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Educational attainment polygenic scores, socioeconomic factors, and cortical structure in children and adolescents

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Abstract

Genome-wide polygenic scores for educational attainment (PGS-EA) and socioeconomic factors, which are correlated with each other, have been consistently associated with academic achievement and general cognitive ability in children and adolescents. Yet, the independent associations of PGS-EA and socioeconomic factors with specific underlying factors at the neural and neurocognitive levels are not well understood. The main goals of this study were to examine the unique contributions of PGS-EA and parental education to cortical structure and neurocognitive skills in children and adolescents, and the associations among PGS-EA, cortical structure, and neurocognitive skills. Participants were typically developing 3- to 21-year-olds (53% male; $N = 391$). High-resolution, T1-weighted magnetic resonance imaging data were acquired, and cortical thickness (CT) and surface area (SA) were measured. PGS-EA were computed based on the EA3 genome-wide association study of educational attainment. Participants completed executive function, vocabulary, and episodic memory tasks. Higher PGS-EA and parental education were independently and significantly associated with greater total SA and vocabulary. Higher PGS-EA was significantly associated with greater SA in the left medial orbitofrontal gyrus and inferior frontal gyrus, which was associated with higher executive function. Higher parental education was significantly associated with greater SA in the left parahippocampal gyrus after accounting for PGS-EA and total brain volume. These findings suggest that education-linked genetics may influence SA in frontal regions, leading to variability in executive function. Associations of parental education with cortical structure in children and adolescents remained significant after controlling for PGS-EA, a source of genetic confounding.

KEYWORDS
brain structure, executive function, genetics, socioeconomic factors

1 | INTRODUCTION

Elucidating genetic and environmental influences on brain development in children and adolescents is an important task for researchers. Recent scientific advances allowing the computation of genome-wide polygenic scores have led to ground-breaking insights into genetic effects on cognitive and health outcomes (Armstrong-Carter et al., 2021; Plomin & von Stumm, 2018). Polygenic scores are derived using genome-wide association studies (GWAS) by aggregating the contributions of all known genetic variants associated with the phenotype of interest (Plomin & von Stumm, 2018). GWAS have identified genetic variants robustly associated with educational attainment (years of education) and led to genome-wide polygenic scores for educational attainment (PGS-EA) that significantly predict years of education (Lee et al., 2018; Okbay et al., 2016, 2022; Rietveld et al., 2013), academic achievement (Selzam et al., 2017; von Stumm et al., 2020; Ward et al., 2014), and general cognitive ability (Allegrini et al., 2019; Belsky et al., 2016; Judd et al., 2020; Wertz et al., 2018) in independent samples. However, the associations between PGS-EA and the underlying factors at the neural and neurocognitive levels in children and adolescents are not well understood.

Building from decades of research demonstrating socioeconomic disparities in cognitive development (McLoyd, 1998), recent studies have shed light on the neural mechanisms underlying these associations (Farah, 2017). Socioeconomic factors, such as parental education and family income, have been repeatedly associated with brain structure in children and adolescents (Farah, 2017; McDermott et al., 2019; Noble et al., 2015; Noble & Giebler, 2020). Socioeconomic factors represent distal markers of aspects of children's environments that influence their development (Merz et al., 2020; Troller-Renfree et al., 2022). Yet, the environments in which children are raised are associated with the genotypes they inherit from their parents (i.e., gene–environment correlation) (Plomin et al., 2016). In one example of a passive gene–environment correlation, more educated parents provide both a genetic propensity for higher educational attainment and cognitively stimulating home environments to their children. Indeed, the associations between socioeconomic factors and children's academic achievement may be partially attributable to genetic transmission (Belsky et al., 2016, 2018; Krapohl & Plomin, 2016; von Stumm et al., 2020). However, the unique role of socioeconomic factors in predicting the underlying neural and neurocognitive measures independent of genetic factors is not well understood. As such, the first main goal of this study was to examine the independent associations of PGS-EA and parental education with cortical structure and neurocognitive skills in children and adolescents.

1.1 | PGS-EA and cortical structure

In recent years, researchers have leveraged GWAS techniques to investigate the genetics of educational attainment (Lee et al., 2018; Okbay et al., 2016, 2022; Rietveld et al., 2013). Educational attainment is a demographic measure collected in most studies, allowing large studies to be conducted on this phenotype. A recent GWAS (EA3) included data from over a million adults of European ancestry and identified 1271 significant single-nucleotide polymorphisms (SNPs) (Lee et al., 2018). A polygenic score derived from the results explained up to 13% of the variance in educational attainment in independent samples (Lee et al., 2018).

To our knowledge, only two neuroimaging studies to date have focused on PGS-EA and cortical structure in children and adolescents. In one study, PGS-EA were significantly positively associated with total brain volume in a large sample of 10-year-olds (Alemany et al., 2019). Cortical volume is a composite of cortical surface area (SA) and cortical thickness (CT), which are genetically, developmentally, and phenotypically independent (Panizzon et al., 2009; Raznahan et al., 2011; Winkler et al., 2010). In a study that examined SA and CT separately, PGS-EA were significantly positively associated with global SA but not significantly associated with global CT in adolescents (Judd et al., 2020). In addition, PGS-EA were significantly associated with regional SA in the right intraparietal sulcus (Judd et al., 2020).

1.2 | Socioeconomic factors and cortical structure

Numerous studies have revealed associations between socioeconomic factors and cortical structure in children and adolescents (Farah, 2017; Noble & Giebler, 2020). In these studies, higher parental education and family income have been significantly associated with greater SA (Judd et al., 2020; McDermott et al., 2019; Noble et al., 2015) and CT (Lawson et al., 2013; Mackey et al., 2015; McDermott et al., 2019; Romeo et al., 2018). These socioeconomic differences in cortical structure have been found to be most prominent in frontal and temporal regions crucial to language, executive function, and memory (McDermott et al., 2019; Noble et al., 2015). Yet, to our knowledge, only one study has examined associations between socioeconomic factors and cortical structure while controlling for PGS-EA in children and adolescents. In this study, parental education remained significantly positively associated with total SA after controlling for PGS-EA in adolescents (Judd et al., 2020).

1.3 | PGS-EA, socioeconomic factors, and neurocognitive skills

Although multiple studies have demonstrated associations between PGS-EA and general cognitive ability (Plomin & von Stumm, 2018), a smaller body of work has shown associations between PGS-EA and specific neurocognitive skills that underlie general cognitive ability. PGS-EA has been significantly associated with vocabulary, executive function (inhibitory control, working memory), and episodic memory in children and adolescents (Domingue et al., 2015; Judd et al., 2020; Loughnan et al., 2021; Rea-Sandin et al., 2021).

In a largely separate literature, greater family income and parental education have been significantly associated with higher levels of these neurocognitive skills (Lawson et al., 2017; Merz et al., 2019;

Noble et al., 2005, 2007). Only a few studies have examined associations between socioeconomic factors and neurocognitive skills while controlling for PGS-EA in children and adolescents. For example, parental education was positively and significantly associated with working memory in adolescents, even when controlling for PGS-EA (Judd et al., 2020). In addition, family income remained significantly associated with associative memory in children while accounting for PGS-EA (Raffington et al., 2019). However, the independent associations of PGS-EA and socioeconomic factors with neurocognitive skills in children and adolescents are not well understood.

1.4 | Current study

The main goals of this study were to examine (1) the independent associations of PGS-EA and parental education with cortical structure and neurocognitive skills and (2) the associations among PGS-EA, cortical structure, and neurocognitive skills in children and adolescents. Participants were typically developing 3- to 21-year-olds ($N = 391$ for analyses of PGS-EA and neuroanatomy). High-resolution, T1-weighted MRI data were acquired, and vocabulary, executive function, and episodic memory were measured. PGS-EA were computed using results from a recent GWAS of educational attainment (Lee et al., 2018). We conducted analyses of global measures of CT and SA and vertex-wise analyses of regional CT and SA. Parental education and family income were examined separately (rather than combined into an SES composite) because they have been associated with distinct aspects of children's environments and relate differentially to children's development (Duncan & Magnuson, 2012). While the main analyses focus on parental education, results for family income are presented in the supplemental material.

We hypothesized that PGS-EA and parental education would be independently associated with SA and possibly CT. Based on previous research (McDermott et al., 2019; Mitchell et al., 2020; Noble et al., 2015), we expected these associations to be most pronounced in frontal and temporal cortical regions. We also hypothesized that both PGS-EA and parental education would uniquely contribute to vocabulary, executive function, and episodic memory. Cortical structure was predicted to mediate associations between PGS-EA and these neurocognitive skills. More specifically, we hypothesized that SA in lateral PFC regions would mediate the association between PGS-EA and executive function (Bari & Robbins, 2013). SA in left hemisphere language regions (e.g., left inferior frontal gyrus, left superior temporal gyrus) was expected to mediate the association between PGS-EA and vocabulary (Friederici, 2011).

Some research has suggested gene-by-SES interactions may predict cognitive ability such that the heritability of intelligence is lower in lower SES family environments and higher in higher SES family environments (Tucker-Drob & Bates, 2016). Thus, we also examined interactions between socioeconomic factors and PGS-EA in predicting cortical structure and neurocognitive skills. In addition, based on previous work (Rabinowitz et al., 2020; Rea-Sandin et al., 2021), we examined whether there were significant interactions between PGS-EA and age for cortical structure and neurocognitive skills. We also examined interactions between socioeconomic factors and age, controlling for PGS-EA, in the prediction of cortical structure and neurocognitive skills.

2 | METHODS

2.1 | Participants

Data were obtained from the Pediatric Imaging, Neurocognition and Genetics (PING) study (http://ping.chd.ucsd.edu/) (Jernigan et al., 2016). The PING study is a large-scale, publicly available data set for investigating neuroimaging, cognition and genetics in typically-developing children and adolescents (Jernigan et al., 2016). Exclusionary criteria in the PING study included neurological disorders; history of head trauma; preterm birth; diagnosis of an autism spectrum disorder, bipolar disorder, schizophrenia, or significant intellectual disability; and contraindications for MRI (Jernigan et al., 2016).

In total, the PING study included cross-sectional data collected from nine different sites across the United States. Participants in the current study ranged from 3 to 21 years of age ($M = 11.53$, $SD = 4.82$), and 53% were male. Family income ranged from $4500 to $325,000 ($M = 121{,}290.35$, $SD = 76{,}743.49$); parental education ranged from 8 to 18 years ($M = 15.73$; $SD = 1.86$).

Written informed consent was provided by parents for all participants younger than 18 years of age and by the participants themselves if they were 18 years or older. Child assent was obtained for 7- to 17-year-old participants. Each site's Institutional Review Board approved the study.

2.2 | Socioeconomic factors

Educational attainment was averaged across parents. Both education and income data were originally collected in bins, which were recoded as the means of the bins for analysis, following from previous work (Noble et al., 2015). Family income was log-transformed to correct for positive skew. Family income and parental education were significantly correlated, $r = .56$, $p < .0001$.

2.3 | Genomic data

The PING data set includes 550,000 SNPs genotyped from saliva samples using Illumina Human660W-Quad BeadChip. Computation of polygenic scores followed steps similar to that of our previous study (Khundrakpam, Vainik, et al., 2020). Steps included preparation of the data for imputation using the "imputePrepSanger" pipeline (https://hub.docker.com/r/eauforest/imputeprepsanger/) and implemented on CBRAIN (Sherif et al., 2014) using Human660W-Quad_v1_A-b37-strand chip as reference. The next step involved data imputation with Sanger Imputation Service (McCarthy et al., 2016) using default

settings and the Haplotype Reference Consortium, HRC (http://www.haplotype-reference-consortium.org/) as the reference panel. Using Plink 1.9 (Chang et al., 2015), the imputed SNPs were then filtered with the inclusion criteria: SNPs with unique names, only ACTG, and MAF > 0.05. All SNPs that were included had INFO scores $R^2 > 0.9$ with Plink 2.0. Next, using polygenic score software PRSice 2.1.2 (Euesden et al., 2015) additional ambiguous variants were excluded, resulting in 4,696,385 variants being available for polygenic scoring. We filtered individuals with 0.95 loadings to the European principal component (GAF_Europe variable provided with the PING data), resulting in 526 participants. These participants were then used to compute 10 principal components with Plink 1.9. Polygenic scores based on the EA3 GWAS (Lee et al., 2018) were used in analyses. We clumped the data as per PRSice default settings (clumping distance = 250 kb, threshold $r^2 = 0.1$).

PGS-EA were computed at different *p*-value thresholds for inclusion of SNPs in the score (e.g., $p < .001$; $p < .01$; $p < .05$; $p < .1$; $p < 1$). Then, the most predictive one was chosen, following previous studies (Alemany et al., 2019; Du Rietz et al., 2018; Dudbridge, 2013; Euesden et al., 2015; Judd et al., 2020). The *p*-value threshold of $p < 1 \times 10^{-7}$ best explained variance in SA. Thus, this conservative *p*-value threshold was used for the main analyses. After matching with available variants in the data, this PGS-EA was based on 694 variants (see Table S1). Results for PGS-EAs calculated based on other *p*-value thresholds were consistent with the results reported.

2.4 | Image acquisition and preprocessing

Each site administered a standardized structural MRI protocol. Imaging data were collected using 3-Tesla scanners manufactured by General Electric, Siemens, and Philips. The imaging protocols and pulse sequence parameters used in the PING study have been published previously (Jernigan et al., 2016; Merz et al., 2018; Noble et al., 2015). T1-weighted images were acquired using a standardized high-resolution 3D RF-spoiled gradient echo sequence (Jernigan et al., 2016).

The raw T1-weighted imaging data for the PING study are publicly shared (https://nda.nih.gov/) for a subset of the sample ($n = 934$). The only difference between the full PING sample and the subsample with raw T1-weighted imaging data was that the full PING sample was older on average than the subsample (Khundrakpam, Choudhury, et al., 2020). We used the CIVET processing pipeline (https://mcin.ca/technology/civet/) developed at the Montreal Neurological Institute to compute CT measurements at 81,924 regions covering the entire cortex. Processing steps included nonuniformity correction of the T1-weighted image and then linear registration to the Talairach-like MNI152 template (created with the ICBM152 data set). After repeating the nonuniformity correction using the template mask, the nonlinear registration from the resultant volume to the MNI152 template is computed, and the transform used to provide priors to segment the image into gray matter, white matter, and cerebrospinal fluid. Inner and outer gray matter surfaces are then extracted using the Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm. CT is then measured in native space using the linked distance between the two surfaces at 81,924 vertices. To impose a normal distribution on the corticometric data and increase the signal to noise ratio, each individual's CT map was blurred using a 30-mm full width at half maximum surface-based diffusion smoothing kernel. Two independent reviewers performed quality control of the data, and only scans with consensus of the two reviewers were used. Exclusion criteria for quality control included: data with motion artifacts, a low signal to noise ratio, artifacts due to hyperintensities from blood vessels, surface-surface intersections, or poor placement of the gray or white matter surface for any reason.

Of the 934 participants with raw T1-weighted MRI data, 29 participants' data failed the quality control procedures. Of these 29, 13 participants' data were excluded before any processing due to severe motion and slicing artifacts. The remaining 16 participants failed the CIVET pipeline for reasons including the presence of bright blood vessels and poor contrast. Thus, 905 participants passed the quality control procedures (Khundrakpam, Choudhury, et al., 2020).

2.4.1 | Sample sizes

Of the 526 participants with polygenic score data, 391 had T1-weighted neuroimaging data and 518 had neurocognitive task data. Thus, 391 participants were included in analyses of associations between PGS-EA and cortical structure, and 518 participants were included in analyses of associations between PGS-EA and neurocognitive skills. For analyses of PGS-EA, cortical structure, and neurocognitive skills, data for 382 participants were available.

2.5 | Neurocognitive tasks

Participants completed tasks from the NIH Toolbox Cognition Battery including the Flanker Inhibitory Control and Attention (Zelazo et al., 2013), List Sorting Working Memory (Tulsky et al., 2013), Picture Sequence Memory (Bauer et al., 2013; Dikmen et al., 2014), and Picture Vocabulary Tests (Gershon et al., 2013, 2014) (see Supplemental Materials). The Flanker and List Sorting Working Memory tasks are measures of inhibitory control and working memory, respectively, core components of executive function (Miyake et al., 2000), and the scores on these tasks were strongly correlated ($r = .76$, $p < .0001$). Thus, they were standardized (*z*-scored) and averaged to create an executive function composite for data reduction purposes and to create a more reliable measure of executive function.

2.6 | Statistical analyses

Multiple linear regression analyses in SAS (version 9.4) were conducted using the general linear model procedure to examine associations of PGS-EA and parental education with global measures of SA

(total SA) and CT (mean CT) and neurocognitive skills. We first investigated whether PGS-EA and parental education were associated with SA, CT, and neurocognitive skills in separate models. Then, we conducted regression models in which they were both included as predictors. Effect sizes (partial eta squared [η_p^2]) are presented, with values of .01, .06, and .14 indicating small, medium, and large effects, respectively (Cohen, 1988; Richardson, 2011). Interactions between socioeconomic factors and PGS-EA were not significant and, as such, were not included in the final regression models.

Vertex-level neuroanatomical variables of interest included SA and CT at each of 81,924 cortical vertices. To examine associations between SA/CT and PGS-EA (or socioeconomic factors), general linear models were conducted for each vertex for SA and CT using the SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/). At every cortical point, the *t*-statistic for the association between cortical structure (SA, CT) and PGS-EA (or socioeconomic factors) was mapped onto a standard cortical surface. Correction for multiple comparisons using random field theory (RFT) (Worsley et al., 2004) was then applied to the resultant map to determine the regions of cortex significantly associated with PGS-EA (or socioeconomic factors). To identify significant clusters, an initial height threshold of $p < .001$ was implemented at the vertex level, and a corrected family-wise error ($p < .05$) was then applied.

2.6.1 | Covariates

Covariates included in the regression models were age, age^2, sex, and scanner/site. In the PING study, 12 MRI scanners were used across the nine data collection sites. Thus, analyses predicting cortical structure included scanner as a covariate, and analyses predicting neurocognitive skills included site as a covariate. Also, to minimize the chance of population structure explaining the polygenic score results, we extracted 10 first principal components (PC10) and used them as covariates. Without controlling for those principal components, random differences in population genomic signature can explain outcomes, if different populations also differ in the outcome (Price et al., 2006). In addition, the main vertex-wise analyses also controlled for total brain volume. Supplemental analyses not adjusting for total brain volume are also presented based on current recommendations (Mills et al., 2016; Vijayakumar et al., 2018) and to compare our results with those of previous studies that did not control for global measures (McDermott et al., 2019; Noble et al., 2015). There is currently no consensus on whether global measures should be included in vertex-wise analyses of SA and CT (Tadayon et al., 2020).

2.6.2 | Mediation

Analyses were also conducted to investigate the extent to which cortical structure may mediate associations between PGS-EA and neurocognitive skills (see Figure S1). Analyses focused on CT or SA measures found to be significantly associated with PGS-EA. We investigated whether these neuroanatomical indices were associated with neurocognitive skills in regression models. For any CT or SA measure found to be associated with both PGS-EA and a neurocognitive outcome, analyses were conducted to examine whether that CT or SA measure mediated the association between PGS-EA and the neurocognitive outcome (MacKinnon et al., 2002). Mediation analyses were conducted using bias-corrected bootstrapping via the PROCESS macro in SAS, with a 95% confidence interval (CI) (Hayes, 2013; Preacher & Hayes, 2008). The effect is significant when the confidence interval does not include zero. To account for the association between PGS-EA and CT/SA potentially biasing the mediation (Kriegeskorte et al., 2009), mediation analyses were also conducted using CT/SA in anatomically defined regions-of-interest (ROIs).

2.6.3 | Moderation

Significant interactions between PGS-EA or parental education and age or age^2 were probed using the PROCESS macro in SAS via the Johnson-Neyman technique (Hayes, 2013). The Johnson-Neyman technique identifies the points along the continuum of the moderator where the conditional effect of X on Y transitions between statistically significant ($\alpha = .05$) and not significant (Bauer & Curran, 2005; Hayes, 2013). Significant interactions involving socioeconomic factors were visualized using ecologically valid groups similar to previous work (Piccolo et al., 2016). In this study, the low and middle parental education groups were collapsed due to small sample size in the low parental education group ($n = 25$), consistent with previous work (Khundrakpam, Choudhury, et al., 2020). Thus, the following parental education groups were used for visualization purposes: less than a high school diploma, completion of high school, or some college (6–14 years of education [$n = 147$]) and 4-year college graduate or professional degree (16–18 years of education [$n = 236$]).

3 | RESULTS

3.1 | Descriptive statistics

Descriptive statistics and zero-order correlations are presented in Table 1. PGS-EA was significantly correlated with parental education ($r = .21$, $p < .0001$) and family income ($r = .10$, $p = .03$). PGS-EA data were normally distributed.

3.2 | PGS-EA, parental education, and SA

3.2.1 | PGS-EA

Higher PGS-EA was significantly associated with greater total SA, $\beta = .11$, $p = .0083$, $\eta_p^2 = .0187$, and remained significantly associated with total SA after accounting for parental education, $\beta = .09$, $p = .0279$, $\eta_p^2 = .0134$. Vertex-wise analyses indicated that PGS-EA

TABLE 1 Descriptive statistics and zero-order correlations

		1	2	3	4	5	6	7	8
1	PGS-EA	–							
2	Parental education (years)	.21***	–						
3	Total SA (mm^2)	.09+	.05	–					
4	Global (average) CT (mm)	.04	.10+	.22***	–				
5	Vocabulary	.03	.03	.10*	−.52***	–			
6	Inhibitory control	−.03	−.03	.17***	−.48***	.72***	–		
7	Working memory	.001	−.003	.16**	−.43***	.77***	.77***	–	
8	Episodic memory	.03	−.01	.04	−.49***	.70***	.70***	.76***	–
	N	526	503	391	391	518	513	516	519
	M (*SD*)	.000043 (.000193)	15.73 (1.86)	200,523.00 (16,564.94)	3.11 (.17)	.89 (1.40)	7.63 (1.84)	17.95 (5.34)	26.22 (11.08)

Abbreviations: CT, cortical thickness; M, mean; PGS-EA, polygenic score for educational attainment; SA, cortical surface area.
Note: *p < .05; **p < .01; ***p < .001; $^{+}$ p < .10.

were significantly (p < .05, RFT-corrected) associated with SA in two clusters. The first cluster consisted primarily of vertices in the left medial orbitofrontal gyrus and rostral ACC. The second cluster consisted of vertices in the left inferior frontal gyrus (IFG), primarily pars triangularis and pars orbitalis (see Figure 1 and Table 2). These associations remained significant after controlling for parental education (see Figure 1 and Table 2). A consistent pattern of results was found when examining PGS-EA computed at different p-value thresholds. There were no significant interactions between PGS-EA and age or age^2 in the prediction of SA.

3.2.2 | Parental education

Higher parental education was significantly associated with greater total SA, $\beta = .13$, $p = .0022$, $\eta_p^2 = .0257$, and remained significantly associated with total SA after accounting for PGS-EA, $\beta = .12$, $p = .0076$, $\eta_p^2 = .0196$. Vertex-wise analyses indicated that higher parental education was significantly (p < .05, RFT-corrected) associated with greater SA in clusters in the left fusiform gyrus and right superior temporal gyrus (see Figure 2 and Table 3). Parental education was significantly associated with SA in a cluster in the left parahippocampal gyrus after controlling for PGS-EA (see Figure 2 and Table 3).

Vertex-wise analyses indicated a significant interaction between parental education and age^2 for SA in the left superior frontal gyrus while controlling for PGS-EA and the other covariates (see Figure S2). Higher parental education was associated with greater SA in the left superior frontal gyrus between 18 and 21 years of age. There were no significant interactions between parental education and age or age^2 in the prediction of total SA. Also, vertex-wise analyses indicated no significant interactions between parental education and age for SA.

Vertex-wise analyses were conducted to examine associations of PGS-EA and parental education with SA without controlling for total brain volume. A similar pattern of results emerged but with significant associations between parental education and SA in more cortical regions (see Figures S3 and S4 and Tables S2 and S3).

3.3 | PGS-EA, parental education, and CT

3.3.1 | PGS-EA

PGS-EA was not significantly associated with global CT, $\beta = .04$, $p = .2195$, or regional CT. There were no significant interactions between PGS-EA and age or age^2 in the prediction of CT.

3.3.2 | Parental education

Although parental education was not significantly associated with global ($\beta = .05$, $p = .1003$) or regional CT in terms of main effects, there was a significant interaction between parental education and age in the prediction of mean CT after controlling for age, age^2, sex, scanner, PGS-EA, PC1-10, and parental education, $\beta = .08$, $p = .0274$, $\eta_p^2 = .0135$ (see Figure S5). The Johnson-Neyman technique indicated that higher parental education was significantly associated with greater mean CT between 13 and 21 years of age.

Vertex-wise analyses indicated a significant interaction between parental education and age for CT localized in the right IFG (primarily pars orbitalis), right calcarine fissure, and right precuneus while controlling for PGS-EA and the other covariates (see Figure S6). The Johnson-Neyman technique indicated that for the right IFG, higher parental education was significantly associated with lower CT between 3 and 7 years of age and with greater CT between 14 and 21 years of age. For the right calcarine fissure, higher parental

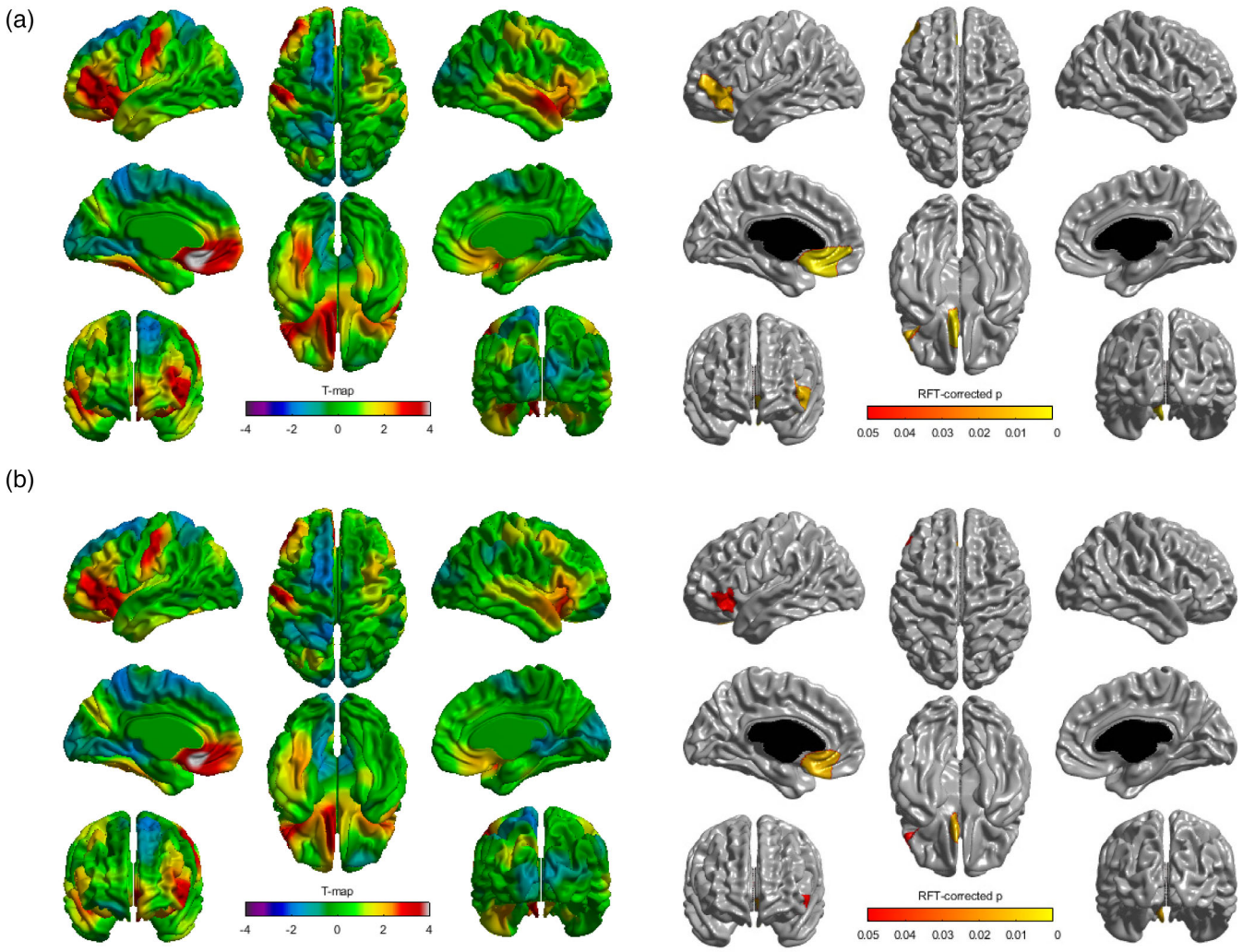

FIGURE 1 Higher educational attainment polygenic scores (PGS-EA) were significantly associated with greater frontal cortical surface area (SA) in children and adolescents (a) without adjusting for parental education and (b) while adjusting for parental education. The left and right panels show *t*-statistics and *p* values ($p < .05$ after correcting for multiple comparisons using random field theory [RFT]), respectively. Covariates were age, age^2, sex, scanner, principal components 1–10, and total brain volume

TABLE 2 Educational attainment polygenic scores (PGS-EA) were significantly associated with cortical surface area (SA)

Cluster #	Cluster-corrected *p*	Cluster size (number of vertices)	Cluster brain label
Without adjusting for parental education			
1	.005	909	Left medial orbitofrontal gyrus, rostral ACC
2	.01	799	Left inferior frontal gyrus
After adjusting for parental education			
1	.009	565	Left medial orbitofrontal gyrus, rostral ACC
2	.04	482	Left inferior frontal gyrus

Abbreviation: ACC, anterior cingulate cortex.
Note: Covariates were age, age^2, sex, scanner, principal components 1–10, and total brain volume.

education was significantly associated with lower CT between 3 and 5 years of age and with greater CT between 12 and 21 years of age. For the right precuneus, higher parental education was significantly associated with lower CT between 3 and 9 years of age and with higher CT between 16 and 21 years of age. There were no significant interactions between parental education and age^2 for CT.

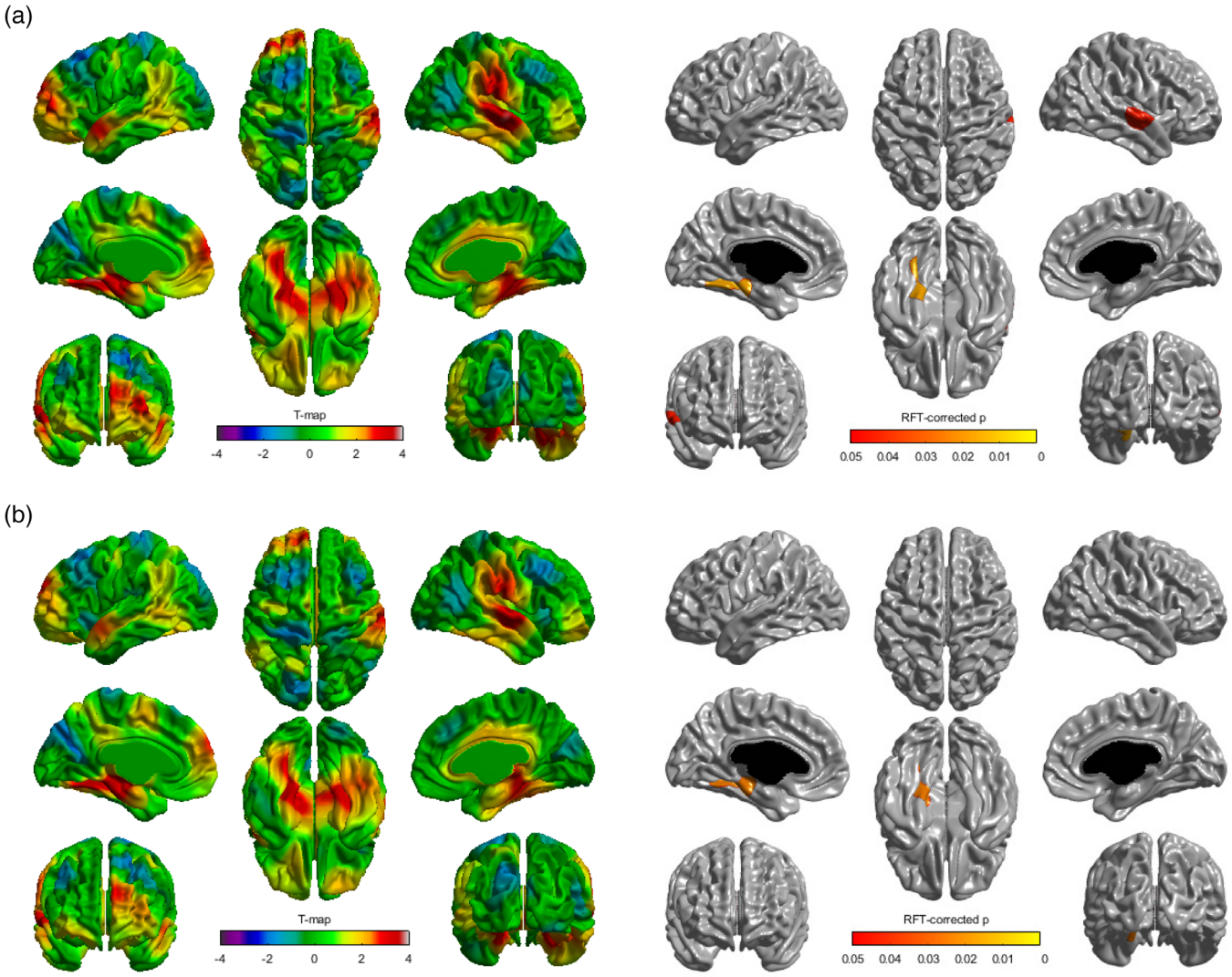

FIGURE 2 Higher parental education was significantly associated with greater cortical surface area (SA) in children and adolescents (a) without adjusting for educational attainment polygenic scores (PGS-EA) and (b) while adjusting for PGS-EA. The left and right panels show *t*-statistics and *p* values ($p < .05$ after correcting for multiple comparisons using random field theory [RFT]), respectively. Covariates were age, age^2, sex, scanner, and total brain volume. Models including PGS-EA also adjusted for principal components 1–10

TABLE 3 Parental education was significantly associated with cortical surface area (SA)

Cluster #	Cluster-corrected *p*	Cluster size (number of vertices)	Cluster brain label
Without adjusting for PGS-EA			
1	.015	574	Left fusiform gyrus
2	.044	493	Right superior temporal gyrus
After adjusting for PGS-EA			
1	.024	503	Left parahippocampal gyrus

Abbreviation: PGS-EA, polygenic score for educational attainment.
Note: Covariates were age, age^2, sex, scanner, total brain volume, and principal components 1–10.

3.4 | PGS-EA, parental education, and neurocognitive skills

3.4.1 | PGS-EA

Higher PGS-EA was significantly associated with greater vocabulary, executive function, and episodic memory (see Table S4). PGS-EA remained significantly associated with vocabulary and episodic memory after controlling for parental education (see Table S4). A similar pattern of results was found for PGS-EA computed at different *p*-value thresholds (see Table S5). There were no significant interactions between PGS-EA and age or age^2 in the prediction of the neurocognitive skills.

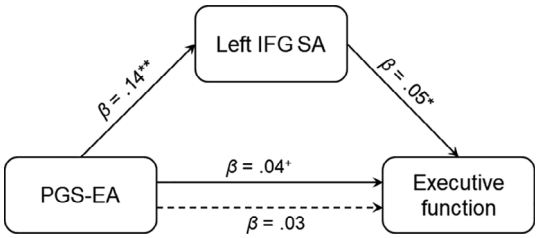

FIGURE 3 Surface area (SA) in the left inferior frontal gyrus (IFG) significantly mediated the association between educational attainment polygenic scores (PGS-EA) and executive function. The solid and dotted lines between PGS-EA and executive function represent the total (*c* path) and direct (*c*′ path) associations, respectively. The line between PGS-EA and left IFG SA represents the *a* path, and the line between left IFG SA and executive function represents the *b* path. $^{+}p < .10$, $^{*}p < .05$, $^{**}p < .01$

3.4.2 | Parental education

Higher parental education was significantly associated with greater executive function, vocabulary, and episodic memory (see Table S4). Parental education remained significantly associated with executive function and vocabulary after controlling for PGS-EA (see Table S4). There were no significant interactions between parental education and age or age^2 in the prediction of the neurocognitive skills.

3.5 | SA as a mediator of associations between PGS-EA and neurocognitive skills

We also investigated whether any of the SA measures found to be significantly associated with PGS-EA (left IFG cluster SA, left medial OFC/rostral ACC cluster SA, total SA) mediated the associations between PGS-EA and neurocognitive skills. Total SA was significantly and positively associated with executive function ($\beta = .06$, $p = .0391$, $\eta_p^2 = .0118$) but not vocabulary or episodic memory after controlling for age, age^2, sex, site, PGS-EA, PC1-10, and parental education. SA in the left medial OFC/rostral ACC cluster was not significantly associated with any of the neurocognitive outcomes. SA in the left IFG cluster was significantly and positively associated with executive function ($\beta = .05$, $p = .0391$, $\eta_p^2 = .0118$) but not vocabulary or episodic memory, after controlling for age, age^2, sex, site, PGS-EA, PC1-10, and parental education. The association between left IFG SA and executive function did not remain significant after additionally controlling for total brain volume ($\beta = .04$, $p = .1414$, $\eta_p^2 = .0061$).

SA in the left IFG cluster significantly mediated the association between PGS-EA and executive function, *ab* path = .02, SE = .01, 95% CI .0005–.0460, although this effect did not remain significant after additionally controlling for total brain volume. Higher PGS-EA was significantly associated with greater left IFG SA, which in turn was significantly associated with higher executive function (see Figure 3). Total SA did not significantly mediate the association between PGS-EA and executive function.

Analyses were also conducted using SA in the anatomically defined parcellations corresponding to the left IFG cluster found to be associated with PGS-EA in the vertex-wise analyses. These analyses focused on SA summed across the left pars orbitalis and pars triangularis, as defined by the Desikan-Killiany-Tourville (DKT) atlas (Klein & Tourville, 2012). Greater SA in this IFG region was significantly associated with higher executive function, $\beta = .06$, $p = .0197$, $\eta_p^2 = .0154$, but was not significantly associated with vocabulary or episodic memory. SA in the left IFG significantly mediated the association between PGS-EA and executive function, *ab* path = .02, SE = .01, 95% CI .0019–.0518. Similar to results shown in Figure 3, higher PGS-EA was associated with greater SA in the left IFG ($\beta = .14$, $p = .0031$) which was associated with greater executive function ($\beta = .06$, $p = .0235$). The total effect (c path) was marginally significant ($\beta = .04$, $p = .0542$), and the direct effect (c′ path) was not significant ($\beta = .03$, $p = .1195$). These associations did not remain significant after additionally controlling for total brain volume.

4 | DISCUSSION

The main goals of this study were to examine (1) the independent associations of educational attainment polygenic scores (PGS-EA) and parental education with cortical structure and neurocognitive skills and (2) the associations among PGS-EA, cortical structure, and neurocognitive skills in children and adolescents. Higher parental education was significantly correlated with higher PGS-EA in children and adolescents, replicating previous findings and suggesting a gene–environment correlation (Belsky et al., 2016, 2018; Judd et al., 2020; Selzam et al., 2017). For example, passive gene–environment correlation may occur because parents create a family environment that corresponds to their genotypes and correlates with the genotypes of their children. Results from this study indicated that PGS-EA and parental education explained unique variability in total cortical surface area (SA) and vocabulary in children and adolescents. These and other novel findings from our study that build on previous work are discussed below.

4.1 | PGS-EA and parental education independently associate with total SA and vocabulary

Socioeconomic factors and PGS-EA made unique contributions to total SA in children and adolescents, consistent with previous work (Judd et al., 2020). Higher parental education (and family income) and PGS-EA were both significantly associated with greater total SA. Associations between socioeconomic factors and total SA were attenuated but remained significant after adjusting for PGS-EA, which accounts for some genetic confounding (Wertz et al., 2020). These findings are consistent with the notion of independent genetic and environmental associations with total SA, although inferences about environmental transmission cannot be made. Evidence from randomized trials of poverty reduction and animal models of chronic stress

and environmental enrichment suggests that at least part of the association between socioeconomic factors and children's cognitive development and brain function may be environmentally mediated (Davidson & McEwen, 2012; Duncan et al., 2017; Troller-Renfree et al., 2022; van Praag et al., 2000). In the current study, associations between socioeconomic factors and SA in children and adolescents, even after accounting for PGS-EA, cannot be interpreted as purely 'environmental' due to other sources of genetic confounding.

4.2 | PGS-EA is associated with frontal cortical surface area

Higher PGS-EA were significantly associated with greater SA in left medial orbitofrontal, rostral anterior cingulate, and inferior frontal cortical regions. These findings are consistent with one previous study of adults (Mitchell et al., 2020) but not another study of adolescents that found a localized association between PGS-EA and SA in the right intraparietal sulcus (Judd et al., 2020).

Greater left IFG SA (and anatomically defined left pars triangularis and pars orbitalis SA) significantly mediated the association between higher PGS-EA and higher executive function, consistent with research documenting involvement of the IFG in executive function (Bari & Robbins, 2013). The association between PGS-EA and left IFG SA may have implications for executive function, potentially partially explaining previously reported associations between PGS-EA and academic achievement (von Stumm et al., 2020). It is noteworthy that these results did not remain significant after accounting for total brain volume. There is a lack of consensus on whether to control for total brain volume (Tadayon et al., 2020), with some recent studies not controlling for this variable (McDermott et al., 2019; Noble et al., 2015). Although the left IFG is also critical to language (Friederici, 2011), left IFG SA was not significantly associated with vocabulary. SA in the medial OFC/rostral ACC cluster was not significantly associated with executive function, vocabulary, or episodic memory.

In addition to cognitive skills (Allegrini et al., 2019; Plomin & von Stumm, 2018; Wertz et al., 2018), PGS-EA have also been associated with "noncognitive" skills (e.g., motivation, persistence, grit) that facilitate academic success (Belsky et al., 2016; Smith-Woolley et al., 2019) (Heckman, 2006). It is possible that the associations of PGS-EA with SA in medial OFC and rostral ACC regions, which have been associated with top-down control over emotional and motivational processes (Etkin et al., 2011; Rolls, 2019), could be due to genetic effects on noncognitive skills that lead to variability in academic achievement. Because the PING data set does not include data on these skills, this possibility was not able to be tested in the current study.

Genetic variants associated with educational attainment have been linked with genes showing elevated expression in neural tissue (Okbay et al., 2016). Genetic propensity to higher educational attainment may include variants that promote optimal cortical development. The cellular processes underlying developmental changes in SA, including synaptic function, have been associated with genes linked with the significant SNPs identified in GWAS of educational attainment (Deary et al., 2021; Okbay et al., 2016). PGS-EA was not significantly associated with mean global CT, consistent with previous research on adolescents and adults (Judd et al., 2020; Mitchell et al., 2020).

4.3 | Socioeconomic factors show associations with frontal and temporal SA and CT after controlling for PGS-EA

4.3.1 | Cortical surface area

Associations between parental education and SA were most prominent in the left parahippocampal gyrus, left fusiform gyrus, and right superior temporal gyrus after adjusting for total brain volume and other covariates. Parental education was significantly associated with SA in the left parahippocampal gyrus after additionally adjusting for PGS-EA. The parahippocampal gyrus, as part of the medial temporal lobe, has been strongly associated with episodic memory (Eichenbaum, 2006), which varies significantly across socioeconomic gradients (Noble et al., 2005, 2007; Noble & Giebler, 2020). In addition, there was a significant parental education-by-age^2 interaction for SA in the left superior frontal gyrus, such that higher parental education was associated with greater SA in the left superior frontal gyrus between 18 and 21 years of age while controlling for PGS-EA. Socioeconomic factors may impact frontal and temporal SA in children and adolescents via multiple proximal environmental factors, including variability in exposure to chronic stress (e.g., household chaos and unpredictability, neighborhood violence, crowding/noise, family conflict) and cognitive and linguistic stimulation (Duncan et al., 2017; Evans & Kim, 2013; Merz et al., 2019; Pace et al., 2017).

When *not* adjusting for total brain volume or PGS-EA, similar to analytic approaches used in previous work (McDermott et al., 2019; Noble et al., 2015), parental education was significantly associated with SA in more cortical regions, including larger portions of the bilateral parahippocampal gyrus, fusiform gyrus, and superior temporal gyrus. In a previous study that also used the PING sample, associations between parental education and SA were more widespread (Noble et al., 2015). These differences in results could be due to methodological factors, such as the current study's inclusion of only participants with European ancestry due to the focus on PGS-EA. Nonetheless, the cortical regions significantly associated with parental education in the current study largely overlapped with those associated with parental education in the larger PING study (Noble et al., 2015) and are associated with cognitive skills such as memory and reading found to be highly susceptible to variability in socioeconomic background (Duncan et al., 2017; Noble et al., 2005, 2007).

4.3.2 | Cortical thickness

Higher family income was significantly associated with greater global (mean) CT, and this association was attenuated but remained

significant after controlling for PGS-EA. In comparison to studies of socioeconomic factors and total SA, associations between socioeconomic factors and mean CT in children and adolescents have been mixed (Noble & Giebler, 2020; Rakesh & Whittle, 2021). When associations have been found, socioeconomic factors have been positively associated with mean CT in children and adolescents (Noble et al., 2015; Rakesh & Whittle, 2021). Although the "main effect" of parental education on global (mean) CT was not significant, there was a significant interaction between parental education and age for mean CT. Vertex-wise analyses indicated significant interactions between parental education and age for CT in the right IFG (primarily pars orbitalis), calcarine fissure, and precuneus. Previous studies using the full PING sample found interactions between parental education and age^2 for mean CT (Piccolo et al., 2016) and CT in the right middle temporal gyrus (Khundrakpam, Choudhury, et al., 2020), whereas we found interactions with age rather than age^2 in our analyses which controlled for PGS-EA. Nonetheless, the overall pattern of results was similar, with higher parental education associated with greater CT in older children and adolescents. In our study, these interactions were found after controlling for PGS-EA. Thus, the current findings extend previous work by suggesting that such associations may not be wholly attributable to genetic confounding.

4.4 | Socioeconomic factors show attenuated associations with neurocognitive skills after controlling for PGS-EA

Higher parental education and family income were significantly associated with higher executive function and vocabulary, and these associations were attenuated but remained significant after accounting for genetic predisposition to educational attainment. These results are consistent with prior work that has frequently documented socioeconomic disparities in language and executive function in children (Lawson et al., 2017; Noble et al., 2005, 2007; Romeo et al., 2018). The current findings extend this work by showing that such associations remain significant even after controlling for children's education-linked genetics. These results are consistent with the notion that SES-related environmental factors (e.g., language input, chronic stress) may be associated with language and executive function above and beyond genetic factors (Duncan et al., 2017).

Several limitations of this study must be taken into account when interpreting the findings. First, due to the cross-sectional, correlational design of this study, causal inferences cannot be made. Second, as in most studies that use genome-wide polygenic scores (Elliott et al., 2019; von Stumm et al., 2020), analyses included only participants of European ancestry. Large-scale GWAS, which are required for identifying genetic variants that are reliably associated with a phenotype, are currently not available in populations with other ancestries. Thus, findings from this study are not generalizable to other ethnicities. Third, mediation questions are best examined using longitudinal data (Cole & Maxwell, 2003; Maxwell & Cole, 2007) and experimental designs (Fiedler et al., 2018), which were not available as part of the data set used in this study. Although our results were consistent with mediation, conclusions about mediation processes cannot be made based on this study. Fourth, educational attainment polygenic scores are vulnerable to biases due to population stratification that the principal components do not fully remove. These biases can be addressed by using within-family difference polygenic score designs, which need larger family-based data sets (Selzam et al., 2019). Fifth, the sample size of this study may have affected power to detect significant effects.

Findings from this study indicated that education-associated genetics and socioeconomic factors accounted for unique variance in total SA and vocabulary in children and adolescents. Educational attainment polygenic scores were most prominently associated with SA in frontal regions, including SA in the inferior frontal gyrus, which was associated with executive function. Associations of socioeconomic factors with total SA, executive function, and vocabulary were attenuated but remained significant after controlling for PGS-EA. These results shed light on the roles of education-linked genetics and socioeconomic factors in contributing to cortical structure and neurocognitive skills in children and adolescents.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data for the PING study are publicly shared (https://nda.nih.gov/).

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SUPPORTING INFORMATION

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