

Corticolimbic Structure–Function Coupling Is Sensitive to Childhood Adversity and Buffers Adversity-Related Symptoms during Development

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Childhood adversity is a potent predictor of mental health problems across the lifespan, and cross-species literature implicates stress-sensitive corticolimbic circuits in adversity-related psychopathology. Structure–function coupling (SFC) is a multimodal marker that is sensitive to developmental plasticity. While emerging evidence suggests cortical SFC is sensitive to adversity exposure during early childhood, it is unknown how SFC in stress-sensitive corticolimbic circuits links adversity exposure with mental health across development. We examined associations between adversity exposure, transdiagnostic symptomatology, and both amygdala–cortical and hippocampal–cortical SFC across development in a large youth sample ($N = 607$, 39% F). Results revealed that adversity exposure moderated the association between age and amygdala–ventromedial prefrontal cortex (vmPFC) SFC (partial $R^2 = 0.015$; $p = 0.007$), such that age was positively associated with amygdala–vmPFC SFC in youth with higher, but not lower, levels of adversity exposure. Furthermore, amygdala–vmPFC SFC moderated the association between adversity exposure and internalizing symptoms (partial $R^2 = 0.015$; $p = 0.012$), such that the adversity–symptoms association was reduced in youth with stronger, but not weaker, amygdala–vmPFC SFC. Separately, higher adversity exposure was associated with weaker hippocampal–limbic SFC (partial $R^2 = 0.019$; $p = 0.037$), which moderated the association between adversity and internalizing symptoms (partial $R^2 = 0.005$; $p = 0.010$) such that the adversity–symptoms association was reduced in youth with weaker, but not stronger, hippocampal–limbic SFC. These findings highlight that neurodevelopment of amygdala–vmPFC and hippocampal–limbic circuits may adapt in distinct ways to support mental health following adversity, with implications for risk and resilience against internalizing psychopathology.

Key words: adversity; development; neuroplasticity; resilience; stress; structure–function coupling

Significance Statement

Delineating how childhood adversity alters neurodevelopment is critical to understanding the origins of adversity-related risk for mental health disorders. Here, we leverage a multimodal marker of the correspondence between brain structure and function to test how corticolimbic circuits are associated with adversity exposure during development. Results reveal that the structure–function coupling of amygdala–vmPFC and hippocampal–limbic circuits is linked with adversity exposure and differentially moderates the association between adversity exposure and internalizing psychopathology. These findings suggest key roles for neural stress regulation and memory circuits in adapting to support optimal functioning following adversity exposure, and highlight the concordance of neural structure and function as an important indicator of individual-level risk and resilience.

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Introduction

Childhood adversity is a potent risk factor for psychopathology at the population level (Felitti et al., 1998; Green et al., 2010; Copeland et al., 2018), but predicting individual risk following adversity remains challenging due to heterogeneous outcomes (Meehan et al., 2022). Experience-dependent neurodevelopmental changes following adversity may contribute to this variability via alterations in brain structure and function (Greenough et al., 1987; Andersen, 2003; McLaughlin and Gabard-Durnam, 2019). Cross-species studies have established that adversity particularly affects stress-sensitive regions such as the hippocampus, amygdala, and ventromedial prefrontal cortex (vmPFC; Mitra et al., 2005; Tottenham and Sheridan, 2010; Eiland et al., 2012; McEwen et al., 2016). Here, we examine how structure–function coupling (SFC) in key corticolimbic circuits develops and relates to adversity and psychopathology.

SFC estimates how structural connectivity relates to functional connectivity at the connectome level (Baum et al., 2020; Fotiadis et al., 2024) and is sensitive to neuroplasticity markers such as myelination and the excitation–inhibition ratio (Fotiadis et al., 2023). SFC strengths change with neurodevelopment. Cortical SFC decreases in early childhood, primarily driven by reductions in sensorimotor regions (Chan et al., 2024; Tooley et al., 2025), and then increases in middle childhood and adolescence, primarily driven by increases in slower-maturing transmodal association regions (Baum et al., 2020; Feng et al., 2024). SFC is also sensitive to environmental input—for example, prenatal adversity is associated with accelerated SFC development in association networks (Chan et al., 2024). However, the majority of SFC studies to date have focused on the cortex, omitting stress-sensitive corticolimbic circuits.

Individuals exposed to adversity show altered functional (Tottenham et al., 2011; van Harmelen et al., 2013; Herringa et al., 2016; McLaughlin et al., 2019; Sisk et al., 2025b) and structural (Eluvathingal et al., 2006; Hanson et al., 2015; Ho et al., 2017; McCarthy-Jones et al., 2018) neurodevelopment in hippocampal–prefrontal and amygdala–prefrontal connections, with implications for cognitive and emotional functioning. Some evidence suggests that adversity alters the timing of corticolimbic neurodevelopment (Callaghan and Tottenham, 2016; McLaughlin and Gabard-Durnam, 2022; Sisk and Gee, 2024). Individual differences in these adversity-related corticolimbic changes may in turn relate to mental health, such that adversity-exposed youth who experience accelerated corticolimbic development have lower psychopathology symptoms (Gee et al., 2013; Herzberg et al., 2021; Chan et al., 2024). At the same time, individual differences in corticolimbic structure or function that predate adversity may also relate to individual differences in psychopathology. Adversity and psychopathology have been associated with differences in corticolimbic structure and function separately, yet it is less clear how they relate to SFC. Given evidence that SFC can predict outcomes above and beyond structure or function alone (Jiang et al., 2019; Gu et al., 2021), addressing this question could advance understanding of heterogeneity in adversity-related outcomes.

Here, we examined three aims in a large youth sample aged 5–18. First, we examined whether age related to SFC across development. As prefrontal SFC increases with age (Baum et al., 2020; Feng et al., 2024) and hippocampal–vmPFC and amygdala–vmPFC connections mature during development (Arruda-Carvalho et al., 2017; Cruz-Sanchez et al., 2026), we hypothesized that hippocampal–vmPFC and amygdala–vmPFC SFC would

increase with age. Second, in line with the theoretical model whereby SFC tracks experience-dependent changes following adversity, we tested whether adversity moderated the association between age and SFC. Given evidence of accelerated cortical SFC development following adversity (Chan et al., 2024), we hypothesized that youth with higher (but not lower) adversity exposure would show hippocampal–vmPFC and amygdala–vmPFC SFC similar to older participants. Finally, we examined whether individual differences in SFC moderated the association between adversity and psychopathology (either via adversity-related changes in SFC or preexisting differences in SFC). As accelerated corticolimbic development may confer resilience to adversity (Gee et al., 2013; Herzberg et al., 2021; Chan et al., 2024), we hypothesized that putatively accelerated SFC would be associated with reduced symptoms.

Materials and Methods

Participants. Participants were 607 youth ages 5–18 (39% female, 61% male) who participated in the Healthy Brain Network (HBN) study (Alexander et al., 2017). Participants were recruited through a community referral model that aimed to capture broad heterogeneity in development and psychopathology (Alexander et al., 2017). Exclusion criteria included acute safety concerns, behavioral or cognitive differences that would hinder study participation, and medical concerns that might confound neuroimaging research (e.g., neurodegenerative disorders). Study procedures were approved by the Chesapeake Institutional Review Board (Alexander et al., 2017). Prior to study participation, 18-year-old participants provided written informed consent, and younger participants provided written assent alongside written informed consent provided by a parent or legal guardian. Participants and a caregiver attended a series of four sessions at one of three sites in the broader New York City area. Sessions included diagnostic interviews, child-report and caregiver-report questionnaires, and an MRI scanning session (Alexander et al., 2017). Detailed demographic information for participants included in the present study is presented in Table 1. We conducted ANOVA tests to ensure that key variables of interest (age, adversity exposure) did not differ systematically by site.

Adversity exposure. Participants' exposure to adversity was queried using the Negative Life Events Scale (NLES; Sandler et al., 1991). The NLES comprises 21 questions assessing life events such as experiencing severe injury or illness, having a caregiver lose a job, or moving schools. The NLES shows satisfactory reliability and construct validity (Sandler et al., 1991). While HBN collects both caregiver- and child-reported NLES questionnaires, we chose to use caregiver-reported NLES scores in the present study to minimize missingness. We used the "total_events" variable, which is a count of the total number of negative life events endorsed.

Clinical measures. The Child Behavior Checklist (CBCL; Achenbach, 1999) is a widely used and well-validated measure that was used to assess clinical symptoms. CBCL *T*-scores from the HBN study were normally distributed and reflected a broad range of symptom severity experienced by participants in the HBN study (Alexander et al., 2017). Given our primary focus on adversity and neurodevelopment, as well as the fact that adversity is associated with transdiagnostic symptoms, we chose to examine *T*-scores representing internalizing, externalizing, and total symptoms rather than disorder-specific subscales. We used *T*-scores rather than raw scores because the *T*-scores (but not the raw scores) met linear model assumptions for normality.

MRI data acquisition. MRI data were acquired using Siemens 3 Tesla scanners; data collected using 1.5 Tesla scanners at the Staten Island site were excluded from this analysis. Data collected at the Rutgers University Brain Imaging Center used a Siemens Tim Trio scanner, and data collected at the CitiGroup Cornell Brain Imaging Center and the CUNY Advanced Science Research Center used Siemens Prisma scanners.

Table 1. Demographics for the sample included in the present study

	Overall (N = 607)
Age (years)	
Mean (SD)	11.720 (3.098)
Range	6.076–17.989
Sex	
Female	237 (39.0%)
Male	370 (61.0%)
Primary caregiver education	
Less than seventh grade	1 (0.2%)
Middle school	3 (0.5%)
Partial high school	7 (1.2%)
High school degree	34 (5.6%)
Partial college	81 (13.3%)
College degree	220 (36.2%)
Graduate School	261 (43.0%)
Total household income	
<\$10,000	9 (1.5%)
\$10,000–\$19,999	12 (2.0%)
\$20,000–\$29,999	23 (3.8%)
\$30,000–\$39,999	19 (3.1%)
\$40,000–\$49,999	16 (2.6%)
\$50,000–\$59,999	16 (2.6%)
\$60,000–\$69,999	28 (4.6%)
\$70,000–\$79,999	21 (3.5%)
\$80,000–\$89,999	35 (5.8%)
\$90,000–\$99,999	31 (5.1%)
\$100,000–\$149,999	100 (16.5%)
>\$150,000	207 (34.1%)
Decline to specify	90 (14.8%)
Ethnicity	
Hispanic or Latino	151 (25.2%)
Not Hispanic or Latino	405 (67.5%)
Unknown	7 (1.2%)
Decline to specify	37 (6.2%)
Missing	7
Race	
Asian	15 (2.5%)
Black or African American	82 (13.9%)
Hispanic or Latinx	58 (9.8%)
Indian	4 (0.7%)
Multiracial	111 (18.8%)
Other race	9 (1.5%)
White	306 (51.7%)
Unknown	2 (0.3%)
Decline to specify	5 (0.8%)
Missing	15
NLES total adverse events	
Mean (SD)	6.730 (3.309)
Range	0.000–17.000
CBCL internalizing T-scores	
Mean (SD)	56.371 (11.448)
Range	33.000–88.000
CBCL externalizing T-scores	
Mean (SD)	52.590 (11.819)
Range	33.000–87.000
CBCL total symptoms T-scores	
Mean (SD)	56.245 (11.139)
Range	24.000–82.000
Site	
CBIC	356 (58.6%)
CUNY	22 (3.6%)
RU	229 (37.7%)

CBCL, Child Behavior Checklist; CBIC, Citigroup Biomedical Imaging Center; CUNY, City University of New York; NLES, Negative Life Events Scale; RU, Rutgers University.

Data were collected using a 32-channel head coil. For detailed information regarding the MRI acquisition parameters, see the original data descriptor paper (Alexander et al., 2017).

Data access. Preprocessed diffusion-weighted imaging data from the HBN study were obtained through a publicly available repository (Richie-Halford et al., 2022). Subsequent reconstruction and connectome creation were performed using QSIREcon (Cieslak et al., 2021, 2025), as described below. Preprocessed resting-state timeseries data and processed anatomical images from the HBN study were obtained from the Reproducible Brain Charts (RBC) project (Shafiei et al., 2024, 2025). Subsequent parcellation and connectome construction were performed using FSL tools (Jenkinson et al., 2012) and custom Python code (van Rossum, 1995).

Quality assessment. Structural and functional imaging data underwent rigorous quality assessment. Diffusion data were assessed through a combination of expert raters, community raters who evaluated images through a web portal, and machine learning models trained on these ratings (Richie-Halford et al., 2022). In the present study, data with a quality score of 0.3 or above were included, and the quality score was included as a covariate in all neuroimaging analyses. Importantly, the results presented below held at varying quality thresholds (e.g., an inclusive threshold of 0.05 and a more stringent threshold of 0.6). Additional detail on the community and expert raters and how their scores were leveraged to train the machine learning algorithm that ultimately produced the quality scores used in this project can be found in the descriptor paper (Keshavan et al., 2019) and the data release paper (Richie-Halford et al., 2022). Functional data image quality was assessed primarily through motion metrics. fMRI runs with framewise displacement (FD) values ≤ 0.2 and normalized cross-correlations greater than or equal to 0.8 were considered adequate for use (Shafiei et al., 2024, 2025). Data that did not meet these criteria were excluded from the present study. T1-weighted (T1w) anatomical images were manually evaluated by 2–5 community raters who participated in “Swipes for Science” (Keshavan et al., 2019). Data were subsequently assigned a rating of “Pass,” “Artifact,” or “Fail” based on these manual reviews. Only data rated as “Pass” were included in the present study.

Anatomical data processing. T1w anatomical images obtained through the RBC data release (Shafiei et al., 2025) were processed using FreeSurfer (Fischl, 2012) and sMRIPrep (Esteban et al., 2024), yielding commonly used measures of brain structure. FreeSurfer derivatives were included in the diffusion image reconstruction pipeline to improve anatomical accuracy.

Diffusion connectome data

Diffusion data reconstruction was performed using QSIREcon version 1.0.0rc3 (Cieslak et al., 2021, 2025), which is based on *Nipype* 1.5.1 (Gorgolewski et al., 2011, 2018), RRID:SCR_002502. The following boilerplate descriptions from QSIREcon are reported in alignment with recommendations for best practices for reproducible neuroscience (Cieslak et al., 2021, 2025). Details on the QSIPrep pipeline used to preprocess these data can be found in the data release paper (Richie-Halford et al., 2022).

MRtrix3 processing. FreeSurfer outputs were registered to the QSIPrep outputs to improve anatomical accuracy. Multitissue fiber response functions were estimated using the dhollander algorithm. Fiber orientation distributions (FODs) were estimated via constrained spherical deconvolution (Tournier et al., 2004, 2008) using an unsupervised multitissue method (Dhollander et al., 2016, 2019). FODs were intensity-normalized using mtnormalize (Raffelt et al., 2017).

Anatomical processing. T1w-based spatial normalization calculated during preprocessing was used to map atlases from template space into alignment with DWIs. Brain masks from antsBrainExtraction

were used in all subsequent reconstruction steps. Cortical parcellations were mapped from template space to DWI data using the T1w-based spatial normalization.

Structural connectome construction. Diffusion data were parcellated using the 4S atlas (<https://github.com/PennLINC/AtlasPack>), which includes 400 cortical parcellations from the original Schaefer atlas in addition to 56 subcortical segmentations from atlases representing thalamic nuclei (Najdenovska et al., 2018), the cerebellum (King et al., 2019), the hippocampus and amygdala (Glasser et al., 2013), and additional subcortical nuclei such as the hypothalamus, caudate nucleus, and putamen (Pauli et al., 2018). Tractography was performed using tckgen, which uses the iFOD2 probabilistic tracking method to generate $1e7$ streamlines with a maximum length of 250 mm, minimum length of 30 mm, and a FOD power of 0.33. Weights for each streamline were calculated using SIFT (Smith et al., 2013), an approach that improves the biological accuracy of the streamline count by using the underlying spherical deconvolution of the diffusion signal to weight streamlines, and were included while estimating the structural connectivity matrix. Structural connectomes were generated representing the streamline counts between all atlas regions, and resulting measures were scaled by the inverse of the node volumes in order to account for the inherently greater number of streamlines that emerge from larger relative to smaller atlas regions (Hagmann et al., 2008; Tournier et al., 2019).

Structural connectome thresholding

To reduce the incidence of potentially spurious streamline connections present in the structural connectivity matrices, we applied a consistency-based thresholding approach (Gong et al., 2009; Li et al., 2012; Roberts et al., 2017; Baum et al., 2020) that retains streamlines that are consistently present across participants regardless of their relative strength. In line with previous work (Baum et al., 2020), we thresholded participants' connectivity matrices at the 75th percentile for edge variability, removing the 25% most inconsistent connections across participants. We subsequently normalized each matrix at the subject level by dividing each edge by the total weight of network connections in order to facilitate comparisons across participants (Baum et al., 2020).

Functional connectome data. Functional imaging data were processed using the Configurable Pipeline for the Analysis of Connectomes (C-PAC; Li et al., 2024) which is based on fMRIPrep (Esteban et al., 2019). A bandpass filter of 0.0125–0.125 Hz was implemented in this version of C-PAC (Version 1.8.5). Additional details on functional data preprocessing can be found in the RBC data release paper (Shafei et al., 2024, 2025).

Functional connectome construction. As resting-state connectivity estimates stabilize with ~ 10 min of data (Gonzalez-Castillo et al., 2014), we concatenated the two 5-min preprocessed resting-state time-series along the time dimension, which was then parcellated using the 456-node 4S atlas. Pearson's correlations were computed between each node's timeseries to generate connectivity matrices for each participant.

Network extraction

Identifying vmPFC nodes. Given our a priori interest in corticolimbic neural architecture, we sought to robustly identify a subset of atlas regions representing the vmPFC. To this end, a vmPFC mask was created by merging all regions of the Mackey Ventromedial Prefrontal Cortical atlas (Mackey and Petrides, 2014) into a single region of interest (ROI). We then estimated the degree of overlap between parcels of the 4S atlas with the Mackey atlas ROI. Parcels from the 4S atlas where 50% or more of voxels overlapped with the Mackey atlas ROI were retained as a part of the "vmPFC" network.

Subcortical-network measures. In order to isolate SFC between cortical and subcortical regions of interest, we extracted several subsets of nodes prior to computing SFC. Specifically, from the functional and structural connectomes, we separately extracted networks representing connectivity among bilateral hippocampal and amygdala segmentations and cortical regions, in the visual, somatomotor, dorsal attention,

salience, limbic, frontoparietal, and default mode networks according to the Yeo 7-network assignments (Yeo et al., 2011). In addition, we extracted node subsets connecting the previously identified vmPFC regions with bilateral hippocampal and amygdala segmentations (Fig. 1).

SFC. SFC was operationalized as the Spearman's correlation coefficient between each atlas region's structural and functional connectivity with every other region (Baum et al., 2020). SFC was computed iteratively for subcortical-cortical network connections. Specifically, for each set of cortical nodes, we created a subset matrix of nodes that comprised a given network (e.g., vmPFC; frontoparietal network) along with a subcortical ROI (i.e., the left or right hippocampus or amygdala). The correlation between the structural and functional vectors representing the subcortical node's connectivity with other cortical nodes in the subsetted matrix was then computed, excluding the self-correlation and edges with a value of zero. The coupling coefficient was then retained for each participant. This process was repeated for each connection of interest (e.g., hippocampus–vmPFC, amygdala–visual network, hippocampus–default mode network). Left and right subcortical region SFC r values were averaged together as we did not have strong hypotheses regarding lateralization and to mitigate the likelihood of Type I errors. These steps yielded a final dataset that included 16 subnetworks, corresponding to amygdala and hippocampal connections to each of the seven Yeo functional networks (Yeo et al., 2011) in addition to the amygdala–vmPFC and hippocampal–vmPFC connections. SFC estimates for each connection were then winsorized across participants to mitigate outlier effects. We chose to winsorize rather than omit outliers in order to preserve sample size but confirmed that all winsorized estimates were correlated at levels >0.95 with the original estimates. Finally, prior to statistical analyses, we corrected SFC measures for site effects using ComBat harmonization while protecting age and adversity exposure as covariates of interest (Fortin et al., 2018).

Statistical analyses

Statistical analyses were conducted in R, version 4.5.1.

Development of subcortical–cortical connections. In order to test the first part of our theoretical model, whereby adversity might be associated with age-related patterns of SFC, we used the *mgcv* package (Wood, 2000) to fit generalized additive models (GAMs) to test for linear and nonlinear age-related effects. GAMs were fitted with a smoothing function applied to the age term, with the number of basis functions set to $k = 3$ as in previous developmental work (Sydnor et al., 2023). This smoothed term generates a spline or a combination of weighted basis functions capable of flexibly capturing linear and nonlinear effects (Wood, 2017; Simonsohn, 2024). To minimize risk of overfitting, increasing complexity of smoothed terms within the GAM model was penalized using restricted maximum likelihood. In order to systematically evaluate age effects on subcortical–cortical SFC, we fitted two models per connection: a null model, estimated without the smoothed age term, and a full model that included the smoothed age term. Model fits for the null model GAM and the full model GAM were compared using an ANOVA. The magnitude of the age effect was quantified by calculating the partial R^2 value between the full and null models. All age-related full and null models controlled for sex assigned at birth, mean whole-brain SFC, average root mean squared displacement during the resting-state scans, mean FD during the diffusion scan, and diffusion quality score. FDR correction was applied to analyses examining age effects on SFC between subcortical regions and the seven Yeo functional networks to account for the seven models fitted for each subcortical ROI.

Interaction effects between age and adversity exposure in subcortical–cortical connections. Given our a priori hypotheses regarding the potential influence of adversity exposure on neurodevelopment, we chose to examine the association between SFC and the interaction between adversity and age. Using a parallel approach to the above, we systematically evaluated potential interaction effects between age and adversity exposure on subcortical–cortical SFC by fitting two models per connection: a null model, which included a smoothed age term but did not include an adversity exposure term, and a full model that included a smoothed

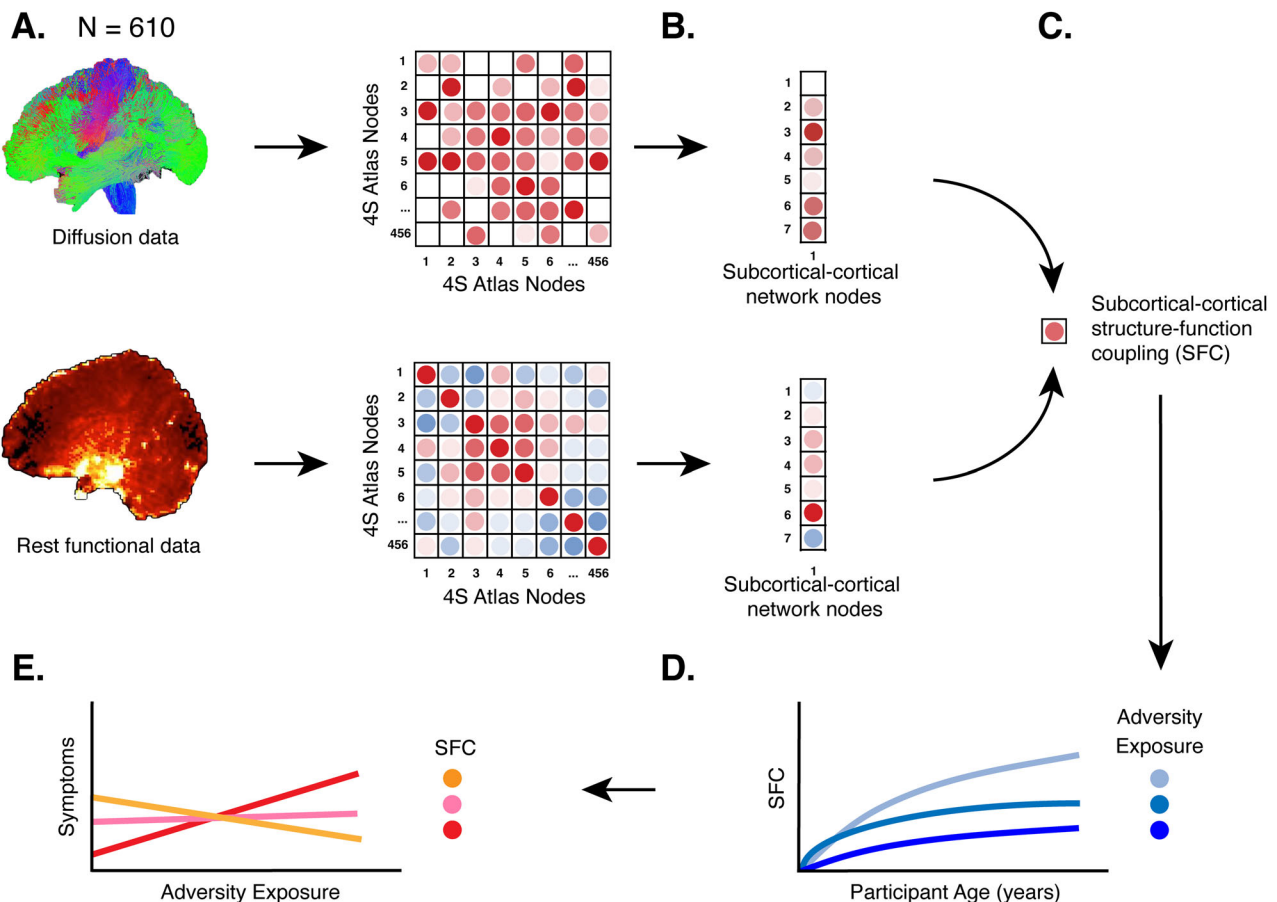


Figure 1. Diagram of analytic workflow. **A**, Structural and resting-state data were parcellated using the 4S atlas to yield structural and functional connectomes. **B**, Subsets of regions for each matrix were selected to reflect structural and functional connectivity, respectively, within specific circuits of interest. **C**, SFC between connectivity vectors was computed, and the value reflecting subcortical-cortical SFC was retained for further analysis. **D**, Generalized additive models were used to assess relations between age, adversity exposure, and subcortical-cortical SFC. **E**, Robust regression models were used to assess the role of subcortical-cortical SFC in moderating associations between adversity and mental health symptoms.

age by adversity interaction term as well as a smoothed age term and a smoothed adversity term. The smoothed interaction term between age and adversity exposure was fitted using a tensor product interaction in order to allow for the possibility of both interactive and main effects (Wood, 2017). The null and full models were compared using an ANOVA, and if including the interaction term and main effects significantly improved model fit, full model statistics were examined. The magnitude of the interaction term effect was quantified by calculating the partial R^2 value between the full and null models. Significant interactions were probed using the Johnson–Neyman (JN) procedure (Johnson and Fay, 1950). For each JN test, the interval of nonsignificance is reported. All full and null interaction models controlled for sex assigned at birth, mean whole-brain SFC, average root mean squared displacement during the resting-state scans, mean FD during the diffusion scan, diffusion quality score, total household income (Noble et al., 2015; Tooley et al., 2021), and the education level of the caregiver participating in the study (Noble et al., 2013). We opted to include proxy measures of socioeconomic status (e.g., caregiver education, combined family income) as covariates in order to estimate the effects of adversity over and above socioeconomic status-related environmental factors (Amso and Lynn, 2017). FDR correction was applied to analyses examining age by adversity interaction effects on SFC between subcortical regions and the seven Yeo functional networks to account for the seven models fitted for each subcortical ROI.

Associations with clinical symptoms. Finally, we tested whether SFC might be related to risk for or resilience against psychopathology following adversity exposure. We first identified the amygdala–cortical and hippocampal–cortical connections that were associated with adversity

exposure. We then examined whether SFC in these connections moderated associations between adversity and psychopathology. We examined these associations using robust regression, an approach that mitigates the influence of outliers on effect estimates (Todorov and Filzmoser, 2009). Specifically, we fit two robust regression models using the *robustbase* R package (Maechler et al., 2025) for each of the three symptom measures: a null model, which included a linear term for adversity exposure but did not include SFC, and a full model that included an interaction between adversity exposure and SFC as well as main effects of adversity exposure and SFC. The null and full models were compared using an ANOVA, and if including the interaction term and main effects significantly improved model fit, full model statistics were examined. The magnitude of the interaction term effect was quantified by calculating the partial R^2 value between the full and null models. Subsequently, significant interactions were probed using the JN procedure (Johnson and Fay, 1950). All models included age, sex assigned at birth, primary caregiver education level, total household income, and primary diagnostic category as covariates. We chose to include primary diagnostic category as a covariate because the HBN sample comprises considerable clinical heterogeneity, including youth diagnosed with conduct disorders, mood disorders, and neurodevelopmental disorders. In particular, a high proportion of the present sample (63%) was diagnosed with a neurodevelopmental disorder, and evidence suggests that the CBCL scale functions differently in youth with neurodevelopmental disorders such as autism (de la Roche et al., 2024; Volk et al., 2025). Thus, we aimed to mitigate potential differences across disorders by including primary diagnostic category as a covariate in all clinical models. In exploratory analyses, we repeated these model comparisons across all seven Yeo network connections with the hippocampus and amygdala, respectively, for each of the three symptom

measures. As in previous analyses, FDR correction was applied to account for the 21 models (seven Yeo network connections $\times$ three symptom measures) fitted for each subcortical ROI.

Data and code accessibility. Preprocessed data used in the present study were obtained through open access repositories (Richie-Halford et al., 2022; Shafiei et al., 2025). Code used to compute the SFC measures used in this study, as well as analysis code, can be found at https://github.com/Yale-CANDLab/Sisk_HBN_StructureFunction.

Results

There were no significant between-site differences for negative life events ($F_{(2,604)} = 0.449$; $p = 0.639$) or age ($F_{(2,604)} = 0.297$; $p = 0.743$).

Amygdala–vmPFC and hippocampal–vmPFC development

Development of subcortical–vmPFC connections

First, we sought to examine the effect of age on SFC in hippocampal–vmPFC and amygdala–vmPFC connections. Inclusion of a smoothed age term did not significantly improve model fit for either amygdala–vmPFC SFC ($p = 0.593$; partial $R^2 < 0.001$) or hippocampal–vmPFC SFC ($p = 0.503$; partial $R^2 < 0.001$), suggesting that the degree to which subcortical–vmPFC functional connectivity is constrained by structural wiring remains largely stable across childhood and adolescence.

Interactions between age and adversity exposure in subcortical–vmPFC connections

We next examined whether there were significant interactive effects between age and adversity exposure that were associated with amygdala–vmPFC SFC and hippocampal–vmPFC SFC. Including a smoothed age by adversity exposure interaction term significantly improved model fit for amygdala–vmPFC SFC ($p = 0.037$; partial $R^2 = 0.015$). Further examination of this model revealed that the smoothed interaction between age and adversity was statistically significant ($F_{(1,000)} = 7.228$; edf =

1.000; $p = 0.007$; Fig. 2B). Neither the smoothed age term ($F_{(1,000)} = 0.350$; edf = 1.000; $p = 0.554$) nor the smoothed adversity term ($F_{(1,878)} = 0.825$; edf = 1.651; $p = 0.353$) was independently significant. As the effective degrees of freedom for the interaction term suggested a linear effect, we used a linear JN test to further probe the interaction. Results revealed that for youth with 10 or more adverse exposures ($n = 119$), there was a positive association between age and amygdala–vmPFC SFC (JN = $[-0.020, 9.990]$; moderator range = $[0.000, 17.000]$; Fig. 2C), whereas for individuals with fewer than 10 adverse exposures ($n = 488$), the association between age and amygdala–vmPFC SFC was not significant. Including a smoothed age by adversity exposure interaction term did not significantly improve model fit for hippocampal–vmPFC SFC ($p = 0.346$; partial $R^2 = 0.007$). These findings suggest that high levels of adversity exposure may be associated with differential age-related change in amygdala–vmPFC SFC in youth.

Associations with clinical symptoms

We next tested whether SFC of amygdala–vmPFC and hippocampal–vmPFC circuits moderated associations between adversity exposure and clinical symptoms. For internalizing symptoms, including an interaction between amygdala–vmPFC SFC and adversity exposure significantly improved model fit relative to the model that included adversity exposure alone ($p = 0.018$; partial $R^2 = 0.015$). The full model showed a significant interaction between adversity exposure and amygdala–vmPFC SFC, such that youth with stronger amygdala–vmPFC SFC showed a reduced association between adversity exposure and internalizing symptoms compared with youth with weaker amygdala–vmPFC SFC ($\beta = -0.102$; SE = 0.041; $t = -2.521$; $p = 0.012$; Fig. 3A). We next probed this interaction using a JN test (Johnson and Fay, 1950) to identify the significant intervals. Results revealed that the association between adversity exposure and internalizing symptoms was significant for individuals with

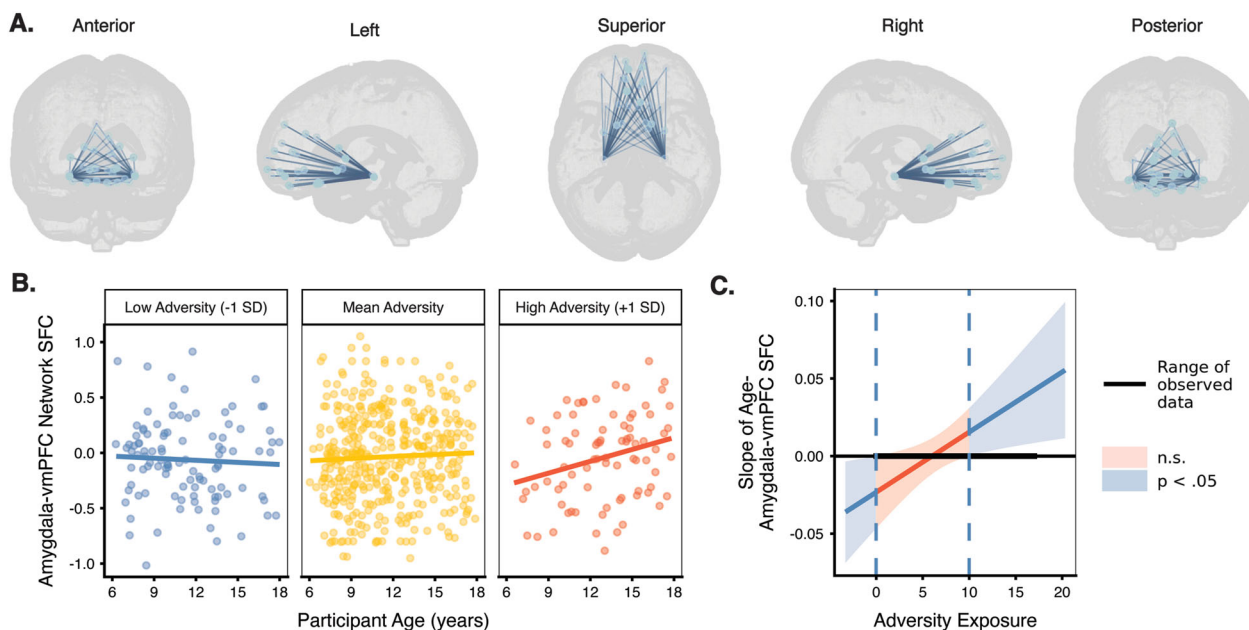


Figure 2. Adversity exposure moderates the association between age and amygdala–vmPFC SFC. **A**, Connections between bilateral amygdalae and nodes included in the vmPFC network. **B**, Amygdala–vmPFC SFC is associated with an interaction between age and adversity exposure. Associations between age and amygdala–vmPFC SFC were stratified across three levels of adversity exposure (for visualization purposes). **C**, A JN plot depicts the statistically significant interval of the interaction. Adversity exposure moderated the association between age and amygdala–vmPFC SFC, such that age was positively associated with amygdala–vmPFC SFC for youth with 10 or more (but not fewer than 10) adverse exposures.

amygdala–vmPFC SFC <0.400 ($JN = [0.400, 4.310]$; moderator range = $[-1.020, 1.050]$; Fig. 3B), whereas for individuals with amygdala–vmPFC SFC >0.400 , SFC buffered the association between adversity exposure and internalizing symptoms such that it was no longer significant. Including an interaction between amygdala–vmPFC SFC and adversity exposure did not significantly improve model fit for externalizing symptoms ($p = 0.318$; partial $R^2 = 0.004$) or total symptoms ($p = 0.225$; partial $R^2 = 0.006$).

With regard to hippocampal–vmPFC SFC, we found that including an interaction between hippocampal–vmPFC SFC and adversity exposure did not significantly improve model fit for internalizing symptoms ($p = 0.159$; partial $R^2 = 0.006$) but did significantly improve model fit for total symptoms ($p = 0.048$; partial $R^2 = 0.008$), and marginally improved model fit for externalizing symptoms ($p = 0.051$; partial $R^2 = 0.009$). Further examination of the full model for total symptoms revealed a significant interaction between adversity exposure and hippocampal–vmPFC SFC, such that youth with stronger hippocampal–vmPFC SFC showed a reduced association between adversity exposure and total symptoms compared

with youth with weaker hippocampal–vmPFC SFC ($\beta = -0.084$; $SE = 0.040$; $t = -2.082$; $p = 0.038$). Examination of this interaction using the JN test revealed that the association between adversity exposure and total symptoms was significant for individuals with hippocampal–vmPFC SFC <0.340 ($JN = [0.340, 13.490]$, moderator range = $[-0.730, 0.700]$), whereas for individuals with hippocampal–vmPFC SFC >0.340 , SFC buffered the association between adversity exposure and total symptoms such that it was no longer significant. Together, these results suggest that greater SFC in the amygdala–vmPFC circuit may buffer specifically against higher internalizing symptomatology, whereas greater SFC in the hippocampal–vmPFC circuit may buffer against higher total symptoms.

Amygdala–functional network and hippocampal–functional network development

Development of subcortical–functional network connections

Next, we sought to characterize age-related change among SFC connections between the amygdala, hippocampus, and the seven Yeo functional networks (Yeo et al., 2011; Fig. 4). Inclusion of a smoothed age term resulted in significantly improved model fit

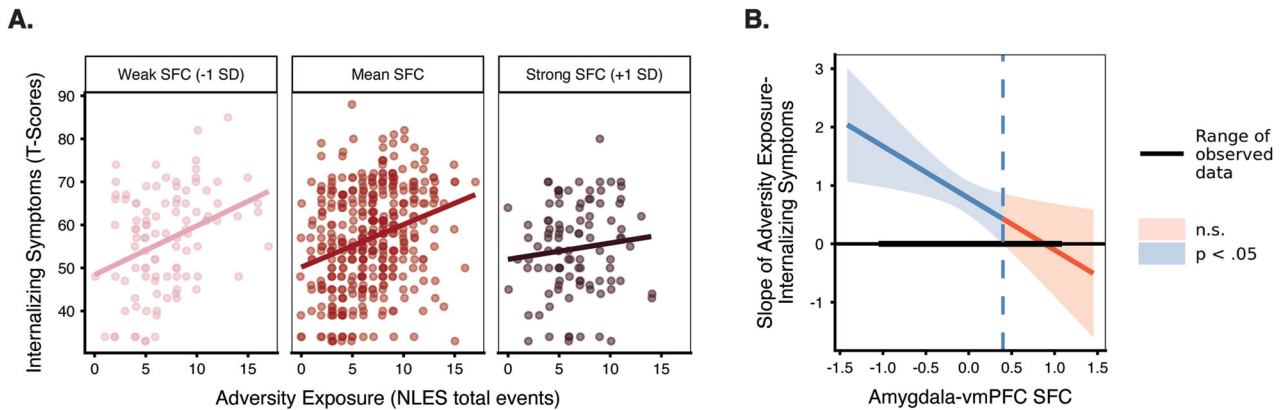


Figure 3. Amygdala–vmPFC SFC moderates the association between adversity exposure and internalizing symptoms. **A**, The interaction between amygdala–vmPFC SFC and adversity exposure was associated with internalizing symptoms. Associations between adversity exposure and internalizing symptoms were stratified across three levels of SFC strength (for visualization purposes). **B**, A JN plot depicts the statistically significant interval of the interaction. Amygdala–vmPFC SFC moderated the association between adversity exposure and internalizing symptoms. Adversity exposure was associated with internalizing symptoms when amygdala–vmPFC SFC was <0.400 , but this association was not significant in youth with amygdala–vmPFC SFC above 0.400.

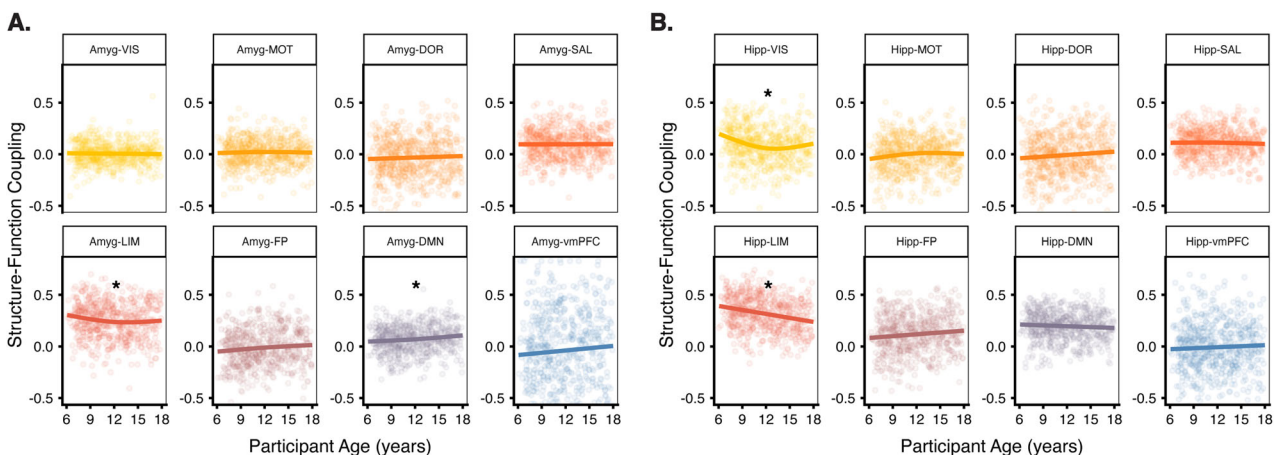


Figure 4. Associations between age and SFC among **(A)** amygdala–cortical and **(B)** hippocampal–cortical connections. Significant age effects are denoted with an asterisk. DMN, default mode network; FP, frontoparietal network; LIM, limbic network; SAL, salience network; DOR, dorsal attention network; MOT, somatomotor network; VIS, visual network; vmPFC, ventromedial prefrontal cortex.

for amygdala–limbic SFC ($p = 0.012$; partial $R^2 = 0.015$), amygdala–default mode SFC ($p = 0.041$; partial $R^2 = 0.007$), hippocampal–limbic SFC ($p < 0.001$; partial $R^2 = 0.046$), and hippocampal–visual SFC ($p < 0.001$; partial $R^2 = 0.040$). Further examination of these models revealed negative associations between age and amygdala–limbic SFC ($F_{(1,950)} = 4.833$; $\text{edf} = 1.777$; $p = 0.020$), hippocampal–limbic SFC ($F_{(1,001)} = 28.700$; $\text{edf} = 1.000$; $p < 0.001$), and hippocampal–visual SFC ($F_{(1,996)} = 11.390$; $\text{edf} = 1.938$; $p < 0.001$). There was a positive association between age and amygdala–default mode SFC ($F_{(1,001)} = 4.159$; $\text{edf} = 1.000$; $p = 0.042$). Age effects for hippocampal–limbic and hippocampal–visual SFC survived FDR correction across the seven network models per subcortical region ($p_{\text{FDR}} < 0.001$).

Interactions between age and adversity exposure in subcortical–functional network connections

In order to test the extent to which the age by adversity exposure interaction was specifically associated with SFC in the amygdala–vmPFC circuit, we next examined whether the interaction between age and adversity exposure was associated with SFC in connections between the hippocampus, amygdala, and the seven Yeo functional networks. Inclusion of a smoothed age by adversity exposure interaction term significantly improved model fit for hippocampal–limbic SFC alone ($p = 0.028$; partial $R^2 = 0.019$). Further examination revealed that the improved model fit was driven by separate main effects of age and adversity exposure. Refitting the model with main effects (excluding the non-significant age by adversity interaction) yielded significant main effects of age ($F_{(1,000)} = 34.227$; $\text{edf} = 1.000$; $p < 0.001$) and adversity exposure ($F_{(1,953)} = 2.933$; $\text{edf} = 1.784$; $p = 0.037$). However, the improvement in model fit afforded by inclusion of the adversity by age interaction and separate main effects was not significant after correcting for the seven models fitted for each of the Yeo functional networks ($p_{\text{FDR}} = 0.196$).

Exploratory analyses

Given that hippocampal–limbic SFC showed a main effect of adversity exposure, we examined whether SFC in this circuit (Fig. 5A) moderated associations between adversity exposure and clinical symptoms. With regard to internalizing symptoms, including an interaction between hippocampal–limbic SFC and adversity exposure significantly improved model fit relative to the model that included adversity exposure alone ($p = 0.034$; partial $R^2 = 0.005$). The full model showed a significant interaction between adversity exposure and hippocampal–limbic SFC for internalizing symptoms, such that youth with weaker hippocampal–limbic SFC showed a reduced association between adversity exposure and internalizing symptoms, compared with youth with stronger hippocampal–limbic SFC ($\beta = 0.098$; $\text{SE} = 0.038$; $t = 2.567$; $p = 0.010$; Fig. 5B). We probed this interaction using the JN test, which revealed that the association between adversity exposure and internalizing symptoms was significant for individuals with hippocampal–limbic SFC > 0.120 (JN = $[-1.470, 0.120]$; moderator range = $[-0.160, 0.740]$; Fig. 5C), whereas for individuals with hippocampal–limbic SFC < 0.120 the association between adversity exposure and internalizing symptoms was no longer significant. With regard to total symptoms, including an interaction between hippocampal–limbic SFC and adversity exposure marginally improved model fit relative to the null model ($p = 0.057$; partial $R^2 = 0.002$) and did not significantly improve model fit for externalizing symptoms ($p = 0.153$; partial $R^2 = 0.004$).

Next, it is plausible that a circuit could moderate associations between adversity and psychopathology even if it was not associated with adversity exposure in previous analyses. Thus, we comprehensively examined whether including an interaction between circuit SFC and adversity exposure as well as separate main effects improved model fit for each of the three symptom measures across each circuit connecting the seven Yeo functional networks with, separately, the hippocampus and the amygdala.

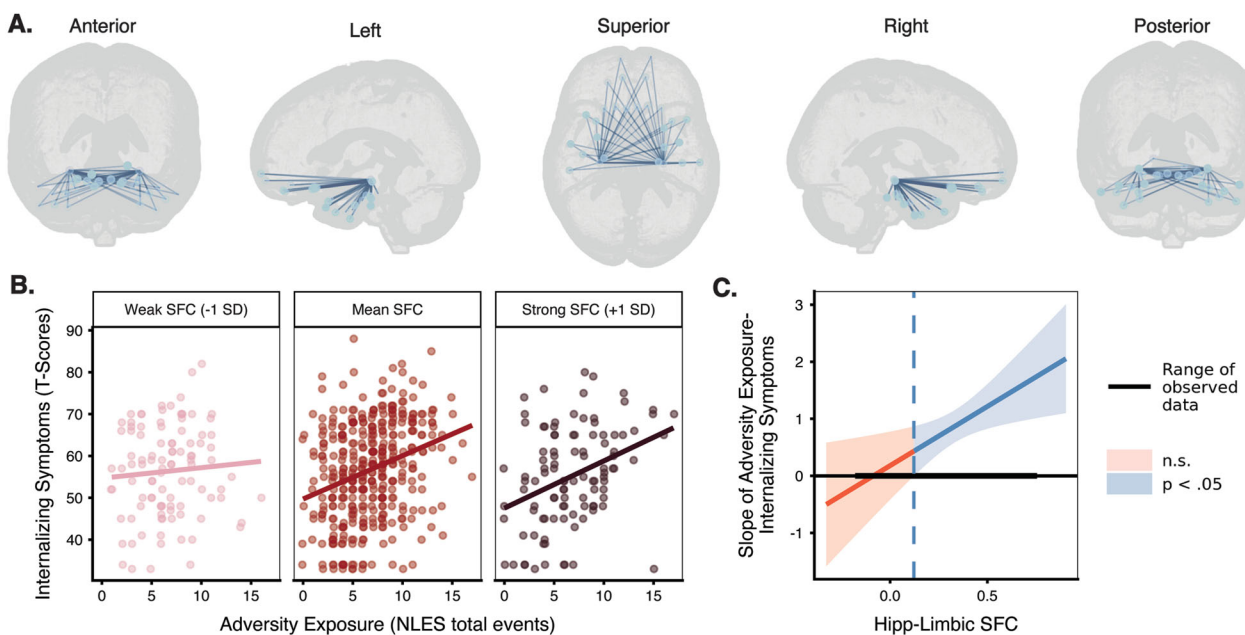


Figure 5. Hippocampal–limbic SFC moderates the association between adversity exposure and internalizing symptoms. **A**, Connections between bilateral hippocampi and nodes comprising the limbic functional network. **B**, The interaction between adversity exposure and hippocampal–limbic SFC was associated with internalizing symptoms. Associations between adversity exposure and internalizing symptoms were stratified across three levels of SFC strength (for visualization purposes). **C**, A JN plot depicts the statistically significant interval of the interaction. Specifically, adversity exposure was associated with internalizing symptoms for youth with hippocampal–limbic SFC > 0.120 , but not for youth with SFC < 0.120 .

In addition to the previously reported interaction between hippocampal–limbic SFC and adversity, we found that including an interaction between adversity exposure and hippocampal–visual SFC as well as separate main effects significantly improved the internalizing symptoms model fit relative to the null model ($p = 0.020$; partial $R^2 = 0.015$). Examination of the full model revealed that this effect was driven by the main effect of hippocampal–visual SFC, rather than the interaction between hippocampal–visual SFC and adversity. We refitted the model without the interaction term, which yielded a significant main effect of hippocampal–visual SFC on internalizing symptoms ($\beta = 0.108$; $SE = 0.041$; $t = 2.637$; $p = 0.009$). However, the model improvement afforded by including the interaction and main effect of hippocampal–visual SFC did not survive FDR correction ($p_{FDR} = 0.320$).

Discussion

Variability in the structural and functional development of connections linking the hippocampus and amygdala with the prefrontal cortex relates to adversity and underlies individual differences in stress responding, cognition, and mental health (Casey et al., 2019). However, structure and function have primarily been examined in isolation. Here, we demonstrate that adversity exposure relates to the coupling of structure and function (i.e., SFC) in amygdala–prefrontal and hippocampal–limbic circuits across development and that SFC in these circuits moderates the link between adversity and mental health. Specifically, we identified age-related increases in amygdala–vmPFC SFC among youth exposed to higher levels of adversity, a pattern that did not emerge in youth exposed to lower levels of adversity. Furthermore, stronger amygdala–vmPFC SFC buffered the association between adversity and internalizing symptoms. In parallel, greater adversity exposure was associated with weaker hippocampal–limbic SFC across development, and weaker hippocampal–limbic SFC attenuated the association between adversity and internalizing symptoms. These effects were circuit-specific and not observed in other amygdala–cortical or hippocampal–cortical connections. These findings suggest that amygdala–prefrontal and hippocampal–limbic SFC may index adversity-related circuit remodeling during development and that adaptive patterns of SFC may differ between stress regulation and memory circuits in ways that moderate risk for or resilience against internalizing psychopathology.

Bidirectional projections between the amygdala and vmPFC undergo dynamic changes over the course of development (Gabard-Durnam et al., 2014; Ojha et al., 2025) and can develop differently following adversity (Gee et al., 2013; Briant et al., 2021; Herzberg et al., 2021). In rodents, neuronal projections from the mPFC to the amygdala mature during the juvenile and early adolescent stages, with adolescent increases in inhibitory neurotransmission suggesting a sensitive period for amygdala–prefrontal circuit development (Arruda-Carvalho et al., 2017). In the present study, youth with higher adversity exposure showed an age-related increase in amygdala–vmPFC SFC. As SFC is sensitive to myelination and the neuronal excitation–inhibition ratio, both putative mechanisms of plasticity restriction (Fotiadis et al., 2023), this pattern may reflect experience-dependent increases in plasticity restriction factors in this circuit. Previous work suggests that stronger inhibitory connectivity within the amygdala–vmPFC pathway facilitates prefrontal regulation of amygdala reactivity (Quirk et al., 2003; Motzkin et al., 2015; Tottenham and Gabard-Durnam, 2017; He et al., 2023), which has been linked with improved stress regulation

(Phelps et al., 2004; Urry et al., 2006) and more resilient functioning (Zhang et al., 2023; van Rooij et al., 2024; Sisk et al., 2025b). In this context, stronger amygdala–vmPFC SFC in youth with higher adversity exposure may represent ontogenetic adaptation that facilitates regulation of neural stress responding. In line with our hypotheses, amygdala–vmPFC SFC buffered the association between adversity and internalizing symptoms, raising the possibility that stronger amygdala–vmPFC SFC contributes to resilience against psychopathology. At the same time, it is also plausible that individual differences in SFC that predate adversity exposure confer risk or resilience, and we cannot distinguish between these two possibilities in the present cross-sectional sample.

Hippocampal–cortical circuits also undergo protracted development that continues into adolescence (Casey et al., 2019; Calabro et al., 2020; Cruz-Sanchez et al., 2026). We observed a developmental decrease in SFC between the hippocampus and the limbic cortical network, primarily comprising entorhinal, parahippocampal, and orbitofrontal cortical regions. Prior studies have observed low SFC in cortical regions within the limbic network (Baum et al., 2020; Fotiadis et al., 2023), and we posit that age-related decreases in hippocampal–limbic SFC may reflect increasing functional signal diversity and flexibility within this circuit (Fotiadis et al., 2023). The present study further found that lower hippocampal–limbic SFC was associated with greater adversity exposure. One interpretation is that this association might represent adversity-related accelerated neurodevelopment within this circuit, beginning at an earlier age not captured in the present sample. Hippocampal–limbic connectivity is involved in cognitive functions such as memory encoding, retrieval, and recall (Chao et al., 2020; Setton et al., 2022; Raud et al., 2023), processes that can be altered in psychopathology (Godsil et al., 2013). Adversity-related changes in the development of SFC within the hippocampal–limbic circuit may be linked with earlier emergence of more mature cognitive functioning (Bath et al., 2016; Callaghan and Tottenham, 2016), potentially alongside adversity-related differences in learning and memory (Pattwell and Bath, 2017; Hardi et al., 2025). However, future longitudinal work incorporating behavioral and cognitive phenotyping will be required to test this hypothesis. Hippocampal–limbic SFC also moderated the association between adversity and internalizing symptoms, such that youth with weaker hippocampal–limbic SFC showed a reduced association between adversity and internalizing symptoms. These results align with longitudinal evidence in primates of adversity-related alterations in hippocampal–prefrontal connectivity predicting reduced anxiety-like symptoms in adulthood (Yuan et al., 2021). Together, these findings suggest that adversity-related neural adaptation within the hippocampal–limbic circuit can also contribute to resilience against psychopathology.

Stronger amygdala–vmPFC SFC and weaker hippocampal–limbic SFC moderated the adversity–internalizing symptoms association, suggesting that both circuits might contribute to resilience against psychopathology, but through opposite patterns of coupling. In other words, neural signatures of risk for or resilience against psychopathology may be multidimensional rather than stronger or weaker SFC being uniformly advantageous. Such nuanced patterns of adaptive SFC may be organized by circuit function and developmental patterning, as illustrated by the distinct roles of amygdala–vmPFC and hippocampal–limbic circuits in stress regulation and memory processes, respectively. In exploratory analyses, we also observed a positive

main effect of hippocampal–visual network SFC on internalizing symptoms. While this effect did not survive multiple-comparisons correction and should thus be interpreted with caution, it aligns with literature suggesting that visual network circuits are linked with internalizing psychopathology in youth (Qu et al., 2025). This finding underscores the possibility that adversity-related shifts in neurodevelopment that are associated with clinical symptoms may coexist alongside neurobiological risk or resilience factors not associated with adversity exposure. Future longitudinal studies are needed to characterize multidimensional neural and behavioral features of resilience over time. Furthermore, prospective assessment of adversity exposure would facilitate better understanding of the respective contributions of neurodevelopmental adaptations to adversity versus intrinsic risk or resilience factors to youth mental health.

The present study has a number of strengths, including a relatively large sample of youth, rigorous characterization of multimodal links between brain structure and function, and robust processing and analytic methods. The sample included individuals with a wide range of adversity exposure and clinical diagnoses, capturing an important cross-section of youth experience that may yield more generalizable findings (Marek and Laumann, 2024). However, there are several important limitations to note. While we used the total adverse events score from the NLES (Sandler et al., 1991), accounting for additional features of adverse events and the contexts in which they occur can help to explain variability in outcomes (McLaughlin et al., 2014; Gee and Casey, 2015; Cohodes et al., 2021; Pollak and Smith, 2021; Ellis et al., 2022). In future work, accounting for features such as developmental timing of adversity (Pechtel et al., 2014; Sicorello et al., 2021; Cohodes et al., 2023; Zhu et al., 2023; Sisk et al., 2025a,b) may yield greater insight into the precise temporal dynamics of neurodevelopment following adversity. We also controlled for differences in caregiver education and total household income in the present study. While this approach isolates the effects of adversity relative to the child's larger family-level environmental context, adversity and socioeconomic status are often intertwined (Mills-Koonce and Towe-Goodman, 2012). This approach may thus dilute the effect size observed for adversity. Inter-regional tractography, as was used to construct the structural connectome, also has known limitations. Streamlines exhibit a relatively high false-positive rate and distance-dependent bias (Reveley et al., 2015; Maier-Hein et al., 2017). While we mitigated these limitations by using a weighted thresholding approach, future advances in estimating correspondence between neural structure and function may improve upon the present methods. Finally, this study is limited to cross-sectional inference into the development of subcortical–cortical SFC, precluding the possibility of conducting mediation analyses. The temporal characteristics of the effects reported here (e.g., whether individual differences in SFC that are related to adversity and psychopathology reflect adaptive neurodevelopmental change or preexisting individual differences) cannot be determined from data collected at a single timepoint. Furthermore, age-related effects observed in cross-sectional studies may differ from effects observed longitudinally over the course of development (Pfefferbaum and Sullivan, 2015). Leveraging data from large-scale longitudinal studies such as the Adolescent Brain Cognitive Development (Casey et al., 2018) and Healthy Brain and Child Development (Volkow et al., 2024) studies to investigate how these patterns emerge within individuals will provide valuable insight into how the present findings may be recapitulated within-person.

Conclusions

The present study identified adversity-related differences in coupling between the structure and function of amygdala–vmPFC and hippocampal–limbic circuits across development. Youth with higher adversity exposure showed greater age-related increases in amygdala–vmPFC SFC, relative to youth with lower exposure, potentially reflecting adaptive neurodevelopmental change. Adversity exposure was also negatively associated with hippocampal–limbic SFC across development. Furthermore, stronger amygdala–vmPFC SFC and weaker hippocampal–limbic SFC moderated the association between adversity and internalizing symptoms. Together, these findings suggest the possibility that adversity exposure may adaptively shape developing brain structure and function in a manner that can promote resilience against internalizing symptomatology. The directionally distinct links between adversity and SFC in amygdala–vmPFC and hippocampal–limbic circuits suggest that putative adversity-related adaptations are circuit-specific rather than reflecting a single neural signature of risk or resilience.

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