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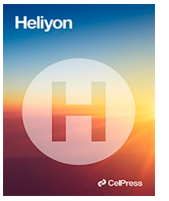

Early life stress modulates the genetic influence on brain structure and cognitive function in children

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ABSTRACT

The enduring influence of early life stress (ELS) on brain and cognitive development has been widely acknowledged, yet the precise mechanisms underlying this association remain elusive. We hypothesize that ELS might disrupt the genome-wide influence on brain morphology and connectivity development, consequently exerting a detrimental impact on children's cognitive ability. We analyzed the multimodal data of DNA genotypes, brain imaging (structural and diffusion MRI), and neurocognitive battery (NIH Toolbox) of 4276 children (ages 9–10 years, European ancestry) from the Adolescent Brain Cognitive Development (ABCD) study. The genome-wide influence on cognitive function was estimated using the polygenic score (GPS). By using brain morphometry and tractography, we identified the brain correlates of the cognition GPSs. Statistical analyses revealed relationships for the gene-brain-cognition pathway. The brain structural variance significantly mediated the genetic influence on cognition (indirect effect = 0.016, $P_{FDR} < 0.001$). Of note, this gene-brain relationship was significantly modulated by abuse, resulting in diminished cognitive capacity (Index of Moderated Mediation = −0.007; 95 % CI = −0.012 ~ −0.002). Our results support a novel gene-brain-cognition model likely elucidating the long-lasting negative impact of ELS on children's cognitive development.

1. Introduction

Early life stress (ELS), such as *abuse*, *neglect*, and *household challenges*, is a major risk factor for maladaptive cognition, behaviors, and psychiatric disorders [1–4] with long-term sequelae [5]. ELS can influence the expression of the genes responsible for stress physiology, emotion regulation, cognitive control, and learning and memory [6–10]. Previous animal literature shows the causal effect of ELS on cognition and behaviors [11–20] and potential epigenetic mechanisms within the brain [21–24]. In humans, ELS is linked to

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maladaptive stress physiology [7], emotion dysregulation [25–27], psychopathology [28,29], deficits in cognitive performance, and abnormal brain function and structure [1,3,8].

Despite the extensive literature, mechanistic insight into how ELS impacts children's cognitive development is needed. Since a number of genetic factors [30,31] influence cognitive development, their interplay with ELS may be a key to understanding how ELS negatively impacts the brain and cognition. However, the complexity of ELS, genes, and cognition makes it challenging to study whether ELS interacts with the genetic factors of cognitive development. To overcome this hurdle, in this study, we take advantage of the genome-wide polygenic score approach to estimate genetic propensities for cognition. Recent studies show a rigorous estimation of the combined effects of the thousands of SNPs associated with cognitive function, explaining up to 13 % of variances in educational attainment and 7–10 % of variances in cognitive performances [31]. This approach allows testing the hypothesis that ELS modulates the inherited genomic influences on children's brain and cognitive development. Since cognitive intelligence is linked to the extensive brain network [32,33], we expect that a number of brain regions are involved with the ELS-gene-brain-cognition relationship. Addressing the relationship will permit much-needed insight into who, when, and where to intervene regarding the impact of ELS on the brain and cognition.

This study had two main questions. First, does the gene-brain-cognition pathway exist during development? If so, does ELS negatively affect the developmental pathway? We investigated these using multimodal data, including genetics, brain imaging, and psychological and cognitive assessment data, in large samples of prepubertal children (ages 9–10 years) with a wide range of socio-demographic information.

2. Methods

2.1. Experimental design

2.1.1. Study participants

Participants were enrolled in the Adolescent Brain Cognitive Development (ABCD) study, an ongoing longitudinal multi-site study of brain development and health of youth in the United States [34]. We used the de-identified neuroimaging, demographic, genetic, and behavioral data from the ABCD 2.0 Data Release. This data was collected across 21 sites from 2015 to 2018. The participants were 11,875 children from the U.S. aged 9–10 years. After performing quality control on both genetic and neuroimaging data, we excluded participants who had missing values in covariates and other assessment domains. In the end, our analyses included 4,26 participants.

2.1.2. Genotype data for genome-wide polygenic scores (GPS)

Saliva samples were collected from study participants and were genotyped using the Affymetrix NIDA Smokescreen array (733,293 SNPs) at the Rutgers University Cell and DNA Repository. We removed any inferiorly genotyped SNPs with genotype call rate<95 % and minor allele frequency (MAF) < 1 %, as well as samples with sample call rate<95 % prior to imputation. We imputed the genotype data using the Michigan Imputation Server [35], based on the 1000 Genome phase 3 reference panel with Eagle ver2.4 phased output [36]. For the imputed 12,046,090 SNPs, we additionally removed data from any individuals with >5 % sample call rate or extreme heterozygosity (F coefficient >3 standard deviation from the population mean) and any SNPs wth <0.4 imputation INFO score, >5 % missingness rate, <1 % MAF, or Hardy-Weinberg equilibrium ($p < 10^{-6}$).

Given the complex ancestry makeup inherent to admixed American populations, our analysis was restricted to individuals with European ancestry to control population stratification. We selected 8027 European-ancestry children out of 10,659 study participants, based on the genetic ancestry information provided by the ABCD cohort and calculated using the fastSTRUCTURE algorithm [37]. We then conducted a series of quality control (QC) procedures to control for familial relatedness and ancestry admixture, using PC-Relate [38] and PC-Air [39].

First, PC-Relate estimated pairwise kinship coefficients using the KING-robust algorithm and a pruned set of 421,316 independent genetic variants (LD threshold of $r^2 < 0.1$ and MAF >1 %). This step allowed us to identify genetically related individuals with closer than 4th-degree relatives (kinship threshold = $2^{(-11/2)}$). We retained only one individual per related pair, resulting in an unrelated set of 6610 individuals after excluding 1417 related individuals.

Subsequently, we performed two rounds of principal component analysis (PCA) using the PC-Air algorithm, which is robust to familial or cryptic relatedness. In the first round, PCs were computed for the 6610 unrelated European-ancestry individuals. We excluded 55 participants whose projected PCs had Mahalanobis distances greater than 6 SDs from further analysis. PC-Relate was then used again to compute new kinship estimates, adjusting for the calculated PCs in the modified unrelated set. The second round of PC-Air computed accurate PCs with the modified unrelated set, resulting in a final genotype dataset of 11,301,999 variant information for 6555 unrelated individuals of European ancestry. Out of these 6555 unrelated individuals, 4276 European-ancestry children had matched neuroimaging data and were included in further analysis. (Supplementary Fig. 1).

To assess the subject-level genetic propensity for cognitive ability, we computed genome-wide polygenic scores (GPS) for cognitive performance (C·P.) and educational attainment (E.A.) using publicly available GWAS summary statistics based on the European population [30]. The scores were computed using PRSice2 software, version 2.0 [40], without applying a specific p-value threshold for SNP selection (GWAS p-value <1; a linkage-disequilibrium clumping threshold r^2 of 0.2 over 500 kb sliding windows based on the 1000 Genome phase3 reference panel), in line with our aim to incorporate the full spectrum of SNPs considering the highly polygenic nature of cognitive ability. While alternative methods may offer different advantages in computing GPSs, we chose PRSice2 due to its widespread use and sustainability for our study's objectives [40]. To control for population stratification, the scores were adjusted for the first ten principal components (PCs) of the genotype data (11,301,999 variants) of 4276 unrelated European-ancestry children,

which were calculated with PC-Air [39] (Supplementary Fig. 1).

2.1.3. Brain imaging-anatomical imaging

We processed T1-weighted (T1w) 3D structural MRI images provided by the ABCD study, following established protocols [34,41]: The gradient nonlinearity distortion correction method was applied to structural MRI scans for the purpose of improving geometric accuracy and image intensity reproducibility [42]. First, intensity nonuniformity was corrected based on tissue segmentation and sparse spatial smoothing. We then resampled the images with 1 mm isotropic voxels into rigid alignment with an atlas-derived brain.

We applied Freesurfer v6.0 (https://surfer.nmr.mgh.harvard.edu) for reconstructing cortical surface [43] followed by skull-stripping [44], white matter segmentation, and initial mesh creation [43], correction of topological defects, surface optimization [45,46], and nonlinear registration to a spherical surface-based atlas [47]. We used Desikan-Killiany and Destrieux atlas to extract 1004 ROI measures, including volumes, surface area, thickness, and mean curvature.

2.1.4. Brain imaging-diffusion spectrum imaging

Diffusion spectrum images were acquired in the ABCD study. We preprocessed the images using the following protocol [48] by the ABCD Data Analysis and Informatics Center (DAIC). Eddy current distortion correction was used with a nonlinear estimation using diffusion gradient orientations and amplitudes to predict the pattern of distortion [49]. Head motion was corrected by registering images synthesized from tensor fit [50]. Diffusion gradients were adjusted for head rotation [50,51]. To identify and replace dark slices due to abrupt head motion, we used robust diffusion tensor estimation [52]. B0 distortion was corrected with the reversing gradient method [53]. Gradient nonlinearity distortion correction was applied [42]. The data were resampled to a standard orientation with an isotropic resolution of 1.5 mm.

We used individual connectome data to estimate accurate brain imaging phenotypes. MRtrix3 [54] was applied for whole-brain white matter tract estimation and individualized connectome generation. We used streamline counts associated with fiber connection strength [55,56] associated with fiber integrity for connectivity metrics. We decreased noise [57] and performed bias correction with the Advanced Normalization Tools (ANTs) pipeline's N4 algorithm [58]. To obtain a connectivity index with a white matter pathway [59], we performed probabilistic tractography by second-order integration over fiber orientation distributions [60], with random seeding across the brain and target streamline counts of 20 million. We filtered these initial tractograms using spherical-deconvolution-informed filtering (2:1 ratio). With a final streamline count of 10 million, we generated each participant's 84 $\times$ 84 whole-brain connectome matrix restricted to their neuroanatomy by using the T1-based parcellation and segmentation in FreeSurfer. We performed the computation on the supercomputers at Argonne Leadership Computing Facility Theta and Texas Advanced Computing Center Stampede2.

2.1.5. Extracting brain representations associated with cognitive capacity genetic scores

To extract brain morphometric representations correlated with genetic influence on intelligence, we first performed a generalized linear model analysis using cognitive capacity GPSs as independent variables and neuroimaging data as dependent variables adjusted for covariates (e.g., age, sex, maternal education, parental income, BMI, study site, and marital status). We separately investigated the associations between two distinct types of cognitive capacity GPSs (educational attainment GPS and cognitive performance GPS) and three distinct types of brain features derived from different neuroimaging modalities (structural MRI, DTI-count, and DTI-FA). At each investigation, we conducted statistical tests equivalent to the number of brain features derived from a given neuroimaging modality. Then, we applied multiple testing correction based on the number of statistical tests we conducted, I.e., the number of brain features derived from a given neuroimaging modality. Among three distinct types of neuroimaging data (structural MRI, DTI-count, and DTI-FA), only brain morphometric features (i.e., structural MRI) showed significant associations with cognitive capacity GPSs ($P_{Bonferroni} < 0.05$; Fig. 3, Supplementary Fig. 2, Supplementary Table 1). We then performed principal component analysis to extract representations from brain morphological features associated with cognitive performance GPS or educational attainment GPS (R version 3.4.1). We used the first principal components as representations of the brain.

2.1.6. NIH Toolbox Cognition Battery data

NIH Toolbox Cognitive Function Tests [61] were used to assess various levels of general cognitive ability of the participants. For each child, summary scores from the NIH Toolbox Cognition Battery were provided, including the crystallized intelligence composite score (an assessment of prior learning and past experiences about language), the fluid intelligence composite score (an assessment of abstract reasoning and learning ability in novel situations), and total intelligence composite score, which is the combination of both crystallized and fluid intelligence composite scores [62]. The crystallized intelligence composite score is a composite of the *Picture Vocabulary Test* and the *Oral Reading Recognition Test* outcomes. The fluid intelligence composite score is a composite of the *Dimensional Change Card Sort Test*, the *Flanker Inhibitory Contro*l and *Attention Test*, the *Picture Sequence Memory Test*, the *List Sorting Working Memory Test*, and the *Pattern Comparison Processing Speed Test* outcomes. Finally, the total intelligence composite score represents general intelligence and is an aggregation of all the tests [62].

2.1.7. Early life stress

We derived ELS measures based on child exposure domains in the ABCD study [63] (Supplementary Table 2). First, ELS measures were divided into three main categories: *household challenges, neglect,* and *abuse*. Subcategories of ELS data were as follows: *parental separation or divorce*, *criminal household member*, *household substance abuse*, *mental illness in the household*, *mother treated violently* in *household challenges*, *emotional neglect*, *physical neglect* in *neglect*, and *physical abuse* and *sexual abuse* in *abuse*. Next, we extracted the

items of each subscale from the following various measurement tools (participant- or parent-reported): ABCD Family Environment Scale-Family Conflict Subscale Modified from PhenX, ABCD Diagnostic Interview for DSM-5 Traumatic Events, ABCD Family History Assessment, ABCD Parent Demographics Survey, ABCD Children's Report of Parental Behavioral Inventory, and ABCD Parental Monitoring Survey. Then, we averaged the measurements for each subcategory and transformed them into z scores. The higher the score, the more stressful the experiences children had.

2.1.8. Statistical analysis

We performed a generalized linear model for three types of relationships — GPS-brain, GPS-intelligence composite scores, and brain-intelligence composite scores. We included the following covariates in those models: age, sex, maternal education, parental income, BMI, study site, and marital status. Family ID was not included because our analysis was performed in the dataset of unrelated individuals after excluding any relatives fourth-degree or closer during the genetic Q.C. process. We utilized the Benjamini-Hochberg procedure as a false discovery rate to correct for multiple testing comparison in each type of relationship.

For path modeling, we first tested an initial mediation model to check whether the key relationship of the GPS-brain-cognition pathway was significant. Before examining the role of ELS in the GPS-brain-cognition pathway, we tested whether ELS directly affects cognition and whether ELS moderates the GPS-cognition pathway. After we determined the potential moderation effect of ELS on the GPS-brain-cognition pathway, we evaluated the first-stage moderated mediation model, and the second-stage moderated mediation models, following the framework of moderated mediation analysis [64–66]. These models assessed how ELS and its interaction with genes or the brain affect the triangular pathway. We repeated the analyses with different subcategories of ELS and compared their effects. After we confirmed the base model through aforementioned path modeling approaches, we performed the step wise-model selection by incorporating the effects of ELS-covariates and GPS-covariates. In a step-wise manner, we iteratively added interaction terms of gene-covariates and ELS-covariates into the base model which examines the impact of Early Life Stress on the gene-brain-cognition pathway without considering the interaction of gene-covariates and ELS-covariates. We selected the best model based on Akaike Information Criterion. Then, we conducted multiple testing comparison by utilizing the Benjamini-Hochberg procedure to control for the false discovery rate as same as aforementioned moderated mediation analysis.

Additionally, we tested another sensitivity analysis for the brain representation within our model. We conducted Pearson's correlation test between the brain representation and global brain morphology variables used for obtaining the brain representation. Subsequently, we replace the brain representation with global brain morphology variables in our best model to examine potential indistinguishability between the brain representation and global brain morphological features. Lastly, we performed moderation analysis as an exploratory analysis to examine how the interactions between ELS and GPS affect behavioral problems with caregiver-reported Child Behavior Checklist (CBCL) from the ABCD study [63].

Mediation and moderated mediation analyses were performed in R environment v3.4.1 using the *lavaan* v0.6-7 package with 1000 bootstrapping samples. Mediation models included the same covariates used in the regression model. Because of model convergence issues, *parental separation or divorce* had to be excluded in a moderated mediation model.

3. Results

3.1. Participants

After quality control, our study cohort comprised 4276 unrelated children of European ancestry with a mean age of 9–10 years from the ABCD study [34]. The demographic characteristics of the patients, stratified by records of ELS experience, are summarized in Table 1 (Supplementary Table 3) and Fig. 1. In addition, several covariates showed significant differences between the ELS and non-ELS groups (Supplementary Table 4).

Table 1
Demographic characteristics of participants with European ancestry (N = 4276). The total participants are divided into five intervals regarding the composite score of ELS.

Sex	Number of subjects				
Male	2271				
female	2005				
Age *(months)*	**Mean**	**Standard deviation**			
	119.28	7.38			
ELS score	**0–20 % (female)**	**20–40 % (female)**	**40–60 % (female)**	**60–80 % (female)**	**80–100 % (female)**
Household Challenges	3711 (46.7 %)	464 (48.7 %)	83 (47.0 %)	15 (40.0 %)	2 (50.0 %)
Neglect	2508 (51.7 %)	1303 (41.8 %)	377 (34.2 %)	81 (40.7 %)	6 (33.3 %)
Abuse	4233 (46.9 %)	27 (55.6 %)	1 (100.0 %)	0 (0)	13 (30.8 %)

Demographic characteristics of participants regarding the composite score of ELS subscales are listed in Supplementary Table 4.

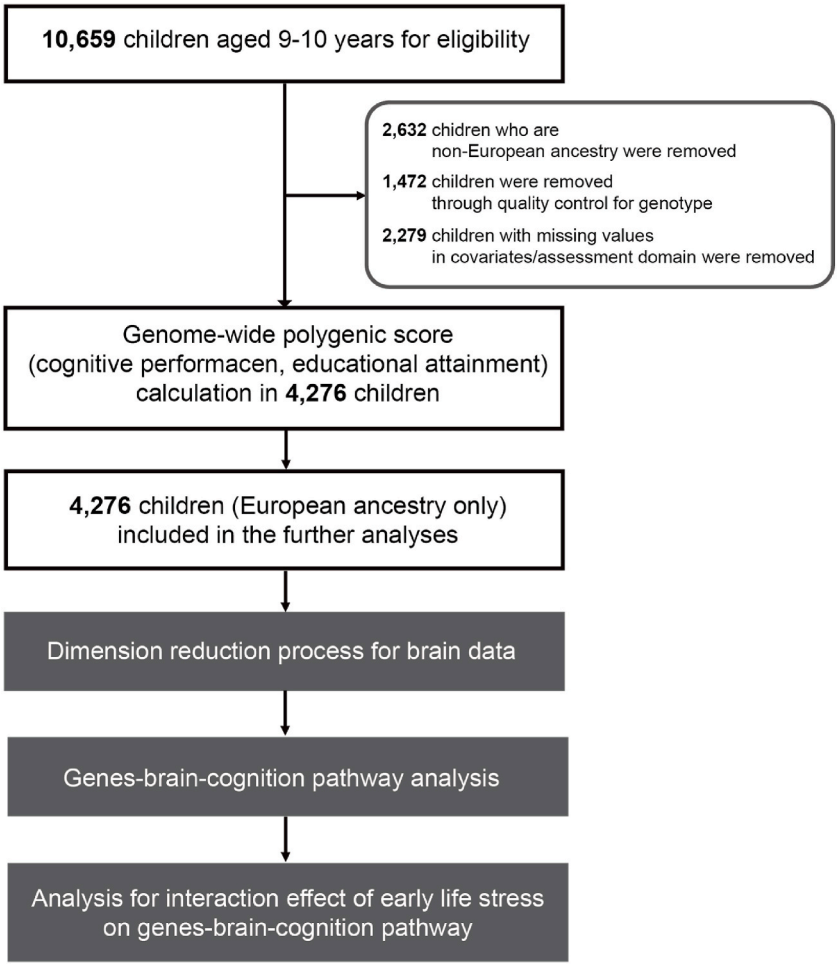


Fig. 1. Flow chart of data selection and research design. From the ABCD 2.0 Data release, genetic, brain imaging, and cognitive assessment data for 11,875 participants were collected. For the 8496 individuals after initial quality control and GPS calculation, we additionally removed samples of non-European ancestry or with any missing values, for a total of 4276 participants included in the analysis.

3.2. Correlation among GPS, brain, and intelligence

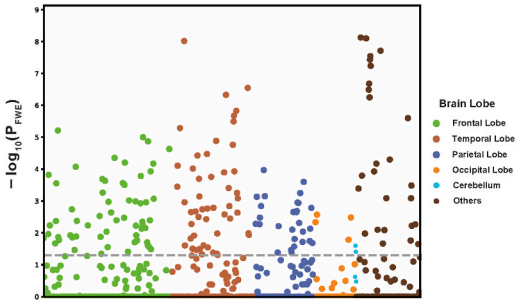
3.2.1. Cognitive capacity GPS-brain

Out of 992 brain morphometric features, 169 and 44 brain features significantly correlated with cognitive performance GPS ($P_{Bonferroni} < 0.05$) and educational attainment GPS, respectively ($P_{Bonferroni} < 0.05$), when adjusted for age, sex, maternal education, parental income, BMI, study site, and marital status (Fig. 2). Of note, global brain features — including total gray matter volume, total cerebral white matter volume, and subcortical gray matter volume — as well as volume and surface area of ROI around the temporal lobe and frontal lobe — including the inferior temporal lobe, superior temporal lobe, orbitofrontal lobe — showed significant associations with both GPSs (Fig. 2, Supplementary Table 1). White matter fiber counts and fractional anisotropy of the structural connectomes showed no significant correlations with either GPS (Supplementary Fig. 2). We performed the principal component analysis with brain morphometric features correlated with each GPS to obtain cognitive capacity GPS-related brain representations. Accounting for the substantial variance of brain morphometric features (correlated with each GPSs) ($Brain_{\text{cognitive performance GPS}}$: 44.5 %; $Brain_{\text{educational attainment GPS}}$: 54.9 %) (Supplementary Figs. 3, 4, 5), the first component significantly correlated with cognitive capacity GPS ($Brain_{\text{cognitive performance GPS}}$: $\beta = 0.10$, $P_{FDR} < 0.001$; $Brain_{\text{educational attainment GPS}}$: $\beta = 0.15$, $P_{FDR} < 0.001$) (Supplementary Table 5).

3.2.2. Brain-intelligence composite score

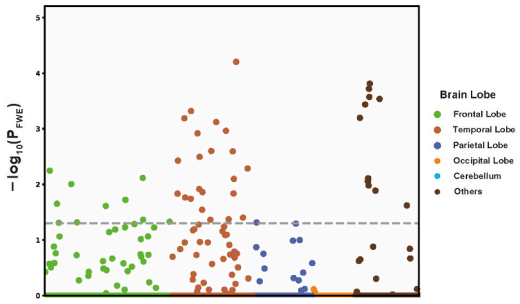
Both $Brain_{cognitive\ performance\ GPS}$ and $Brain_{educational\ attainment\ GPS}$ significantly correlated with all three types of intelligence composite scores ($P_{FDR} < 0.001$). Among the several types of intelligence composite scores, the brain representations showed the highest effect size on crystallized intelligence composite scores ($Brain_{cognitive\ performance\ GPS}$: $\beta = 0.18$; $Brain_{educational\ attainment\ GPS}$: $\beta = 0.18$), with the lowest effect size on fluid intelligence composite scores ($Brain_{cognitive\ performance\ GPS}$: $\beta = 0.05$; $Brain_{educational\ attainment\ GPS}$: $\beta = 0.05$). Total intelligence composite score moderately correlated with brain representations ($Brain_{cognitive\ performance\ GPS}$: $\beta = 0.12$; $Brain_{educational}$

A. Brain structural features associated with CP GPS



Brain morphology features	β	P	P_{BONF}	Lobe
white matter volume of right hemisphere inferior temporal lobe	0.088	9.62e-12	9.55e-09	temporal
volume of right hemisphere inferior temporal lobe	0.085	2.86e-10	2.84e-07	temporal
area of left hemisphere lateral superior temporal gyrus	0.086	4.72e-10	4.69e-10	temporal
area of left hemisphere superior temporal lobe	0.082	1.49e-09	1.48e-06	temporal
area of left hemisphere inferior temporal lobe	0.078	2.14e-09	2.12e-06	temporal
area of right hemisphere middle temporal lobe	0.078	3.22e-09	3.19e-06	temporal
white matter volume of right hemisphere middle temporal lobe	0.079	5.21e-09	5.17e-06	temporal
area of right hemisphere middle frontal gyrus	0.082	6.18e-09	6.14e-06	frontal
area of left hemisphere superior frontal lobe	0.078	9.99e-09	9.92e-06	frontal
volumee of left hemisphere superior temporal lobe	0.080	1.31e-08	1.30e-05	temporal

B. Brain structural features associated with EA GPS



Brain morphology features	β	P	P_{BONF}	Lobe
area of left hemisphere superior temporal lobe	0.083	6.27e-08	6.23e-05	temporal
volume of rigth hemisphere temporal pole	0.081	4.83e-07	4.80e-04	temporal
white matter volume of right hemisphere inferior temporal lobe	0.073	6.54e-07	6.49e-04	temporal
volume of left hemisphere superior temporal lobe	0.078	7.65e-07	7.59e-04	temporal
area of right hemisphere temporal pole temporal	0.071	3.23e-06	3.21e-04	temporal
white matter volume of right hemisphere superior temporal lobe	0.073	3.77e-06	3.74e-04	temporal
volume of right hemisphere inferior temporal lobe	0.069	5.21e-06	5.17e-04	temporal
volume of right hemisphere rostral middle frontal lobe	0.071	7.73e-06	5.67e-04	frontal
area of left hemisphere medial orbito frontal lobe	0.065	7.81e-06	7.68e-04	frontal
area of right hemisphere inferior temporal lobe	0.066	8.05e-05	7.99e-04	temporal

Fig. 2. Neural correlates of cognitive performance GPS (CP GPS) and educational attainment GPS (EA GPS). A, Brain structural features associated with cognitive performance GPS and the list of the ten most significant brain structural features. B, Brain structural features associated with educational attainment GPS and the list of the ten most significant brain structural features. The dotted line indicates the significance threshold for bonferroni corrected p value ($\alpha_{Bonferroni} = 0.05$).

attainment GPS: $\beta = 0.12$) (Supplementary Table 6).

3.2.3. GPS-intelligence composite score

Both cognitive performance and educational attainment GPS significantly correlated with the outcomes of all three types of intelligence measures ($P_{FDR} < 0.05$). Crystallized intelligence showed the strongest association with both GPSs (cognitive performance *GPS: $\beta = 0.17$; educational attainment GPS: $\beta = 0.15$*), followed by total intelligence composite scores (cognitive performance *GPS: $\beta = 0.14$; educational attainment GPS: $\beta = 0.10$*) and the fluid intelligence composite score (cognitive performance *GPS: $\beta = 0.09$; educational attainment GPS: $\beta = 0.05$*) (Supplementary Table 6).

3.2.4. Relationships of GPS, brain, and cognition

Mediation analyses of the GPS-brain-cognition pathway (Fig. 3-A) showed that the brain morphometry significantly mediated the effect of both GPSs on cognitive intelligence ($P_{FDR} < 0.001$). Both GPSs showed the strongest direct effect on the crystallized intelligence composite score (direct effect of cognitive performance GPS: $\beta = 0.15$; direct effect of educational attainment GPS: $\beta = 0.13$) compared to that on fluid intelligence (direct effect of cognitive performance GPS: $\beta = 0.09$; direct effect of educational attainment GPS: $\beta = 0.04$) and total intelligence (direct effect of cognitive performance GPS: $\beta = 0.13$; direct effect of educational attainment GPS: $\beta = 0.09$). The GPS-Brain-Intelligence indirect (mediation) effects were also the strongest to crystallized intelligence (indirect effect of cognitive performance GPS: $\beta = 0.016$; indirect effect of educational attainment GPS: $\beta = 0.016$), compared to fluid intelligence (indirect effect of cognitive performance GPS: $\beta = 0.004$; indirect effect of educational attainment GPS: $\beta = 0.005$) and total intelligence (indirect effect of cognitive performance GPS: $\beta = 0.010$; indirect effect of educational attainment GPS: $\beta = 0.010$) (Table 2, Supplementary Table 7).

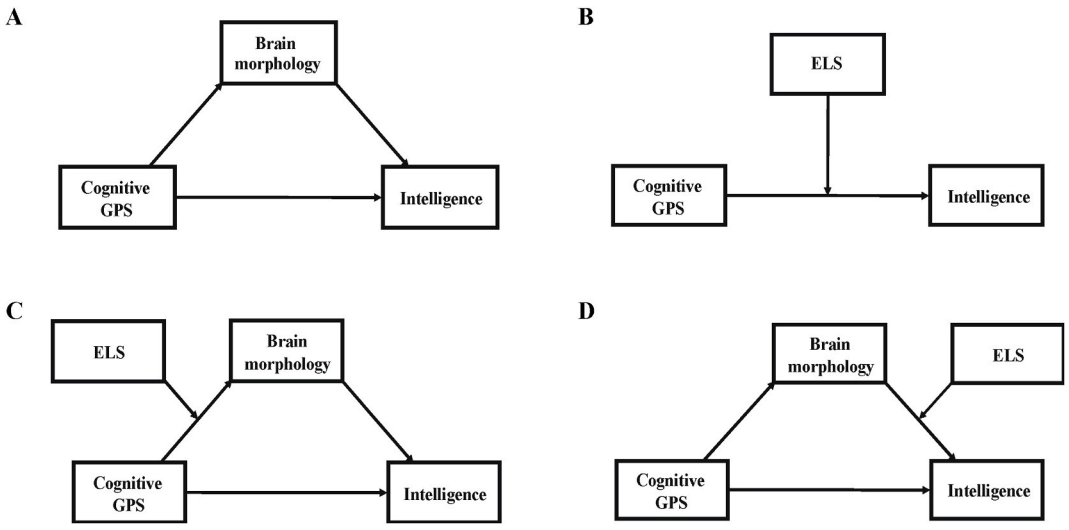


Fig. 3. Schematic overview of the tested path models. A, The baseline mediation model has the brain factor as a mediator. B, The moderation model has ELS as a moderator. C, The first-stage moderated mediation model for testing the moderating role of ELS on the relationship between the brain and genomic factors. D, The second-stage moderated mediation model for testing the moderating role of ELS on the relationship between the brain and intelligence composite scores.

Table 2
Results of mediation analysis.

Intelligence type	Crystallized Intelligence		Fluid Intelligence		Total Intelligence	
	CP GPS	EA GPS	CP GPS	EA GPS	CP GPS	EA GPS
coefficient [95 % CI]						
$X \rightarrow M$	0.101*** [0.075, 0.126]	0.094*** [0.066, 0.122]	0.101*** [0.076, 0.129]	0.081*** [0.065, 0.124]	0.101*** [0.077, 0.127]	0.094*** [0.067, 0.122]
$M \rightarrow Y$	0.155*** [0.128, 0.176]	0.168*** [0.139, 0.196]	0.041*** [0.012, 0.071]	0.059*** [0.020, 0.079]	0.099*** [0.072, 0.127]	0110*** [0.082, 0138]
$X \rightarrow M \rightarrow Y$ *(Indirect)*	0.016*** [0.011, 0.021]	0.016*** [0.010, 0.021]	0.004** [0.001, 0.008]	0.005** [0.002, 0.008]	0.010*** [0.007, 0.014]	0.010*** [0.007, 0.014]
$X \rightarrow Y$ *(Direct)*	0.151*** [0.126, 0.172]	0.134*** [0.107, 0.163]	0.087*** [0.061, 0.115]	0.035* [0.017, 0.074]	0.130*** [0107, 0.152]	0.093*** [0.057, 0.103]
R [2]						
$X \rightarrow M$	0.286	0.279	0.286	0.279	0.286	0.279
$X \rightarrow Y$	0.252	0.243	0.147	0.140	0.248	0.236

*False Discovery Rate (Benjamin-Hochberg procedure) corrected p value. *p < 0.05, **p < 0.01, ***p < 0.001*. Standardized regression coefficients for each path and standardized regression coefficients for indirect/direct path are reported. 95 % Confidence Intervals are listed in the square bracket below coefficient values. CP GPS = Cognitive Performance GPS; EA GPS = Educational Attainment GPS. X (Independent variable) = GPS; M (Mediator) = the first principal component of GPS-related brain morphology features; Brain; Y (Dependent variable) = Intelligence Composite Scores. Note: N = 4267.

3.2.5. Moderated mediation effect of ELS on GPS-brain-cognition pathway

Before moderated mediation analysis, we performed moderation analysis to test whether ELS moderated the effect of cognitive capacity GPSs on intelligence composite scores (Fig. 3-B). No significant moderation effects of the ELS variables were detected ($P_{FDR} > 0.05$) (Supplementary Tables 8 and 9).

First-stage moderated mediation analysis (Fig. 3-C) showed the significant negative moderation effect of *abuse* on the educational attainment GPS-brain-intelligence composite score relationship (Fig. 4-A). Notably, *abuse* itself did not affect educational attainment GPS-related brain morphometry; however, the interaction between educational attainment GPS and *abuse* showed a significant negative association with brain morphometry ($\beta = -0.04$, 95 % CI = -0.07 ~ -0.014, $P_{FDR} < 0.05$). Crystallized intelligence was the most severely affected by the modulatory effect of ELS on the cognitive capacity GPSs-brain morphometry pathway (*Index of Moderated Mediation = -0.007, 95 % CI = -0.012 ~ -0.002*) compared to fluid intelligence (*Index of Moderated Mediation = -0.002, 95 % CI = -0.004~0.0*) and total intelligence (*Index of Moderated Mediation = -0.005, 95 % CI = -0.009 ~ -0.002)* (Fig. 4-B, Table 3, Supplementary Table 10). In second-stage moderated mediation models (Fig. 3-d), we found no significant interactions between the brain and ELS on intelligence composite scores (Supplementary Table 11). Taken together, the negative moderation effect of *abuse* on the pathway from GPS to cognitive intelligence was observed only when the brain served as the mediator. This moderated mediation effect was only significant for *abuse,* but not for other ELS, including subscales (Supplementary Tables 12 and 13). After investigating the

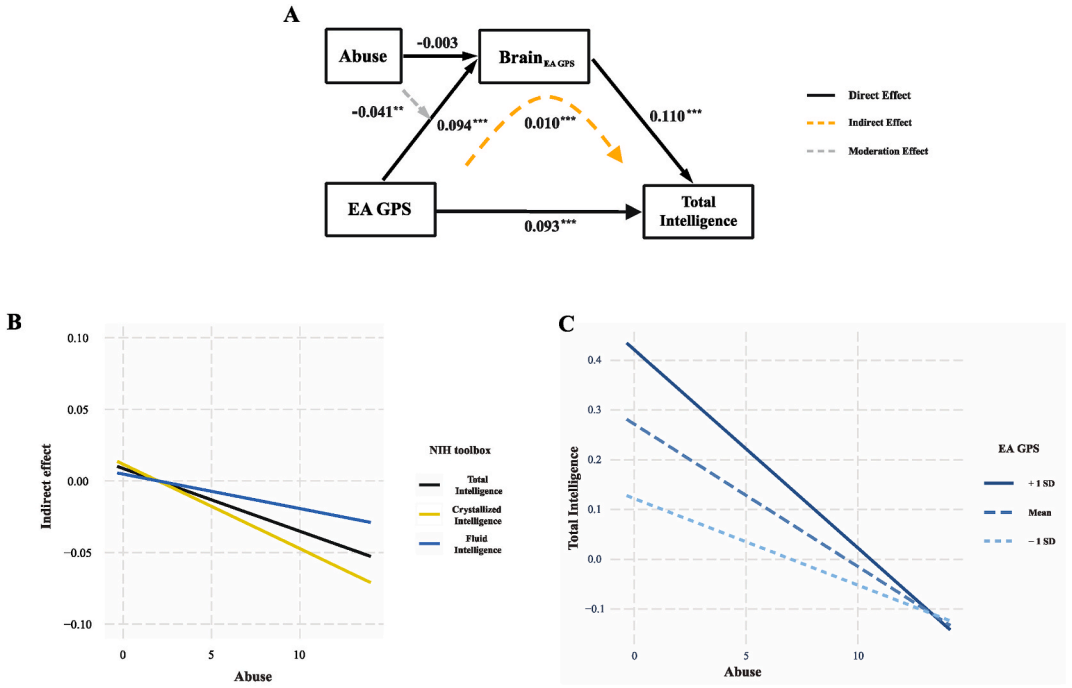


Fig. 4. The impact of interaction effect between educational attainment GPS (EA GPS) and abuse on genes-brain-cognition pathway. A, Diagram of our pathway model. B, Slope of lines indicate moderation effects of abuse on the indirect effect of genes-brain-cognition (i.e., Index of moderated mediation) with regards to types of intelligence. C, Differential impact of interaction between educational attainment GPS and abuse on genes-brain-cognition pathway according to the level of educational attainment GPS.

Table 3
Moderated Mediation effect of *Abuse* on Educational Attainment GPS-Brain-Cognition.

Intelligence	Crystallized Intelligence	Fluid Intelligence	Total Intelligence
coefficient [95 % CI]			
$X \rightarrow M$	0.094*** [0.066, 0.124]	0.094*** [0.064, 0.123]	0.094*** [0.064, 0.122]
$W \rightarrow M$	−0.003 [-0.03, 0.022]	−0.003 [-0.032, 0.021]	−0.003 [-0.029, 0.023]
$X \times W \rightarrow M$	−0.041* [-0.074, −0.014]	−0.041* [-0.073, −0.015]	−0.041* [-0.074, −0.014]
$M \rightarrow Y$	0.168*** [0.139, 0.195]	0.048*** [0.017, 0.078]	0.110*** [0.083, 0.137]
$X \rightarrow M \rightarrow Y$ *(Indirect)*	0.016*** [0.011, 0.022]	0.005** [0.001, 0.008]	0.010*** [0.007, 0.014]
$X \rightarrow Y$ *(Direct)*	0.134*** [0.106, 0.159]	0.046*** [0.018, 0.075]	0.093*** [0.053, 0.104]
Index of Moderated Mediation	−0.007 [-0.012, −0.002]	−0.002 [-0.004, 0.0]	−0.005 [-0.009, −0.002]
R [2]			
X & $W \rightarrow M$	0.281	0.281	0.281
$X \rightarrow Y$	0.243	0.140	0.236

*False Discovery Rate (Benjamin-Hochberg) corrected p-value. *p < 0.05, **p < 0.01, ***p < 0.001.* Standardized regression coefficients for each path and standardized regression coefficients for indirect/direct path are reported. X (Independent variable) = Educational Attainment GPS; M (Mediator) = the first principal component of Educational Attainment GPS-related brain morphology features; Brain; Y (Dependent variable) = Intelligence Scores; W (Moderator) = Early Life Stress; X × W = interaction term of GPS and ELS. Note: N = 4276. *household challenges*: case/control = 4198/78; *neglect*: case/control = 3960/316; *abuse*: case/control = 1303/2973.

impact of the interaction between educational attainment GPS and *abuse* on the gene-brain-cognition pathway, we conducted a step-wise model selection to identify the optimal model that characterized the influence of *abuse* on the gene-brain-cognition pathway, while also accounting for the interaction effects of educational attainment GPS-covariates and *abuse*-covariates. Upon the step-wise model selection, we confirmed significance of the interaction between educational attainment GPS and *abuse* on the gene-brain-cognition pathway with the existence of additional interactions involving educational attainment GPS-covariates and *abuse*-covariates, including sex, maternal education, parental income, BMI, study site, and marital status as covariates. These findings remained statistically significant even following multiple testing comparison (Supplementary Tables 10–c).

Following model confirmation, we performed sensitivity analysis for brain representation within our model. As results from Pearson's correlation test, the brain representation derived from educational attainment GPS-related brain morphological features were highly correlated with educational attainment GPS-related global brain morphological features (Pearson's $r > 0.9$), including total brain volume, total gray matter volume, and total cerebral white matter volume. However, when replacing the brain

representation with global brain morphological features in our model to examine the impact of ELS on the gene-brain-cognition pathway, we found that the interaction between ELS and educational attainment GPS did not significantly affect these global brain morphological features, even after accounting for the influence of the interaction of educational attainment GPS-covariates and ELS-covariates (Supplementary Table 14).

3.2.6. Relationships of abuse on behavioral outcomes: exploratory analyses

Lastly, we explored whether *abuse* affected non-cognitive domains using the Child Behavior Checklist. *Abuse* significantly correlated with internalizing behavior problems ($\beta = 0.05$, $P_{FDR} < 0.01$), externalizing behavior problems ($\beta = 0.05$, $P_{FDR} < 0.01$) and total behavior problems ($\beta = 0.06$, $P_{FDR} < 0.01$) when adjusted for covariates. Of note, we found a significant negative interaction of *abuse* and educational attainment GPS on internalizing behavior problems ($\beta = -0.04$, $P_{FDR} < 0.05$) and on total behavior problems ($\beta = -0.05$, $P_{FDR} < 0.05$). That is, with the existence of *abuse*, a child with a higher educational attainment GPS showed a lower behavioral problem compared with a child with a lower educational attainment GPS, alluding to a protective effect of educational attainment GPS against *abuse*. The interaction effect remained significant when including total intelligence scores and its interaction with *abuse*, which also correlated with total behavior problems. Furthermore, when we additionally included the interactions of educational attainment GPS-covariates and ELS-covariates — educational attainment GPS-parental income, educational attainment GPS-maternal education, educational attainment GPS-sex, *abuse*-parental income, *abuse*-maternal education, *abuse*-sex — into the above analyses, internalizing behavior problems and total behavior problems were significantly correlated with the interaction effect between educational attainment GPS and *abuse* (Supplementary Figures 6~8, Supplementary Table 15).

4. Discussion

In this research, we elucidated the relationships between the genetic influences on brain and cognitive function and how ELS affects the gene-brain-cognition pathway. We performed an integrative, multimodal analysis by leveraging genetic, neuroimaging, and cognitive assessment data of 4276 children of European descent. In the gene-brain-cognition pathway, the brain's gray matter morphometry mediated the genomic influence on cognitive function. It is noteworthy that no other types of ELS showed such effects. Therefore, the comprehensive, multimodal analysis used in this study offers a mechanistic understanding of the detrimental effects of abuse on cognitive function in children.

Extending the literature reporting the unidirectional influence of genetics on the brain and cognition [3,67–72], our study shows a comprehensive multifactorial model in which brain structural development mediates the genome-wide influence on cognitive function in children. Of note, the association of the cognitive capacity GPS was significant only with gray matter morphology, primarily cortical regions, but not with white matter connectivity. This finding may be associated with the developmental characteristics observed during preadolescence (9–10 years old), i.e., marked changes in gray matter, followed by white matter maturation in the later developmental stage [73]. In the future, it may be interesting to assess how the genetic influence of cognitive capacity is linked to longitudinal brain changes throughout the developmental trajectory.

Several key contributions of this study should be noted. First, by integrating genetics, brain imaging, and behavioral datasets, we showed that *abuse* negatively modulated the genome-wide influence on the brain and cognitive function and identified extensive cortical regions (including the frontal, temporal, and parietal areas) associated with this modulatory effect. This finding may account for the potential mechanism of the long-term impact of ELS on cognitive deficits or delays in development in humans [74,75]. The discovery of the ELS modulatory effect and the widespread cortical mediator was enabled by our novel application of the biologically informed model of the gene-brain-cognition pathway instead of the direct correlation of ELS to the brain or cognitive estimates as in some prior studies. Our model might lead to a more precise and detailed stratification of the risk of ELS on cognitive function by considering the variability of children's genetic predispositions.

Our observations support that the modulatory effect of ELS on the influence of the cognitive capacity GPS on the brain structure is in line with its influence on other domains, such as affective processing, stress physiology, and the relevant brain system [3,67–72]. Likewise, animal studies show that *abuse* negatively impacts genetic regulation of the brain systems, such as hippocampal glucocorticoid receptors, neurogenesis, and regulation of brain development [6,7,9,76]. Indeed, the modulatory effect of ELS might be linked to epigenetics. Animal and human research show that ELS induces epigenetic modification of the genes associated with a wide array of neural events and brain morphology, such as neurotransmitter biosynthesis, neurological system processes, glial cell proliferation, neurogenesis in the hippocampus, neural migration in the cerebral cortex, neuroplasticity, and neurodevelopmental delay: *FKBP5*, *SLC64A*, *SHC2*, *IMPACT*, *GRIN2D*, and *DIP2C* [76–82]. Many of these events are related to cognitive development. Our findings are noteworthy as they revealed that ELS had a significant modulatory effect on the relationship between cognitive capacity GPS and brain structure in children even after adjusting for sex. Recent study show that epigenetic modifications induced by ELS in children persist when controlling for sex [76]. These results indicate that ELS may negatively affect the gene-brain-cognition relationship regardless of sex. Although we could not examine sex differences due to limited sample size, it will be valuable to investigate the potential role of sex in the modulatory effects of ELS on the relationship between genetic predisposition and neurocognitive development [76].

Our study indicates the modes of action whereby *abuse* modulates the educational attainment GPS's influence may differ on cognitive and behavioral outcomes. In the absence of *abuse*, the educational attainment GPS positively correlates with the brain structural estimates (a greater cortical thickness, surface area, and volumes) and cognitive intelligence as expected. However, the existence of *abuse* weakens the education attainment GPS' influence on the brain and cognition. As a result, a child with a higher education attainment GPS ends up having a greater negative impact of abuse on cognitive intelligence, that is, a smaller genetic influence on the brain structure and cognition. This reflects that the negative effects of *abuse* on cognitive capacity may override the

genetic influence. This consequence might seem counterintuitive, considering the literature reporting high cognitive capacity (e.g., education attainment, intelligence quotient) as a resilience factor for mental health against ELS [83–85]. However, looking deeper, it becomes clearer. Children with *abuse* and higher educational attainment GPS still show higher cognitive intelligence than children with lower educational attainment GPS (consistent with the literature [6–10]). However, the impact of abuse on the behavioral domain shows the opposite pattern. In CBCL behavioral problems, which *abuse* is positively correlated with, a child with a high educational attainment GPS shows fewer behavioral problems than a child with a low educational attainment GPS. Unlike the cognitive domain, in the behavioral domain, a high education attainment GPS may serve as a protective factor against *abuse* (a low education attainment GPS is a vulnerability factor). This point may support the diathesis-stress model [86,87]. Taken together, this study, compared with the existing literature, reveals the more detailed nature of the impact of *abuse* on the genetic pathway to the neurocognitive domain and the behavioral domain.

Our application of the GPS allows a novel assessment of the impact of the gene networks on the brain and cognitive development and the modulatory effects of ELS. In line with the previous study reporting the association of cognitive capacity genetic scores and total brain volume in adults [68], our study extends that the association is shown as early as in prepubertal childhood. Additionally, we show that the extensive brain network contributes to the association with the cognitive capacity genetic scores. This includes the cortical regions, prefrontal cortex volume/area (i.e., medial orbitofrontal cortex, rostral middle frontal cortex, and anterior cingulate cortex), the key to executive function, decision making, and learning and memory [88–90], volume and area of the inferior temporal cortex, superior temporal cortex, and temporal pole, key to language processing, social intelligence, and learning and memory [91].

The indirect effect of cognitive capacity GPSs on cognition mediated by brain morphometry was about 10 % of the direct effect. Note that the gray matter representations derived from ROI-level morphometry may only partially account for the gene-to-brain effects. Indeed, a morphometric analysis may not fully detect subtle changes in the brain tissues under the control of epigenetic (or any other environmental) mechanisms, such as vascularization, neurogenesis, and synaptogenesis. Future research may elucidate more sensitive brain representations related to genetic influence and environmental modulation.

Another explanation of the smaller indirect effect on the brain may be related to the limitations of linear models in testing complex nonlinear relationships. We used PCA to extract the brain representation (i.e., principal components) from thousands of brain morphometric variables. We used this method for the ease of statistical modeling (mediation analysis). However, since this method uses a linear orthogonal transformation of data, we admit that this representation might be limited in capturing nonlinear relationships among the brain variables.

Importantly, our results from sensitivity analysis, aimed at examining whether the brain representation is indistinguishable with global brain morphology, indicate that the brain representation extends beyond mere reflection of global brain morphological characteristics, such as total brain volume, total gray matter volume, and total cerebral white matter volume. Our study revealed that the brain representation comprehensively encapsulated brain morphological features associated with cognition, which could capture the impact of interaction between educational attainment GPS and *abuse* on the brain.

Our study showed the utility of our multi-trait (cognitive performance and educational attainment) genomic approach for revealing the different patterns of genetic influences on the brain and cognition. Years of education (educational attainment, E.A.) is a widely used proxy for an intelligence phenotype. This is because of its high genetic correlation with intelligence and the ease of assessment compared to an evaluation of cognitive ability that would require behavioral tests (hence, it is unfavorable in large GWASs). For example, the literature shows that education attainment GPS correlates with cognitive function [92] and the development of behaviors [93].

Although both cognitive capacity GPSs showed significant effects on the gene-brain-cognition pathway, only educational attainment GPS showed a significant modulatory effect of ELS on the pathway; cognitive performance GPS did not have a notable effect on the pathway. This observed ELS effect on educational attainment GPS might be related to genetic loading for cognitive capacity and noncognitive skills and traits needed for successful educational attainment [94]. On the other hand, cognitive performance GPS correlated with a greater number of brain morphometric features than education attainment GPS did. This may reflect that cognitive performance GPS indicates the genetic influence primarily on biological processes (i.e., brain development) linked to cognitive performance, but not so much on noncognitive processes. These points may guide future studies examining the gene-environment interaction in cognitive development.

Our results show greater magnitudes of the genetic influence on crystallized intelligence than on fluid intelligence during development. Crystallized intelligence is the ability to apply prior knowledge to problem-solving; fluid intelligence is the ability to reason in novel situations without prior knowledge [95–97]. Since the genetic influence (direct and indirect) was up to three times larger on crystallized intelligence compared to that on fluid intelligence, the impact of ELS via the gene-brain pathway was proportionally greater on crystallized intelligence than on fluid intelligence. This finding, thus, adds granularity to the specificity of ELS's impact.

Limitations of the study should be noted. First, it was not within the scope of this study to examine brain function, which ELS influences through the triangular relationship. It is well known that ELS leads to changes in brain function [3,8]. Previous animal studies support the idea that the function of adaptive gene-brain-cognition feedback systems may be affected by ELS [8]. Thus, the comprehensive impact of ELS on this triangular relationship needs to be further investigated in terms of brain function to reveal all the causal mechanisms. Second, we created composite scores of ELS with several proxy measures instead of using the established measure for childhood trauma, i.e., the Adverse Childhood Experiences (ACE) questionnaire [98]. This was due to the unavailability of the ACE questionnaire data in the ABCD study. However, it is of note that we included questionnaires like those of the ACE questionnaire and several ELS-related measurements [63], thus, aggregating various adverse environmental factors. Third, the mediation and moderated mediation analyses could only provide insight into the putative causal pathway if all potential unmeasured confounding effects are not adequately controlled for. In our mediation and moderated mediation model, we involved Genome-wide Polygenic Scores, known to

be susceptible to confounding by environmental influences, mirroring the confounding effects observed in Genome-wide Association Studies due to environmental factors. Thus, our findings only reveal a possible causal pathway consistent with previous studies in animal and human. However, it is of note that our study controlled for confounding effects by only involving a large number of American children with European ancestry in our analyses and adjusting the effects of influential covariates (I.e., age, sex, maternal education, parental income, BMI, study site, marital status, and genetic population structure) available in ABCD study. We expect that replication of our findings with an independent dataset could enhance the robustness of our findings.

Data availability

The ABCD data can be accessed via NIMH Data Archive (https://abcdstudy.org/scientists/data-sharing/).

Code availability

Codes (including detailed results from correlation among structural brain features, I.e., structural MRI and diffusion tensor MRI, and cognitive genome-wide polygenic scores) are freely available for reproducibility.

CRediT authorship contribution statement

Hee-Hwan Wang: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Seo-Yoon Moon:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Hyeonjin Kim:** Data curation. **Gakyung Kim:** Data curation. **Woo-Young Ahn:** Data curation. **Yoonjung Yoonie Joo:** Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing. **Jiook Cha:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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