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Triple Interactions Between the Environment, Brain, and Behavior in Children: An ABCD Study

Dongmei Zhi, Rongtao Jiang, Godfrey Pearlson, Zening Fu, Shile Qi, Weizheng Yan, Aichen Feng, Ming Xu, Vince Calhoun, and Jing Sui

ABSTRACT

BACKGROUND: Environmental exposures play a crucial role in shaping children's behavioral development. However, the mechanisms by which these exposures interact with brain functional connectivity and influence behavior remain unexplored.

METHODS: We investigated the comprehensive environment-brain-behavior triple interactions through rigorous association, prediction, and mediation analyses, while adjusting for multiple confounders. Particularly, we examined the predictive power of brain functional network connectivity (FNC) and 41 environmental exposures for 23 behaviors related to cognitive ability and mental health in 7655 children selected from the Adolescent Brain Cognitive Development (ABCD) Study at both baseline and follow-up.

RESULTS: FNC demonstrated more predictability for cognitive abilities than for mental health, with cross-validation from the UK Biobank study (N = 20,852), highlighting the importance of thalamus and hippocampus in longitudinal prediction, while FNC+environment demonstrated more predictive power than FNC in both cross-sectional and longitudinal prediction of all behaviors, especially for mental health (r = 0.32–0.63). We found that family and neighborhood exposures were common critical environmental influencers on cognitive ability and mental health, which can be mediated by FNC significantly. Healthy perinatal development was a unique protective factor for higher cognitive ability, whereas sleep problems, family conflicts, and adverse school environments specifically increased risk of poor mental health.

CONCLUSIONS: This work revealed comprehensive environment-brain-behavior triple interactions based on the ABCD Study, identified cognitive control and default mode networks as the most predictive functional networks for a wide repertoire of behaviors, and underscored the long-lasting impact of critical environmental exposures on childhood development, in which sleep problems were the most prominent factors affecting mental health.

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Adolescence has long been known as an important time for developing cognitive skills and is also a period when most mental disorders initially manifest (1). Moreover, a child's brain undergoes a growth spurt in structural and functional maturation, building a foundation for behavioral outcomes (2). Despite the well-known fact that environmental exposures play a critical role in influencing behaviors, we have a very limited understanding of how these exposures interact with the brain and in turn shape our behaviors, especially during adolescence (3).

Recent years have seen rapid growth of interest in examining the neural basis through which environmental exposures can have enduring effects on behaviors (4–6). Nevertheless, research in this context has been dominated by brain structural features in children (4,7), with less focus on brain functional measures. This is partly due to the easier access and feasibility of structural magnetic resonance imaging (MRI) scans, though functional features have shown more predictive power for high-order cognition (8). As a measure that can well characterize individual variability (9,10), functional network connectivity (FNC) quantifies the temporal statistical dependencies between functional activation among different brain networks, providing insightful correlations between heterogeneous personal behaviors with the brain (11). The limited evidence available on relationships between brain, environment, and behaviors (5,12) calls for a more comprehensive investigation into how different brain functional networks may connect or even mediate associations between diverse environmental exposures and a wide range of childhood behaviors.

Furthermore, previous environment-behavior association studies often focused on a single behavioral domain (e.g., cognitive ability) or only a few environmental domains (4,6,13), thus not capturing the broader relationships between various factors. For example, sufficient sleep (14) and high socioeconomic status (4) may improve cognitive ability, while long-term exposure to air pollution (15) and low family income (5) can have the opposite impact. Perinatal factors such as birth weight and postnatal growth have been associated with cognitive ability but not mental health (16), whereas higher community noise impaired both (17). Additionally, Alnæs *et al.*

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(18) revealed 3 brain anatomical covariation patterns associated with perinatal complications, sociocognitive stratification, and urbanicity, and Modabbernia *et al.* (12) found that socioeconomic circumstances, perinatal events, and cognition had the most reliable covariations with multiple brain measures. However, a comprehensive exploration of environment-brain-behavior triple interactions, which may provide constructive insights into risky and protective environmental exposures for children's brain and behavioral development, is still lacking.

Beyond association analysis, by revealing the predictive power of FNC patterns and environmental exposures on multiple behaviors, thereby establishing their utility in longitudinal individual evaluation, we may identify imaging signatures with promising translational impact that could be missed by existing studies (19,20). We applied NeuroMark (9), a fully automated independent component analysis framework, to the resting-state functional MRI (fMRI) data to generate the data-adaptive FNC patterns that serve as the predictive brain signatures. Further exploration of how these patterns mediate the effects of environmental exposures on cognition and mental health may facilitate the elucidation of the neural underpinnings of positive and negative developmental trajectories in children.

Specifically, we included 7655 typically developing children from the Adolescent Brain Cognitive Development (ABCD) Study with 41 environmental exposures across 5 domains [spanning perinatal, family, school, neighborhood, and individual lifestyle (12)] and 23 behaviors of two types—10 cognitive abilities and 13 mental health measures—both at baseline and longitudinally. Figure 1 displays the whole research design including 4 steps (more details in Figure S1 in Supplement 1): 1) identify the FNCs most susceptible to environmental influences and determine the environmental exposures impacting most FNCs by association analysis; 2) build environment-behavior association maps and identify the shared and unique environmental exposures affecting cognitive abilities and mental health, both at baseline and longitudinally; 3) characterize dominating functional networks, FNC signatures, and critical environmental exposures that support individual-level prediction of cognitive abilities and mental health (at baseline and longitudinally), which were also externally validated via UK Biobank data; and 4) examine whether and to what extent this predictome (21) of FNC signatures mediates the environment-behavior associations.

METHODS AND MATERIALS

Participants From the ABCD Study

This study used data from a population-based sample of 9- to 10-year-olds from 21 U.S. study sites in the ongoing ABCD Study (release 3.0), including neuroimaging and behavioral data collected at baseline and longitudinally (22). Informed written consent was obtained from children and their parents, with ethical approval from each research site's institutional review boards. The current study included 7655 participants after rigorous data quality control (Figure S2 in Supplement 1) (23).

fMRI Data Acquisition and Processing

Resting-state fMRI data from the ABCD Study were acquired and preprocessed as previously described and detailed in Supplement 1 (22). The preprocessed data were decomposed into 53 subject-specific independent components (Figure S3 in Supplement 1) and their corresponding time courses via a spatially constrained single-subject independent component analysis method with the Neuromark_fMRI_1.0 template as spatial references (available in GIFT at http://trendscenter.org/software/gift) (9). Paired correlations of the independent components were calculated by Pearson correlation and transformed using Fisher *z* transformation, in which the upper triangle elements of the FNC matrix (53 × 52/2 = 1378) were extracted for further analysis.

Phenotypic Measures

We examined a total of 41 summarized environmental exposures as done by Modabbernia *et al.* (12), consisting of 5 domains (Table S2 in Supplement 1): 13 perinatal/early

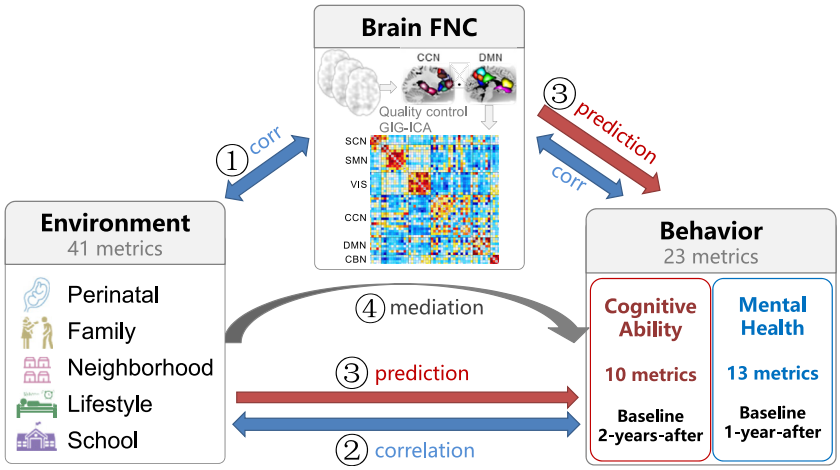

Figure 1. Research design. Environment-brain-behavior triplet correlations 1) between environmental exposures and whole-brain functional network connectivity (FNC) and 2) between environmental exposures and multibehaviors (baseline, 1-year follow-up, 2-year follow-up). 3) Building behavior (baseline and follow-up) prediction models using FNCs, environmental exposures, and their combinations, identifying the most predictive functional network modules and environmental exposures. 4) Examining the mediating effect of the identified predictive FNCs for significant associations between environmental exposures and 2 types of behaviors. CBN, cerebellum network; CCN, cognitive control network; DMN, default mode network; GIG-ICA, group-information guided independent component analysis; SCN, subcortical network; SMN, somatomotor network; VIS, visual network.

development events, 7 life events/lifestyle, 12 family characteristics, 6 neighborhood variables, and 3 school environment variables. For cognitive abilities, we used 10 scores from a well-validated NIH Toolbox at baseline and 2-year follow-up (24). For mental health, we used 11 metrics from the parent-reported Child Behavior Checklist and 2 additional metrics (prodromal symptom and subsyndromal mania) at baseline and 1-year follow-up (25), which were selected via balancing the sample size and information completeness (Tables S3, S5, and S6 in Supplement 1).

Baseline and Longitudinal Association Analysis Between Environment, Brain, and Behavior

Linear mixed-effects models were adopted to examine the associations between 41 environmental exposures and 1378 whole-brain FNC pairs, 10 cognitive abilities, and 13 mental health measures at baseline (Figure 1). Specifically, each FNC edge, cognitive ability, or mental health measure was modeled as the dependent variable; environmental exposures and the nuisance covariates were modeled as fixed effects; and the family structure nested within sites was modeled as a random effect (13). The nuisance covariates included age, sex, body mass index, puberty, ethnicity, handedness, and mean framewise displacement (for the FNC analyses only), in which sex, ethnicity, and handedness were coded as dummy variables. The correlation r value, t statistic, and effect size (Cohen's d) were estimated for each linear mixed-effects model to reflect the association of specific environmental exposure with the dependent variable. The same analytical framework was employed to investigate the longitudinal associations between environmental exposures and follow-up cognitive abilities and mental health measures separately but additionally included the baseline outcomes as a covariate.

Baseline and Longitudinal Behavior Prediction Using FNC and Environmental Exposures

Beyond brain-behavior correlations, to identify key predictive FNC signatures that support individual-level prediction of behaviors, we built an FNC-based predictive model using partial least squares regression for each cognitive ability and mental health metric. Ten-fold nested cross-validation with 200 random loops was utilized to avoid circularity bias. Model performance was assessed by averaging Pearson's correlation and coefficient of determination (COD) across 200 repetitions between observed and predicted scores for all subjects (11,26). We then evaluated the most average contributing FNC at the edge, node, and network levels across all repetitions (27,28). Furthermore, to examine the promotion degree of environmental exposures on behavior prediction, we constructed independent prediction models using only FNC, only environment, and FNC+environment. The most critical environmental exposures contributing to predictions were estimated and compared between cognitive abilities and mental health.

To examine the predictability of follow-up cognitive abilities and mental health by FNC, environment, or FNC+environment at baseline, we implemented the above predictive procedure, in which the baseline outcomes and confounding variables in the association analysis were set as covariates in the predictive model (29).

Cross-Validation Using the UK Biobank Dataset

To further validate the generalizability of the FNC-based behavior prediction, 20,852 participants were selected from the UK Biobank for cross-dataset validation who had both FNC and fluid intelligence after rigorous quality control (Figures S4 and S5 in Supplement 1). The same predictive procedure for fluid intelligence was constructed within and across the ABCD and UK Biobank datasets.

Mediation Analysis

Standard mediation analysis in an R toolbox (30) was used to examine whether and to what extent the predictome FNC signatures mediated the significant environment-behavior associations. To distinguish connectivity features with positive and negative contributions in the predictive models (31), the predictive FNCs were separated into positive-weighted and negative-weighted connectivity sets. A standard 3-variable path model was implemented for every mediation analysis (32), adjusting for the same confounding variables in the association analysis, in which the predictor was an environmental exposure, the outcome variable was one cognitive ability or mental health measure, and the mediator was either positive-weighted or negative-weighted FNC.

Multiple-Comparison Correction

We performed false discovery rate correction ($q < .05$) to determine significant environment-brain associations, and the p-value threshold was 2.3×10^{-4}, with a total of 1378×41 tests. Bonferroni correction was used to determine significant environment-behavior associations, and the p-value threshold was 1.0×10^{-3}, with a total of 41 tests for each behavior. For prediction, we performed 10,000 permutation tests for the prediction accuracy, and the p-value threshold was 1.0×10^{-4}. Moreover, we used 95% bias-corrected CIs with 10,000 bootstrap tests in the mediation analysis, and the p-value threshold was .05. When reporting p values, the uncorrected p values are reported.

RESULTS

The Subcortical Network Was the Most Vulnerable to Environmental Exposures

As shown in Figure 2A, family income ($r_{absolute}$ = 0.05–0.09) and caregiver education ($r_{absolute}$ = 0.04–0.07) were the top 2 ranked exposures influencing more FNC numbers, which manifest similar FNC architectures, especially the cross-module connections. Meanwhile, the thalamus ($r_{absolute}$ = 0.04–0.08) stood out as the brain region with the most environmental susceptibility, followed by the precuneus ($r_{absolute}$ = 0.04–0.08) and superior temporal gyrus ($r_{absolute}$ = 0.04–0.09) (Figure 2B). Specifically, environmental exposures showed the most influence on FNC connections in the thalamus–temporal gyrus and thalamus–postcentral gyrus (Figure 2C). From the perspective of the functional network module, the subcortical network (SCN) stood out with the highest

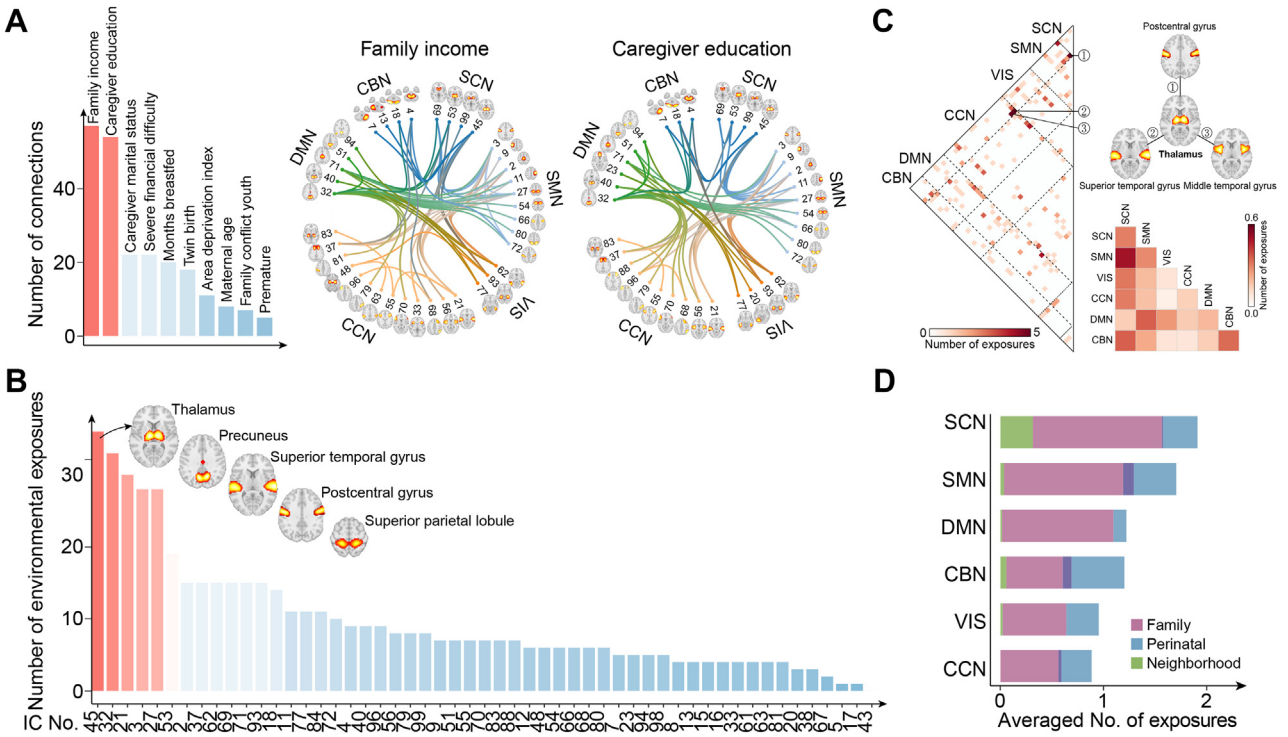

Figure 2. Summary of associations between whole-brain functional network connectivity (FNC) and 41 environmental exposures (false discovery rate–corrected, $p < .05$). **(A)** Ranking of environmental factors influencing more FNC pairs, and the top 2 FNC patterns. **(B)** Ranking of FNC nodes associated with more exposures, and the top 5 nodes (independent component [ICs]). **(C)** Mapping of the number of environmental exposures correlated with each FNC, and within each network module, in which the top FNC nodes are illustrated. **(D)** Distribution of environmental exposures correlated with each FNC module. CBN, cerebellum network; CCN, cognitive control network; DMN, default mode network; SCN, subcortical network; SMN, somatomotor network; VIS, visual network.

vulnerability to environment, mainly in domains of family, perinatal, and neighborhood exposures (Figure 2D).

Critical Environmental Exposures Associated With Behavior at Baseline and Longitudinally

We next tested the environment-behavior associations to unveil the diversity in the impact of environmental exposures on cognitive ability and mental health both at baseline and longitudinally. At baseline (Figure 3A), 9 environmental exposures were commonly correlated with 80% or more behaviors, in which family income, caregiver education, caregiver marital status, neighborhood security, and area deprivation index significantly correlated with nearly all behaviors, all of which belong to the family and neighborhood domains. In contrast, 11 environmental exposures were linked to more mental health problems, while 2 were linked to more cognitive abilities. Specifically, months breastfed and delayed verbal development were uniquely associated with cognitive abilities, while sleep problems, family conflict parents, school environment, secondary caregiver warmth, maternal substance use, and screen use during weekdays uniquely linked to psychiatric problems. Detailed association maps for the 2 most representative behavior measures—cognition total composite and Child Behavior Checklist total problems (Figure 3B)—and other behaviors are illustrated in Figures S6 and S7 in Supplement 1. Notably, these significant associations did not change appreciably after controlling for the participants' diagnosis status of mental disorders (Tables S8 and S9 in Supplement 1).

When summarizing the findings at the environmental level, we observed that 3 psychiatric assessments, i.e., Child Behavior Checklist total problems, withdrawn/depressed syndrome, and social problems, were significantly associated with the most environmental exposures (31 out of 41). Similarly, the cognition total, oral reading, and crystallized composite were linked to the most environmental factors, while pattern comparison and flanker inhibitory control and attention were linked to the least number of exposures.

Most importantly, at follow-up (Figure 3C), it was remarkable that sleep problems showed prominent associations with all mental health problems. Five baseline environmental exposures, i.e., family income, caregiver education, severe financial difficulty, caregiver marital status, and area deprivation index, were commonly correlated with more than 5 follow-up behaviors, which primarily fell in the family and neighborhood domains. In contrast, 5 exposures, particularly sleep problems, family conflict, parental psychopathology, and number of people living, uniquely linked to more 1-year-later mental health problems, while 2 exposures, i.e., delayed verbal development and months breastfed, specifically linked to more 2-year-later cognitive abilities. Interestingly, school domains and multiple pregnancy measures linked to almost all baseline mental problems, especially 1-year-later prodromal symptom.

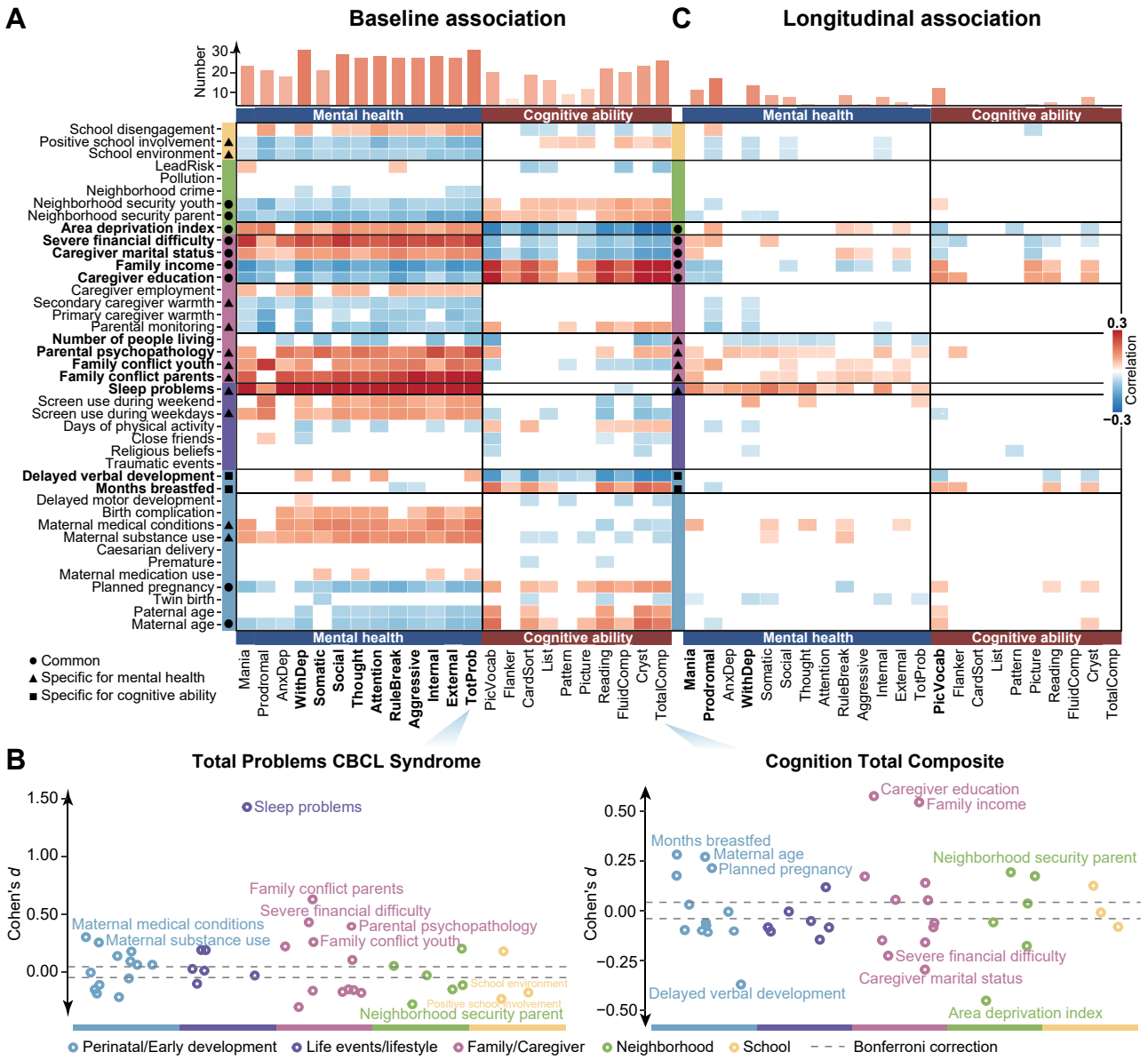

Figure 3. Environment-behavior association. The summarized correlation mapping between 5 domains of environmental exposures and 23 behaviors, both **(A)** at baseline and **(C)** longitudinally, in which the triangle, square, and round black dots denote the mental health–specific, cognition-specific, and shared environmental exposures, respectively. The bar above denotes the number of environmental exposures significantly correlated with each of the 23 behavioral items (Bonferroni corrected, $p < .05$). **(B)** Environmental exposures significantly associated with the cognition total composite and Child Behavior Checklist (CBCL) total problems syndrome in which the top 10 most associated exposures were annotated, and the dots outside the dotted line represent significant correlations passing the Bonferroni correction ($p < .05$), with Cohen's *d* displayed.

Overall, prodromal symptom, subsyndromal mania, and withdrawn/depressed syndrome were the 3 follow-up mental problems most associated with baseline exposures, along with picture vocabulary as a measure of cognitive ability.

The Dominating Role of Environmental Exposures in Predicting Multiple Behaviors

The results demonstrated that all 10 cognitive abilities and 13 mental health measures can be significantly predicted by whole-brain FNC ($p < 1.0 \times 10^{-4}$, 10,000 permutation tests) (Table S10 in Supplement 1), in which the prediction accuracies for most cognitive abilities were much higher than those for mental health measures. Similar results were revealed by the connectome-based predictive modeling (31) and random forest (33) models (Figure S10). Specifically, cognition total composite showed the highest predictability among all behaviors (r = 0.39, COD = 0.14) (Figure 4A–C). Notably, these predictions remained significant even after controlling for multiple covariates and data harmonization via ComBat (Figure 4B) (34).

Obviously, the environmental exposures themselves can achieve much higher prediction accuracy than using only FNCs for most cognitive abilities (r_{max} = 0.47, COD = 0.22) and all mental health measures (r_{max} = 0.63, COD = 0.40) (Table S10 in Supplement 1) with $p < 1.0 \times 10^{-5}$ (10,000 permutations). We note that their combination further improved the prediction accuracy of multiple behaviors (Figure 4), whose accuracies were significantly higher than using only FNC ($p < .001$, false discovery rate–corrected), and such an improvement was more remarkable in mental health (r = 0.32–0.63, Δr = 0.17–0.53) (Figure 4E) than in cognitive ability (r = 0.12–0.47, Δr = 0.00–0.08) (Figure 4F) at $p < 1.0 \times 10^{-5}$ (10,000 permutations), suggesting the prominent role of environmental exposures on developmental risks of adolescent mental health.

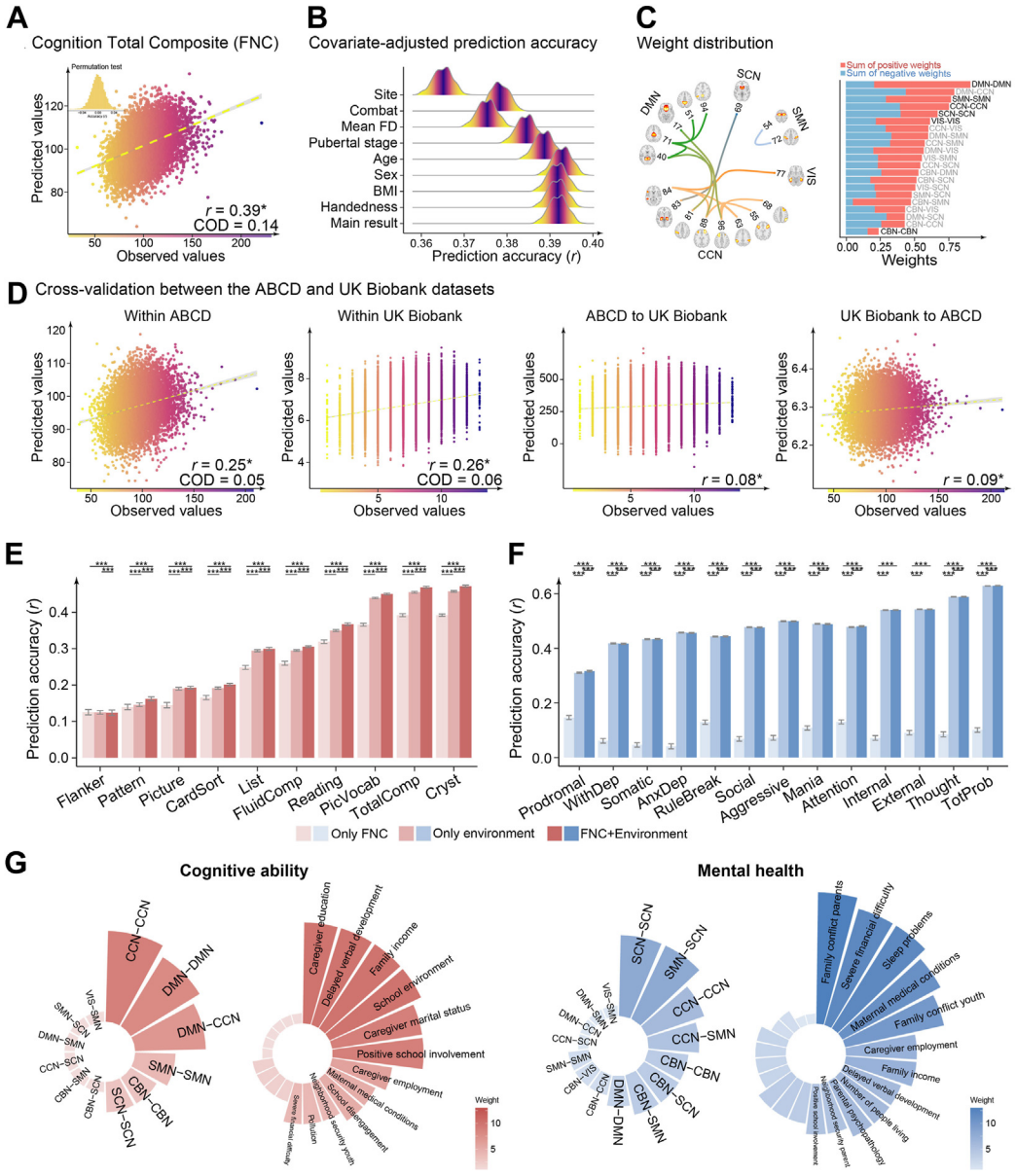

Figure 4. The prediction results for behaviors. Prediction of cognition total composite **(A)** based on functional network connectivity (FNC) only and **(B)** after adjusting for covariates including site, harmonization by ComBat, mean framewise displacement (FD), pubertal stage, age, sex, body mass index (BMI), and handedness across 200 repetitions of 10-fold cross-validation. **(C)** The top 1% predictive connections and network modules for cognition total composite after averaging across 2000 cross-validation rounds. **(D)** Cross-validation between the ABCD (Adolescent Brain Cognitive Development) and UK Biobank datasets for prediction of fluid intelligence using FNC. Comparison of prediction accuracy using only FNC, only environment, or their combination for **(E)** 10 types of cognitive abilities and **(F)** 13 types of mental health measures. **(G)** The summarized top-contributing FNC modules and environmental exposures for predicting cognition or mental health. *$p < .05$, ***$p < .001$, false discovery rate–corrected. CBN, cerebellum network; CCN, cognitive control network; COD, coefficient of determination; DMN, default mode network; SCN, subcortical network; SMN, somatomotor network; VIS, visual network.

Figure 4G summarizes the most contributing functional network modules and environmental exposures for either the 10 cognitive abilities or 13 mental health measures. Results showed that FNCs in cognitive control network–cognitive control network (CCN-CCN), default motor network–default motor network (DMN-DMN), and DMN-CCN showed the most predictive power for cognitive abilities, while FNCs in the SCN-SCN, somatomotor network–SCN, and CCN-CCN contributed most to mental health. This suggests that CCN-CCN within-network connections are shared crucial predictors for both domains. In contrast, FNCs within the DMN contributed more to cognition, while FNCs within the SCN primarily contributed to mental health.

Furthermore, caregiver education, caregiver marital status, delayed verbal development, family income, and school environment were the top 5 environmental exposures for cognitive prediction, whereas family conflict parent/youth, severe financial difficulty, sleep problems, and maternal medical conditions were the top 5 predictive environmental adversities for mental health, which are highly overlapped with those most associated exposures in Figure 3A. For each metric, the prediction results, FNC signatures, and critical environmental exposures are provided in Table S10 and Figures S11 to S13 in Supplement 1, with high stability of the predictive weights (Figure S14).

Cross-Validation Using the UK Biobank Dataset

The fluid intelligence can be significantly predicted within both the ABCD Study (r = 0.25, COD = 0.05) and UK Biobank (r = 0.26, COD = 0.06) datasets using FNC (Figure 4D). More importantly, when directly applying the FNC-based prediction model trained on the ABCD Study to UK Biobank data, significant predictions can still be achieved (r = 0.08, $p < 1.0 \times 10^{-30}$), and vice versa (r = 0.09, $p < 1.0 \times 10^{-15}$).

Longitudinal Behavior Prediction Using FNC and Environmental Exposures

Results showed that four 2-year-later cognitive abilities can be significantly predicted with $r > 0.13$ ($p < 1.0 \times 10^{-5}$) (Table 1) using only FNC, especially picture vocabulary (r = 0.27) and crystallized composite (r = 0.22). However, prodromal symptom was the most predictable (r = 0.12, $p < 1.0 \times 10^{-5}$) in 1-year-later mental health. Similar to baseline prediction, longitudinal prediction accuracy with only environment or FNC+environment was much higher than only FNC, especially for mental health. Specifically, the prediction accuracy for picture vocabulary increased most in all cognitive abilities, from r = 0.27 to r = 0.44, while thought syndrome increased most in all mental health, i.e., from r = 0.05 to r = 0.45.

The top 5 most predictive independent component nodes and environmental exposures are listed in Table 1, in which the hippocampus, precuneus, thalamus, and caudate played a prominent role in the longitudinal behavior prediction. Consistent with the baseline critical exposures, we found that family conflict and sleep problems uniquely contributed most to mental health measures, while delayed verbal development was specifically prominent for cognitive abilities in the longitudinal prediction. Particularly, the number of people living played a more important role in longitudinal prediction than cross-sectional prediction of mental health, as an increased number of people living at baseline can decrease mental health problems 1 year later. Moreover, family income and severe financial difficulty were shared high-contributing predictors for longitudinal cognition and mental health.

Mediation Analysis

Results demonstrated that positive-weighted predictive FNCs mediated more cognitive abilities, whereas negative-weighted predictive FNCs mediated more mental health (Figure 5). Specifically, crystallized composite, cognition total, and picture vocabulary can be mediated by positive-weighted FNCs from the most number of environmental exposures. A similar condition exists for prodromal symptom and attention problem in mental health, but by negative-weighted FNCs. In terms of common and unique exposures linked to two types of behaviors, the shared influential exposures were primarily in the domains of family and neighborhood. In contrast, sleep problems and family conflict parents specifically affected mental health, whereas maternal age, months breastfed, and delayed verbal development specifically affected cognitive abilities, mainly in the domain of perinatal/early development. The significant mediation results for all cognitive abilities and mental health measures are provided in Tables S11 and S12 in Supplement 2 and Figures S15 and S16 in Supplement 1.

DISCUSSION

This work revealed comprehensive environment-brain-behavior triple interactions within a large longitudinal sample of typically developing children. We found common critical environmental exposures that have substantial and long-lasting importance on cognitive ability and mental health, which mainly fall in family and neighborhood domains, especially the family domain linked most to children's brain function (Figure 2D). This aligned with the concept that high socioeconomic status (family income and caregiver education) reflects a home environment conducive to learning and high-quality parent-child interactions (35), while such long-term stimulation may effectively support children's functional brain development (36) and may be linked to behavioral development (37,38). Extending previous studies, we underscore the importance of the area deprivation index, a measure of neighborhood-level socioeconomic status (39) and neighborhood security, which can be changed practically by improving public environmental sanitation or enhancing children's safety education to reduce risk factors rapidly for certain mental health.

For unique influencers, healthier perinatal exposures such as longer months breastfed and earlier verbal development promise better cognitive abilities in adolescents, which also shows strong lasting links to the children's brain connectome in all network modules. This may be because the infant brain is marked by rapid development of neurons and explosive growth of cortex and thus is highly vulnerable to environmental exposures (40), suggesting that healthy perinatal development is an irreplaceable protective factor for evolving cognitive function. On the other hand, more sleep problems, family conflict, and adverse school environment were especially link to increased risk of mental health (Figure 3), both at baseline

Table 1. Longitudinal Prediction of Follow-Up Behaviors Using FNC and Environmental Exposures

	Only FNC		Only Environment		FNC+Environment		Most Predictive Features	
Variable	*R*	*p*	*R*	*p*	*R*	*p*	Top 5 fMRI ICs	Top 5 Exposures
Thought Syndrome (CBCL)	0.05 ± 0.01	$<1 \times 10^{-3}$	0.46 ± 0.01	$<1 \times 10^{-5}$[a]	0.45 ± 0.01	$<1 \times 10^{-5}$[a]	Caudate Precuneus Superior frontal gyrus Postcentral gyrus Left postcentral gyrus	Family conflict parents Number of people living School environment Maternal medical condition Sleep problems
Total Problems (CBCL)	0.04 ± 0.01	<.05	0.44 ± 0.01	$<1 \times 10^{-5}$[a]	0.42 ± 0.01	$<1 \times 10^{-5}$[a]	Hippocampus Precuneus Middle temporal gyrus Right inferior frontal gyrus Middle cingulate cortex	Family conflict parents Number of people living School environment Maternal medical condition Sleep problems
Attention Problems (CBCL)	0.06 ± 0.01	$<1 \times 10^{-4}$[a]	0.36 ± 0.01	$<1 \times 10^{-5}$[a]	0.37 ± 0.01	$<1 \times 10^{-5}$[a]	Middle temporal gyrus Middle cingulate cortex Middle temporal gyrus Left postcentral gyrus Inferior parietal lobule	Family conflict parents Number of people living School environment Delayed verbal development Maternal medical condition
Rule-Breaking Behavior (CBCL)	0.05 ± 0.01	<.01	0.35 ± 0.01	$<1 \times 10^{-5}$[a]	0.35 ± 0.01	$<1 \times 10^{-5}$[a]	Thalamus Caudate Hippocampus Middle temporal gyrus Sub/hypothalamus	Family conflict parents Family conflict youth Severe financial difficulty Caregiver marital status Family income
Prodromal Symptoms	0.12 ± 0.01	$<1 \times 10^{-5}$[a]	0.29 ± 0.01	$<1 \times 10^{-5}$[a]	0.28 ± 0.01	$<1 \times 10^{-5}$[a]	Caudate Precuneus Superior temporal gyrus Middle occipital gyrus Cerebellum	Family conflict youth Severe financial difficulty Family income Caregiver education Caregiver marital status
Anxious/ depressed Syndrome (CBCL)	0.04 ± 0.01	<.05	0.29 ± 0.01	$<1 \times 10^{-5}$[a]	0.28 ± 0.01	$<1 \times 10^{-5}$[a]	Precuneus Precentral gyrus Supplementary motor Right inferior frontal gyrus Paracentral lobule	Family conflict parents Number of people living Days of physical activity Severe financial difficulty Sleep problems
Picture Vocabulary	0.27 ± 0.01	$<1 \times 10^{-5}$[a]	0.43 ± 0.02	$<1 \times 10^{-5}$[a]	0.44 ± 0.02	$<1 \times 10^{-5}$[a]	Hippocampus Precuneus Superior medial frontal gyrus Superior parietal lobule Cerebellum	Delayed verbal development Severe financial difficulty Family income Caregiver education Caregiver marital status
Crystallized Composite	0.22 ± 0.01	$<1 \times 10^{-5}$[a]	0.38 ± 0.03	$<1 \times 10^{-5}$[a]	0.37 ± 0.03	$<1 \times 10^{-5}$[a]	Thalamus Hippocampus Putamen Superior medial frontal gyrus Inferior frontal gyrus	Delayed verbal development School environment Family income Caregiver education Caregiver marital status
Oral Reading Recognition	0.13 ± 0.01	$<1 \times 10^{-5}$[a]	0.24 ± 0.03	$<1 \times 10^{-5}$[a]	0.24 ± 0.03	$<1 \times 10^{-5}$[a]	Thalamus Hippocampus Superior parietal lobule Posterior cingulate cortex Superior temporal gyrus	Delayed verbal development School environment Severe financial difficulty Positive school involvement Caregiver education
Picture Sequence Memory	0.13 ± 0.01	$<1 \times 10^{-5}$[a]	0.20 ± 0.01	$<1 \times 10^{-5}$[a]	0.21 ± 0.01	$<1 \times 10^{-5}$[a]	Precuneus Superior temporal gyrus Paracentral lobule Middle occipital gyrus Cerebellum	School environment School disengagement Severe financial difficulty Family income Caregiver marital status

The longitudinal prediction accuracy by only FNC, only environment, and the combination of FNC and environmental exposures are represented by mean ± SD across 200 repetitions of 10-fold cross-validation, with the top 5 ICs and environmental exposures displayed.

CBCL, Child Behavior Checklist; fMRI, functional magnetic resonance imaging; FNC, functional network connectivity; IC, independent component.

[a]The longitudinal prediction is significant across all 200 repetitions ($p < 1 \times 10^{-4}$).

and longitudinally. Previous studies have found that sleep problems were associated with high emergence of depressive problems (6,13,14). Similarly, family conflict was identified to be one of the most robust risk factors for suicidality (41), which resonated with our results linking family conflict with the emergence of baseline or follow-up mental health problems.

More importantly, environmental exposures played a much more dominating role than brain connectivity in predicting all behaviors, especially in longitudinal prediction, among which sleep problems emerged as the most prominent factor affecting all mental health. In longitudinal prediction (Table 1), we again found that family income was the shared key predictor;

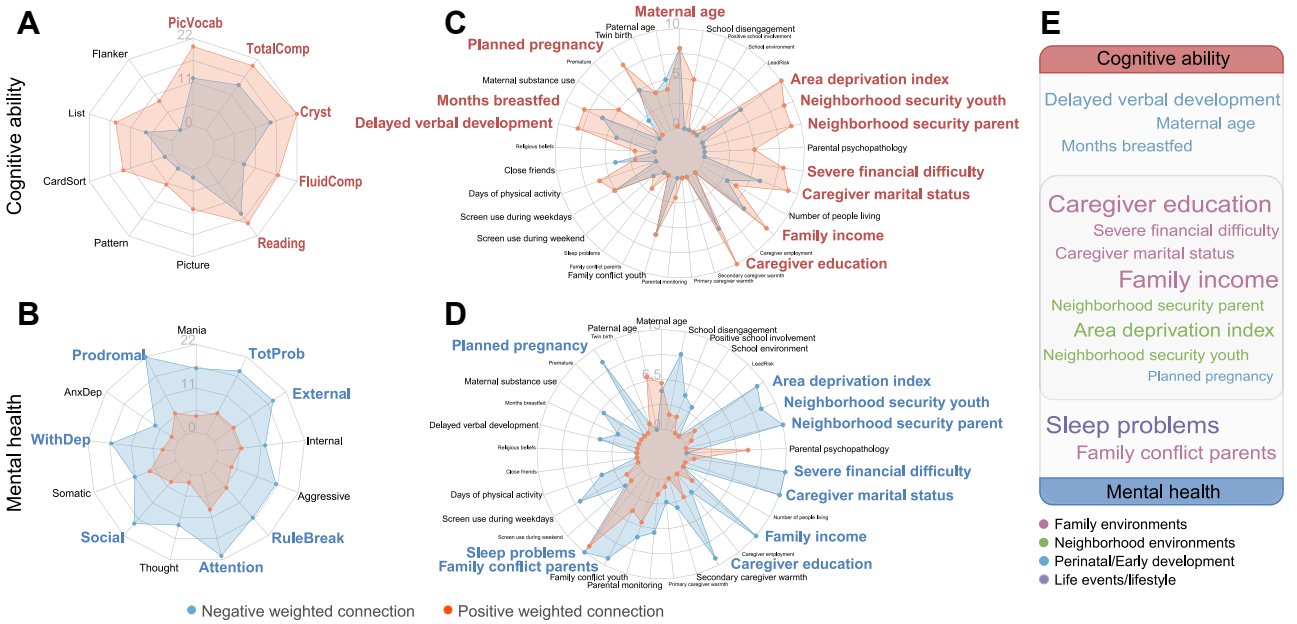

Figure 5. The mediating effects. We further tested whether the identified predictive functional network connectivities can mediate associations from environment to multiple behaviors. For each of the **(A)** cognitive and **(B)** mental health measures, the radar maps show the number of environmental exposures that can be significantly mediated by functional network connectivity (10,000 bootstrap tests at $p < .05$). Similarly, for each environmental exposure, radar maps display how many **(C)** cognitive metrics or **(D)** mental health measures can be significantly mediated by functional network connectivities, in which the top factors are highlighted in bold. **(E)** The common and specific environmental influencers between cognitive abilities and mental health in mediations. The more mediation involved, the bigger the text size.

family conflict and sleep problems uniquely contributed most for predicting 1-year-later mental health, while delayed verbal development specifically worked for 2-year-later cognitive ability prediction, highlighting their respectively dominating roles in the 2 types of behavioral development (6,42). Interestingly, unlike the association results, we discovered that a greater number of people living promised fewer follow-up mental health problems in middle childhood, suggesting that a larger number of household members, especially older siblings, is a protective factor for reducing risks of psychopathology due to more family member communication and interaction (43). Furthermore, school environment appears in the top 5 predictors in 6 out of 10 follow-up behaviors, implicating that constructing a positive school environment could be one of the most effective public health interventions for reducing psychiatric risk and improving cognitive ability in practice (44).

Intriguingly, when looking into the predominant exposures, we found that cognitive abilities in middle childhood were influenced most by environmental exposures that are relatively fixed such as parents' education, perinatal exposures, and family income. However, lifestyle and school environmental exposures that are flexible and changeable in childhood influenced mental health substantially. Particularly, more sleep problems, family conflict, and adverse school environment increased the risk for baseline and 1-year-later mental health problems. Note that these exposures can be modified immediately by improving sleep habits, providing harmonious family relationships, or creating a positive school environment.

In contrast, the brain connectome could mainly predict cognitive abilities and baseline mental health but showed weaker links to 1-year-later mental health prediction, with the exception of prodromal syndrome, which may be due to the fact that mental health is measured through parental observation and consequently may be influenced by participants' subjective feelings (25). FNCs in the DMN and CCN showed the most predictive power for cognitive ability, especially the important role of the DMN in longitudinal prediction (Figure 4, Table 1). This is not surprising because the DMN and CCN have been considered widely involved in different aspects of cognition (8,45,46). In comparison, FNCs in the SCN contributed the most to mental health. Abnormalities in the DMN have been consistently revealed to be implicated in adult psychiatric disorders (47). Our results further revealed the critical role of the SCN in mental health problems in adolescents. The SCN has been implicated in impulsivity, attention deficits, and emotional regulation (45,48). One interesting finding is that the hippocampus and thalamus manifest as prominent brain nodes in predicting 2-year-later comprehensive reading and crystal intelligence. Specifically, the hippocampus plays a crucial role in long-term episodic memory, which can mediate behaviors that allow learning to take place (49), so as to contribute most to the follow-up cognitive ability. The thalamus, which conveys subcortical-cortical information (50), acts as a bridge between sensory perception and cognition (51), which are involved in widespread deficits in behaviors. Moreover, the predictive FNCs significantly mediate the environment-behavior associations, implying the potential environment-brain-behavior plasticity loops (4).

There are several limitations in this study. First, there may exist potential collinearity among environmental exposures or

behavior outcomes, deserving further investigation via exploratory factor analysis in the future (52); however, this was not the emphasis of the current study. Second, the study is primarily based on association analysis and does not allow for causal inferences about the environment-brain-behavior relationships without further validation using randomized controlled trials. Nevertheless, it offers a critical first step for future studies to examine the neurobiological mechanisms underlying behaviors. In addition, FNC matrices for adolescents from the ABCD datasets were estimated using the NeuroMark template derived from adults, which may underestimate the divergence of spatial network distribution configurations between adolescents and adults (53–56). Nevertheless, this concern is lessened given the generalization of models between the ABCD and UK Biobank datasets and the applicability of the NeuroMark template across different age groups (57–59). Individualized atlas developed for different age groups deserve further exploration. Furthermore, it is worth noting that ethnicity was only considered as a covariate. Future research can establish ethnicity-specific models to examine the disparities of the environment-brain-behavior relationships across different ethnicities.

Collectively, the present study unveiled comprehensive environment-brain-behavior triple interactions based on the ABCD Study both at baseline and longitudinally; identified the CCN, DMN, and SCN as the most predictive functional networks for a wide repertoire of behaviors; and emphasized the long-term importance of critical environmental exposures to promote brain and behavioral development in children, especially the attainable targets with family conflict, sleep quality, and school and neighborhood environments, to promote the healthy development of adolescents.

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DZ and JS conceived and designed the experiment. DZ performed the analyses with support from RJ, ZF, SQ, WY, AF, and MX; JS, RJ, and SQ provided guidance on result interpretation. DZ and JS wrote the article with contributions from VC, RJ, and GP and comments from all other authors.

Neuroimaging and behavioral data from the ABCD dataset were obtained from https://nda.nih.gov/abcd with the approval of the ABCD consortium. The data from UK Biobank used in this study are publicly accessible via their standard data access procedure at https://www.ukbiobank.ac.uk/. MATLAB and R scripts written to perform most of the analyses are available from the authors upon request.

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ARTICLE INFORMATION

From the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China (DZ, JS); Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, Connecticut (RJ); Department of Psychiatry and Neurobiology, Yale School of Medicine, New Haven, Connecticut (GP); Tri-institutional Center for Translational Research in Neuroimaging and Data Science, Georgia Institute of Technology, Emory University, and Georgia State University, Atlanta, Georgia (ZF, VC, JS); College of Computer Science and Technology, Nanjing University of Aeronautics and Astronautics, Nanjing, China (SQ); National Institute on Alcohol Abuse and Alcoholism, Lab of Neuroimaging, National Institutes of Health, Bethesda, Maryland (WY); Brainnetome Center and National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing, China (AF, MX); and School of Artificial Intelligence, University of Chinese Academy of Sciences, Beijing, China (AF, MX).

DZ and RJ contributed equally to this work.

Address correspondence to Jing Sui, Ph.D., at kittysj@gmail.com, or Vince Calhoun, Ph.D., at vince.calhoun@ece.gatech.edu.

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