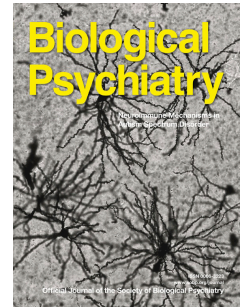


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**Stress-related psychopathology shapes episodic memory development in youth:
Network-level brain predictors and relations with early-life stress**

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Short title: Stress and brain connectivity predict memory in youth

Keywords: early-life stress, episodic memory, development, connectome predictive modeling

Abstract

Background: Episodic memory processes and their underlying neural circuitry have been closely linked with stress-related psychopathology; however, the temporal and directional nature of these links remains unclear. Understanding how large-scale brain networks and psychopathology symptoms relate to changes in episodic memory across development is important for identifying at-risk youth and guiding developmentally-tailored interventions.

Methods: We used latent change score modeling to examine longitudinal associations between stress-related psychopathology and episodic memory in $N = 3,466$ youth aged 9-10 from the Adolescent Brain Cognitive Development (ABCD) Study. We then trained and tested resting-state functional connectivity (rsFC) networks to predict changes in episodic memory using connectome-based predictive modeling, and examined how these networks and stress-related psychopathology mediate links between early-life stress and memory.

Results: Stress-related psychopathology emerged as a leading predictor of change in episodic memory in youth. Whole-brain rsFC networks successfully predicted developmental changes in episodic memory. Specifically, stronger connectivity in the visual association area, primary visual cortex, and secondary visual cortex predicted less improvement in episodic memory over two years, whereas stronger connectivity in the cerebellum and subcortical networks predicted greater improvement in episodic memory over two years. Finally, rsFC and stress-related psychopathology mediated the association between higher early-life stress and less improvement in episodic memory.

Conclusions: Together, these findings suggest that early-life stress, network connectivity, and stress-related psychopathology contribute to episodic memory development. The identification of these neurobiological and early environmental predictors may contribute to better understanding

of potential interventions targeting maladaptive memory processes in youth with stress-related psychopathology.

INTRODUCTION

Episodic memory, the capacity to form and retrieve specific memories of past events, undergoes dynamic changes throughout development (1–4). Prior work suggests that episodic memories are altered in stress-related psychopathology, such as post-traumatic stress disorder (PTSD; 5). However, whether these alterations provide a possible mechanistic account of stress symptom etiology or occur as a consequence of the onset of psychopathology is unclear from the literature, which in general is dominated by cross-sectional rather than longitudinal studies. While alterations in episodic memory may emerge after the onset of stress-related psychopathology (6), disruptions in key memory-related neural systems may also serve as a premorbid risk factor for the development of PTSD (7). These memory-related neural systems include cortical networks such as the frontoparietal (8) and default mode networks (9), and subcortical structures such as the hippocampus (1,2). Notably, during childhood and adolescence, hippocampal networks undergo significant developmental changes, with increasing structural (10) and functional integration (11) between the hippocampus and prefrontal and parietal cortices, particularly during middle childhood (often defined as ages 6-11; 2). Middle childhood and early adolescence, in particular, are characterized by both improvements in episodic memory (2) and the onset of internalizing psychopathology (12).

Given shared underlying neurobiology between stress-related psychopathology and memory (e.g., hippocampal structure and function; 13), it may also be the case that external factors, such as exposure to early-life stress, shape trajectories of both constructs. Cross-species research supports the notion that early-life stress exposure can alter memory encoding and retrieval, with resultant effects on fear- and depression-related behaviors (14–16). Mechanistically, early-life stress may shape key neural circuits that support memory processes,

leading to altered memory functioning, as well as increased risk for stress-related psychopathology. However, studies of the nature and direction of these links have been limited by a dearth of longitudinal data, measurement of only one or a limited number of types of episodic memory, and small sample sizes. Longitudinal datasets, such as the Adolescent Brain Cognitive Development (ABCD;17) Study, provide opportunities to examine changes in memory and psychopathology at multiple timepoints during development. The current study leveraged data from the ABCD Study to examine neurobehavioral predictors of episodic memory development in youth.

The first aim of this study was to clarify the longitudinal associations between episodic memory and stress-related psychopathology in youth. Based on prior work, we hypothesized that there would be either a significant link between baseline stress-related psychopathology and change in episodic memory or baseline episodic memory and change in stress-related psychopathology. Our second aim was to identify the neural predictors of episode memory development. Here, we chose to employ connectome-based predictive modeling (CPM; 18). Compared to multivariate methods (e.g., canonical correlation analysis), CPM prioritizes network interpretability, allowing for more straightforward investigations of brain-behavior associations. We hypothesized that large-scale networks that include the prefrontal cortex and hippocampus would emerge as predictive of episodic memory development. Our third aim was to examine how early-life stress relates to these identified predictors (i.e., stress-related symptoms and neural connectivity) of episodic memory, and we hypothesized that stress-related symptoms and brain networks would mediate associations between early-life stress and episodic memory.

METHODS

Data were drawn from the Adolescent Brain Cognitive Development (ABCD) Study, an ongoing longitudinal study of 11,878 youth across 21 study sites in the United States (17). We used baseline and two-year follow-up data from $N = 3,466$ youth from the 5.0 data release. Participants were excluded if 1) their baseline resting-state data did not pass the inclusion quality control criteria from the ABCD analytic core, and 2) they had missing baseline or two-year follow-up data for variables used in the current analyses. Sample demographics are presented in **Table 1**. Additional ABCD procedures are presented in the Supplement.

Measures

Episodic memory

Our measure of episodic memory incorporated participants' performance on several standard episodic memory measures, described below and further in the Supplement.

NIH Toolbox Picture Sequence Memory Test

At baseline and the two-year follow-up, youth participants completed the NIH Toolbox Picture Sequence Memory Test (20). The Picture Sequence Memory Test assesses visuospatial sequencing and memory by requiring participants to recall increasingly lengthy series of pictures depicting activities/events. For both timepoints, total uncorrected (i.e., non-age-corrected) task scores (i.e., total correct) were used in analyses.

Rey Auditory Verbal Learning Test

At baseline and the two-year follow-up, youth participants completed the Rey Auditory Verbal Learning Test (RAVLT; 21). This test requires participants to listen to and recall a list of 15 unrelated words on each of five learning trials. For both timepoints, performance (i.e., total correct) on the delayed recall trial (i.e., RAVLT Trial VII) was used in analyses.

Emotional N-back task: Recognition memory test

At baseline and the two-year follow-up, youth participants completed the Emotional N-back (EN-back) task followed by a recognition memory test (17). This test included 48 old stimuli presented during the EN-back task and 48 new stimuli, with equal numbers of each emotion category in the old and new stimulus sets (12 each of happy, fearful, and neutral facial expressions, and places as control stimuli). For both timepoints, d-prime (i.e., the relative proportion of hits to false alarms) for each of the 4 stimulus sets was used separately in analyses.

Stress-related psychopathology

At baseline and the two-year follow-up, parents of youth participants completed the Child Behavior Checklist (CBCL) (22), which assesses dimensional psychopathology symptoms. For both timepoints, we used the standardized Total Stress Problems score, a sum score of items that assess stress-related symptoms, such as alterations in mood and somatic complaints, in analyses.

Early-life stress

At baseline, parents completed the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-5; 23). Items from the PTSD module were used to determine cumulative exposure to potentially traumatic events (1 = yes; 0 = never experienced). Total early-life stress was calculated by summing the number of endorsed events for each participant.

Resting-state functional connectivity

At the baseline visit, youth completed four 5-minute resting-state fMRI scans (procedures described in detail, 17). Data were preprocessed by the ABCD Consortium's data analytic core using the Human Connectome Project pipeline (24,25). We used the resting-state fMRI data preprocessed by the ABCD-Brain Imaging Data Structure Community Collection team (26). Tabulated imaging data from the NDA 5.0 release were used in sensitivity analyses only (data used for these sensitivity analyses were not subject to the noted error in the 5.0 release, which

was relevant only for tabulated imaging data representing rsfMRI correlations between cortical networks and subcortical ROIs). Further details regarding imaging procedures are detailed in the Supplement.

Analytic plan

Bivariate latent change score model

To examine change in memory scores across time, we computed multiple indicator univariate latent change scores within a structural equation modeling framework using the lavaan package in R. Latent change score models allow for the modeling of change at the construct level and are especially useful for testing cross-domain couplings (27). Here, we used observed measures of episodic memory administered at each timepoint (baseline and two-year follow-up) to model change in latent episodic memory. Specifically, we modeled a latent change in episodic memory factor using six observed measurements of episodic memory: the NIH Toolbox Picture Sequence Memory Test, the Rey Auditory Verbal Learning Test (RAVLT), and the four stimulus types from the EN-back recognition test.

We extended our univariate latent change score model to a bivariate latent change score model (BLCSM) by including a second domain of interest, stress-related psychopathology. In order to test the robustness of our findings (28), we ran the BLCSM with both maximum likelihood and Bayesian estimation methods. Metrics of fit and results from our maximum likelihood model are described in the Supplement. Maximum likelihood models controlled for propensity weights and sibling relatedness. Factor scores for change in episodic memory were extracted for each participant as an estimate of latent episodic memory change where higher scores reflect greater improvements in episodic memory. All subsequent analyses used this factor score representing individual change in episodic memory.

Functional connectivity matrix construction

CPM was implemented in a manner consistent with prior work (18). We constructed static whole-brain resting-state functional connectivity (rsFC) matrices using baseline fMRI data. Unlike hypothesis-driven analyses that focus on predefined resting-state networks, the networks identified from CPM are empirically-defined, built on parcels from a chosen atlas. Consistent with previous studies using CPM (18), network nodes were defined using the Shen 368-node atlas (29,30), which includes anatomical subcortical segmentations and functional cortical parcellations. See Supplement for additional information on the matrix construction procedure.

Connectome-based predictive modeling

Leave-one-out-cross-validation (LOOCV) was used to build models testing the associations between rsFC and latent change in episodic memory. As previously described (18), after CPM model fitting, edges that were significantly correlated with the outcome variable above a feature selection threshold of $p < 0.01$ were selected using p-threshold filtering. We collected edges that survived this thresholding across all models, and we separated LOOCV-surviving edges into positive coefficient and negative coefficient networks and created network-level averages for rsFC. This separation of positive and negative edges is in line with standard approaches employing CPM (18). Specifically, edges exhibiting a significant positive association with change in episodic memory comprise the positive predictive network, whereas edges exhibiting a significant negative association comprise the negative predictive network. It is important to note that these designations refer to the direction of the edge-behavior association and not to positive or negative functional connectivity between brain regions. This data-driven method requires no a priori selection of networks, with the model building procedure separately identifying edges for which connectivity is positively or negatively correlated with memory

scores above the feature selection threshold of $p < 0.01$. These edges are allocated to positive and negative predictive networks respectively. While the positive and negative networks are topologically distinct and edges cannot overlap by definition, they may share nodes. Average rsFC values of the positive and negative networks were then included as independent variables in linear mixed-effects models with change in episodic memory as the outcome variable. We extracted average rsFC across the same edges from each hold-out participant from LOOCV, and then used the linear model to predict each outcome variable. Model performance was assessed as the Pearson correlation between the predicted and observed values of the outcome variable in the full hold-out sample. P -values for model performance were estimated with permutation testing, repeating the above procedure using 1,000 randomly-shuffled values of the outcome variable and comparing true model performance to this null distribution.

Parallel mediation models

Parallel mediation models were tested using the PROCESS Macros (31) in R. Early-life stress served as the predictor variable and latent change in episodic memory served as the outcome variable. Individual “network strength” was calculated by averaging the edges in the positive and negative networks separately, which were then used as mediators alongside baseline stress-related psychopathology. Two separate models were run, one for the CPM-identified positive network and one for the CPM-identified negative network. Sex assigned at birth, age at scan, and scanner site were included as covariates.

Sensitivity analyses

We ran sensitivity analyses using BLCSMs to examine whether the relation between stress-related psychopathology and episodic memory extended to working memory or executive functioning. We also tested whether change in episodic memory could be detected with

alternative established networks derived from the Gordon parcellation. Finally, we examined linear associations between stress-related psychopathology and the rsFC networks.

RESULTS

Directionality of the relationship between episodic memory and stress-related psychopathology

Using six separate observed indices of episodic memory and an observed index of stress-related psychopathology, BLCSM (shown in **Figure 1**) showed adequate fit with Bayesian estimation methods (DIC = 196,570.8, WAIC = 196,587.4, BGamHat = 0.924). Baseline stress-related psychopathology predicted change in episodic memory ($B = -0.045$, 90% CI = -0.067 – -0.025). We also observed that change in stress-related psychopathology was correlated with change in episodic memory ($B = -0.80$, 90% CI = -1.372 – -0.252). However, we did not find evidence that baseline episodic memory predicted change in stress-related psychopathology ($B = 0.075$, 90% CI = -0.004 – 0.155) or for a transactional model. Fit for the multiple indicator univariate latent change score model (i.e., the episodic memory measurement model) and distributions for our observed and latent variables can be found in the Supplement.

Figure 1. Multiple indicator bivariate latent change score model. Coefficients using Bayesian estimation methods. NIH TPS = NIH Toolbox Picture Sequence Task; RAVLT = Rey Auditory Verbal Learning Test; EN-BACK REC = Emotional N-back recognition memory task; EM = Episodic memory; SX = Stress-related symptoms; CBCL = Child Behavior Checklist. Bolded coefficients have confidence intervals that exclude 0. The red arrow indicates that the Z path is significant. Note: Stimulus sets (i.e., positive, negative, neutral, place) for the Emotional N-back recognition memory task are collapsed into one indicator for visualization purposes. Parameter estimates for the episodic memory measurement model are provided in the Supplement.

Brain networks predicting change in episodic memory

CPM significantly predicted change in episodic memory relative to chance (**Figure 2**). Specifically, both the positive and negative network predicted change in episodic memory in a cross-validated framework (positive model, $r_s = .069$, permuted $p < .001$; negative model, $r_s = .084$, permuted $p < .001$). Supplementary analyses using 20-fold cross-validation yielded similar prediction results for the positive ($r_s = .086$, permuted $p < .001$) and negative network ($r_s = .081$, permuted $p < .001$). The identified positive network contained 1,219 edges, while the identified negative network contained 1,718 edges. Notably, the negative network included a greater proportion (adjusted for network size) of edges connected to the visual association area, primary visual cortex, and secondary visual cortex relative to the positive network, which included a greater proportion of edges connected to the cerebellum and subcortical networks (**Figure 3**).

Figure 2. CPM predicted change in episodic memory. This predictive model yielded two brain networks: a positive network (left) associated with greater improvement in episodic memory ($r_s = .069$, permuted $p < .001$) and a negative network (right) associated with lower improvement in episodic memory ($r_s = .084$, permuted $p < .001$).

Figure 3. Edges identified in the CPM predicting change in episodic memory. **A)** Plot of the positive (red) and negative (blue) networks predicting change in episodic memory. The positive network contained fewer edges (or connections) than the negative network (1,219 vs 1,718). Each line represents a network connection, and each circle represents nodes in the network. Node size corresponds to node degree (number of connections attached to the particular node). **B)** Proportion of edges belonging to specific subnetworks. The negative network included a greater proportion (adjusted for network size) of edges connected to the visual association area, primary visual cortex, and secondary visual cortex relative to the positive network, which included a greater proportion (adjusted for network size) of edges connected to the cerebellum and subcortical networks. Networks identified: Cerebellum (Cer), Default Mode Network (DMN), Fronto Parietal (FP), Medial Frontal (MF), Motor, Subcortical (SC), Salience Network (SN), Visual Association (Vas), Visual I (VI), Visual II (VII).

Mediating roles of brain networks and stress-related psychopathology in the association between early-life stress and episodic memory

We next considered how identified predictors of episodic memory (i.e., stress-related psychopathology and functional network connectivity) related to early-life stress. Here, we tested for a mediating role of stress-related psychopathology in the association between early-life stress and change in episodic memory, as well as the mediating role of network connectivity (within

the memory change-predictive networks identified via CPM) on the associations between early-life stress and change in episodic memory.

In our model run with the negative CPM network, we observed a significant positive direct effect of early-life stress on stress-related psychopathology ($B = 0.87, p < .001$), with more early-life stress predicting greater stress-related psychopathology (**Figure 4**). We also observed a significant positive direct effect of early-life stress on network connectivity in the negative network, with more early-life stress predicting stronger connectivity in this network ($B = 0.002, p = .043$). The direct effect of early-life stress on change in episodic memory was not significant ($B = -0.05, p = .117$). However, early-life stress was associated with change in episodic memory indirectly through both stress-related psychopathology ($B = 0.03, 95\% \text{ CI } [0.017, 0.051]$) and connectivity in the negative network ($B = -0.01, 95\% \text{ CI } [-0.027, -0.003]$).

In our model run with the positive CPM network, we again observed a significant positive direct effect of early-life stress on stress-related psychopathology ($B = 0.87, p < .001$). We also observed a significant negative direct effect of early-life stress on network connectivity in the positive network, with more early-life stress predicting weaker connectivity in this network ($B = -0.004, p < .001$). The direct effect of early-life stress on change in episodic memory was not significant ($B = -0.04, p = .271$). However, early-life stress was associated with change in episodic memory indirectly through both stress-related psychopathology ($B = 0.03, 95\% \text{ CI } [0.017, 0.051]$) and connectivity in the positive network ($B = -0.03, 95\% \text{ CI } [-0.045, -0.018]$; **Figure 5**). Unstandardized coefficients for the indirect effects in both models are displayed in **Table 2**.

Figure 4. Parallel mediation model with early-life stress and the negative network. Unstandardized beta coefficients from the direct paths are shown here. Stress-related psychopathology ($B = 0.03$, 95% CI [0.017, 0.051]) and connectivity in the negative network ($B = -0.01$, 95% CI [-0.027, -0.003]) mediate the association between early-life stress and change in episodic memory. $*p < .05$, $***p < .001$.

Figure 5. Parallel mediation model with early-life stress and the positive network. Unstandardized beta coefficients from the direct paths are shown here. Stress-related psychopathology ($B = 0.03$, 95% CI [0.017, 0.051]) and connectivity in the positive network ($B = -0.03$, 95% CI [-0.045, -0.018]) mediate the association between early-life stress and change in episodic memory. $*p < .05$, $***p < .001$.

Sensitivity analyses

Sensitivity analyses suggest we cannot reliably examine change in working memory or executive functioning with the available ABCD measures due to poor model fit ($CFI = 0.624$, $RMSEA = 0.515$, $SRMR = 0.270$, and $CFI = 0.624$, $RMSEA = 0.484$, $SRMR = 0.243$, respectively). Results also showed that Gordon parcellation-defined rsFC within the default mode network significantly predicted change in episodic memory ($B = 1.95$, $p = .001$). In addition, separate linear models showed that there was no significant association between rsFC and stress-related psychopathology for the negative network ($B = 0.00$, $p = .736$) or positive network ($B = 0.00$, $p = .563$). Full sensitivity analyses are reported in the Supplement.

DISCUSSION

In the current study, we examined neurobehavioral and early environmental predictors of episodic memory development in youth. Our findings point to changes in stress-related psychopathology over development as a leading indicator of changes in episodic memory in youth, and identify important roles of whole-brain connectivity and early-life stress exposure in memory development. Specifically, we show that early-life stress predicts change in episodic memory through both stress-related psychopathology and whole-brain resting-state functional networks identified using CPM. Overall, our findings support the important roles that both stress-related symptoms and brain networks play in shaping memory systems during key neurodevelopmental periods.

Using latent change score modeling, we found that greater stress-related psychopathology preceded and predicted less improvement in episodic memory performance. This finding extends previous research on the association between stress-related psychopathology and episodic memory. While previous findings have shown that stress-related psychopathology, such as PTSD, is associated with reduced episodic recollection of both

1 traumatic (32) and non-traumatic (33) events, the directionality of this relationship, particularly
2 in childhood, has remained unclear. The current findings suggest a leading role of stress-related
3 psychopathology in relation to episodic memory development in youth, consistent with the view
4 that the presence of mental health symptoms earlier in life can shape long-term cognitive
5 functioning (34,35). We also observed that change in stress-related psychopathology was
6 correlated with change in episodic memory, suggesting these variables may exhibit co-occurring
7 trajectories, potentially reflecting shared underlying neurobiological processes. We did not see
8 reliable evidence that the association with stress-related symptoms held for working memory and
9 executive functioning. Given that prior work has found associations between stress and these
10 processes (36–38), future work should examine whether stress-related symptoms predict
11 developmental change in cognitive functions beyond episodic memory.

12 Applying CPM revealed that patterns of whole-brain connectivity could predict change in
13 episodic memory. We identified predictive positive and negative networks, whereby greater
14 connectivity predicted more improvement and less improvement in episodic memory,
15 respectively. As is standard with CPM, the identified predictive networks comprise connections
16 distributed across multiple canonical brain networks rather than a single predefined functional
17 network. We note that CPM is not intended to support strong claims about specific functional
18 connections (18) and, given the lack of behavioral data during the scans, that interpretation of the
19 functional significance of the identified networks would rest on reverse inference (39). Still, we
20 contextualize some of the current findings in prior literature in order to contribute to hypothesis
21 generation for future, more mechanistic investigations of these processes. Although the positive
22 and negative networks are topologically distinct and edges cannot overlap by definition, they do
23 share some key “hubs.” For instance, both networks include a significant number of connections

with the dorsolateral prefrontal cortex (dlPFC), but the regions that are functionally coupled with the dlPFC diverge: the positive network includes dlPFC connectivity with the hippocampus, whereas the negative network includes dlPFC connectivity with the visual association area. Connections between the prefrontal cortex and hippocampus have been proposed to play a critical role in episodic memory functioning, with the hippocampus contributing to the organization of memories within the context in which they are experienced, and the prefrontal cortex supporting the retrieval of context-appropriate memories (40). More so, disruptions in functional connectivity between the hippocampus and the prefrontal cortex have been implicated in altered memory processes (41,42). These findings build on prior work showing that developmentally-normative increases in hippocampal-prefrontal connectivity are associated with improvements in episodic memory functioning (43,44). The negative network exhibited a greater proportion of edges with connections to the visual association area, primary visual cortex, and secondary visual cortex relative to the positive network. While speculative, in the context of prior work showing a developmental shift from reliance on the visual system to reliance on prefrontal regions during episodic encoding (45), a lower reliance on visual-specific processes for episodic memory in middle childhood may be adaptive for memory functioning.

Finally, we observed significant indirect effects, where both stress-related psychopathology, as well as the identified positive and negative episodic memory networks, mediated the link between early-life stress and change in episodic memory. The link between early adversity and memory development in youth has been well-documented (46,47), and our findings suggest that stress-related symptoms and neural connectivity play key mechanistic roles in these associations. There is evidence that youth exposed to early-life stress exhibit alterations in memory-relevant neural regions, such as the hippocampus, and that these alterations may lead

1 to decreased episodic memory performance (48). Prior work has also shown that alterations in
2 verbal memory are associated with PTSD in youth, but not with trauma exposure in the absence
3 of PTSD, suggesting stress-related symptoms may be critical for observed alterations in memory
4 functioning following trauma exposure (49). In addition, given that the association between
5 connectivity and stress-related psychopathology was not significant, our results suggest that the
6 effect of stress-related psychopathology on change in episodic memory is distinct from the effect
7 of rsFC on change in episodic memory. This finding was expected given that the measure of
8 rsFC was extracted from the CPM used to predict change in episodic memory, not change in
9 stress-related psychopathology. It may be the case that neurobiological systems more canonically
10 relevant to stress-reactivity, such as prefrontal connectivity with the amygdala and hippocampus
11 (50,51), contribute to associations between stress-related symptoms and memory processes.

12 The findings should be considered in light of several limitations. First, although we
13 successfully identified predictive whole-brain functional networks at rest, this may preclude an
14 understanding of the real-time functional role of the identified network connections, and future
15 work may benefit from examining task-based neural correlates of episodic memory. Second, we
16 focused on parent-reported stress-related symptoms and early-life stress given the lack of child
17 self-reported symptom data at the necessary timepoints (i.e., baseline and the two-year follow
18 up). However, given evidence of discrepancies in parent- and youth-reported mental health
19 symptoms (52), future work would benefit from considering youth reports as well. Third, it is
20 important to note that there is somewhat limited variability in early-life stress and stress-related
21 psychopathology in the current sample, which is expected given that the ABCD Study includes a
22 community sample of youth who were not selected based on any criteria such as stress exposure.
23 Future work in samples with higher stress exposure and in clinical populations will be important

to understand to more fully understand the relations between stress-related symptoms and episodic memory following early-life stress. Fourth, we focused on a narrow age range (9-11 years old). Past research has shown that episodic recall processes exhibit significant improvements from ages 8-11 years old (2,3). Prior to this middle childhood period, episodic memories are often prone to forgetting, particularly before 3 years old, though the ability to recall contextual details associated with events shows improvement between 4 and 6 years of age (53,54). As such, predictors of memory changes identified in this study would almost certainly differ if examined in youth younger or older than these ages. Fifth, it is possible that the positive and negative networks identified here represent dissociable mechanisms, or that they represent two subcomponents of a single underlying mechanism. While CPM summarizes edges according to the sign of their associations with behavior, this method cannot distinguish between these possibilities. As such, future work comparing CPM with other multivariate predictive approaches would be valuable for determining whether the positive/negative network distinction reflects meaningful neurobiological organization or represents subcomponents of a single network. Finally, consistent with the increased statistical power to observe small effects in large samples such as the ABCD Study, the effect sizes in this study are small as in other ABCD fMRI studies (e.g.,55). Future work is needed to determine the potential clinical implications of these small effects.

In conclusion, our study examined neurobehavioral and environmental predictors of memory trajectories in a large sample of youth. We clarified the directionality of the relationship between stress-related symptoms and episodic memory in this sample, and found that both stress-related psychopathology and distinct patterns of resting-state network connectivity predicted changes in episodic memory during development. The relationship between early-life stress and

change in episodic memory was mediated by resting-state connections and baseline stress-related psychopathology. Though further investigation is needed, the identification of these neurobiological and early environmental predictors may have implications for understanding links between stress-related symptoms and episodic memory across development.

Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

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listing of the study investigators can be found at https://abcdstudy.org/consortium_members/.

ABCD consortium investigators designed and implemented the study and/or provided data but

did not necessarily participate in analysis or writing of this report. This manuscript reflects the

views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium

investigators. The ABCD data repository grows and changes over time. The ABCD data used in

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Data Transparency: Code to facilitate reproducibility can be found here:

<https://github.com/Yale-CANDLab>.

Supplement Description:

Supplement Methods, Results, Figures S1-S6, Table S1

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Characteristic	Baseline (T1)	1-year follow-up (T3)	2-year follow-up (T5)
	M (SD)	M (SD)	M (SD)
Age	9.96 (7.51)	10.86 (5.23)	11.79 (5.45)
Sex assigned at birth	n (%)	—	—
Male	1,760 (50.78%)	—	—
Female	1,706 (49.22%)	—	—
Race and Ethnicity ^a	n (%)	—	—
Asian	198 (5.71%)	—	—
Black	527 (15.20%)	—	—
Hispanic	573 (16.53%)	—	—
Native Hawaiian, Pacific Islander, Alaskan Native, American Indian, or Multiracial	131 (3.78%)	—	—
White	2,843 (82.03%)	—	—
NIH Toolbox Picture Sequence Memory Test	104.28 (11.79)	—	110.19 (11.89)
Rey Auditory Verbal Learning Test	9.58 (3.04)	—	9.36 (2.84)
Emotional N-back (positive)	0.56 (0.84)	—	0.92 (0.94)
Emotional N-back (negative)	0.54 (0.82)	—	0.87 (0.90)
Emotional N-back (neutral)	0.45 (0.79)	—	0.78 (0.88)
Emotional N-back (place)	0.96 (1.06)	—	1.46 (1.15)
Stress-related psychopathology	52.92 (5.58)	—	52.76 (5.32)
Early-life stress	0.48 (0.93)	—	—

Table 1. Demographic, behavioral, and clinical characteristics of the sample across timepoints. Means and standard deviations (continuous variables), and frequencies and percentages (categorical variables) displayed. ^aPercentages for race/ethnicity do not sum to 100% due to multiracial reporting (i.e., some participants endorsed more than 1 race/ethnicity category).

Indirect effect (negative network)	<i>B</i>	SE	LLCI	ULCI
Stress-related psychopathology	0.03	0.009	0.017	0.051
Resting-state network connectivity	-0.03	0.007	-0.045	-0.018
Indirect effect (positive network)				
Stress-related psychopathology	0.03	0.009	0.017	0.051
Resting-state network connectivity	-0.01	0.006	-0.027	-0.003

Table 2. Results from mediation models that demonstrate the indirect effects of early-life stress on change in episodic memory through stress-related psychopathology and resting-state network connectivity (with separate effects for the negative and positive network). *B* = unstandardized beta; SE = standard error; LLCI = lower limit confidence interval; ULCI = upper limit confidence interval

