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Pathways link environmental and genetic factors with structural brain networks and psychopathology in youth

Anqi Qiu [1,2,3,4,5]✉ and Chaoqiang Liu[1]

Adolescence is a period of significant brain development and maturation, and it is a time when many mental health problems first emerge. This study aimed to explore a comprehensive map that describes possible pathways from genetic and environmental risks to structural brain organization and psychopathology in adolescents. We included 32 environmental items on developmental adversity, maternal substance use, parental psychopathology, socioeconomic status (SES), school and family environment; 10 child psychopathological scales; polygenic risk scores (PRS) for 10 psychiatric disorders, total problems, and cognitive ability; and structural brain networks in the Adolescent Brain Cognitive Development study (ABCD, $n = 9168$). Structural equation modeling found two pathways linking SES, brain, and psychopathology. Lower SES was found to be associated with lower structural connectivity in the posterior default mode network and greater salience structural connectivity, and with more severe psychosis and internalizing in youth ($p < 0.001$). Prematurity and birth weight were associated with early-developed sensorimotor and subcortical networks ($p < 0.001$). Increased parental psychopathology, decreased SES and school engagement was related to elevated family conflict, psychosis, and externalizing behaviors in youth ($p < 0.001$). Increased maternal substance use predicted increased developmental adversity, internalizing, and psychosis ($p < 0.001$). But, polygenic risks for psychiatric disorders had moderate effects on brain structural connectivity and psychopathology in youth. These findings suggest that a range of genetic and environmental factors can influence brain structural organization and psychopathology during adolescence, and that addressing these risk factors may be important for promoting positive mental health outcomes in young people.

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INTRODUCTION

It is well-established that adolescence is a critical period for the emergence of many psychiatric disorders. Many psychiatric disorders, including neurodevelopmental disorders, anxiety, and fear-related disorders, schizophrenia, and mood disorders, tend to have their onset during adolescence or early adulthood [1]. A combination of genetics and early life experiences and environments can influence the development of the brain and the risk of psychopathology in adolescents. Early identification of environmental and genetic factors that may increase the risk of psychiatric disorders can be essential for optimizing neurodevelopment and minimizing the risk of psychopathology in young people.

During adolescence, the brain undergoes significant structural changes that are thought to be related to the maturation and specialization of brain function [2, 3]. These changes are reflected in changes in brain anatomy as seen on magnetic resonance imaging (MRI) scans, including changes in gray and white matter volume and integrity. Brain gray matter volume tends to decrease during adolescence, while white matter increases [4, 5]. The changes in gray and white matter volumes during adolescence are thought to be related to the pruning of unnecessary neural connections and the strengthening of important ones and to the process of myelination, in which the axons of neurons are coated with myelin [6, 7]. These processes contribute to the specialization and segregation of brain function that occurs during adolescence [2, 3]. Additionally, white matter integrity is thought to mature during adolescence in association and projection fibers that support cortico-cortical and cortico-cerebellum integration [8, 9]. These changes in brain structure during adolescence may be important for the emergence of adolescent brain transformation.

There are many environmental factors that can influence brain development and psychopathology during adolescence, including exposure to prenatal adversity reflected as birth weight and prematurity [10–12], parental factors (e.g., parental psychopathology, maternal substance use) [13–17], socio-economic status (SES, household and neighborhood) [18–22], and social environment (e.g., school and family environment) [23]. Most existing studies assess these environmental factors and their influences on brain and psychopathology separately [10–12, 18–23]. These environmental factors play an important role in neurodevelopment and tend to covary highly with each other, which makes it difficult to parse out which environmental factor contributes most to neurodevelopmental outcomes. In addition, the number and type of potential environmental factors adjusted for in previous

[1]Department of Biomedical Engineering, National University of Singapore, Singapore, Singapore. [2]The N.1 Institute for Health, National University of Singapore, Singapore, Singapore. [3]NUS (Suzhou) Research Institute, National University of Singapore, Suzhou, China. [4]Institute of Data Science, National University of Singapore, Singapore, Singapore. [5]Department of Biomedical Engineering, The Johns Hopkins University, Baltimore, MD, USA. ✉email: anqi.qiu.sg@gmail.com

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analyses vary widely [10–12, 18–23]. More studies are needed to examine multifaceted environmental factors jointly. Also, more research is needed to understand how environmental factors interact with genes that may be particularly influential in the development of brain and psychopathology in adolescence.

This study capitalized upon a comprehensive environmental, genetic, and imaging dataset available in the Adolescent Brain Cognitive Development (ABCD) study (version 3.0) in youth aged 9-to-11 years [24]. We aimed to explore a comprehensive map that describes possible pathways among multifaceted environments, genetic risks, structural brain organization, and psychopathology in youth. Here, we computed polygenic risk scores (PRS) to characterize the genetic contribution to susceptibility for psychiatric disorders with onset age in adolescence, total problems, and cognitive ability. The PRS appears to reflect the cumulative influence of multiple genetic variants [25, 26], which allows the easy assessment of polygenic impacts on various psychiatric disorders. As adolescence is a critical period of myelination and synaptic pruning, we characterized the adolescent brain using the structural connectivity between brain regions derived from diffusion MRI. We derived transdiagnostic dimensions of psychopathology to represent comorbid characteristics across psychiatric disorders in youth. It has been suggested that dimensional approaches to studying psychopathology in children and youth are beneficial for characterizing the clinical phenomenology [27]. We took univariate and multivariate analyses and considered comprehensive interplay among environmental factors, polygenic risks, brain structural organization, and dimensional psychopathology in youth. This study provided a comprehensive map describing the contribution of individual aspects of environmental factors and genetic risks to brain structural networks and psychopathology, which is a necessary step toward early identification of at-risk youth and might ultimately allow for interventions to achieve improved functional outcomes.

MATERIALS AND METHODS

Participants

Participant data were obtained from the open baseline from the ongoing Adolescent Brain Cognitive Development study (https://abcdstudy.org/). Youth ($n = 11{,}875$) 9–11 years of age were recruited for this study, forming a similar proportion of males and females living in the United States. The sample selection criteria were targeted to reflect the sociodemographic proportion of the population as described in the ABCD study design [28]. The brain images, genotypes, psychopathology, demographics, and environmental factors were obtained from all participants at the same visit [28]. The institutional review board approved the research protocol at each data collection site [29] (https://abcdstudy.org/study-sites/). Written informed consent was obtained from all parents and adolescents.

This study included participants with good structural and diffusion-weighted images (see the image quality check below), environmental factors, child psychopathology, and genotype data. Figure S1 illustrates the flow chart of the subject selection. As a result, this study included 9168 subjects.

Environmental factors

This study included environmental items, such as developmental adversity, maternal substance use, parental psychopathology, socioeconomic status (SES), and school and family environment. The design and acquisition protocol of questionnaires were detailed in [28, 30].

Developmental adversity. The parent-report developmental History Questionnaire [28] was used to assess prematurity, birth weight, pregnancy complications, and birth complications. The Modified Ohio State University Traumatic Brain Injury Screen-Short Version [31] was employed to assess the parent-report overall brain injury/concussion during child development.

Maternal substance use. The developmental History Questionnaire [28] was used to assess maternal substance use before knowing about the pregnancy, including drinking, smoking, and marijuana.

Parent psychopathology. Parent psychopathology symptoms were assessed using the Adult Self Report (ASR) [32] and Family History Assessment Module Screener (FHAM-S) questionnaires [33]. Parents reported these questionnaires. The ASR provided 8 empirically-based syndrome scales (anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior, and intrusive). FHAM-S reported the presence/absence of symptoms associated with alcohol and drug use, depression, and mania in all 1st and 2nd degree "blood-relatives" of the youth. The accumulated presence of depression and mania is scored as the family psychopathology risk of mental illness. The presence of alcohol and drug use problems in the child's relatives was defined as the family psychopathology risk of substance use disorders.

Socioeconomic status (SES). The parent-report demographics battery from the PhenX toolkit measured the social demographics of the parental highest education, family income, and partner (do you have a partner) [34]. Economic insecurity and area deprivation index were also employed to provide additional information about socioeconomic influences [35].

The "Safety from Crime" items from the PhenX Toolkit were used to assess neighborhood safety and crime reports [36].

School environment. Children reported their school risk and protective factors via a 12-item Inventory for School Risk and Protective Factors of the PhenX toolkit [37]. Three measures were selected to assess a child's connectedness to his/her school, including school teacher and classroom environment, personal involvement in school, and school disengagement from academic goals.

Family environment. The child-reported parent monitoring and acceptance and the family conflicts were included to measure the family environment. Parent monitoring was accessed by a 5-item summary score of the Parental Monitoring Scale [38]. Parent acceptance was evaluated by the Acceptance Scale, a subscale of the Child Report of Behavior Inventory (CRPBI) [39]. To assess family conflicts, the ABCD protocol utilizes a 9-item Family Conflict subscale of the Family Environment Scale (FES) for the baseline protocol [40]. The psychosocial behavior of youth was assessed using the child-reported Strengths and Difficulties Questionnaire [41].

Child psychopathology

Child psychopathology was dimensionally assessed based on the parent report of Child Behavior Checklist (CBCL), the ten-item Mania Scale derived from the Parent General Behavior Inventory for Children and Adolescents [42], and the Prodromal Questionnaire Brief Version [43]. This project included 8 empirically-based syndrome scales from CBCL (anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior, social competence), mania in mood and behavior, and a severity score of psychosis risk symptoms.

MRI acquisition

The ABCD imaging protocol was harmonized for three 3 T scanner platforms (*Siemens Prisma, General Electric (GE) 750, and Philips)* and use of multi-channel coils capable of multiband echo planar imaging (EPI) acquisitions, using a standard adult-size coil [44]. This study only employed T1-weighted MRI and diffusion-weighted images (DWIs). T1-weighted MRI and echo planar DWIs were acquired with the following sequence parameters. The T1-weighted MRI was acquired with repetition time (TR) = 2500 ms; echo time (TE) = 2–2.9 ms; flip angle = 8°; field of view = 256 mm × 256 mm; matrix size = 256 × 256; 176–225 slices; and voxel size = 1 × 1 × 1 mm. DWIs were acquired in 6 directions at b = 500 s/mm^2, 15 directions at b = 1000 s/mm^2, 15 directions at b = 2000 s/mm^2, and 60 directions at b = 3000 s/mm^2 using TR = 4100–5300 ms; TE = 81.9–89 ms; flip angle = 77–90°; field of view = 240 mm × 240 mm; matrix size = 140 × 140; voxel size = 1.7 × 1.7 × 1.7 mm; and 81 slices. Eight images were acquired at b = 0 s/mm^2. The imaging protocol was detailed in Casey et al. [44].

MRI analysis and brain structural networks

FreeSurfer longitudinal analysis pipeline (a bug-fixed version 5.3.0) was used to analyze T1-weighted images and segment the brain into three tissue types, gray matter, white matter, and cerebrospinal fluid (CSF) [45]. A post-processing quality check was conducted by one well-trained

researcher based on the instruction given at https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData.

Diffusion-weighted images (DWIs) were processed using principal component analysis (PCA)-based denoising [46], manual removal of motion-corrupted volumes following visual inspection, eddy current distortion correction with outlier replacement and intra-volume movement correction [47–49], and bias field correction [50]. The diffusion tensor model was fitted for each subject, and fractional anisotropy (FA) was calculated using the *dwi2tensor* and *tensor2metric* commands from the MRtrix3 package. For each subject, the T1-weighted image was aligned with the first diffusion $b = 0$ s/mm^2 image using rigid registration with 6 degrees of freedom [51, 52]. Its white matter and gray matter masks were used to guide tractography using the probabilistic approach given in MRtrix3 package. This probabilistic tractography constructs a possible streamline based on the local tract orientation at each voxel. Multi-modal LDDMM mapping [53, 54], was employed to align the structural and diffusion tensor image (DTI) data into the JHU atlas space [55], where intensity-corrected T1-weighted image, cortical surfaces, and FA image were taken as input for mapping. This non-linear transformation was used to align the tracts into the atlas space.

The DWI data quality was checked via the following steps: (1) removing the DWI data with more than 20% volumes with head motion greater than 0.5 mm or/and missing signal; (2) removing the DWI data with mapping errors; (3) removing the DWI data whose tracts were not in the white matter mask.

A structural brain network was computed for individual subjects based on the brain parcellation given in Shen et al. [56], where the brain was divided into 268 regions. This study employed this functional atlas due to the structure-function coupling in the brain networks [57, 58]. The structural connectivity of two brain regions was computed as the number of tracts going through them and normalized by their volumes. This study employed the structural connectivity of any two brain regions as a brain structural network measure in the following statistical analysis.

Genotype data analysis and polygenic risk score

This study employed the genotype data of the ABCD study (release version 3.0). The saliva and blood sample was collected at the baseline visit. DNA was extracted in RUCDR. The Smokescreen™ Genotyping array [59] was assayed. To maximize the number of quality-checked SNPs, both SNPs from saliva and blood, whichever had higher successful calls, higher none-missing, matched genetic sex, and less excessive IBS, have been merged. The imputation was performed on the quality-checked genotype data using the TOPMed imputation server. Pre-imputation steps were followed as instructed at https://topmedimpute.readthedocs.io/en/latest/prepare-your-data/. The imputation was performed using mixed ancestry and Eagle v2.4 phasing. The imputed data contained 11099 unique individuals with 8,833,408 SNPs.

This study computed polygenic risk score (PRS) using PLINK (version 1.9) based on the imputed SNPs of the ABCD study and meta-analysis GWAS results retrieved from the Psychiatric Genomics Consortium (PGC, https://www.med.unc.edu/pgc). The SNPs of the ABCD sample were selected with low linkage disequilibrium to each other ($r^2 < 0.25$ within 200 kb window), minimum allele frequency [60] greater than 0.01, and not deviating from Hardy-Weinberg Equilibrium (HWE; $p < 1e{-}6$). Among these SNPs, those that survived at the p values of 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 obtained from the existing GWAS study were used to incorporate the proportion of variation in disease risk explained through their additive effects [61–63]. The PRS was calculated for ten psychiatric disorders, including Autism, ADHD, anxiety, social anxiety, panic disorder, phobia, bipolar disorder, major depressive disorder (MDD), schizophrenia, insomnia, and total problems as well as cognitive ability, to represent the genetic risks of youth for these disorders and cognitive ability. We chose these disorders since their onset was in childhood or adolescence.

Statistical analysis

Univariate analysis. This study first employed univariate analysis to examine the influences of individual environmental items and polygenic risks on brain structural connectivity and child psychopathology. For this, each score of environmental items, child psychopathology, and PRS was first standardized with zero mean and unit variance using rank-based inverse Gaussian transformation. A linear mixed effect model took one of the structural connectivities as a dependent variable and one of the environmental items, child psychopathology, or PRS scores, as an independent variable. Here, the structural connectivity quantified the structural connection between two brain regions. Bonferroni correction was used to determine the significance of statistical tests (35778 connectivities x (32 environmental factors + 10 child psychopathology scores + 12 PRS scores)) at $p < 10e{-}5$.

Covariates in univariate models. The above univariate models included age, sex, and ethnicity as covariates. The information of twins, non-twin siblings, and 22 different research sites was entered as random effects.

SEM analysis. We employed structural equation modeling (SEM, lavaan package in R) to examine potential pathways that link environmental/genetic factors with child brain structural networks and transdiagnostic dimensions of psychopathology. We employed principal component analysis (PCA) on environmental items to identify environmental factors and to avoid multilinearity in SEM due to the high correlation among environmental items. PCA was further examined to determine the transdiagnostic dimensions of child psychopathology. We used SEM to model (1) the pathways from all environmental and genetic factors to the structural connectivities of individual brain networks and transdiagnostic dimensions of child psychopathology; (2) the pathways from the structural connectivities of individual brain networks to transdiagnostic dimensions of child psychopathology; (3) pathways from SES to maternal factors (psychopathology and substance use) and child developmental adversity; (4) pathways from maternal factors to child developmental adversity and family environment. Here, 268 brain regions were grouped into 14 brain networks, where the structural connectivity was averaged to quantify the structural connectivity strength at a network level. The 14 brain networks were defined via spectral clustering of the brain functional connectivity matrix (268 × 268) (see Fig. S2 [58]). We summarized the SEM used in this study as follows:

brain ~ six environmental factors + 12 PRS scores + covariates

child psychopathology ~ brain + six environmental factors + 12 PRS scores + covariates

maternal factors ~ SES + covariates

child developmental adversity ~ SES + maternal factors + covariates

family environment ~ SES + maternal factors + school environment + child developmental adversity + covariates

Bonferroni correction was used to determine the statistical significance of pathways (14 connectivities x (6 environmental factors + 12 PRS scores + 3 transdiagnostic dimensions of psychopathology) + 12 pathways among 6 environmental factors + 3 transdiagnostic dimensions x (6 environmental factors + 12 PRS scores)) at $p < 0.01$.

Covariates in SEM. The above SEM models included age, sex, and ethnicity as covariates. The information of twins, non-twin siblings, and 22 different research sites was also entered as covariates.

RESULTS

Demographics

This study included 9168 youths aged 9–11 years (9.92 ± 0.62 years). Among them, 4838 were males (52.8%). This sample comprised 54.4% white, 14.5% black, 19.4% Hispanic, 1.3% Asian, and 10.3% others. Table S1 (Support Document) lists the descriptive statistics for (1) 32 environmental factors related to developmental adversity, maternal substance use, parental psychopathology, SES, school and family environment; (2) 10 child psychopathological scales; (3) polygenic risk scores (PRS) for psychiatric disorders (Autism, ADHD, anxiety, social anxiety, panic disorder, phobia, bipolar disorder, major depressive disorder (MDD), schizophrenia), as well as total problems and cognitive ability.

Environment-wide associations with brain structural connectivities

We first investigated associations of individual environmental items with brain structural connectivities via univariate analysis while controlling for age, gender, ethnicity, and mixed effects of family and study sites. Figure 1A illustrates the Manhattan plot of environment-wide associations with the structural connectivities between 268 brain regions defined in Shen's atlas [56]. Prematurity and birth weight from developmental adversity,

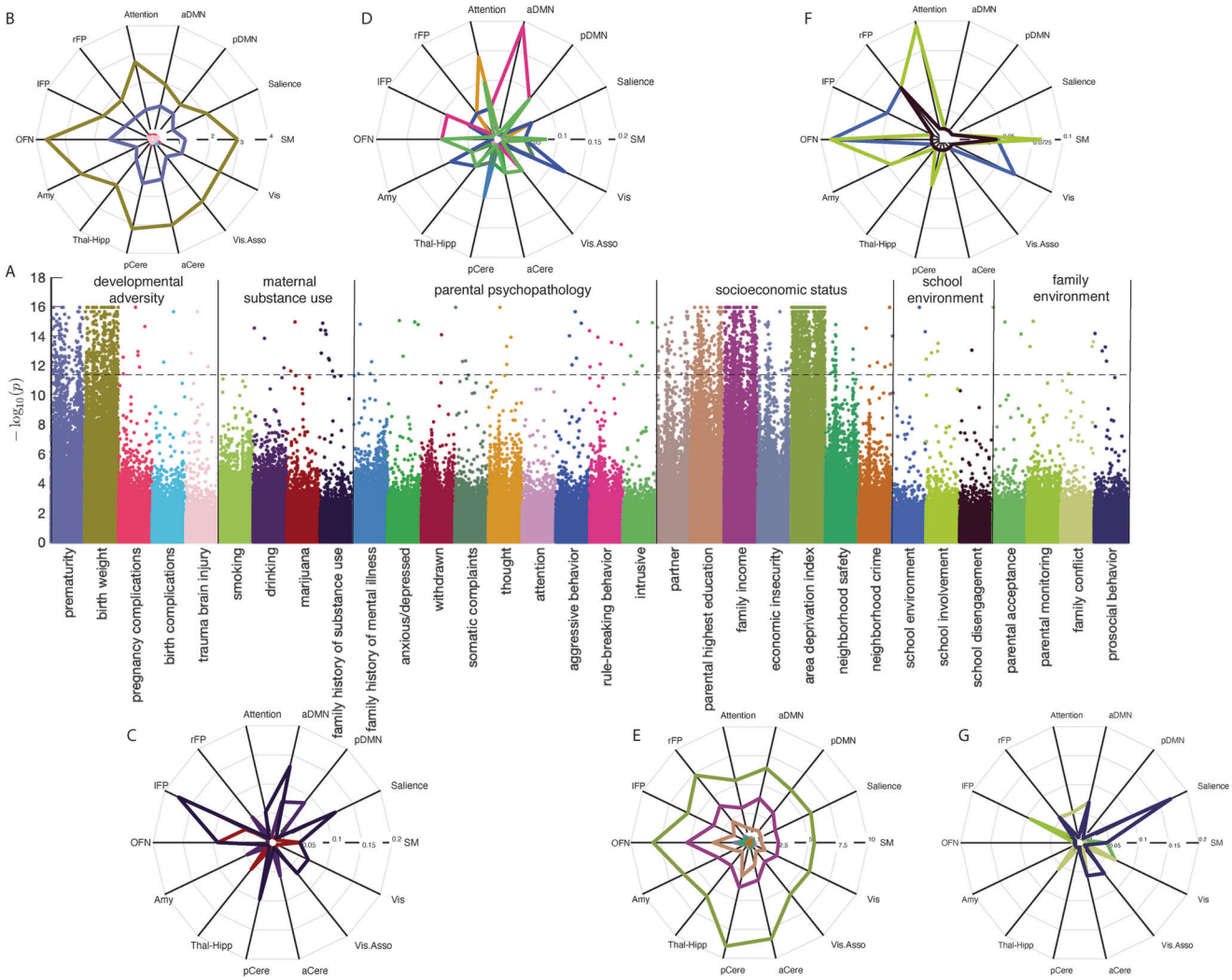

Fig. 1 Environment-wide associations with brain structural connectivities. A The Manhattan plot illustrates the associations of individual environmental factors with the structural connectivities between any two brain regions. The dashed line indicates Bonferroni corrected *p* value at a level of 1e−05. **B**–**G**, The pie charts show the number of structural connectivities per region averaged over each brain network that was statistically significant for developmental adversity, maternal substance use, parental psychopathology, socioeconomic status (SES), school environment, and family environment, respectively. **B**–**G** employ the same color scheme as in (**A**). OFN orbitofrontal network, lFP left frontoparietal, rFP right frontoparietal, aDMN and pDMN anterior and posterior default mode network, SM, sensorimotor, Vis visual, Vis.Asso visual association, aCere and pCere anterior and posterior cerebellum, Thal.Hipp thalamus and hippocampus, Amy amygdala.

parental highest education, family income, and area deprivation index of SES were most associated with the structural connectivities.

There were 138, 338, 7, 2, and 3 structural connectivities associated with prematurity and birth weight, pregnancy complications, birth complications, and traumatic brain injury, respectively. When summarizing the significant environmental associations as the number of structural connectivities per region in each brain network, prematurity and birth weight were more associated with the connectivities in primary networks, including sensorimotor (SM) and visual (Vis) networks, cerebellar networks, and orbitofrontal network (OFN, Fig. 1B).

Likewise, 51, 206, 417, 34, 876, 21, and 6 structural connectivities were associated with partnership, parental highest education, family income, economic insecurity, area deprivation index, neighborhood safety, and neighborhood crime, respectively. Figure 1E illustrates the number of structural connectivities per brain region averaged over each brain network that were significantly associated with SES. Area deprivation index, family income, and parental highest education showed widespread associations across all brain networks in the order of the anterior and posterior cerebellar networks (aCere and pCere), executive networks (right frontoparietal (rFP) and OFN, left FP (lFP)), attention (Att), amygdala (Amy), anterior and posterior default mode networks (aDMN, pDMN), salience network and primary networks (Thalamus-hippocampal network (Thal.Hipp), SM, Vis, visual associate network (Vis.Asso)).

Maternal substance use (13 connectivities, Fig. 1C), parental psychopathology (32 connectivities, Fig. 1D), school environment (8 connectivities, Fig. 1F), and family environment (12 connectivities, Fig. 1G) showed environment-specific associations with only a few structural connectivities predominantly in the executive networks (lFP, Att, OFN), DMN, and salience.

PRS-wide associations with brain structural connectivities

We then investigated the influences of the PRS scores on brain structural connectivities. The PRS score at 0.01 gave the most statistical power among all the *p* values (0.001, 0.01, 0.05, 0.1–0.5) investigated in this study. Therefore, only the findings of PRS at 0.01 were reported in the following. Figure 2A shows the

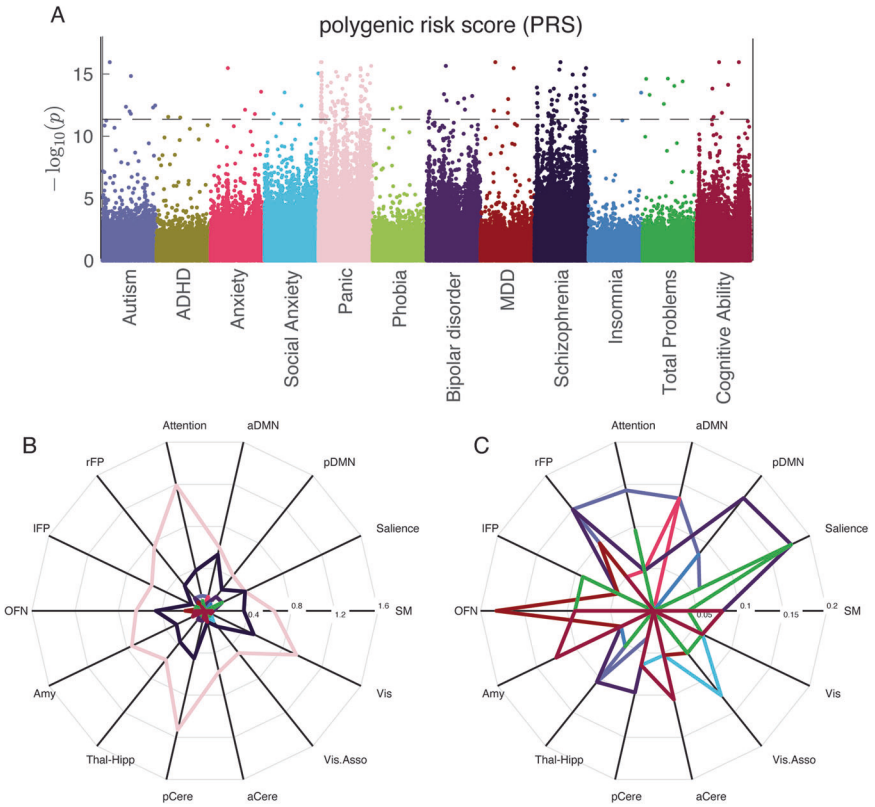

Fig. 2 PRS-wide associations with brain structural connectivities. A The Manhattan plot illustrates the associations of individual PRS scores with the structural connectivities between any two brain regions. The dashed line indicates Bonferroni corrected *p* value at a level of 1e–05. **B** The pie chart shows the number of structural connectivities per brain region averaged over each brain network that was statistically significant for PRS. **C** The enlarged pie chart illustrates the associations of the PRS scores, except for panic disorder and schizophrenia, with brain structural connectivities. All the panels employ the same color scheme.

Manhattan plot of PRS-wide association with all the structural connectivities. The PRS scores for schizophrenia and panic disorder showed relatively strong associations with 97 and 45 brain structural connectivities (Fig. 2B), respectively. The PRS for panic disorder was most related to the structural connectivities in the Att, pCere, Vis, and Amy networks (pink curve in Fig. 2B). The PRS for schizophrenia was predominately associated with the structural connectivities in the aDMN, salience, and OFN networks, the primary visual network, the subcortical and cerebellar networks (Amy, Thal-Hipp, and pCere) (black curve in Fig. 2B).

The PRS for the other disorders, total problems, and cognitive ability show distinct patterns of the PRS-wide associations with the brain structural connectivities (Fig. 2C). The number of structural connectivities ranged from 2 to 10. The PRS for Autism was most associated with the connectivities in the Att, rFP, and aDMN. Moreover, the PRS for anxiety and social anxiety were most associated with the connectivities in the aDMN and the visual associate network (Vis.Asso), respectively. Furthermore, the PRS for bipolar disorder was predominantly associated with the connectivities in the rFP, pDMN, and salience networks while the PRS for MDD was related to the OFN and rFP. Finally, the PRS for total problems and cognitive ability were associated with the connectivities in the salience and amygdala networks. In summary, the strongest PRS-wide associations for psychiatric disorders, total problems, and cognitive ability occurred most in the executive networks (rFP, Att, OFN), DMN, and salience. Nevertheless, the number of structural connectivities per region that contributed to PRS-wide associations was smaller than that for the environment-wide associations (Figs. 1B, 1E, and Fig. 2B).

Child psychopathology-wide associations with brain structural connectivities

Figure 3A illustrates the Manhattan plot of the associations between child psychopathology and brain structural connectivities. The number of structural connectivities ranged from 1 to 80. The structural connectivity of the OFC was most associated with mania (Fig. 3B). On the other hand, the structural connectivities of the lFP and pDMN were most associated with psychosis (Fig. 3B).

Pathways among environmental factors, PRS, brain structural connectivity, and psychopathology

We employed multivariate analysis to identify the pathways that quantify the environmental and genetic contributions to structural brain networks and the transdiagnostic dimension of psychopathology. PCA identified six environmental factors (51.4% of total variance) that represented parental psychopathology, school environment, SES, developmental adversity, maternal substance use, and family environment (Fig. S2 in Support Document). Figure S3 (Support Document) illustrates three transdiagnostic dimensions of child psychopathology (68.7% of total variance), including externalizing, psychosis, and internalizing dimensions. Figure 4 shows the heat map among the six environmental factors, three transdiagnostic dimensions of child psychopathology, and child PRS at corrected $p < 10e{-}5$. The environmental factors, except developmental adversity, were highly correlated with child internalizing, externalizing, and psychosis. Increased developmental adversity was associated with increased psychosis. Only SES was correlated with most of the PRS, except for ADHD, Phobia, insomnia, and cognitive ability. Child psychosis was correlated with child PRS for panic disorder and schizophrenia.

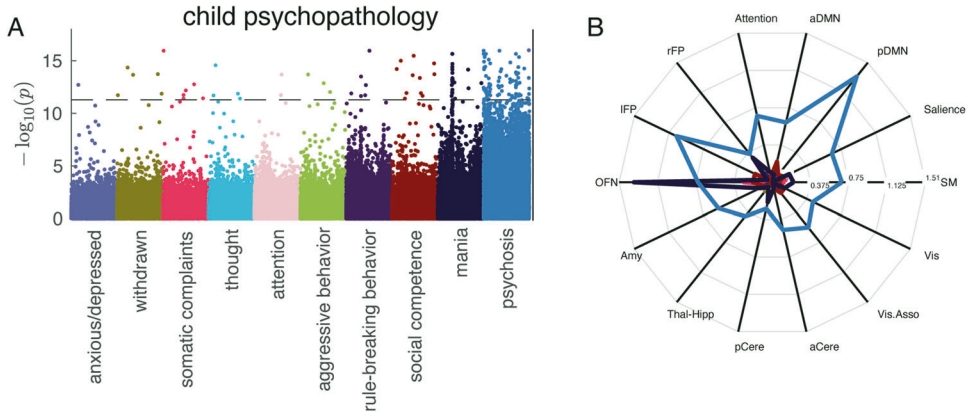

Fig. 3 Child psychopathology-wide associations with brain structural connectivities. A The Manhattan plot illustrates the associations of individual child psychopathological scales with the structural connectivities between any two brain regions. The dashed line indicates Bonferroni corrected p-value at a level of 1e−05. **B** The pie chart shows the number of structural connectivities per region in each brain network that was statistically significant with child psychopathological scales.

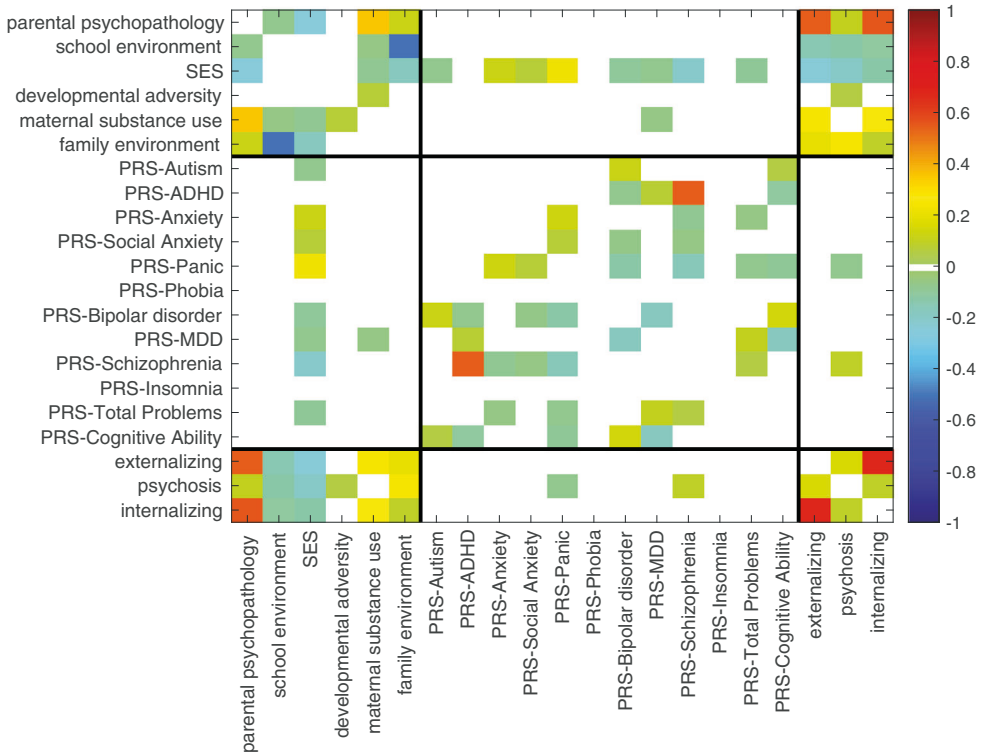

Fig. 4 Heatmap among the environmental factors, polygenic risk scores, and child transdiagnostic dimensions of psychopathology. The correlation values less than corrected $p < 10e{-}5$ are shown.

Figure 5 illustrates the pathways that link environmental factors, genetic risks, brain structural connectivity, and transdiagnostic dimensions of psychopathology in youth via SEM. Comparative fit index (CFI) indicates the goodness of fit of our SEM model (CFI = 0.968) [64]. Among six environmental factors, increased SES ($ß = -16.1$, corrected $p < 0.001$) and school engagement ($ß = -55.1$, corrected $p < 0.001$), decreased parental psychopathology ($ß = 5.58$, corrected $p < 0.001$) predicted reduced family conflicts and increased family monitoring. Moreover, increased maternal substance use ($ß = 4.61$, corrected $p = 0.001$) predicted increased developmental adversity (e.g., earlier prematurity, lower birth weight).

Developmental adversity positively predicted the structural connectivities in early developing brain networks, such as the Thal.Hipp network ($ß = 4.39$, corrected $p = 0.004$), but negatively predicted the structural connectivities in the SM ($ß = -4.38$, corrected $p = 0.004$) and Amy networks ($ß = -4.33$, corrected $p = 0.005$). Moreover, increased SES predicted decreased structural connectivities in the Vis ($ß = -6.07$, corrected $p < 0.001$), Amy ($ß = -4.23$, corrected $p = 0.008$), aCere ($ß = -5.04$, corrected $p < 0.001$), OFN ($ß = -5.12$, corrected $p < 0.001$), and salience network ($ß = -4.37$, corrected $p = 0.004$) but increased structural connectivities in the pDMN ($ß = 5.58$, corrected $p < 0.001$). While controlling for all the environmental factors, age, gender, and race, only the PRS for social anxiety predicted less structural connectivities in the Vis.Asso ($ß = -5.06$, corrected $p < 0.001$) and OFN ($ß = -4.93$, corrected $p < 0.001$).

The environmental factors and structural brain networks but not polygenic risks for psychiatric disorders predicted the

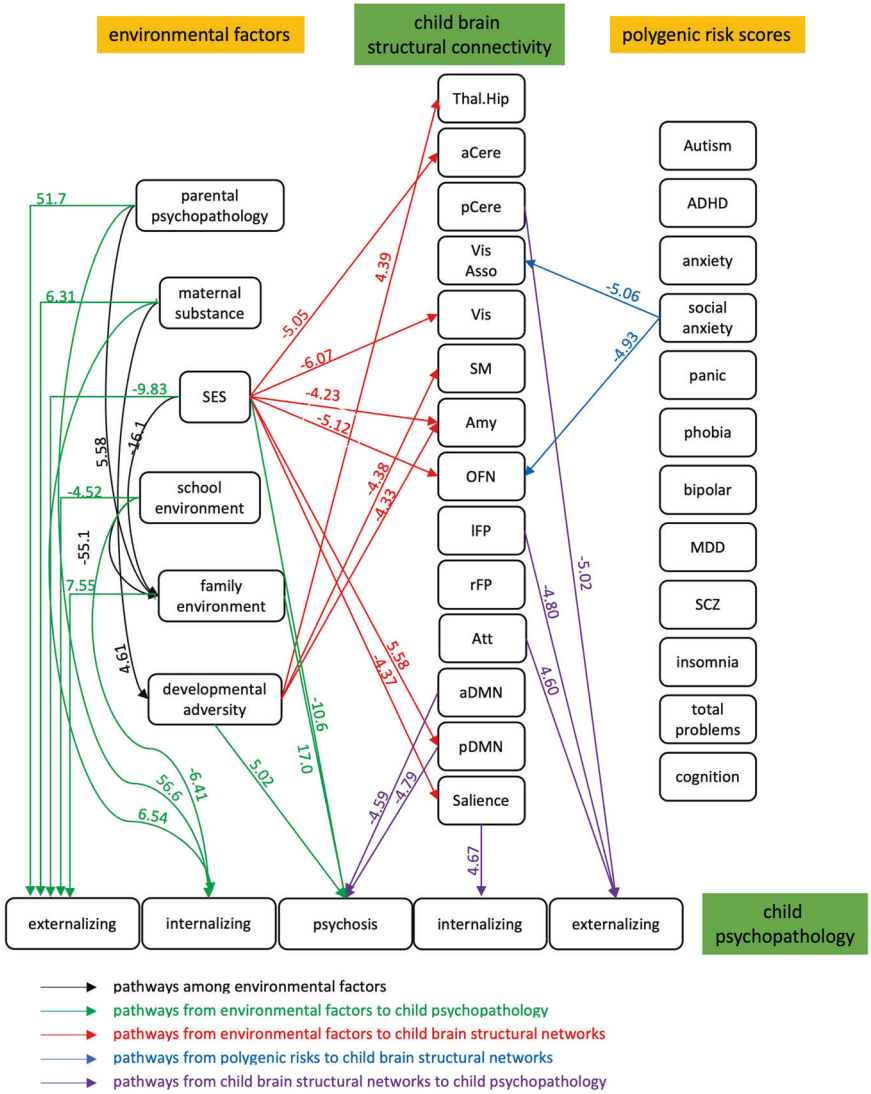

Fig. 5 Pathways link environmental factors and polygenic risk scores with the brain structural connectivity and transdiagnostic dimensions of psychopathology in youth. For visualization, we repeatedly represent child internalizing and externalizing on the bottom row. Statistical coefficients are given for each path. All statistical significance passes Bonferroni correction ($p < 10e{-}5$). The values for each path denote the standardized beta coefficients.

transdiagnostic dimension of psychopathology in youth. Increased externalizing problems were predicted by increased parental psychopathology ($ß = 51.7$, corrected $p < 0.001$), maternal substance use ($ß = 6.31$, corrected $p < 0.001$), and family conflict ($ß = 7.55$, corrected $p < 0.001$), decreased SES ($ß = -9.83$, corrected $p < 0.001$) and school engagement ($ß = -4.52$, corrected $p = 0.002$), as well as decreased structural connectivities in the pCere ($ß = -5.02$, corrected $p < 0.001$) and lFP ($ß = -4.80$, corrected $p < 0.001$) but increased structural connectivities in the Att ($ß = 4.60$, corrected $p = 0.001$). Moreover, increased internalizing problems were predicted by increased parental psychopathology ($ß = 56.6$, corrected $p < 0.001$), maternal substance use ($ß = 6.54$, corrected $p < 0.001$), decreased school engagement ($ß = -6.41$, corrected $p < 0.001$), and increased structural connectivities in the salience network ($ß = 4.67$, corrected $p < 0.001$). Last, increased psychosis was predicted by increased family conflict ($ß = 17.0$, corrected $p < 0.001$) and developmental adversity ($ß = 5.02$, corrected $p < 0.001$), decreased SES ($ß = -10.6$, corrected $p < 0.001$) and structural connectivities in the aDMN ($ß = -4.59$, corrected $p = 0.002$) and pDMN ($ß = -4.79$, corrected $p < 0.001$).

DISCUSSION

This study discovered a possible comprehensive map that links environmental factors, genetic risks, brain structural networks, and dimensional psychopathology in youth. Environmental factors and genetic risks contributed independently to child brain structural networks in youth with environmental factors having a stronger influence, in particular developmental adversity and SES. Developmental adversity predicted the structural connectivities in the SM and subcortical networks, while SES was linked with the subcortical, cerebellar, and primary visual networks, pDMN, and salience. Moreover, the triple structural networks and cerebellar networks showed distinct patterns of associations with externalizing, internalizing, and psychosis in youth. Furthermore, six environmental factors showed different associations with externalizing, internalizing, and psychosis in adolescents. Our findings suggested direct and indirect pathways of environmental factors and genetic risks influencing brain structural organization and dimensional psychopathology in youth.

This study included the multifaceted constructs of SES, including household and neighborhood SES. Among the 32 environmental measures, SES (e.g., area deprivation index, family

income, parental highest education) had the strongest independent associations with the structural connectivities dispersed across brain networks. Using the same sample, Sripada et al. [21] demonstrated that the SES score, a composite of both household and neighborhood SES, highly correlated to the functional connectivities broadly distributed across brain networks. Household and neighborhood SES also demonstrated common effects on resting-state functional connectivities, particularly in sensory systems and cognitive executive networks [65]. Previous work found that neighborhood SES is more predictive of cognitive performance than parental education [66] and moderates the development of functional brain segregation in youth [20]. Our study demonstrated that area deprivation index had the most impact, providing new evidence on the importance of neighborhood SES in modifying the brain structural organization in youth.

Our pathway analysis demonstrated that the SES factor had direct and indirect influences on the structural brain networks and the three transdiagnostic dimensions of psychopathology in youth while covarying the polygenic risks, other environmental factors, age, gender, and race. The direct link between lower SES and worse externalizing and psychosis was highly consistent with previous findings [18, 19]. The two indirect pathways linked SES, brain, and psychopathology, suggesting that lower SES predicted (1) lower pDMN structural connectivity and more severe psychosis, (2) greater salience structural connectivity and more severe internalizing in youth. The DMN is vital in monitoring the internal mental landscape [67], while the salience network plays a crucial role in the attentional capture of relevant events and the engagement of frontoparietal systems for working memory and higher-order cognitive control [68]. Increasingly, the DMN and salience networks have been identified as disease volumetric and functional connectomic "fingerprints" that are commonly disrupted across distinct forms of mood, psychosis, fear behaviors in adolescents [69, 70] or schizophrenia, depression, anxiety in adults [71]. Our findings suggested that SES might be a crucial environmental factor for reconfiguring the common core of brain structural organization in psychiatric disorders and hence improving psychopathology in youth.

Prematurity and birth weight are the purported proxies for adverse prenatal exposure. Our study found their dominant associations with the early-developed brain networks, such as the SM and subcortical networks. The sensorimotor cortex and subcortical structures, such as the thalamus, amygdala, and hippocampus, are mature in childhood [4]. Weaker functional connectivity strength in the SM network is found in preterm children and adolescents [72]. Volume reductions in the thalamus and hippocampus have been found in individuals with low birth weight [12, 73]. These findings suggest long-lasting alterations in brain morphology, structural and functional organization due to developmental adversity. Such an impact is related to the timing of exposure and the stage of brain development.

Nevertheless, this study did not find a direct relationship between family and school environment and brain structural connectivity. This is consistent with previous research, which has also not found a relationship between school environment and fractional anisotropy values of white matter tracts in the same cohort [74].

Our pathway analysis also demonstrated the interleaved relationship among the six environmental factors and their direct and indirect associations with psychopathology in youth. Increased parental psychopathology, decreased SES and school engagement was associated with increased family conflict and psychosis, and externalizing behaviors in youth. Likewise, increased maternal substance use predicted increased developmental adversity, internalizing, and psychosis. These findings indicated the importance of SES, parental, and school social factors in improving family social interactions, parenting, and developmental adversity.

Our findings further suggest that the polygenic risks for psychiatric disorders, total problems, and cognitive ability moderately affected brain structural connectivity and psychopathology in youth. While considering the environmental complexity, variations in structural connectivity and transdiagnostic dimensions of psychopathology were largely associated with environmental factors rather than polygenic risks. Judd et al. [75] recently also found that parental education predicted cognitive function and total cortical surface area, independent of the polygenic risk score for years of education in adolescents. This might result from fine-tuning synapses [7], brain morphology and functional organization associated with environmental complexity [20], or stress-induced alterations in neuroendocrine pathways [76] in adolescence.

Despite the large sample size and the comprehensive data analysis in this study, several limitations are worth considering. Our SEM model did not incorporate individual environmental items due to their collinearity. This study used univariate analysis to provide complementary information on the contributions of individual environmental items. Moreover, this study was a cross-sectional study. Longitudinal data would be needed to investigate the timing and influence of environmental factors on the developmental trajectory of brain structural connectivity and psychopathology during adolescence. Another limitation is that the study only included participants aged 9–11 years, which may limit the generalizability of the finding to other age groups. Finally, the study found moderate effects of polygenic risks on brain structural organization. But, the offspring of parents with elevated psychopathological problems were up to 50 times more likely to develop externalizing and internalizing behaviors, suggesting some form of heritability. Advanced genetic analysis methods may need to be developed for future investigation.

Our study provided a unique and comprehensive map that shows pathways linking environmental factors, genetic risks, brain structural connectivity, and psychopathology in youth. They highlight some risks to optimal development, including SES, parental psychopathology, maternal substance use during pregnancy, and school engagement, which can interfere with other environmental factors and the reconfiguration of brain structural connections unique to dimensional psychopathology. These findings suggest that a range of genetic and environmental factors can influence brain structural organization and psychopathology during adolescence, and that addressing these risk factors may be important for promoting positive mental health outcomes in young people.

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AUTHOR CONTRIBUTIONS

AQ designed the study, conducted the analyses, interpreted the findings, and drafted the manuscript. CL made substantial contributions to the DTI analysis. All authors gave their final approval of the version to be published and agreed to be accountable for all aspects of the work.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Anqi Qiu.

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