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

Shared and unique lifetime stressor characteristics and network connectivity predict adolescent anxiety and depression

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Key Words: Major life stressor characteristics, resting-state functional networks, longitudinal prediction, anxiety, depression, adolescence

Abstract

Background

Exposure to major life stressors and aberrant brain functioning have been related to anxiety and depression, especially during adolescence. However, whether these associations differ based on the specific characteristics of the stressors experienced, and/or the functional networks engaged, remains unclear.

Methods

We used baseline lifetime stressor exposure and resting-state functional magnetic resonance imaging data from a longitudinal sample of 150 adolescents enriched for anxiety and depressive disorders. We examined the cumulative lifetime stressor frequency and severity of five stressor characteristics: physical danger, interpersonal loss, humiliation, entrapment, and role change/disruption. Anxiety and depression symptoms were assessed at three time points: baseline, 6-month and 12-month follow-ups. Linear mixed-effect models tested if the lifetime frequency and severity of these stressor characteristics and functional connectivity within and between frontoparietal, default, and ventral attention networks at baseline predicted anxiety and depression symptoms at three time points.

Results

Lifetime frequency and severity of humiliation and entrapment predicted both anxiety and depression symptoms. Lifetime frequency and severity of entrapment exposures predicted anxiety and depression symptoms after accounting for baseline depression and anxiety symptoms, respectively. Resting-state functional connectivity between default, frontoparietal and ventral attention networks did not predict either anxiety or depression symptoms after correcting for multiple comparisons.

Conclusions

Our study highlights lifetime exposures to humiliation and entrapment stressors as central stressor characteristics predictive of prospective anxiety and depression symptoms in adolescence. Our results also suggest that resting-state functional connectivity within and between default, frontoparietal and ventral attention networks may be relatively weak predictors of prospective anxiety and depression symptoms in adolescence.

Introduction

Exposure to major life stressors is a strong risk factor for the onset and subsequent recurrence of affective disorders (Faravelli & Pallanti, 1989; Francis et al., 2012; Kendler et al., 1999; Kessler, 1997; Miloyan et al., 2018), especially in adolescence when there is increased brain plasticity and heightened vulnerability to the emergence of psychopathology (Casey et al., 2008; March-Llanes et al., 2017; Merikangas et al., 2010, 2010; Paus et al., 2008). However, stressors come in many different forms and are diverse with respect to both their characteristics and associations with mental health outcomes (Bonanno et al., 2023; Cohen et al., 2019; A. H. Lee et al., 2025; Slavich, 2019). Results from large-scale, prospective cohort studies have suggested that exposures to certain characteristics of major life stressors may preferentially increase risk for specific clinical outcomes such as anxiety and depression. For instance, stressor characteristics that involve devaluation of the self, such as interpersonal loss and humiliation, are theorized to preferentially heighten risk for depression (Asselmann et al., 2015; Farmer & McGuffin, 2003; Finlay-Jones & Brown, 1981; Keller et al., 2007; Kendler et al., 2003). In contrast, stressor characteristics marked by a threat to one's physical integrity, such as danger, are theorized to be stronger predictors of anxiety (Asselmann et al., 2015; Ayazi et al., 2014; Finlay-Jones & Brown, 1981; Kendler et al., 2003). Stressors characterized by feelings of failure without any means of escape, such as entrapment, predict both anxiety and depression (Griffiths et al., 2014; Kendler et al., 2003). Although distinct stressor characteristics are not mutually exclusive from each other (e.g. a stressor can be both dangerous and humiliating), prior studies have often examined each stressor characteristic in isolation. Therefore, the *unique contributions* of each stressor characteristics to the prediction of anxiety and depression symptoms on top of each other remains unclear. Furthermore, very few studies examined the associations between lifetime stressor exposures and psychopathology in adolescence.

With respect to the brain, prior studies have linked altered brain functioning with anxiety and depression in early life. Specifically, resting-state functional connectivity (RSFC) within and between the frontoparietal, default and ventral attention networks, which are theorized to underlie dysfunctional executive (Cole et al., 2014; Kaiser et al., 2015; Menon, 2011; Williams & Goldstein-Piekarski, 2020; Xu et al., 2019; Z. Zhang et al., 2025), self-referential (Berman et al., 2011; Kaiser et al., 2015; Menon, 2011; Williams & Goldstein-Piekarski, 2020; Xu et al., 2019; Z. Zhang et al., 2025) and salience processing (Manoliu et al., 2014; Menon, 2011; Williams & Goldstein-Piekarski, 2020; Xu et al., 2019) respectively, have been associated with both anxiety and depression in pre-adolescent children and adolescents (Ho et al., 2015; Pawlak et al., 2022; Perino et al., 2021; Rzepa & McCabe, 2018; Sievertsen et al., 2025; Willinger et al., 2024).

However, only a few studies have examined RSFC correlates of anxiety and depression symptoms using longitudinal samples of pre-adolescent children and adolescents (Connolly et al., 2017; Huang et al., 2023; Jalbrzikowski et al., 2017; Jin et al., 2020; Lopez et al., 2018; Pawlak et al., 2022; Qu et al., 2021; Strikwerda-Brown et al., 2014). Therefore, it remains unclear if certain RSFC patterns may precede changes in anxiety and depression symptoms during these critical developmental periods.

Present Study

To address these gaps in knowledge, we first investigated if lifetime exposures (self-reported number of exposures [henceforth referred as “frequency”] and subjective severity ratings [henceforth referred as “severity”]) to any characteristics of major life stressors assessed at baseline predicted anxiety and depression symptoms at each of the three time points—baseline, 6-month and 12-month follow-up assessments. We then analyzed if any RSFC metric within and between the frontoparietal, default, and ventral attention networks assessed at baseline predicted anxiety and depression symptoms at these three time points. These analyses were conducted using linear mixed-effects (LME) models in a longitudinal sample of adolescents recruited from school-based and hospital-based child treatment programs (Hubbard et al., 2024). Most participants had a current diagnosis of at least one anxiety or depressive disorder at the time of baseline assessment. Our results showed that lifetime frequency and severity of humiliation and entrapment stressors predicted both anxiety and depression symptoms over time. Furthermore, lifetime frequency and severity of entrapment exposures are differentially associated with prospective anxiety and depression symptoms, respectively. These findings indicate that among all stressor characteristics we assessed, humiliation and entrapment exposures are the strongest predictors of anxiety and depression in adolescence. Whether such exposures are differentially associated with specific mental health outcomes may depend on the exact measure (frequency or severity) used. Although our study showed that RSFC within the default network, between default and frontoparietal networks and between ventral attention and frontoparietal networks predicted prospective anxiety symptoms, the main effects of these associations did not survive the false discovery rate (FDR) corrections. These findings indicate that RSFC within and between the default, frontoparietal, and ventral attention networks may have limited predictability for prospective anxiety and depression symptoms in adolescence.

Methods and Materials

Participants

Data were collected from 215 adolescents (M_{age} = 15.44, range = 14-17 years old) enrolled in the Boston Adolescent Neuroimaging of Depression and Anxiety (BANDA) study (Hubbard et al., 2024) and assessed at 6-month intervals after the initial visit for up to 12 months. The present analyses were restricted to data from the baseline, 6-month follow-up and 12-month follow-up assessments. Resting-state functional magnetic resonance imaging (rsfMRI) data were available for 202 participants at baseline (Hubbard et al., 2024). Out of these 202 adolescents, 150 had available behavioral measures of interest at baseline, 6- and 12- month follow-up assessments and were included in the final sample for statistical analyses involving stressor characteristics and symptom measures (**Table 1**). Of these 150 participants, 65% (*n* = 98) had a current diagnosis of at least one anxiety or depressive disorder. Diagnostic group of each participant was given by a blinded, licensed clinical psychologist based on the Diagnostic and Statistical Manual of Mental Health Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013) and reached moderate to substantial inter-rater agreement (Hubbard et al., 2024).

Table 1. Demographic characteristics for the final analytical sample (*n* = 150)

	Baseline	
Demographics	*M/n*	*SD/%*
Age	15.44	0.85
Sex, (% female)	92	61.33
Mean parental education [a]	6.11	1.27
Diagnostic group	*n*	*%*
Anxiety [b]	58	38.67
Control	52	34.67
Depression [c]	40	26.67
Race	*n*	*%*
African American	3	2.00
Asian	3	2.00
Hawaiian	1	0.67
White	121	80.67
Ethnicity	*n*	*%*
Hispanic	11	7.33
Lifetime frequency of stressor characteristics	*M*	*SD*
Entrapment	4.36	3.18
(Range: 0-14; Possible range: 0-28)		
Humiliation	5.85	4.60
(Range: 0-20; Possible range: 0-40)		
Interpersonal loss	5.08	3.92
(Range: 0-20; Possible range: 0-61)		
Physical danger	1.98	2.18
(Range: 0-10; Possible range: 0-46)		
Role change/disruption	2.99	2.47
(Range: 0-15; Possible range: 0-24)		
Lifetime severity ratings of stressor characteristics	*M*	*SD*
Entrapment	13.65	12.01
(Range: 0-54; Possible range: 0-95)		
Humiliation	8.88	7.92
(Range: 0-36; Possible range: 0-60)		

Interpersonal loss	12.09	9.57
(Range: 0-45; Possible range: 0-85)		
Physical danger	5.87	6.81
(Range: 0-38; Possible range: 0-60)		
Role change/disruption	7.20	6.51
(Range: 0-32; Possible range: 0-60)		
Clinical symptoms	*M*	*SD*
Anxiety symptoms	26.05	18.24
(Range: 0-73; Possible range: 0-93)		
Depression symptoms	16.84	15.28
(Range: 0-56; Possible range: 0-66)		
Six-month follow-up		
Clinical symptoms	*M*	*SD*
Anxiety symptoms	24.86	17.51
(Range: 0-79; Possible range: 0-93)		
Depression symptoms	17.14	14.60
(Range: 0-58; Possible range: 0-66)		
Twelve-month follow-up		
Clinical symptoms	*M*	*SD*
Anxiety symptoms (0-93)	21.72	15.24
(Range: 0-62; Possible range: 0-93)		
Depression symptoms (0-66)	14.95	13.90
(Range: 0-53; Possible range: 0-66)		

Note: [a] Mean parental education = the average of the highest education degree achieved across both parents for each subject. [b] Anxiety = having a current diagnosis of at least one anxiety disorder and no depressive disorder based on DSM-5. [c] Depression = having a current diagnosis of at least one depressive disorder based on DSM-5.

Measures of social-psychological characteristics of life stressors

At the baseline assessment, the Stress and Adversity Inventory for Adolescents (STRAIN; Slavich et al., 2019) assessed each participant's total lifetime frequency and severity ratings of exposures to five social-psychological stressor characteristics—physical danger, interpersonal loss, humiliation, entrapment, and role change/disruption—by quantifying both the frequency and subjective severity ratings of self-reported acute and chronic stressors across the life course (see https://www.strainsetup.com). Examples of stressors linked to each of these five characteristics have been described elsewhere (Slavich et al., 2019). The mean lifetime frequency and severity of each stressor characteristic within each diagnostic group at baseline assessment are illustrated in **Supplementary Figure 1**. Self-reported severity ratings is a good complementary measure to frequency of major life stressors because subjective ratings do not assume that all stressors are perceived equally by all individuals and may thus index important individual differences in stress vulnerability (Shields et al., 2023). Total lifetime frequency and severity for these five characteristics were used to predict the levels of anxiety and depression symptoms at each of the three time points (baseline, 6-month and 12-month follow-up assessments). Brief definitions for these stressor characteristics are as follows (Brown et al., 1995; Finlay-Jones & Brown, 1981; Kendler et al., 2003; Slotter & and Walsh, 2017):

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

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

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

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

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

The STRAIN has demonstrated excellent test-retest reliability, good concurrent and discriminant validity, as well as predictive utility in relation to various clinical outcomes including anxiety and depression (Slavich et al., 2019; Slavich & Shields, 2018).

Measures of anxiety and depression symptoms

For each participant, anxiety and depression symptoms were assessed at three time points: baseline, 6-month and 12-month follow-ups. The mean anxiety and depressive symptoms within each diagnostic group at each of the three time points is illustrated in **Supplementary Figure 2**.

Self-reported anxiety symptoms were assessed by the Revised Children's Anxiety and Depression Scale (RCADS; Chorpita et al., 2000). The RCADS has exhibited excellent internal consistency, test-retest reliability, convergent and discriminant validity (Chorpita et al., 2000). The RCADS have six subscales: separation anxiety disorder, social phobia, generalized anxiety, panic disorder, obsessive-compulsive disorder and low mood. Total anxiety symptoms for each participant were computed by summing the four anxiety subscales (Separation Anxiety Disorder, Social Phobia, Generalized Anxiety and Panic Disorder).

Self-reported depression symptoms were assessed by the Mood and Feelings Questionnaire (MFQ; Angold et al., 1995; Costello & Angold, 1988). Prior studies have found the MFQ to be a reliable and valid measure of adolescent depression in both clinical and non-clinical samples across different populations (Burleson Daviss et al., 2006; Sund et al., 2001; Thabrew et al., 2018; Wood et al., 1995). We used the total MFQ score as the measure of depression symptoms for each participant.

Neuroimaging

Data acquisition and processing

Functional and anatomical neuroimaging data were acquired at baseline assessment using a 3-Tesla Siemens Prisma scanner with a 2D multi-band gradient-recalled echo-planar imaging (EPI) sequence. Each participant underwent four 5.8-minute resting-state functional MRI (rsfMRI) runs, consisting of two runs with opposite phase encoding directions (AP/PA). Each rsfMRI scan was acquired using 2mm isotropic resolution and a TR of 800ms. Full details of the acquisition protocol can be found elsewhere (Siless et al., 2020).

The acquired rsfMRI data then went through the previously established Human Connectome Project (HCP) minimal preprocessing pipelines (Glasser et al., 2013). Minimally preprocessed T1w images (Glasser et al., 2013) went through bias- and distortion- correction using the *PreFreeSurfer* pipeline and registered to MNI space. Cortical surface reconstruction was conducted using FreeSurfer v5.2 using recon-all adapted for high-resolution images. The reconstructed surface meshes were then registered to the Conte69 surface template (Van Essen et al., 2012). During preprocessing, the fMRI data were first corrected for gradient-nonlinearity-induced distortions. The fMRI time series in each frame were then realigned to the single-band

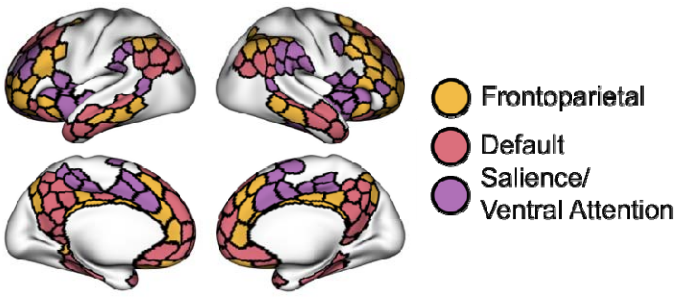
reference image to correct for subject motion using rigid body transformation (Jenkinson et al., 2002; Jenkinson & Smith, 2001) with FSL. The resulting single-band image underwent spline interpolation to correct for distortions and was then registered to the T1w image (Greve & Fischl, 2009). The registered fMRI volumes then went through nonlinear registration to the Conte69 surface template (Van Essen et al., 2012) and mapped to the standard CIFTI grayordinate coordinate space. Further details about the HCP minimal preprocessing pipelines of structural and functional images can be found elsewhere (Glasser et al., 2013). The minimally preprocessed rsfMRI data for each run were then denoised using ICA+FIX (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014) pre-trained using HCP_hp2000.RData and aligned across participants using MSMAll multi-modal surface registration (Glasser et al., 2016; Robinson et al., 2014). The ICA-FIXed rsfMRI data were further processed by detrending and regressing out the 12 motion parameters within each run using customized Python code. Out of the 202 participants with available rsfMRI data, we excluded participants (n = 51) if their mean framewise displacement (Power et al., 2012) was greater than 0.30mm, if more than 20% of their volumes had FD > 0.30 mm, or if any single volume exceeded 5mm FD (Parkes et al., 2018; Satterthwaite et al., 2013). Consequently, our final sample for statistical analyses involving RSFC and symptom measures comprised 114 participants.

Resting-state functional connectivity

We defined 400 cortical regions of interest (ROIs) using the Schaefer's Parcellation (Schaefer et al., 2018). Within each of the 4 rsfMRI runs, resting-state functional connectivity (RSFC) was measured by Pearson's r correlations between the mean time series of each pair of ROIs. The average FC matrix across all runs in each participant was computed after applying Fisher Z-transformation and used for subsequent analyses.

Specifically, this study focused on RSFC within and between the frontoparietal, default, and ventral attention networks (**Figure 1**) according to the 17-network solution (Thomas Yeo et al., 2011) as predictors of anxiety and depression symptoms at three time points (baseline, 6-month follow-up and 12-month follow-up). Within-network connectivity was assessed by averaging the pairwise RSFC of all regions assigned to that network, resulting in three within-network connectivity values per individual. "Between" network connectivity was assessed by computing the pair-wise correlations of each ROI in one network (e.g., frontoparietal) to each ROI in the other network (e.g., default) and averaging across them, resulting in three between network connectivity values per individual.

Figure 1. The functional network organization of the human cerebral cortex revealed through intrinsic functional connectivity. Colors reflect regions estimated to be within the same network. Cortical regions-of-interest (ROIs) defined by Schaefer's parcellation (Schaefer et al., 2018) and assigned to frontoparietal (yellow), default (red), and salience/ventral attention (purple) networks (Thomas Yeo et al., 2011).



Covariates

The following covariates were dummy coded, converted to factors and entered into each LME model: participant's ethnicity (Hispanic: Yes=1, No=0), sex (female=0, male=1). The following covariates were continuous and entered into each LME model: The mean parental education (computed as the average of the highest education degrees across both parents), participant's age at baseline. We further included baseline depression symptoms in each LME model predicting anxiety symptoms and baseline anxiety symptoms in each LME model predicting depression symptoms as continuous covariates to parse out differential predictors of each symptom (i.e., anxiety, depression) over time.

Imputation of missing data

Missing values in the behavioral data were imputed using the *missForest* algorithm (Stekhoven & Bühlmann, 2012), an iterative imputation method based on random forest. The *missForest* algorithm was selected for its ability to impute both numeric and factor data and for its superior performance compared to 15 other common imputation algorithms as evaluated by the *missCompare* framework (Varga, 2020). Under the *missCompare* framework, 50 simulated datasets matching multivariate characteristics and missingness patterns of the original data were generated. The missing data in each simulated dataset were then imputed using a curated list of 16 algorithms. The computation time and imputation accuracy of each algorithm were hitherto assessed by calculating Root Mean Square Error (RMSE), Mean Absolute Error (MAE) and Kolmogorov-Smirnov (KS) values between the imputed and the simulated data points (**Supplementary Figure 3**). These metrics were compared under three conditions: Missing Completely At Random (MCAR), Missing At Random (MAR), and Missing Not At Random or Non-Ignorable (MNAR). Finally, post-imputation diagnostics, including visual examination of data distributions and stability of correlation coefficients between measures, before and after imputation, were examined, showing minimal impact of imputation (**Supplementary Figure 4**).

Statistical analyses

We constructed linear mixed-effect (LME) models with random intercepts using the *lme4* package in Rv4.2.0 (Bates et al., 2015) to assess if lifetime frequency and severity of any stressor characteristics and functional connectivity within and between frontoparietal, default, and ventral attention networks at baseline assessment predicted each symptom (i.e., anxiety, depression) at each of the three time points (baseline, 6-month and 12-month follow-up assessments). Each LME model used one of the following three sets of predictors: (a) total

lifetime frequency of five stressor characteristics [formula: $Symptom \sim PhysicalDangerFrequency + InterpersonalLossFrequency + HumiliationFrequency + EntrapmentFrequency + RoleDisruptionFrequency + BaselineAge + Sex + Ethnicity + MeanParentalEducation + Time + (1|SubjectID)$]; (b) total lifetime severity ratings of five stressor characteristics [formula: $Symptom \sim PhysicalDangerSeverity + InterpersonalLossSeverity + HumiliationSeverity + EntrapmentSeverity + RoleDisruptionSeverity + BaselineAge + Sex + Ethnicity + MeanParentalEducation + Time + (1|SubjectID)$]; and (c) each of the six RSFC metrics within and between the frontoparietal, default, and ventral attention networks [formula: $Symptom \sim RSFCwithinFPN$ (or $RSFCwithinDN, RSFCwithinVAN, RSFCbetwFPN\text{-}DN, RSFCbetwFPN\text{-}VAN, RSFCbetwDN\text{-}VAN$) $+ BaselineAge + Sex + Ethnicity + MeanParentalEducation + Time + (1|SubjectID)$] to predict anxiety or depression symptoms at each of the three time points, resulting in sixteen LME models in total. We accounted for covariates in each LME model to assess if the fixed effects of these stressor characteristics and RSFC metrics were robust to the inclusion of potential confounders. Continuous predictors and covariates were standardized to make the beta estimates more interpretable. We used the participant ID as the random intercept, meaning that the intercept estimates were allowed to vary across participants while the beta estimate for each predictor was constant across participants.

Despite the strong intercorrelations among the five stressor characteristics (*r*s > 0.50; **Supplemental Table 1**), LME models including all stressor characteristics as predictors showed variance inflation factors (VIFs) smaller than 5, demonstrating no multicollinearity issues. However, when the six RSFC metrics within and between the three functional networks were included as predictors in the same LME models, we observed moderate multicollinearity issues (4 < *VIF*s < 10). Hence, we entered these RSFC metric as separate predictors of anxiety and depression symptoms (*VIF*s < 2). Since the model residuals exhibit non-normality and heteroscedasticity (**Supplementary Figures 5-8**), square-root transformation was applied to the symptom variables to achieve normality and homoscedasticity (**Supplementary Figures 9-12**). Hence, all results presented and discussed in this manuscript are based on square-root transformations. For ease of interpretation, we back-transformed the beta coefficient associated with each bivariate association.

Results

Greater total lifetime frequency and severity of humiliation and entrapment exposures predict higher prospective anxiety and depression symptoms

We first used total lifetime frequency and severity ratings of all stressor social-psychological characteristics (i.e., physical danger, interpersonal loss, humiliation, entrapment, role change/disruption) at baseline to predict each symptom (i.e., anxiety, depression) at each of the three time points (baseline, 6-month and 12-month follow-up assessments). After accounting for lifetime frequency of four other stressor characteristics and other potential confounding covariates, greater total lifetime frequency of humiliation and entrapment exposures at baseline assessment prospectively predicted higher anxiety (Humiliation: $\beta = 0.35$, $\beta_{back-transformed} = 0.18$, $p_{uncorrected} = 0.0073$, $p_{FDR} = 0.018$; Entrapment: $\beta = 0.78$, $\beta_{back-transformed} = 0.42$, $p_{uncorrected} = 2.87 \times 10^{-7}$, $p_{FDR} = 1.44 \times 10^{-6}$, **Figure 2**) and depression (Humiliation: $\beta = 0.38$, $\beta_{back-transformed} = 0.20$, $p_{uncorrected} = 0.0042$, $p_{FDR} = 0.011$; Entrapment: $\beta = 0.77$, $\beta_{back-transformed} = 0.39$, $p_{uncorrected} = 1.15 \times 10^{-6}$, $p_{FDR} = 5.73 \times 10^{-6}$, **Figure 2**) symptoms.

Results from LME models assessing total lifetime severity of the five stressor characteristics as predictors showed similar patterns. After accounting for lifetime severity of four other stressor characteristics and other potential confounding covariates, greater humiliation and entrapment severity at baseline assessment prospectively predicted higher anxiety symptoms (Humiliation: $\beta = 0.47$, $\beta_{back-transformed} = 0.25$, $p_{uncorrected} = 0.0083$, $p_{FDR} = 0.021$; Entrapment: $\beta = 0.62$, $\beta_{back-transformed} = 0.33$, $p_{uncorrected} = 0.0019$, $p_{FDR} = 0.0095$, **Figure 3**). Although the prospective associations between the lifetime severity of both stressor characteristics and depression symptoms were also positive and significant before correcting for multiple comparisons, only the main effects of entrapment severity survived FDR corrections (Humiliation: $\beta = 0.39$, $\beta_{back-transformed} = 0.20$, $p_{uncorrected} = 0.035$, $p_{FDR} = 0.088$; Entrapment: $\beta = 0.86$, $\beta_{back-transformed} = 0.44$, $p_{uncorrected} = 5.76 \times 10^{-5}$, $p_{FDR} = 0.00029$, **Figure 3**).

Overall, these results show that both self-reported frequency and severity of exposures to humiliation and entrapment stressors predict prospective anxiety and depression symptoms at all three time points, suggesting that humiliation and entrapment may be the stressor characteristics most strongly related to anxiety and depression in adolescence.

Figure 2. Comparison of standardized β estimates (± 95% confidence intervals) from LME models predicting anxiety and depression symptoms at three time points from total lifetime frequency of five stressor characteristics at baseline assessment. The vertical dashed line represents $\beta = 0$. All LME models include a random intercept for each participant and adjust for potentially confounding covariates. Positive β estimates indicate that greater stressor frequency is associated with higher symptom scores. *: $q_{FDR} < 0.05$

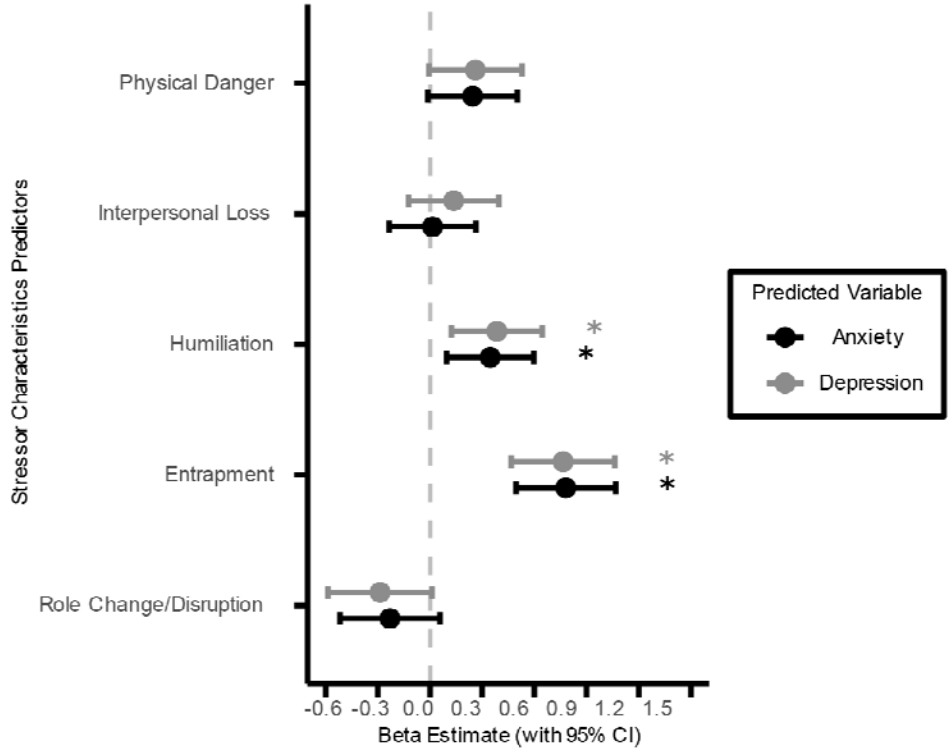
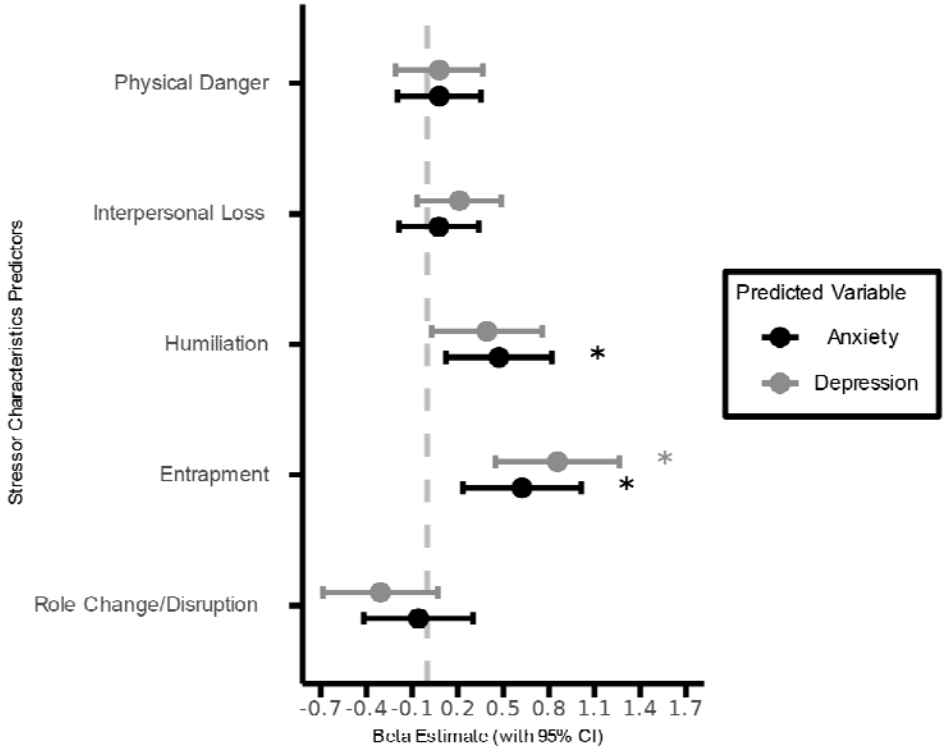


Figure 3. Comparison of standardized β estimates (± 95% confidence intervals) from LME models predicting anxiety and depression symptoms at three time points from total lifetime severity of five stressor characteristics at baseline assessment. The vertical dashed line represents $\beta = 0$. All LME models include a random intercept for each participant and adjust for potentially confounding covariates. Positive β estimates indicate that greater stressor severity is associated with higher symptom scores. *: $q_{FDR} < 0.05$



Total lifetime frequency and severity of entrapment differentially predict prospective anxiety and depression symptoms

We further tested if total lifetime frequency of any stressor social-psychological characteristic differentially predicted each symptom at three time points by including the other symptom measure at baseline assessment as an additional covariate in each LME model. We found that total lifetime frequency of entrapment stressors differentially predicted anxiety symptoms at all three time points ($\beta = 0.56,\ \beta_{back-transformed} = 0.30,\ p_{uncorrected} = 7.63 \times 10^{-5}$, $p_{FDR} = 0.00038$, **Supplementary Figure 13**), but not depression symptoms ($\beta = 0.37$, $\beta_{back-transformed} = 0.19,\ p_{uncorrected} = 0.010$, $p_{FDR} = 0.052$, **Supplementary Figure 13**).

We then conducted similar analyses using total lifetime severity of the five stressor characteristics as differential predictors of prospective anxiety and depression symptoms at three time points. After accounting for baseline depression symptoms, the main effects of humiliation and entrapment severity predicting prospective anxiety symptoms were not significant (Humiliation: $\beta = 0.29,\ \beta_{back-transformed} = 0.15,\ p_{uncorrected} = 0.086$; Entrapment: $\beta = 0.34,\ \beta_{back-transformed} = 0.18,\ p_{uncorrected} = 0.075$, **Supplementary Figure 14**). On the contrary, greater total lifetime severity of entrapment differentially predicted higher depression symptoms after including baseline anxiety symptoms as a covariate (Entrapment: $\beta = 0.50$, $\beta_{back-transformed} = 0.26,\ p_{uncorrected} = 0.0087$, $p_{FDR} = 0.043$, **Supplementary Figure 14**).

These results suggest that exposures to entrapment stressors may be a shared risk factor for both anxiety and depression in adolescence, but whether it is differentially associated with one or the other outcome depends on the measure used to assess such exposures. The number of entrapment exposures differentially predicted prospective anxiety symptoms, whereas the subjective severity rating of entrapment exposures differentially predicted prospective depression symptoms

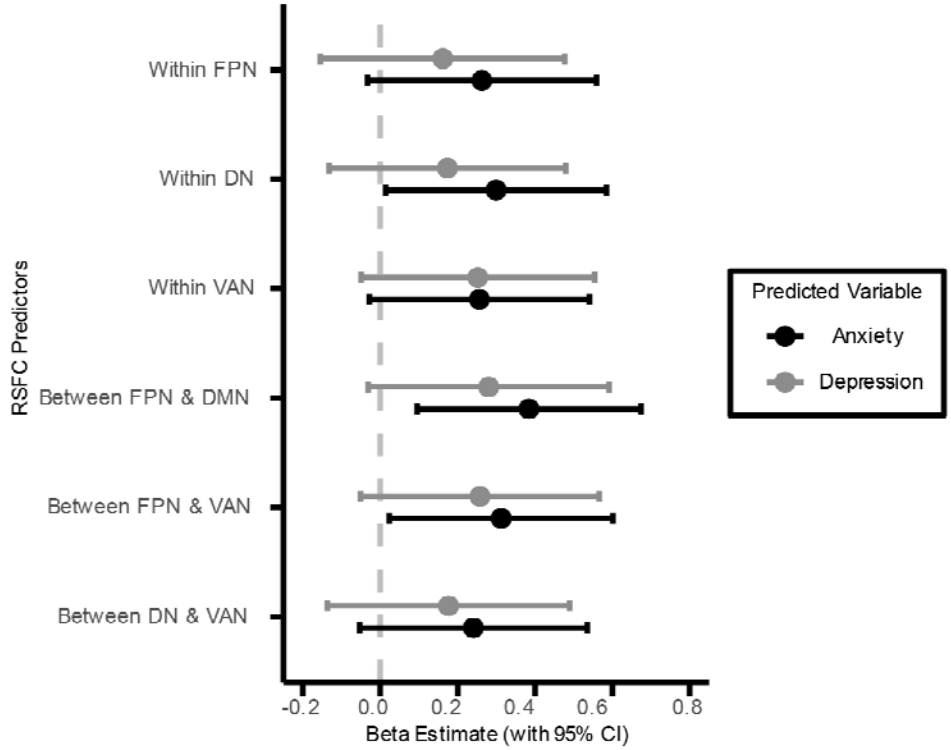
RSFC between frontoparietal, default and ventral attention networks does not predict prospective anxiety and depression symptoms

Finally, we assessed if RSFC within and between default, frontoparietal and ventral attention networks at baseline predicted each symptom (i.e., anxiety, depression) at each of the three time points (baseline, 6-month and 12-month follow-up assessments). These RSFC metrics were entered as separate predictors (see **Materials and Methods**). After accounting for potential confounding covariates, more positive/less negative RSFC within the default network ($\beta = 0.30,\ \beta_{back-transformed} = 0.16,\ p_{uncorrected} = 0.040$, $p_{FDR} = 0.079$, **Figure 4**), between frontoparietal and default networks ($\beta = 0.38,\ \beta_{back-transformed} = 0.21,\ p_{uncorrected} = 0.0097$,

$p_{FDR} = 0.058$, **Figure 2**), and between frontoparietal and ventral attention networks ($\beta = 0.31$, $\beta_{back-transformed} = 0.17$, $p_{uncorrected} = 0.034$, $p_{FDR} = 0.079$, **Figure 4**) predict higher prospective anxiety symptoms. However, the main effects of these associations failed to survive FDR corrections. All prospective associations between RSFC and depression symptoms did not reach statistical significance ($p_{uncorrected} > 0.05$, **Figure 4**).

We further assessed if RSFC within and between default, frontoparietal and ventral attention networks at baseline differentially predicted each symptom by accounting for the other symptom measure at baseline assessment in each LME model. As before, RSFC metrics were entered as separate predictors (see **Materials and Methods**). After accounting for potential confounding covariates and depression symptoms at time of baseline assessment, more positive/less negative RSFC between frontoparietal and default networks differentially predict higher prospective anxiety symptoms ($\beta = 0.22$, $\beta_{back-transformed} = 0.12$, $p_{uncorrected} = 0.046$, $p_{FDR} = 0.14$, **Supplemental Figure 15**). All other differential associations between RSFC and either symptom did not reach statistical significance ($p_{uncorrected} > 0.05$, **Supplemental Figure 15**). Taken together, our results suggest that RSFC between the frontoparietal, default, and ventral attention networks have limited predictive value for future anxiety and depression symptoms and do not differentiate between the two symptom outcomes.

Figure 4. Comparison of standardized β estimates (± 95% confidence intervals) from LME models predicting anxiety and depression symptoms at three time points from RSFC at baseline assessment. Six RSFC metrics are listed on the y-axis: within-network connectivity of the frontoparietal (FPN), default (DN), and ventral attention (VAN) networks, and between-network connectivity of FPN–DN, FPN–VAN, and DN–VAN. The vertical dashed line represents $\beta = 0$. All LME models include a random intercept for each participant and adjust for potentially confounding covariates. Positive β estimates indicate that greater RSFC is associated with higher symptom scores. *: $q_{FDR} < 0.05$



Discussion

Despite a wealth of prior research examining associations between stress exposures, neurobiology and internalizing psychopathology, it remains unknown if exposures to major life stressors with specific characteristics and exhibiting certain resting-state functional connectivity patterns predict future anxiety and depression symptoms in adolescence. To investigate, we acquired functional neuroimaging at baseline and tracked a sample of adolescents longitudinally for one year, more than half of whom were currently diagnosed with at least one depressive or anxiety disorder at time of initial assessment. We first tested if lifetime frequency and severity of exposures to five stressor characteristics at the time of baseline assessment predicted each symptom (anxiety, depression) at each of the three time points (baseline, 6-month and 12-month follow-up assessments). We then assessed if RSFC within and between the frontoparietal, default, and ventral attention networks at the time of baseline assessment predicted each symptom at the three time points.

Results from the LME models revealed that (a) higher total lifetime frequency and severity of humiliation and entrapment exposures at baseline predicted higher prospective anxiety symptoms; (b) higher total lifetime frequency of humiliation, total lifetime frequency and severity of entrapment exposures at baseline predicted higher prospective depression symptoms; (c) higher total lifetime frequency of entrapment exposure at baseline differentially predicted higher prospective anxiety symptoms above and beyond baseline depression symptoms; (d) higher total lifetime severity of entrapment exposure at baseline differentially predicted higher prospective depression symptoms above and beyond baseline anxiety symptoms; and (e) RSFC within and between frontoparietal, default, and ventral attention networks did not predict either anxiety or depression symptoms. These findings identify humiliation and entrapment as key stressor characteristics predicting future anxiety and depression symptoms in adolescence, while also suggesting that functional interactions among the frontoparietal, default, and ventral attention networks offer limited predictive value for these outcomes.

As opposed to prior studies suggesting that exposure to major life stressors characterized by danger is a specific risk factor for anxiety (Asselmann et al., 2015; Ayazi et al., 2014; Finlay-Jones & Brown, 1981; Kendler et al., 2003), we failed to find a significant association between lifetime exposures to physical danger and prospective anxiety symptoms. Moreover, our results did not reveal differential prediction of depressive symptoms by lifetime exposures to loss stressors, as has been previously shown (Asselmann et al., 2015; Farmer & McGuffin, 2003; Finlay-Jones & Brown, 1981; Keller et al., 2007; Kendler et al., 2003). Unlike prior studies that conducted bivariate analyses between specific stressor characteristics and mental health

outcomes, our study examined the *unique contributions* of each stressor characteristics to the prediction of anxiety and depression symptoms after accounting for all other stressor characteristics. Taken together, these results suggest that the differential association between physical danger/interpersonal loss and prospective anxiety/depression symptoms may be fully explained by the main effects of exposures to other stressor characteristics.

Our results are consistent with prior studies implying that exposures to humiliation and entrapment may contribute to both anxiety and depression (Griffiths et al., 2014; Kendler et al., 2003; Li et al., 2024; Taylor et al., 2011). Humiliation is theorized as perceived devaluation of the self arising from being unfairly harmed by others (Klein, 1991; D. A. Lee et al., 2001). Exposures to humiliation may heighten anxiety and depression by increasing vigilance towards potential future harm by others and viewing the self as worthless. Common examples of humiliation stressors include public shaming, peer bullying, social exclusion, rejection and revelation of infidelity. We found that humiliation frequency predicted both anxiety and depression symptoms over time, but differentially predicted neither. Humiliation severity at baseline predicted prospective anxiety symptoms, while the prospective associations between humiliation severity and depression symptoms failed to survive FDR corrections. On the other hand, entrapment refers to the feelings of being chronically trapped in a stressful situation despite having a strong desire to escape (Gilbert & Allan, 1998). Exposures to entrapment stressors may provoke anxiety and depression by fostering a sense of diminished control and reinforcing perceptions of futility, consistent with the concept of learned helplessness. Examples of entrapment stressors include persistent food and financial insecurity, unsafe housing and overwhelming demands at work or school. We found that entrapment frequency and severity predicted both anxiety and depression symptoms over time. Results from the present study highlight the potentially long-lasting impacts of humiliating and socio-structural stressors on both anxiety and depression. Another interesting observation from our findings is that frequency and severity measures of entrapment exposures are differentially associated with anxiety and depression symptoms respectively. This suggests that more frequent entrapment exposures, irrespective of severity, may be more anxio-genic by encouraging hypervigilance sustaining anticipation of further threat. On the other hand, isolated occurrences of severe entrapment stressors can exhaust one’s coping resources and perpetrate the belief that any escape is futile.

Finally, we uncovered nominally significant associations between RSFC within the default network, between frontoparietal and default networks, and between frontoparietal and ventral attention networks and prospective anxiety symptoms. Our results are not consistent with the formulation that abnormal interactions between functional networks theorized to support

executive control (i.e. frontoparietal), self-referential processing (i.e. default) and salience processing (i.e. ventral attention) are associated with anxiety and depression (Al-Ezzi et al., 2021; Berman et al., 2011; Duan et al., 2020; Ho et al., 2015; Kaiser et al., 2015; Leech & Sharp, 2014; Manoliu et al., 2014; Nejad et al., 2013; Pawlak et al., 2022; Perino et al., 2021; Rzepa & McCabe, 2018; Sievertsen et al., 2025; Willinger et al., 2024; Y. Zhang et al., 2024). The lack of significant associations may arise from methodological differences compared to the prior literature. For example, while our study examined prospective associations between RSFC and affective symptoms, most previous studies focused on cross-sectional associations (Al-Ezzi et al., 2021; Ho et al., 2015; Kaiser et al., 2015; Manoliu et al., 2014; Perino et al., 2021; Rzepa & McCabe, 2018, 2018; Willinger et al., 2024; Y. Zhang et al., 2024). Among the longitudinal studies, most focused on functional connectivity involving isolated network ROIs, especially subcortical ROIs, as predictors of anxiety and depression symptoms at follow-up (Connolly et al., 2017; Davey et al., 2015; Edalati et al., 2023; Lopez et al., 2018; Pawlak et al., 2022), while we computed RSFC across multiple cortical ROIs for each network of interest (Schaefer et al., 2018). Aside from methodological differences, the lack of significant findings in our study may also be attributed to the limited size of our current sample that may not afford sufficient power for detecting certain prospective brain-behavior associations with small effect sizes (Marek et al., 2022). Lastly, our study did not find differential associations of any RSFC within and between the frontoparietal, default and ventral attention networks with respect to either anxiety or depression symptoms. These results suggest that there may not be any symptom-specific RSFC predictor.

Strengths and Limitations

Several strengths and limitations of this work should be noted. In terms of strengths, we leveraged a longitudinal sample of adolescents enriched for clinical diagnosis of anxiety and depressive disorders with a narrow age range. This enabled us to examine prospective associations between exposure to major life stressors, neurobiology, and clinical symptoms during the developmental stage characterized by heightened vulnerability to stress-related psychopathology (Casey et al., 2008; Larsen & Luna, 2018; March-Llanes et al., 2017; Merikangas et al., 2010; Paus et al., 2008). We assessed a rich repertoire of theoretically relevant stressors occurring across the entire life course using distinct dimensions of social-psychological characteristics assessed by the STRAIN. Our study had a novel focus on using subjective severity ratings besides the number of exposures to stressor characteristics. In this way, we demonstrated the validity of these stressor characteristic indices in predicting internalizing psychopathology over time. We included all five social-psychological characteristics

and the potential confounding variables into the same LME model when predicting anxiety/depression symptoms at three time points. This ensured that any prospective association between a stressor characteristic and clinical symptom is robust to the inclusion of other inter-correlated stressor characteristics. Lastly, each participant in our study underwent 23.2 minutes of rsfMRI. The scan duration of our rsfMRI data goes far beyond that of most previous rsfMRI studies and should afford relatively high reliability (Birn et al., 2013).

Several limitations should also be noted. First, the sample was relatively small (*n* = 150), which did not afford us sufficient statistical power to assess RSFC involving other functional networks such as the dorsal attention and the limbic networks as well as the subcortical structures such as the amygdala, which have also been associated with anxiety and depression (Brandl et al., 2022; Connolly et al., 2017; Cullen et al., 2014; Kaiser et al., 2015; Liu et al., 2021; Sylvester et al., 2012; Xu et al., 2019; Z. Zhang et al., 2025). Future high-powered analyses would benefit from a whole-brain approach. Although small sample size is a common issue with richly-phenotyped, longitudinal datasets involving clinical samples, findings from the present study should be validated by larger samples in future studies. Since the fMRI protocol of the current dataset was harmonized with other HCP studies (Siless et al., 2020), other HCP datasets may provide valuable resources for this purpose. Second, the vast majority (79.33%) of participants were White, came from highly educated families, and endorsed relatively low exposures to stressors characterized by danger and role change/disruption (**Table 1**) compared to previous studies on autistic adults (Moseley et al., 2025) and sexual minority adults of color (Parra et al., 2023). Although our study assessed moderate-to-severe life stressors, and previous research suggests that exposure to a single severe stressor can trigger depressive episodes in over half of individuals (Monroe et al., 2007; Shapiro, 1979), further research is still needed to confirm whether our findings generalize to populations with greater exposure to stressors involving danger and significant role disruptions. Lastly, although we included a number of covariates such as age, race and ethnicity, baseline symptoms, and diagnostic status in our LME models to ensure that our findings could not be explained by these confounders, other potential confounders such as medication use and family history of psychopathology were unavailable in this dataset and may be relevant.

Conclusion

Notwithstanding these limitations, through the use a longitudinal sample of adolescents, over half of whom met clinical cut-offs for at least one anxiety or depressive disorder, the present study demonstrate that lifetime frequency and severity of humiliation and entrapment exposures

predict both anxiety and depression symptoms at baseline, 6 months, and 12 months later. These results imply that among all characteristics of major life stressors examined by the Adolescent STRAIN, humiliation and entrapment may be the most important predictive characteristics of both anxiety and depression over time. Follow-up analyses showed that lifetime frequency of entrapment exposures differentially predicts anxiety symptoms, whereas lifetime severity differentially predicts depression symptoms, suggesting that distinct measures of stressor exposures may be associated with different mental health outcomes. Finally, our results showed no association between RSFC among the frontoparietal, default, and ventral attention networks and anxiety or depression symptoms across all three time points, indicating that these connectivity patterns may be relatively weak predictors of adolescent internalizing symptoms. Looking forward, additional research is needed to elucidate how lifetime stressor exposure interacts with brain activity and connectivity—as well as peripheral biological processes—to predict other forms of psychopathology in adolescence and across the life course.

Financial Support

G.M.S. was supported by grant OPR21101 from the California Governor's Office of Planning and Research/California Initiative to Advance Precision Medicine. S.C. was supported by the McKenzie Fellowship from the University of Melbourne. The study was made possible by National Institute of Mental Health grant R01 MH120080 to A.J.H. The findings and conclusions in this article are those of the authors and do not necessarily represent the views or opinions of these organizations, which had no role in designing or planning this study; in collecting, analyzing, or interpreting the data; in writing the article; or in deciding to submit this article for publication. This manuscript has been posted as a preprint on bioRxiv: https://www.biorxiv.org/content/10.1101/2024.10.25.620373v1.

Disclosures

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

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