme4* package in Rv4.2.0 (75)
251 with restricted maximum likelihood estimation (REML) to test our hypotheses. Each hypothesis-
252 driven LME model assessed if total lifetime severity for each stressor social-psychological
253 characteristic (i.e., physical danger, interpersonal loss, humiliation, entrapment) at baseline
254 predicted each symptom (i.e., anxiety, depression) at two 6-month follow-ups. We used the
255 *cAIC4* package v1.0 (76) to determine whether each of these models yielded lower conditional
256 Akaike information criterion (cAIC) when fitted with a random intercept or with a random slope
257 plus a random intercept. We also included covariates in each model to test if the fixed effects of
258 these stressor characteristics were robust to the inclusion of potential confounders. Continuous
259 predictors, covariates and outcome variables were standardized to make the beta estimates
260 more interpretable and to avoid multicollinearity.

261 Finally, we included the total lifetime severity of all stressor characteristics, all RSFC
262 metrics and their interactions in a single "unified LME model" predicting each symptom (i.e.,
263 anxiety, depression) at two 6-month follow-ups. In each unified LME model, we explored if total
264 lifetime severity of any stressor characteristics, any RSFC metrics within and between the
265 frontoparietal, default, and ventral attention networks, and their interactions emerged as
266 significant predictors of each symptom. Each unified LME model was fitted either with a random

267 intercept or with a random intercept plus a random slope. Potential confounders were included
268 in each unified LME model and all continuous variables were standardized. As an example, the
269 formula for the unified LME model predicting prospective anxiety symptoms with a random slope
270 and intercept was:

271
272 $AnxietySx \sim (PhysicalDanger + InterpersonalLoss + Humiliation + Entrapment +$
273 $RoleReversal) * (RSFCwithinFPN + RSFCwithinDN + RSFCwithinVAN + RSFCbetwFPN-DN +$
274 $RSFCbetwFPN-VAN + RSFCbetwDN-VAN) + DepressionDx + AnxietyDx +$
275 $BaselineDepressionSx + Race + Ethnicity + BaselineAge + sex + time + (1 + time | Subject).$

276
277 The unified LME model predicting prospective depression symptoms with only a random
278 intercept was:

279
280 $DepressionSx \sim (PhysicalDanger + InterpersonalLoss + Humiliation + Entrapment +$
281 $RoleReversal) * (RSFCwithinFPN + RSFCwithinDN + RSFCwithinVAN + RSFCbetwFPN-DN +$
282 $RSFCbetwFPN-VAN + RSFCbetwDN-VAN) + DepressionDx + AnxietyDx +$
283 $BaselineAnxietySx + Race + Ethnicity + BaselineAge + sex + time + (1 | Subject).$

284
285 Since total lifetime severity scores for the five stressor characteristics were highly
286 intercorrelated (**Supplemental Table 1**), as expected, the resulting unified LME models may
287 exhibit high multicollinearity ($VIF \geq 5$) despite standardization of predictor and outcome variables.
288 Hence, for each unified LME model, we started with including all five stressor characteristics,
289 iteratively removing different subsets of one to four stressor characteristics, rerunning the model
290 and recomputing cAIC. We selected the optimal subset of stressor characteristics yielding the
291 lowest conditional Akaike information criterion (cAIC) for each unified LME model. The
292 conditional R^2 captured by each optimal unified LME model was determined using the
293 *performance* package (77) in Rv4.2.0.

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Results

297 **Total lifetime severity of stressor characteristics differentially predicts prospective** 298 **anxiety and depression symptoms**

299 Across all hypothesis-driven LME models predicting anxiety symptoms at two 6-month
300 follow-ups, the models fitted with random slopes plus random intercepts yielded lower cAICs
301 than the corresponding models fitted with only random intercepts (**Supplemental Table 3**). On
302 the other hand, all hypothesis-driven LME models predicting prospective depression symptoms
303 were singular when fitted with both random slopes and random intercepts (**Supplemental Table**
304 **4**). Therefore, we will focus on results from LME models fitted with random slopes and
305 intercepts when prospective anxiety symptoms is the predicted variable and focus on results
306 from LME models fitted with only random intercepts when prospective depression symptoms is
307 the predicted variable.

308 Consistent with our hypothesis that lifetime physical danger severity is a specific
309 predictor of anxiety, the LME analyses revealed that greater lifetime severity of physical danger
310 at baseline predicted higher anxiety ($\beta = 0.25$, $p = 3.63 \times 10^{-5}$; **Supplemental Table 4**) but not
311 depression symptoms ($\beta = -0.0079$, $p = 0.90$; **Supplemental Table 5**) at follow-up, after
312 accounting for potentially confounding covariates.

313 Failing to support our second hypothesis theorizing interpersonal loss as a specific
314 predictor of depression, the second set of hypothesis-driven LME models indicated that the
315 main effects of lifetime severity of interpersonal loss on both anxiety ($\beta = 0.039$, $p = 0.55$;
316 **Supplemental Table 6**) and depression symptoms were not robust to the inclusion of
317 potentially confounding covariates ($\beta = 0.057$, $p = 0.29$; **Supplemental Table 7**). These results
318 suggest that individual differences in the lifetime severity of interpersonal loss does not predict
319 prospective depression symptoms above and beyond anxiety symptoms and depression
320 diagnosis at baseline.

321 Contrary to our third hypothesis, the third set of hypothesis-driven LME models revealed
322 that greater lifetime severity of humiliation at baseline predicted higher anxiety ($\beta = 0.31$, $p =$
323 2.56×10^{-6} ; **Supplemental Table 8**) but not depression symptoms ($\beta = 0.034$, $p = 0.62$;
324 **Supplemental Table 9**) at follow-up, after accounting for potentially confounding covariates.
325 These data suggest that lifetime severity of humiliation may be a specific risk factor for anxiety
326 rather than depression.

327 Finally, the fourth set of hypothesis-driven LME models revealed that greater total
328 lifetime severity of entrapment predicted both anxiety ($\beta = 0.39$, $p = 5.20 \times 10^{-8}$; **Supplemental**
329 **Table 10**) and depression symptoms at two 6-month follow-ups, after accounting for potentially

330 confounding covariates ($\beta = 0.15$, $p = 0.05$; **Supplemental Table 11**). These results suggest
331 that lifetime severity of entrapment may be a shared risk factor for both anxiety and depression.

332

333 **Total lifetime severity of stressor characteristics, large-scale brain networks and** 334 **symptoms of anxiety and depression**

335 Next, we sought to determine if prospective associations between stressor
336 characteristics and clinical symptoms are moderated by patterns of functional connectivity within
337 and between the large-scale brain networks theorized to underlie the expression of affective
338 illness. To this end, we used two unified LME models to explore if total lifetime severity of any
339 stressor characteristics, any RSFC metrics within and between the frontoparietal, default, and
340 ventral attention networks, and their interactions emerged as significant predictors of
341 prospective anxiety and depression symptoms. The unified LME model predicting prospective
342 anxiety symptoms yielded the lowest cAIC when fitted with both a random slope and intercept
343 and when total lifetime severity for physical danger and entrapment were entered as predictors
344 along with all RSFC metrics (**Supplemental Table 12**). The optimal unified model for anxiety
345 had a conditional R^2 of 0.873. The unified LME model predicting prospective depression
346 symptoms yielded the lowest cAIC when fitted with only a random intercept and when total
347 lifetime severity entrapment was the only stressor characteristic in the model (**Supplemental**
348 **Table 13**). The optimal unified model for depression had a conditional R^2 of 0.759. Below, we
349 focus on the results from the optimal unified LME models.

350 Results from the optimal unified model for anxiety revealed that total lifetime severity of
351 entrapment at baseline was positively associated with anxiety symptoms at two follow-up
352 assessments ($\beta = 0.36$, $p = 3.10 \times 10^{-4}$), and the association was stronger when RSFC within
353 the default network was higher (**Table 2; Figure 3A&C**). When considering depression, the
354 optimal unified model indicated that RSFC between the frontoparietal and default network
355 ($\beta = 0.18$, $p = 8.20 \times 10^{-4}$) and total lifetime severity of entrapment stressor exposure ($\beta = 0.17$,
356 $p = 0.05$) at baseline were positively associated with depression symptoms levels at two follow-
357 up assessments (**Table 3; Figure 3B&D**). These results demonstrate that entrapment severity
358 remained to be a shared predictor for both anxiety and depression even after accounting for
359 main and interaction effects involving within- and between-network RSFC metrics, further
360 supporting its importance in predicting both anxiety and depression.

361 **Table 2.** Results of unified LME models testing if anxiety symptoms at two 6-month follow-ups
 362 can be predicted from total lifetime severity of physical danger, total lifetime severity of
 363 entrapment, and RSFC within and between functional networks at baseline

Predictor	Estimate	SE	95% CI		t	p
			LL	UL		
wFPN FC	-0.057	0.065	-0.17	0.053	-0.87	0.39
wVAN FC	0.076	0.063	-0.029	0.18	1.22	0.23
wDN FC	-0.024	0.060	-0.13	0.082	-0.40	0.69
bFPN-DN FC	-0.12	0.070	-0.24	-0.0014	-1.71	0.091
bFPN-VAN FC	0.089	0.059	-0.0096	0.19	1.52	0.13
bDN-VAN FC	-0.023	0.053	-0.11	0.066	-0.43	0.67
Physical danger	0.083	0.086	-0.062	0.23	0.97	0.33
Entrapment	0.36	0.095	0.20	0.52	3.78	0.0031***
Baseline depression symptoms	0.41	0.093	0.25	0.57	4.42	3.14×10⁻⁵****
Diagnosis of Depression	-0.032	0.18	-0.34	0.28	-0.17	0.86
Diagnosis of Anxiety	0.46	0.13	0.24	0.67	3.59	0.00057****
White	0.016	0.51	-0.84	0.87	0.032	0.97
African American	0.19	0.62	-0.86	1.24	0.30	0.76
Asian	-0.060	0.62	-1.10	0.98	-0.097	0.92
Ethnic group	-0.28	0.20	-0.62	0.065	-1.36	0.18
Baseline age	0.072	0.054	-0.021	0.17	1.34	0.18
Sex	-0.30	0.11	-0.49	-0.11	-2.70	0.0085**
Time	-0.088	0.037	-0.16	-0.015	-2.37	0.020*
wFPN FC:Physical danger	0.17	0.094	0.0076	0.33	1.77	0.080
wFPN FC:Entrapment	-0.15	0.086	-0.30	-0.010	-1.80	0.076
wVAN FC:Physical danger	-0.029	0.069	-0.15	0.088	-0.42	0.68
wVAN FC:Entrapment	0.012	0.076	-0.12	0.14	0.15	0.88
wDN FC:Physical danger	-0.10	0.064	-0.22	0.0074	-1.63	0.11
wDN FC:Entrapment	0.27	0.077	0.14	0.40	3.52	0.00073****
bFPN-DN FC:Physical danger	-0.0039	0.12	-0.21	0.20	-0.033	0.97
bFPN-DN FC:Entrapment	-0.022	0.11	-0.21	0.16	-0.21	0.84
bFPN-VAN FC:Physical danger	-0.14	0.088	-0.29	0.0026	-1.65	0.10

bFPN-VAN FC:Entrapment	0.10	0.094	-0.058	0.26	1.07	0.29
bDN-VAN FC:Physical danger	0.045	0.086	-0.10	0.19	0.52	0.60
bDN-VAN FC:Entrapment	0.048	0.066	-0.063	0.16	0.73	0.47
Intercept	-0.024	0.51	-0.88	0.83	-0.047	0.96

364 Note. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$; **** $p < 0.001$. FC = functional connectivity. bFPN-DN =
365 between frontoparietal and default network, bDN-VAN = between default network and ventral
366 attention network. bFPN-VAN = between frontoparietal and ventral attention network.
367 wFPN = within frontoparietal network. wDN = within default network. wVAN = within ventral
368 attention network

369 **Table 3.** Results of the unified LME model testing if depression symptoms at two 6-month
 370 follow-ups can be predicted from total lifetime severity of entrapment and RSFC within and
 371 between functional networks at baseline

Predictor	Estimate	SE	95% CI		<i>t</i>	<i>p</i>
			LL	UL		
wFPN FC	0.089	0.065	-0.025	0.20	1.37	0.17
wVAN FC	-0.086	0.061	-0.19	0.021	-1.41	0.16
wDN FC	0.088	0.059	-0.015	0.19	1.50	0.14
bFPN-DN FC	0.18	0.067	0.064	0.30	2.71	0.0082**
bFPN-VAN FC	-0.049	0.056	-0.15	0.050	-0.87	0.39
bDN-VAN FC	0.0066	0.053	-0.087	0.10	0.12	0.90
Entrapment	0.17	0.086	0.023	0.32	2.02	0.046*
Baseline anxiety symptoms	0.45	0.091	0.29	0.61	4.98	3.35×10⁻⁶****
Diagnose of Depression	0.58	0.16	0.31	0.86	3.71	0.000372****
Diagnosis of Anxiety	-0.028	0.14	-0.27	0.22	-0.20	0.84
White	-0.55	0.51	-1.45	0.34	-1.08	0.28
African American	0.50	0.64	-0.62	1.61	0.78	0.44
Asian	-0.60	0.63	-1.71	0.52	-0.94	0.35
Ethnic group	0.25	0.21	-0.11	0.62	1.22	0.22
Baseline age	0.12	0.053	0.031	0.22	2.34	0.022*
Sex	-0.048	0.11	-0.25	0.15	-0.41	0.68
Time	-0.038	0.034	-0.11	0.029	-1.11	0.27
wFPN FC:Entrapment	-0.070	0.068	-0.19	0.048	-1.04	0.30
wVAN FC:Entrapment	-0.025	0.065	-0.14	0.089	-0.39	0.70
wDN FC:Entrapment	0.015	0.061	-0.092	0.12	0.25	0.80
bFPN-DN FC:Entrapment	0.056	0.086	-0.096	0.21	0.65	0.52
bFPN-VAN FC:Entrapment	-0.068	0.056	-0.17	0.031	-1.21	0.23
bDN-VAN FC:Entrapment	-0.0026	0.055	-0.098	0.093	-0.047	0.96
Intercept	0.39	0.51	-0.51	1.29	0.76	0.45

372 Note. **p* < 0.05; ***p* < 0.01; ****p* < 0.005; *****p* < 0.001. FC = functional connectivity. bFPN-DN =
 373 between frontoparietal and default network, bDN-VAN = between default network and ventral
 374 attention network. bFPN-VAN = between frontoparietal and ventral attention network.

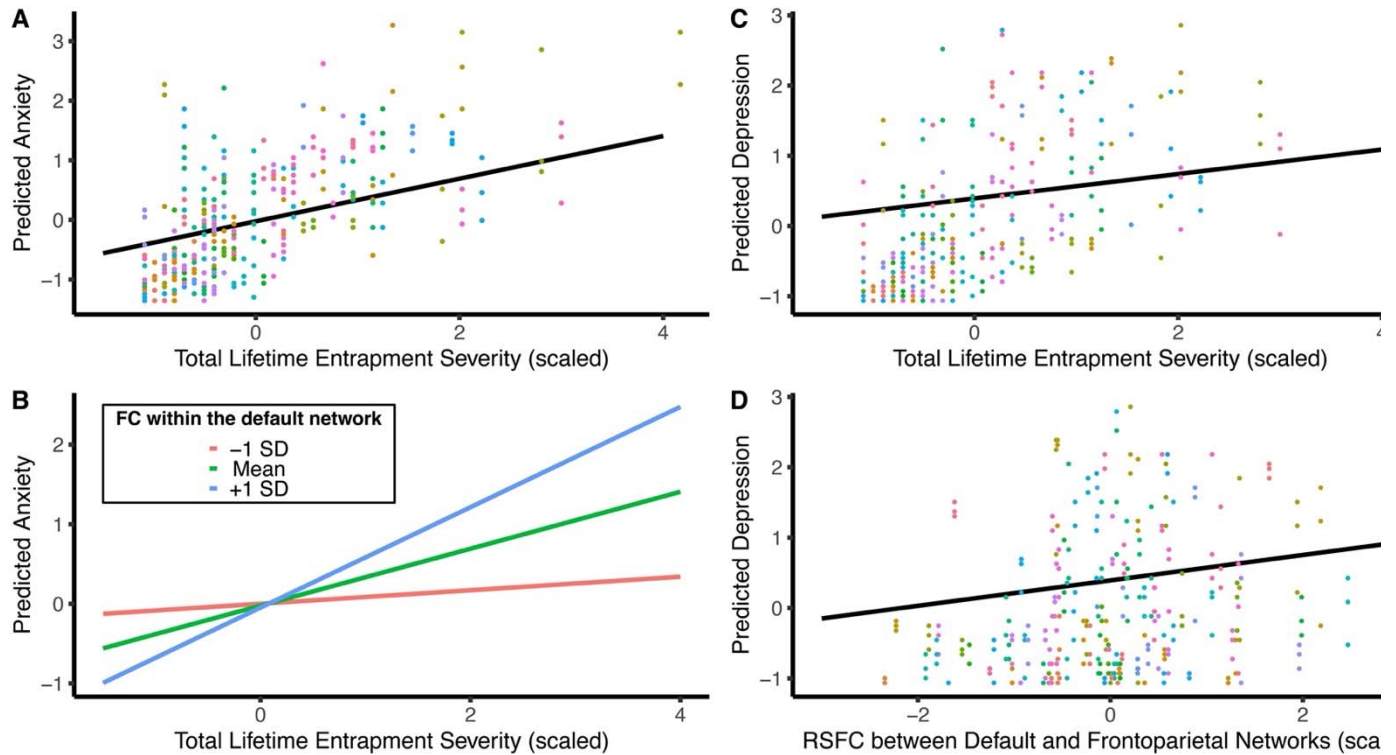
375 wFPN = within frontoparietal network. wDN = within default network. wVAN = within ventral

376 attention network

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381 **Figure 3.** (A) The association between total lifetime severity of entrapment and the sums of
382 marginal fit and conditional residuals from the fitted LME models predicting anxiety symptoms
383 depression symptoms at two 6-month follow-ups; (B) The association between total lifetime
384 severity of entrapment and anxiety symptoms at different levels of functional connectivity within
385 the default network. The association between (C) total lifetime severity of entrapment, (D)
386 functional connectivity between the frontoparietal and default networks and the sums of
387 marginal fit and conditional residuals from the fitted LME models predicting depression
388 symptoms at two 6-month follow-ups. Different colors represent different participants.

389

390

Discussion

391 Despite a wealth of prior research examining associations between stress, neurobiology
392 and internalizing psychopathology, it remains unknown if the lifetime severity of distinct life
393 stressor characteristics differentially predicts future anxiety and depression in adolescence, and
394 if such prospective associations are moderated by large-scale network connectivity. To
395 investigate, we acquired functional neuroimaging at baseline and tracked a sample of
396 adolescents longitudinally for one year, more than half of whom were currently diagnosed with at
397 least one depressive or anxiety disorder at time of initial assessment. We first tested our
398 hypotheses associating lifetime severity of specific stressor characteristics differentially with
399 anxiety or depression symptoms at two 6-month follow-up. We then explored if distinct stressor
400 characteristics and RSFC within and between large-scale networks acted independently or jointly
401 to predict prospective anxiety and depression symptoms.

402 Results from the hypothesis-driven LME models revealed that (a) higher total lifetime
403 severity of physical danger and humiliation predicted higher levels of anxiety but not depression
404 symptoms; (b) higher total lifetime severity of entrapment predicted higher levels of both anxiety
405 and depression symptoms; and (c) total lifetime severity of interpersonal loss predicted neither
406 anxiety or depression symptoms. Results from the exploratory unified LME models additionally
407 included fixed and interaction effects of RSFC metrics within and between large-scale functional
408 networks and showed that (a) the main effects of higher total lifetime severity of entrapment still
409 predicted higher levels of both anxiety and depression symptoms at the two 6-month follow-ups;
410 (b) more positive RSFC between the frontoparietal and the default networks uniquely predicted
411 higher levels of depression symptoms at the two 6-month follow-ups; and (c) the association
412 between total lifetime severity of entrapment and anxiety symptoms at the two 6-month follow-
413 ups was more pronounced (i.e., more positive) among adolescents who had more positive
414 RSFC within the default network. These results thus support the importance of including major
415 life stressors, as well as both RSFC within and between large-scale functional networks, in
416 models aiming to predict changes in anxiety and depression in adolescence over time.

417 The results from the hypothesis-driven LME models are consistent with the prior studies
418 suggesting that exposure to major life stressors characterized by danger, which implies threat to
419 one's physical integrity, is a specific risk factor for anxiety (13,15,16,18). However, these data
420 did not reveal unique associations between loss, humiliation, and depression, as has been
421 previously theorized (13–17). Such a discrepancy may have arisen from differences in sample
422 characteristics. For example, although most prior studies have focused on adults recruited from
423 the community, we used an adolescent sample, around 60% of whom were already diagnosed

424 with anxiety and depressive disorders at the time of baseline assessment. Indeed, having formal
425 diagnoses of anxiety and depressive disorders are strong predictors of prospective anxiety and
426 depression symptoms (**Supplemental Tables 5-12**) and may have obscured the associations
427 between loss, humiliation and depression. Nevertheless, the fixed effects of total lifetime
428 entrapment severity were not obscured by including anxiety and depression diagnoses in the
429 LME models predicting prospective anxiety and depression symptoms, implying that entrapment
430 severity predicts both anxiety and depression regardless of diagnostic status.

431 These results are consistent with prior studies implying entrapment as a shared risk
432 factor for both anxiety and depression (13,19). Exposure to entrapment, which refers to chronic
433 difficulties that are unlikely to be resolved, has been associated with the onset of depressive (53)
434 or mixed major depression-generalized anxiety episode (13). Self-reported feelings of
435 entrapment have been associated with longitudinal changes in anxiety and depression
436 symptoms at 1-year follow-up in clinically depressed and healthy adolescents (19). Results from
437 the present study are thus consistent with these findings by showing that higher total lifetime
438 severity of entrapment exposure was associated with higher levels of anxiety and depression
439 symptoms at two 6-month follow-up assessments, highlighting entrapment as the most central
440 shared risk factor for anxiety and depression among all stressor characteristics we examined.
441 More broadly, they are consistent with a stressor characteristics perspective on stress, which
442 argues that the effects of stressors on health are not uniform across different of stressors (77).

443 In turn, results from the unified LME model predicting anxiety symptoms showed that
444 higher total lifetime severity of entrapment exposure at baseline prospectively predicted even
445 higher anxiety symptoms at the follow-ups for among participants who had more positive RSFC
446 within the default network. A meta-analysis found converging evidence that hyperconnectivity
447 within the default network was associated with anxiety symptoms across multiple anxiety
448 disorders, including social anxiety, generalized anxiety and panic disorders (78). Findings from
449 this meta-analysis are consistent with our results, where anxiety symptoms were computed by
450 summing across subscales related to separation anxiety, social phobia, generalized anxiety and
451 panic disorder symptoms. A few other studies have found that more positive intra-network
452 RSFC within the default network in anxiety disorder (79,80). Aspects of the default network,
453 including the posterior cingulate and the precuneus, are hypothesized to support internally-
454 related cognition (81–83) such as rumination. Therefore, although speculative, participants
455 displaying hyperconnectivity within the default network may exhibit higher tendency to engage in
456 anxiety-related internal rumination and experience higher levels of anxiety symptoms over time
457 after exposure to stressful life events (84,85).

458 Finally, results from the unified LME model predicting depression symptoms showed that
459 total lifetime entrapment severity did not interact with any RSFC metric, suggesting that
460 entrapment severity and RSFC within and between functional networks independently predicted
461 prospective depression symptoms. The model also revealed a positive fixed effect of RSFC
462 between the frontoparietal and the default networks in predicting prospective depression
463 symptoms. This finding is consistent with prior studies finding hyperconnectivity between the
464 default and the frontoparietal network in depressed adolescents and adults (45,86–88). Since
465 anti-correlation between the default and the frontoparietal networks is theorized to reflect
466 competition between internally-oriented and externally-oriented modes (89), the more positive
467 RSFC between the default and the frontoparietal networks may reflect difficulty disengaging
468 from internally-oriented thoughts to meet executive demands (90).

469

470 **Strengths and Limitations**

471 Several strengths and limitations of this work should be noted. In terms of strengths, we
472 leveraged a longitudinal sample of adolescents enriched for clinical diagnosis of depressive and
473 anxiety disorders with a narrow age range. This enabled us to examine associations between
474 exposure to major life stressors, neurobiology, and clinical symptoms during the developmental
475 stage characterized by heightened vulnerability to stress-related psychopathology (6–10). We
476 also assessed exposure to a variety of different types of theoretically relevant stressors across
477 the entire life course using distinct dimensions of social-psychological characteristics. Lastly, we
478 included all five social-psychological characteristics, all six RSFC metrics within and between the
479 three *a priori* functional networks, as well as the potential confounding variables into the same
480 LME model when predicting anxiety/depression symptoms at follow-up. This ensures that any
481 prospective association between a stressor characteristic or RSFC metric and clinical symptom
482 is robust to the inclusion of other inter-correlated stressor characteristics or RSFC metrics.

483 Several limitations should also be noted. First, the sample was relatively small, which
484 limits the statistical power to detect the complex associations between stressful life event
485 exposure, RSFC patterns, and clinical symptoms. Although this is a common issue with richly-
486 phenotyped, longitudinal datasets involving clinical samples, findings from the present study
487 should be validated by larger samples in future studies. Since the fMRI protocol of the current
488 dataset was harmonized with other HCP studies (63), other HCP datasets may provide valuable
489 resources for this purpose. Second, the vast majority (95.33%) of participants were White, and
490 additional research is needed to examine the generalizability of these findings to other
491 populations and demographic groups. Third, considering the limited sample size, our

492 hypothesis-driven analyses focused on RSFC within and between the default, frontoparietal and
493 ventral attention networks. RSFC involving other functional networks such as the dorsal
494 attention and the limbic networks as well as the subcortical structures such as the amygdala
495 have also been associated with anxiety and depression (45,91–94), and future high-powered
496 analyses would benefit from a whole-brain approach. Fourth, although we included a number of
497 covariates such as age, race and ethnicity, baseline symptoms, and diagnostic status in our
498 LME models to ensure that our findings could not be explained by these confounders, other
499 potential confounders such as medication use and family history of psychopathology were
500 unavailable in this dataset and may be relevant.

501

502 **Conclusion**

503 Through the use a longitudinal sample of adolescents, over half of whom met clinical
504 cut-offs for at least one depressive or anxiety disorder, the present analyses demonstrate that
505 greater total lifetime severity of entrapment exposure predicts higher levels of in anxiety and
506 depression symptoms at two subsequent 6-month follow-up time points. Lifetime entrapment
507 exposure prospectively predicted anxiety symptoms in participants with more positive default
508 network connectivity. Heightened RSFC between the frontoparietal and the default network
509 specifically predicted higher levels of depression symptoms at the two 6-month follow-ups.
510 These results imply that among all characteristics of major life stressors that we examined using
511 the STRAIN, entrapment may be the most important risk factor for both anxiety and depression.
512 Our results also suggest that more positive connectivity in the default network may be a specific
513 risk factor for anxiety when an individual is exposed to entrapment, and that more positive
514 connectivity between the frontoparietal and default network may be a specific risk factor for
515 depression.

516

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Disclosures

The authors declare no conflicts of interest with respect to this work.

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