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Socioeconomic factors, brain-derived neurotrophic factor Val66Met polymorphism, and cortical structure in children and adolescents

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Variability in associations between socioeconomic status and cortical gray matter may be due in part to the common, functional brain-derived neurotrophic factor (BDNF) Val66Met polymorphism, which alters BDNF signaling. In this study, we examined whether BDNF Val66Met genotype moderated the associations between socioeconomic factors (family income, parental education) and cortical surface area (SA) and thickness (CT) in two large independent samples of typically-developing children and adolescents. Participants were 3- to 21-year-olds (*N* = 383; 47% female) from the Pediatric Imaging, Neurocognition, and Genetics (PING) study and 11- to 14-year-olds (*N* = 2566; 46% female) in the Adolescent Brain Cognitive Development (ABCD) study. High-resolution, T1-weighted magnetic resonance imaging data were acquired in both studies. Analyses were conducted on global and regional SA and CT. In the PING sample, BDNF Val66Met genotype significantly moderated the association between family income and total SA and SA in the left fusiform gyrus. In the ABCD sample, there were no significant interactions for global or regional SA or CT. Collectively, these results suggest that BDNF Val66Met genotype may not explain variability in associations between socioeconomic factors and SA or CT in children and adolescents.

Keywords Family income, Parental education, Gene-by-environment interaction, Cortical surface area, Cortical thickness, Neurotrophins

Socioeconomic disadvantage during childhood is prevalent in the United States and worldwide[1]. Early socioeconomic disadvantage has been consistently found to predict lower academic achievement and an increased likelihood of mental and physical health problems[2–5]. However, it has long been observed that outcomes vary widely following early socioeconomic disadvantage, with some individuals exhibiting resilience[5,6]. Similar patterns have emerged at the neural level. Although socioeconomic disadvantage has been repeatedly associated with reduced cortical gray matter in children and adolescents[7,8], there is wide variability in cortical gray matter metrics among those with the same socioeconomic background[9,10]. These results point to the role of moderators in these associations. Among possible genetic moderators, the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is a strong candidate. This common, functional single nucleotide polymorphism (SNP) in the prodomain of the BDNF gene, leading to a valine-to-methionine substitution at codon 66, alters BDNF signaling through reduced activity-dependent secretion of BDNF[11,12]. To our knowledge, no research has examined this SNP as a moderator of socioeconomic disparities in cortical structure.

Socioeconomic factors and cortical structure

Socioeconomic status (SES) is a multidimensional construct that reflects access to economic resources and social and human capital. Socioeconomic gradients have been identified in which lower SES consistently associates with worse academic and mental and physical health outcomes[2–5]. Family income and parental educational

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attainment are commonly used measures reflecting SES of children and adolescents; they are correlated but distinct socioeconomic factors[7,13–15].

In large-scale studies, lower levels of family income and parental education have been repeatedly associated with reduced global and regional cortical volume, thickness (CT), and surface area (SA) in children and adolescents[7,8,16–18]. Cortical volume is the product of CT and SA, which are distinct in their genetic underpinnings and developmental trajectories[19,20]. Thus, studies of CT and SA provide more specific structural information compared to studies focused solely on cortical volume. Lower levels of family income and parental education have been more consistently associated with reduced total SA than with lower mean CT in children and adolescents[9,10,21–23]. In addition to these results for global measures, socioeconomic differences in CT and SA have been found across widespread cortical regions, including sensorimotor and association regions[10,22,24,25].

SES is robustly linked with variability in children's environmental experiences. For example, lower SES is associated with greater exposure to adversity, chronic stressors (e.g., family conflict, crowding/noise, household unpredictability, neighborhood violence), environmental toxins and pollutants, and reduced cognitive stimulation (e.g., trips to museums and libraries, books and toys in the home, language input)[26–30]. These proximal environmental factors have been found to mediate associations between SES and cortical structure[8,24,31].

Alongside these findings, researchers have examined moderators of socioeconomic differences in SA and CT in children and adolescents. It is well-established that genetic factors make important contributions to brain structure and development, including SA and CT[19,32,33]. Furthermore, genetic factors have been theorized and found to moderate the effects of early environmental factors on various outcomes (e.g., risk for psychopathology) and partially explain variability in outcomes following exposure to early adversity[34–36]. Yet, few studies have examined possible genetic moderators of associations between socioeconomic factors and cortical structure[37].

BDNF Val66Met polymorphism

The BDNF Val66Met polymorphism stands out as a potential moderator of socioeconomic differences in cortical gray matter. BDNF is widely expressed throughout the brain and essential to neuronal development and plasticity[38–41]. BDNF regulates neuronal survival and synaptic growth in the developing brain and modulates synaptic plasticity[42,43]. The BDNF Val66Met polymorphism has been found to alter intracellular trafficking of BDNF, reduce activity-dependent release of BDNF[11,12,44], and initiate Met prodomain-specific actions[45,46]. In animal models, this SNP has been found to alter dendritic morphology and synaptic function in prefrontal cortical regions and the hippocampus[44,47–49] and to increase susceptibility to the synaptic effects of chronic stress[50]. Research has indicated developmental changes in the ratio of proBDNF (precursor form of BDNF) to mature BDNF (mBDNF) expression across childhood and adolescence, with increased mBDNF expression by adolescence and adulthood[51]. In addition, the Met prodomain exhibits delayed developmental expression[45], and findings suggest that some effects of BDNF Val66Met genotype may be specific to adolescence[52–54].

BDNF Val66Met polymorphism as a moderator

BDNF Val66Met genotype has been investigated as a moderator of associations between early environmental factors (e.g., adversity) and behavioral phenotypes, such as risk for psychopathology (e.g., depression)[55–58]. However, only a few studies have examined interactions between early adversity and BDNF Val66Met genotype for cortical structure in healthy or typically-developing individuals[59]. In these studies, participants were grouped as either Met carriers (Val/Met, Met/Met) or Val homozygotes, which is a common practice due to relatively low Met allele frequency in those of European ancestry[60,61]. All of these studies focused on adults, except one study focused on a small sample of children and adolescents[62]. Some findings suggest that the Met allele increases susceptibility to the effects of early adversity on cortical structure[63,64]. For example, in healthy adults, Met carriers with exposure to childhood adversity had reduced subgenual anterior cingulate cortical (ACC) volume compared to Met carriers without childhood adversity and Val homozygotes with childhood adversity[64]. Other studies have shown different patterns of interaction effects. For instance, adults who were maltreated as children and had Val/Val genotypes had decreased rostral ACC CT compared to non-maltreated adults with Val/Val genotypes, whereas rostral ACC CT did not significantly differ as a function of childhood maltreatment in Met carriers[65]. In another study, adults who were maltreated as children and had Val/Val genotypes had reduced CT in the left fusiform and transverse temporal gyri compared to non-maltreated adults with Val/Val genotypes, whereas CT in these regions did not differ as a function of childhood maltreatment in Met carriers[56]. Inconsistencies in results across these few studies could be due to variability in the neural phenotype of interest; racial/ethnic composition of the sample; and age range of the sample. In addition, the sample sizes in all these studies were below 300 (see Table S1). And some studies only analyzed a few specific cortical regions of interest.

Research on gene-by-environment interactions has been conducted from the perspective of diathesis-stress and differential susceptibility (environmental sensitivity) models[34,36]. It is possible that BDNF Val66Met genotype increases vulnerability to the effects of negative environmental factors (consistent with the diathesis-stress model) or increases malleability to both positive and negative environmental factors (consistent with the differential susceptibility model). Results from prior studies suggest that BDNF Val66Met genotype may be a marker of differential susceptibility to context for outcomes at the behavioral level[57,58,66]. Yet, to our knowledge, no previous studies have examined BDNF Val66Met genotype as a moderator of socioeconomic differences in cortical structure.

Reproducibility and replication

Major issues with reproducibility and replication in candidate gene and MRI research have been identified[67–69]. Findings from candidate gene studies have been found to be difficult to replicate[61,70]. Inconsistent findings in MRI research are likely driven, in part, by the reliance on small sample sizes, which have low statistical power[71].

In fact, MRI studies with large sample sizes are more equipped to yield replicable findings[72]. Thus, in our study, we conducted analyses using two large independent samples to assess reproducibility.

Current study

The goal of this study was to examine whether BDNF Val66Met genotype moderated associations between socioeconomic factors (family income, parental education) and CT and SA in two large independent samples of typically-developing children and adolescents. High-resolution, T1-weighted MRI data were acquired in both studies. Family income and parental education were examined separately as they may influence children's environments and development in distinct ways[14,15]. Analyses of global and regional SA and CT were conducted.

We hypothesized that an interaction effect would be found between socioeconomic factors and BDNF Val66Met polymorphism for SA during adolescence. We predicted that positive associations between socioeconomic factors and SA would be stronger for Met allele carriers than for Val homozygotes. We did not have hypotheses about specific cortical regions as BDNF is widely distributed across the cortex, and the BDNF Val66Met polymorphism has been associated with the structure of many different cortical regions[73,74].

Methods

Participants

Participants were 3- to 21-year-olds ($N = 383$) from the Pediatric Imaging, Neurocognition, and Genetics (PING) study[75] and 11- to 14-year-olds ($N = 2566$) from the Adolescent Brain Cognitive Development (ABCD) study[76].

For the PING study, typically-developing participants were recruited across nine university-based data collection sites in the United States[75]. Individuals with neurological disorders; history of head trauma; preterm birth; diagnosis of autism spectrum disorder, bipolar disorder, schizophrenia, or intellectual disability; pregnancy; or contraindications for MRI were excluded[75]. Participants ranged from 3.17 to 21.00 years of age (47% female; see Table 1 for sample characteristics). Given that BDNF allele frequencies and patterns of findings differ significantly by racial/ethnic background[55,56,59,60,77,78], analyses included only participants of European ancestry (0.95 loadings to the European principal component).

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-olds. Each site's Institutional Review Board approved the study.

The ABCD study (http://abcdstudy.org) included 21 data collection sites in the United States[76,79] and uses a longitudinal design. Data were collected using school-based recruitment. Participants with contraindications for MRI, intellectual, medical, or neurological issues, or poor English-language proficiency were excluded. Data from ABCD Release 5.1 were used for this study. Written informed consent was obtained from parents, and children separately completed a written assent. The ABCD study was approved by the Institutional Review Board of the University of California, San Diego (IRB# 160091). In addition, Institutional Review Boards at each site approved the procedures. All methods were performed in accordance with Declaration of Helsinki ethical guidelines and regulations.

We analyzed ABCD study data from time 2 because participants' ages at this timepoint correspond to early adolescence, which is when BDNF Val66Met genotype has been reported to be influential[47,53]. Using data from time 2 allowed for focusing on adolescence while preserving sample size, given attrition in the ABCD study over time[80]. Excluded from analyses were those with neurological disorders, similar to previous analyses using this sample[81]. We randomly selected one family member for inclusion in analyses. Only participants of European ancestry were included in analyses based on the rationale described above. Also excluded were all outliers in SA and CT based on the following criterion: 2.2 interquartile range below the first quartile or above the third

	PING ($N = 383$)			ABCD ($N = 2566$)		
	M	**SD**	**Range**	**M**	**SD**	**Range**
Age (years)	12.05	4.76	3.17–21.00	11.97	0.65	10.58–13.75
Family income (U.S. dollars)	119,648.83	75,234.71	4500.00-325,000.00	128,704.80	53,373.75	2500.00-200,000.00
Parental education (years)	15.67	1.88	8.00–18.00	16.23	2.25	6.00–22.00
Total SA (mm^2)	200,509.75	16,584.43	159,472.12–246,539.70	192,983.00	19,275.10	141,593.00-241,755.00
Mean CT (mm)	3.11	0.17	2.61–3.61	2.71	0.07	2.48–2.95
	%	***n***	**Range**	**%**	***n***	**Range**
Sex (female)	47.26	181	--	46.34	1189	--
BDNF Val66Met genotype						
Val/Val	65.54	251	--	63.09	1619	--
Val/Met	30.29	116	--	33.32	855	--
Met/Met	4.18	16	--	3.59	92	--

Table 1. Descriptive statistics for sample characteristics, BDNF Val66Met genotype, SA, and CT. SA, cortical surface area; CT, cortical thickness; BDNF, brain-derived neurotrophic factor; U.S., United States; PING, Pediatric Imaging, Neurocognition, and Genetics study; ABCD, Adolescent Brain Cognitive Development study; --, not applicable.

quartile[82,83]. These exclusions resulted in 2566 11- to 14-year-olds (46% female) included in analyses (see Table 1 for sample characteristics).

Socioeconomic factors

In both samples, both family income and parental education data were originally collected in bins, which were recoded to create continuous variables, following from previous work[9,10,25,84]. Parental education was recoded into years of education and averaged across parents[10,25,85]. As expected, family income and parental education were significantly correlated (e.g., PING sample: $r = .56$, $p < .0001$).

BDNF Val66Met genotyping

In the PING study, genome-wide genotyping was performed on DNA extracted from saliva samples using the Illumina Human660 W-Quad BeadChip (San Diego, CA), from which rs6265 genotype data were obtained using PLINK 2.0[86].

In the ABCD study, DNA extracted from saliva samples was used for genotyping across sites[87]. The biospecimen storage, DNA extraction, and genotyping calls were performed at the Rutgers University Cell and DNA Repository (RUCDR)[88]. After basic biospecimen quality controls, RUCDR used the Affymetrix Axiom Smokescreen Array[89] as the genotyping platform. BDNF rs6265 genotype for each individual was obtained using PLINK 2.0[86].

Image acquisition and processing

PING

Each site administered a standardized structural MRI protocol[75,90]. Imaging data were collected using 3-Tesla scanners manufactured by General Electric (GE), Siemens, and Philips. The PING study imaging protocols and pulse sequence parameters have been published previously[10,75]. T1-weighted images were acquired using a standardized high-resolution 3D RF-spoiled gradient echo sequence[75].

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 publicly-shared raw T1-weighted imaging data was that the full PING sample was older on average than the subsample[91]. Using this publicly shared raw data, the CIVET processing pipeline (https://mcin.ca/technology/civet/) was employed to compute CT and SA. 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[91]. In the PING sample, there were no outliers for total SA or mean CT as defined by datapoints being 2.2 interquartile range below the first or above the third quartile[82,83]. Analyses of global SA and CT were followed by analyses of regional SA and CT in 31 regions per hemisphere defined by the commonly used Desikan-Killiany-Tourville (DKT) atlas[92].

ABCD

Imaging data were collected using 3-Tesla scanners manufactured by Siemens, GE, and Philips. Data collection was harmonized across all acquisition sites by using standardized hardware (e.g., 32-channel head coils) and adjusting acquisition sequences for each scanner manufacturer. As described previously[93], 3-dimensional T1-weighted imaging data with 1-mm voxel resolution were acquired. FreeSurfer (version 5.3)[94] was used for cortical surface reconstruction and parcellation[95]. We examined regional CT and SA data corresponding to DKT atlas parcellations[92]. Visual inspection of raw and processed data was conducted to ensure that only images with no processing errors were included in the dataset. Only data that passed ABCD study quality control[95] were included in analyses.

Statistical analyses

PING

Multiple linear regression analyses were conducted in SAS (version 9.4) to examine the interaction between socioeconomic factors and BDNF Val66Met genotype (Met carrier or Val homozygote) for global and regional SA and CT. Separate regression models were run for family income and parental education. Covariates were age, age-squared, sex, and scanner/site (dummy-coded). The first 10 principal components (PC1–10) were also included as covariates to control for population stratification[96], similar to previous studies[65]. All variables were

standardized prior to running the regression models. Effect sizes (partial eta squared, η_p^2) are presented for significant results, with values of 0.01, 0.06, and 0.14 indicating small, medium, and large effects, respectively[97,98].

Analyses of regional specificity were conducted by examining the interaction effect for SA and CT in each of the 62 parcellations of the DKT atlas (31 parcellations per hemisphere)[92]. False discovery rate (FDR)[99] corrections were applied to account for multiple comparisons. These corrections were applied separately for SA and CT in 62 regions. Significant interactions were probed using simple slopes, which were computed using the PROCESS macro in SAS[100]. Significant interactions were also plotted to visualize the association between socioeconomic factors and SA or CT in Met carriers and Val homozygotes.

Although many studies of regional SA have included whole brain volume as a covariate in analyses, since SA scales with head size[101], controlling for whole brain volume may bias results[102]. In line with these findings, some studies of regional SA have not included this covariate[103,104]. Thus, analyses of regional SA were conducted with and without controlling for whole brain volume.

Because of the PING sample's wide age range, three-way socioeconomic factor × BDNF Val66Met genotype × age interactions were examined. Given low power for detecting a three-way interaction, we also examined whether the socioeconomic factor × BDNF Val66Met genotype interaction was significant during childhood (< 11 years) and adolescence (≥ 11 years) based on our hypothesis that the interaction would be significant during adolescence and not childhood.

ABCD

A nearly identical multiple linear regression approach was used to examine our research questions in the ABCD study sample. Analyses were conducted using R (v. 4.3.1) and the *lm* function. These analyses used the same set of covariates included in analyses of the PING sample. SA and CT data for the DKT atlas parcellations were used in analyses of regional specificity. Standardized regression coefficients were calculated using the *lm.beta* library in R. ComBat harmonization software was used to remove site variability from the SA and CT data[105]. A *p*-value threshold of 0.05 (two-tailed) was used for all analyses, with FDR correction then applied in analyses of regional SA and CT. Surface visualizations of results for cortical regions were created using ggseg in R.

Results

Descriptive statistics

Descriptive statistics for BDNF Val66Met genotype, total SA, and mean CT are provided in Table 1. In the PING sample, Met carriers did not differ significantly from Val homozygotes in family income, $t(381) = 1.44$, $p = .15$; age, $t(381) = 0.95$, $p = .34$; or sex, $\chi^2(1, N = 383) = 0.12$, $p = .73$. Parents of Met carriers had higher levels of educational attainment compared to parents of Val homozygotes, $t(381) = 2.19$, $p = .03$. In the ABCD sample, Met carriers did not differ significantly from Val homozygotes in family income, $t(2012) = 0.90$, $p = .37$; age, $t(2030) = -0.95$, $p = .34$; sex, $\chi^2(1, N = 2566) = 0.01$, $p = .91$; or parental education, $t(2024) = -0.16$, $p = .87$. Allele frequencies did not deviate from Hardy–Weinberg equilibrium in the PING sample ($p = .95$) or ABCD sample ($p = .99$).

PING sample

SA

There was a significant interaction between family income and BDNF Val66Met genotype for total SA (see Table 2), with a small effect size ($\eta_p^2 = 0.02$). Lower family income was significantly associated with reduced total SA in Met carriers, $t = 3.34$, $p = .0009$, but not in Val homozygotes, $t = 0.73$, $p = .47$ (see Figure S1). The interaction was not significant for parental education.

When not controlling for whole brain volume, the interaction between family income and BDNF Val66Met polymorphism was significant for SA in the left fusiform gyrus ($\eta_p^2 = 0.03$; see Table S2), and the pattern of simple slopes was the same as that for total SA (see Figure S2). The t-values are presented in Fig. 1. This interaction was not significant for SA in any cortical regions when controlling for whole brain volume (see Table S3). The interaction was not significant for parental education with or without controlling for whole brain volume (see Tables S4 and S5).

CT

There were no significant interactions between family income or parental education and BDNF Val66Met genotype for mean CT (see Table 2) or regional CT (see Tables S6 and S7).

	PING						ABCD					
	Total SA			Mean CT			Total SA			Mean CT		
	β	SE	*p*	β	SE	*p*	β	SE	*p*	β	SE	*p*
BDNF Val66Met genotype × family income	0.22	0.09	0.0135	0.004	0.06	0.9496	0.02	0.04	0.50	0.03	0.04	0.35
BDNF Val66Met genotype × parental education	0.03	0.11	0.7853	0.07	0.08	0.4057	0.001	0.04	0.97	0.007	0.04	0.82

Table 2. BDNF Val66Met genotype × socioeconomic factor interaction results for total SA and mean CT. SA, cortical surface area; CT, cortical thickness.

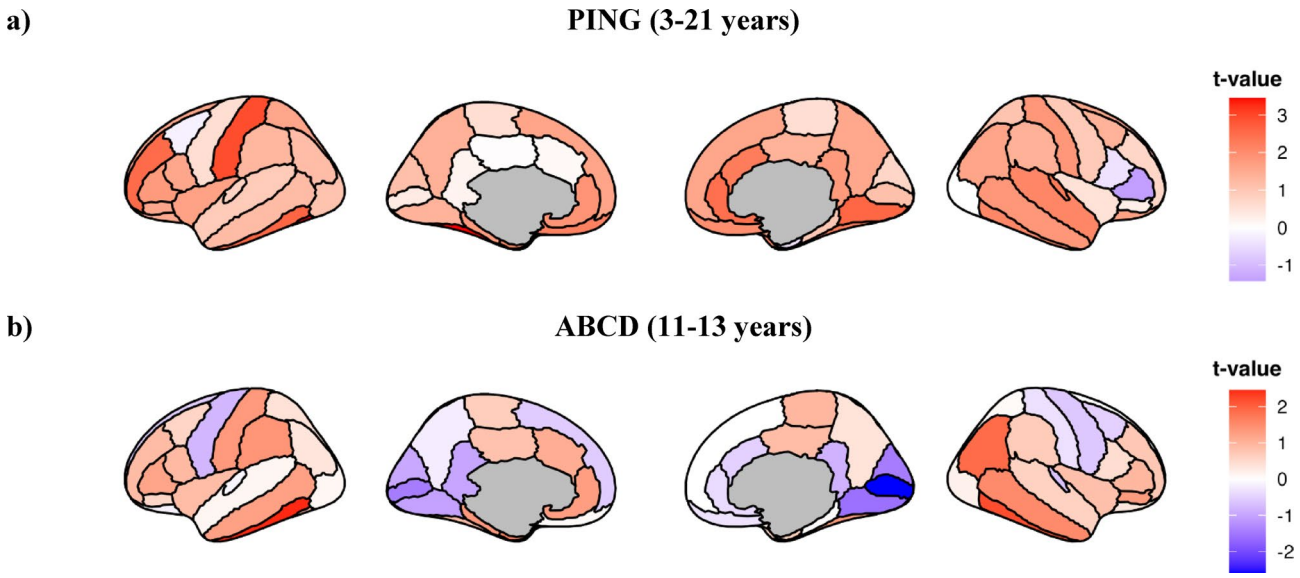

Fig. 1. Family income × BDNF Val66Met polymorphism interaction term t-values for regional cortical surface area (SA) without controlling for whole brain volume in the **(a)** Pediatric Imaging, Neurocognition, and Genetics (PING) sample and **(b)** Adolescent Brain Cognitive Development (ABCD) sample. Brain map parcellation is according to the Desikan-Killiany-Tourville atlas. Interaction terms were non-significant after false discovery rate (FDR) correction for all regions in the ABCD sample and for all regions except the left fusiform gyrus in the PING sample.

ABCD sample

SA

In the ABCD sample, the interactions between family income and BDNF Val66Met polymorphism and between parental education and BDNF Val66Met polymorphism were not significant for total SA (see Table 2) or regional SA (see Tables S2-S5 and Fig. 1).

CT

Interactions between family income and BDNF Val66Met polymorphism and between parental education and BDNF Val66Met polymorphism were also not significant for mean CT (see Table 2) or regional CT (see Tables S6 and S7).

Sensitivity analyses

In the PING sample, there were no significant three-way interactions with age or age-squared. The interaction between family income and BDNF Val66Met genotype was significant for total SA in adolescence, $\beta = 0.35$, $p = .0056$, $n = 210$, $\eta_p^2 = 0.04$, but not childhood, $\beta = 0.01$, $p = .9196$, $n = 173$. Using ComBat to control for site in analyses of the PING sample did not change the results.

Discussion

The goal of this study was to examine whether BDNF Val66Met genotype moderated associations between socioeconomic factors and SA and CT in two large independent samples of children and adolescents. Findings suggest that BDNF Val66Met genotype may not moderate these associations. In line with our hypotheses, an interaction was found between family income and BDNF Val66Met genotype for total SA in the PING sample (3- to 21-year-olds), which was specific to adolescence. However, no significant interactions were found for SA or CT in the larger ABCD sample (11- to 14-year-olds).

Inconsistent results for cortical surface area across independent samples

In animal models, significant effects of BDNF Val66Met genotype have been found during adolescence. Some effects of BDNF Val66Met genotype on neuronal morphology, social functioning, and anxiety may be specific to adolescence[45,47,52,53]. BDNF availability during adolescence may be especially important to neuronal development in cortical regions and outcomes in these domains. Research has demonstrated delayed developmental expression of the Met prodomain[46] and developmental changes in the ratio of proBDNF to mBDNF expression across childhood and adolescence[51]. Results from the current study suggested that the interaction effect for total SA in the PING sample was specific to adolescence, but analyses of the ABCD sample that focused on 11- to 14-year-olds failed to reveal any significant interactions.

We examined regional SA controlling for and not controlling for total brain volume, as there is a lack of consensus on including this covariate in analyses of regional SA[102–104]. When it was not included, in the PING sample, interaction effects were found for SA in the left fusiform gyrus, but this result was no longer significant

once whole brain volume was included as a covariate, and interaction effects for regional SA were not found in the ABCD sample. Taken together, these results suggest that BDNF Val66Met genotype does not moderate socioeconomic differences in regional SA during childhood and adolescence.

These results for SA align with previous work indicating non-replicable findings in candidate gene studies[68–70]. Research has indicated that main effects of the BDNF Val66Met polymorphism on psychiatric phenotypes are difficult to replicate[61]. Although relatively fewer studies have examined interaction effects, one large-scale study that included BDNF Val66Met did not find any candidate gene polymorphism-by-environment moderator effects for depression[67]. These candidate gene replication difficulties also extend to intermediate neural phenotypes[106]. The result for SA in the PING sample may have been a false positive potentially due to low statistical power[107] since it could not be replicated in the larger ABCD study sample. These results are also consistent with genome-wide association studies, which indicate that individual SNPs have small effects on SA and CT[32,33].

Non-significant results for cortical thickness

In both the PING and ABCD samples, there were no significant interactions between socioeconomic factors and BDNF Val66Met genotype for global or regional CT. Thus, results were consistent across samples in suggesting that BDNF Val66Met genotype does not moderate socioeconomic differences in CT in children and adolescents. Although two previous studies found that BDNF Val66Met genotype moderated the associations between early trauma and CT in adults[56,65], the same pattern was not found for socioeconomic differences in CT in children and adolescents.

There are several possible reasons for these non-significant results for both SA and CT. We cannot rule out the possibility that the moderating role of BDNF Val66Met genotype is specific to or only observable for SA measured during later adolescence or early adulthood. Non-significant results could be due in part to sex differences[54] as BDNF signaling is modulated by gonadal hormones, including estrogens[51,61]. In addition, interactions between BDNF Val66Met genotype and gene expression could have affected the results. Future research should simultaneously examine both BDNF SNPs and gene expression in relation to cortical structure. Research based on animal models[108] has indicated that both socioeconomic disadvantage and BDNF genetic polymorphisms may influence cortical structure through epigenetic influences on BDNF gene expression (DNA methylation)[109,110]. This study also focused on key measures of family-level SES that were available for both samples. Results could be different for neighborhood-level socioeconomic factors, which have been significantly associated with cortical structure[9,18,25,85].

Strengths and limitations

This study had several strengths, including its focus on children and adolescents; analyses using two large independent samples; and lack of reliance on retrospective report of childhood adversity. Analyses of two socioeconomic measures were conducted rather than focusing solely on a single socioeconomic factor[13–15]. In alignment with robust research practices aiming for reproducible science[71], this study included a replication attempt, and through its publication, reduces publication bias in human neuroscience. In addition, the large samples used in this study were typically developing, reducing the possibility of confounds due to participants having serious psychiatric disorders or other medical conditions.

There are also limitations that should be taken into account when interpreting the results of this study. First, analyses were cross-sectional and correlational. Second, all participants included in analyses were of European ancestry. In studies of the BDNF Val66Met polymorphism, results have been found to depend on the racial/ethnic background of the participants[55,56,78]. Thus, these results cannot be generalized to individuals of other racial or ethnic backgrounds. Third, the frequency of Met homozygotes (Met/Met) in these samples was too low to examine these individuals as a separate group and so they were combined with the Val/Met heterozygotes to create a single group of Met carriers. Further research is needed that examines these interaction effects using all three BDNF Val66Met genotypes; some research has indicated dose-dependent effects of the Met allele on brain structure, although results have been inconsistent[74,111,112].

Conclusion

In this study, results indicated a significant interaction between family income and BDNF Val66Met genotype for total SA in 3- to 21-year-olds, which was specific to adolescence. Yet, no significant interactions were found for global or regional SA or CT in a larger sample of 11- to 14-year-olds. Thus, BDNF Val66Met genotype most likely does not moderate associations between socioeconomic factors and SA or CT during childhood or early adolescence. This study makes an important scientific contribution to research aiming to identify genetic moderators of the effects of early environmental factors on brain structure and function.

Data availability

Data used in this study are publicly available through the NIMH Data Archive (https://nda.nih.gov/).

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Author contributions

EM conceptualized the study, conducted the main analyses, and wrote and edited the manuscript. FM conducted the main analyses and wrote and edited the manuscript. MH created figures and wrote and edited the manuscript. JS assisted with analyses and wrote and edited the manuscript. LJ wrote and edited the manuscript. UV extracted genotype data, provided guidance, and wrote and edited the manuscript. MS extracted genotype data and wrote and edited the manuscript. BM provided guidance and wrote and edited the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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