Title: Genetic associations with brain structure are not correlated with individual and state-level economic differences

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Abstract

Using data from the Adolescent Behavior and Cognitive Development (ABCD) study, we investigate whether neural, cognitive, and psychopathology phenotypes that are more strongly related to genetic differences are less strongly associated with family- and state-level economic contexts (N = 5,374 individuals with 1KG-EUR-like genotypes, plus 870 twins). We estimated the twin- and SNP-based heritability of each phenotype, as well as its association with an educational attainment polygenic index (EA PGI). We further examined associations with family socioeconomic status (SES) and tested whether SES-related differences were moderated by state cost of living and social safety net programs (Medicaid expansion and cash assistance). SES remained broadly associated with cognition, psychopathology, brain volumes, and cortical surface areas, even after controlling for the EA PGI. Brain phenotypes that were more heritable or more strongly associated with the EA PGI were not, overall, less related to SES, nor were SES-related differences in these phenotypes less moderated by macroeconomic context and policy. Informing a long-running theoretical debate, and contra to widespread lay beliefs, results suggest that aspects of child development that are more strongly related to genetic differences are not, in general, less associated with socioeconomic contexts and policies.

1. Introduction

Genetic differences are associated with differences in nearly every aspect of child development, including brain structure and function, as well as with symptoms of psychopathology and cognitive abilities (Blokland et al., 2012; Polderman et al., 2015). Some academics have argued that, if genetic differences substantially contribute to variation in child development, then interventions and policies aiming to improve cognition, academic achievement, well-being, or behavior problems will generally be ineffective (Jensen, 1969; Murray, 2020). Consistent with this idea, some evolutionary biologists have proposed a trade-off between how heritable a trait is (i.e., how much variation in a trait is due to genetic differences) and how plastic the trait is to changes in environmental context (Tonsor et al., 2013). Similarly, among the lay public, the belief that there are "biogenetic" influences on a trait or behavior is associated with greater pessimism about the possibility of change (Haslam & Kvaale, 2015; Lebowitz & Appelbaum, 2019). In contrast, other theorists have emphasized that even very highly heritable phenotypes can, in some cases, be intervened upon environmentally, as the examples of shortsightedness and phenylketonuria illustrate (Burt et al., 2019; Goldberger, 1979; Harden, 2021; Haworth & Davis, 2014). But are these exceptions that prove the rule? Few studies have empirically investigated whether aspects of child development that are more strongly associated with genetic differences are, on average, less responsive to differences in environmental context. Here, using data from the Adolescent Behavior and Cognitive Development (ABCD) study, we test whether brain structure, cognitive, and psychopathology phenotypes that are more strongly associated with genetic differences between children are, on average, less associated with parental socioeconomic status (SES) and whether SES-related differences are less moderated by state-level economic contexts and policies.

The few studies that have investigated whether phenotypes with stronger genetic associations are less responsive to environmental changes have used twin designs, which estimate heritability by leveraging theoretical differences in genetic relatedness between monozygotic and dizygotic twins, asking whether monozygotic twins are more similar than dizygotic twins. These studies yielded mixed conclusions. An early study of attitude change found that people showed greater physiological stress following interventions targeting more heritable compared to less heritable attitudes, and that average intervention effects were smaller as the heritability of the attitude increased (Tesser et al., 1998). In contrast, two twin studies found that brief in-laboratory manipulations (namely, an acute psychosocial stressor test and a growth mindset intervention) produced marked changes in physiological and psychological

phenotypes (cortisol output and growth mindset, respectively) irrespective of their heritability estimates (Burgoyne et al., 2020; Raffington et al., 2022).

In addition to twin data, genetic associations with a phenotype can be estimated from data that directly measure genomic variants, most commonly single nucleotide polymorphisms (SNPs). Genomic heritability studies leverage differences in measured genomic similarity across SNPs between pairs of unrelated individuals, asking whether people who are more genetically similar are also more phenotypically similar. Whereas twin heritability estimates are putatively based on all forms of genetic variation, SNP heritability estimates are based solely on common genetic variants (Young, 2019). Yet another method for estimating genetic associations is to use a polygenic index (PGI), which uses results from large-scale genome-wide association studies on SNPs to create a summary measure of an individual's overall genetic liability for a given trait (Choi et al., 2020).

Of particular interest to child development researchers has been the educational attainment (EA) PGI, which can now be calculated from the results of a genome-wide association study of years of completed formal schooling in over 3 million people (Okbay et al., 2022). Prior studies have reported that the EA PGI is robustly correlated with children's brain structure, cognition, and academic achievement, as well as with SES, both within- and between families (e.g., Isungset et al., 2022; Merz et al., 2022; Okbay et al., 2022). Some studies have found limited overlap between the brain regions associated with SES and those associated with the EA PGI in adolescents (Judd et al., 2020; Merz et al., 2022), but a larger study in adults revealed substantial convergence between brain regions associated with SES and an EA PGI (Kweon et al., 2022). In this study, we use all three methods – twin modeling, SNP heritability, and PGI – to add to the small empirical literature examining whether phenotypes that are more strongly associated with genetic differences between people are, as has been hypothesized, generally less responsive to economic context.

The ABCD study is an ideal dataset to test this hypothesis as it includes twins, genomic data, neuroimaging data, cognitive and psychopathology measures, and a range of individual and state-level environmental variables. Previous research with the ABCD cohort has documented that many aspects of brain development, as well as internalizing and externalizing psychopathology symptoms and cognitive abilities, are associated with adolescent's environmental context, including parental SES (Dennis et al., 2022; Judd et al., 2020; Taylor et al., 2020). These SES-related differences in adolescent development might be moderated by macroeconomic contexts and policies, including social safety net programs which are designed to provide financial assistance, support, and resources to low-income individuals and

households (Bitler et al., 2017). For instance, SES-related differences in hippocampal volume and internalizing symptoms were found to be moderated by state-level average cost of living and by two safety net programs: Medicaid expansion after the passage of the Affordable Care Act in 2010 and average cash assistance to low-income households (Weissman et al., 2023). Studying the ABCD cohort thus provides a unique opportunity to examine whether the genetic measures of a phenotype are correlated with a phenotype's association with individual economic context and the moderation of SES by macroeconomic contexts and policies that differ between US states.

In summary, this study aims to provide a more comprehensive examination of how variation across adolescent neurobiological phenotypes in the strength of their genetic associations is related, or unrelated to their associations with economic contexts and policies in the US. This relationship, between the parameters estimated from genetic analyses and those estimated from analyses of variation across socioeconomic contexts, has long been an object of theoretical speculation and public interest but has rarely been investigated empirically as we do here.

2. Methods

The preregistration and code are available here: osf.io/mg63h.

2.1. Sample

The Adolescent Brain and Cognitive Development (ABCD) study is a longitudinal cohort study that enrolled 11,876 youth at baseline across 21 sites in 17 states. Mental and physical health were assessed at annual visits (Volkow et al., 2018; https://abcdstudy.org/). The sample includes many siblings as well as a twin sub-sample consisting of 840 pairs of same-sex twins recruited from state birth registries at four sites (Garavan et al., 2018). ABCD study imaging procedures were harmonized across sites (Casey et al., 2018). The study protocols were approved by the University of California, San Diego Institutional Review Board. The data used in this study were obtained from the year 1 assessment (data release 4.0).

Regression analyses were conducted on a maximum of 5,370 individuals (mean age = 9.925 years, SD = 0.631, N females = 2,559) who: (1) identified as white and non-Hispanic; (2) had genotypes most similar to the 1000 Genomes EUR panel ("1KG-EUR-like" individuals), as compared to people sampled from other regions of the world; (3) had available demographic data; and (4) had data on at least one cognition, psychopathology, or neuroimaging measure. The number of participants included in the regression analyses differed across investigated phenotypes, ranging from N = 5,189 to 5,370 (**Supplemental Material)**. To facilitate comparisons between twin- and SNP-based estimates of heritability, we performed analyses on a subset of same-sex twins with 1KG-EUR-like genotypes, including a maximum of 382 MZ (N females = 190) and 492 DZ twins (N females = 236; **Supplementary Table 1)**.

2.2. Measures

2.2.1. *Polygenic index*

We calculated an educational-attainment PGI (EA PGI) using results from the EA genome-wide association study (GWAS) on 3 million individuals, including 23andMe Data, Inc. (Okbay et al., 2022). Participant inclusion, genotyping, imputation, principal component analyses, and quality checks are described in the **Supplementary Material**. Briefly, PGIs were computed using PRS-CS, a Bayesian approach that incorporates all SNPs (*i.e.*, no p-value thresholding) and uses an external linkage disequilibrium reference panel to account for correlations between SNPs (Ge et al., 2019).

2.2.2. *Demographics*

Demographic variables included self-reported age, biological sex, genomic principal components, and socioeconomic status (SES) as measured by the income-to-needs ratio. To calculate income-to-needs ratio, caregivers selected one of the ten income ranges, and the midpoint of the range was selected as the family income for each participant. The ratio was calculated by dividing the family income by the 2017 federal poverty threshold for a family of that size (U.S. Census Bureau, 2022; **Supplementary Table 2**) and was log-transformed.

2.2.3. *Brain structure*

We conducted analyses on 164 neuroimaging phenotypes generated by the ABCD study (Hagler et al., 2019): 68 cortical mean thicknesses, 68 cortical surface areas, 17 subcortical grey matter volumes, and 11 other brain volumes (i.e., corpus callosal volumes, cerebellar grey and white matter volumes, and whole brain white matter volumes). All brain segmentations were performed using FreeSurfer v5.3 on T1-weighted MRI volumes. Additional global measures included total brain volume (TBV), total cortical surface area (TSA), and total mean cortical thickness (TMCT). Cortical measures were segmented using the Desikan-Killiany atlas (Desikan et al., 2006) implemented in Freesurfer (Fischl, 2012).

We evaluated the distribution of genetic and SES associations across cortical mean thicknesses and surface areas in comparison with three parcellations of the cortex: (1) the sensorimotor-axis ranking defined by Syndor and colleagues (Sydnor et al., 2021), which reflects cortical development based on macrostructural, microstructural, functional, metabolic, and transcriptomic features; (2) the cytoarchitectonic classes defined by von Economo and Koskinas (Economo & Koskinas, 1925), which categorize cortical regions based on cellular composition and arrangement; and (3) the functional networks derived by Yeo and Krienen (Yeo et al., 2011), which group cortical regions by their involvement in coordinated neural activities. We measured the correlation between the sensorimotor-axis ranking and SES and genetic associations using a Spearman correlation test and tested differences in the distribution of SES and genetic associations across functional networks and cytoarchitectonic classes using a Kruskal-Wallis test. P values were calculated using a spin permutation test (**Supplementary Material)**.

2.2.4. *Cognitive ability*

Given that fluid and crystallized measures of cognitive ability differ slightly in their genetic architectures (de la Fuente et al., 2021), we included the fluid and crystallized measures of cognitive ability provided by the NIH Toolbox (**Supplemental Material**).

2.2.5. Psychopathology

Internalizing and externalizing behaviors were measured with parent reports on the school-age version of the Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001), a validated DSM-oriented scale. The ABCD study provided CBCL composite scores for internalizing and externalizing behaviors for participants who responded to any of the 112 items, regardless of missingness (**Supplemental Material**).

2.2.6. State-level economic context and policies

As previously described (Weissman et al., 2023), we calculated state-level economic context and policies. State-level economic context was measured by the state's cost of living based on Regional Price Parity (RPP) for the year 2017 – the median year in which the ABCD baseline data was collected – and obtained from the U.S. Bureau of Economic Analysis. State-level economic policies were assessed by economic policies, including cash assistance and Medicaid expansion. The state's mean cash assistance program was measured as the mean of the average monthly Earned Income Tax Credit (EITC) and Temporary Assistance for Needy Families (TANF) benefit in each state (**Supplemental Material**). Medicaid expansion was measured as a dichotomous variable indicating whether that state had expanded Medicaid eligibility through the Affordable Care Act by the end of 2017.

2.3. Statistical Analyses

Analyses were conducted in three steps in R (R Core Team, 2022). First, we estimated twin and SNP heritabilities, and the associations of the EA PGI with brain, psychopathology, and cognitive outcomes. Second, we investigated the association of SES with each brain, psychopathology, and cognitive outcome, with and without adjusting for the EA PGI. We then tested whether the magnitude of SES-related disparities in outcomes varied across states. For regions that did show variation across states, we examined whether state-level economic context and policies moderated the SES-outcome association. Third, we examined the convergence between results of genetic and SES analyses: do outcomes that show higher heritabilities and/or stronger associations with measured genotypes show weaker associations with SES and/or less moderation of SES by economic policies and contexts?

Regression analyses were conducted using linear mixed-effects models with the *lmerTest* package (Kuznetsova et al., 2017). We controlled for age, sex (genetic sex: males coded -0.5 and females 0.5), age*sex, study site (random intercept), and family ID (random intercept). Brain-related analyses were conducted with the MRI manufacturer as a categorical covariate (0: Siemens, N= 3,440; 1: GE Medical Systems, N=1,061; 2: Philips Medical systems, N = 688). We ran the analyses of regional brain phenotypes with and without adjusting for the region's global measure (i.e., TBV for volumes, TSA for surface areas, and TMCT for

mean thicknesses). The first ten ancestral principal components were included as covariates across analyses including the EA PGI as a fixed effect.

We report results in the main text that are significant ($p < 0.05$) after applying a False Discovery Rate (FDR) correction to the p values of the coefficients of interest in each analysis (**Supplemental Material**). The p value significance threshold for global brain measures was set to 0.017 (0.05/ 3). All betas and standard errors (SE) are standardized and can be interpreted as the change in SD of the cognition, brain, or psychopathology phenotype for a change of 1 SD in the predictor variable (e.g., SES).

2.3.1. Genetic analyses

We estimated twin heritability with a 2-group Cholesky ACE twin model using the *umx* package (Bates et al., 2019). The ACE model estimates the proportions of total phenotypic variation that is due to variation in additive genetics (A; i.e., heritability), shared environment, which includes all environmental factors shared by twins raised in the same home that serve to make twins similar to one another regardless of zygosity (C), and non-shared environment (E), which includes all environmental factors that make twins different from one another regardless of zygosity, plus measurement error. We estimated SNP heritability using genome-wide complex trait analysis - genome-based restricted maximum likelihood (GCTA-GREML) on 6,303,056 SNPs (Yang et al. 2011). We estimated associations with the EA PGI using linear mixed-effects models.

2.3.2. SES analyses

We estimated associations with SES using linear mixed-effects models. Next, we ran regression models including both SES and the EA PGI, to examine whether the SES-phenotype associations were robust to adjusting for genes associated with educational attainment.

To reduce the number of phenotypes included in moderation analyses with state-level economic context and policies, we first examined whether the association between SES and each phenotype varied by study site. Given that study sites are distributed across states, variations in the SES association across sites may be driven by state-level differences in economic context and policy. We conducted a linear mixed effects model that estimated a random slope of SES, and identified which phenotypes had a significant random slope by comparing the fit of the model with and without including SES as a random slope using ANOVA. A significant ANOVA test (p <0.05) indicated that the model with SES as a random slope fit the data better, suggesting that the SES gradient varied by site, and in turn, by state.

Focusing on the subset of phenotypes that showed significant variation in the SES association across states, we then estimated the extent to which the state's economic context

(cost of living) and economic policy (i.e., Medicaid Expansion or mean cash assistance) moderated the associations with SES. Both economic policies were positively associated with family SES (**Supplemental Material**). All models included the main effects of SES, the state's cost of living, and an economic policy (either Medicaid Expansion or the state's mean cash assistance) and their interactions. Coefficients of interest for the multiple comparison corrections included 2- and 3-way interactions. We repeated these analyses adjusting for the EA PGI.

2.3.3. *Convergence between results of genetic and SES analyses*

The analyses described above produced two estimates of environmental associations with each phenotype: (1) the regression on SES and (2) the moderation of the SES association by economic context and policies. They also produced three estimates of genetic influences: (1) twin heritability, (2) SNP heritability, and (3) regression coefficients for the EA PGI. Our final analysis examined convergence between these parameters across phenotypes, to test whether phenotypes with stronger genetic associations were less associated with SES and with changes in state-level economic context and policies. When evaluating the spatial correspondence of cortical maps, we used a permutation-based "spin" test that accounted for the spatial contiguity and hemispheric symmetry of the cortex (Grotzinger et al., 2023).

3. Results

3.1. Genetic Analyses

3.1.1. Brain, cognition, and psychopathology phenotypes are heritable

Twin heritability estimates were greater than SNP heritability estimates for crystallized ($h^2_{Twin} = 0.61$, $h^2_{SNP} = 0.42$) and fluid ($h^2_{Twin} = 0.52$, $h^2_{SNP} = 0.19$) intelligence and externalizing ($h^2_{Twin} = 0.72$, $h^2_{SNP} = 0.18$) and internalizing ($h^2_{Twin} = 0.19$, $h^2_{SNP} = 0.03$) psychopathology scores.

Twin heritability estimates for brain outcomes ranged from 0.44 to 0.95 for volumes (median $h^2_{Twin} = 0.73$), from 0.22 to 0.78 for cortical surface areas (median $h^2_{Twin} = 0.56$), and from 0.10 to 0.76 for cortical mean thicknesses (median $h^2_{Twin} = 0.52$). SNP heritability estimates were generally smaller than twin estimates, ranging from 0.12 to 0.41 for volumes (median $h^2_{SNP} = 0.29$), from 0.02 to 0.38 for cortical surface areas (median $h^2_{SNP} = 0.17$), and from 0.02 to 0.43 for cortical mean thicknesses (median $h^2_{SNP} = 0.18$; **Figure 1**).

Correlations between cortical sensorimotor-axis ranks (Syndor et al., 2021) and the present study's cortical heritability estimates revealed that mean thicknesses from lower-order, primary, and unimodal cortices with sensory and motor functions were more heritable ($\rho_{Twin} = -0.30$, $\rho_{SNP} = -0.50$) than higher-order transmodal association cortices subserving executive, socioemotional, and mentalizing functions. No association between heritability and sensorimotor-axis rank was found for cortical surface areas (**Supplementary Material)**.

Cortical mean thickness heritability estimates generally varied across cortical functional networks ($p_{Twin} < 0.01$; $p_{SNP} < 0.001$) but did not vary as a function of cortical cytoarchitecture (**Supplementary Material).** Similar results were observed for SNP heritability and surface areas ($p_{SNP} < 0.001$).

Measures of global brain size (TBV, TSA, and TMCT) were also heritable ($h^2_{Twin} = 0.78$, 0.73, and 0.78, and $h^2_{SNP} = 0.25$, 0.20, and 0.31, respectively; **Supplemental Table 3**).

3.2. Brain, cognition, and psychopathology phenotypes are broadly associated with the EA PGI

Higher EA PGI was associated with higher fluid ($\beta = 0.13$, SE = 0.01) and crystallized ($\beta = 0.23$, SE = 0.01) intelligence scores and with lower internalizing ($\beta = -0.07$, SE = 0.01) and externalizing ($\beta = -0.15$, SE = 0.01) scores (**Supplemental Table 4)**.

A higher EA PGI was associated with greater left and right cerebral white matter volume ($\beta = 0.06$, SE = 0.01, and $\beta = 0.06$, SE = 0.01, respectively) and cerebellar white ($\beta = 0.04$, SE = 0.01, and $\beta = 0.04$, SE = 0.01) and grey matter volume ($\beta = 0.06$, SE = 0.01, for both).

Individuals with a higher EA PGI had greater regional size in all subcortical volumes (median |β| = 0.06), all cortical surface areas (median β= 0.07) and were associated with a thicker cortex in 5/68 regions (median β= 0.01; **Figure 1**).

Correlations between cortical sensorimotor-axis ranks (Syndor et al., 2021) and the EA PGI beta coefficient indicated that the EA PGI was more strongly related to mean thickness in lower-order regions (sensory and motor functions) compared to higher-order transmodal association regions (executive, socioemotional, and mentalizing functions; ρ = -0.31). The opposite pattern was observed for surface area (ρ = 0.23). Moreover, associations between the EA PGI and regional mean thicknesses varied as a function of cytoarchitectonic classes (p < 0.05), but no such relationship was observed for surface areas (**Supplementary Material).**

Regarding global measures, the EA PGI was associated with TBV (β= 0.11, SE = 0.01) and TSA (β= 0.10, SE = 0.01) but not TMCT (**Supplemental Table 5**). Of the 96 brain measures with significant associations with the EA PGI, less than a quarter (17%, 16/96) were still significant after adjusting for their respective global measure, indicating that the association of the EA PGI with brain structure is largely related to macroscale organization (**Supplementary Table 4**).

3.3. SES Analyses

3.3.1. Brain, cognition, and psychopathology phenotypes are broadly associated with SES, even after adjusting for the EA PGI

Higher SES was associated with higher fluid (β= 0.13, SE = 0.02) and crystallized (β = 0.21, SE = 0.01) intelligence scores and with lower internalizing (β = -0.13, SE = 0.02) and externalizing (β = -0.20, SE = 0.01) scores (**Supplemental Table 6)**.

Higher SES was associated with greater left and right brain white matter volume (β = 0.06, SE = 0.01 for both) and cerebellar white (β = 0.06, SE = 0.01 and β = 0.04, SE = 0.01) and grey matter volume (β = 0.08, SE = 0.01, and β = 0.07, SE = 0.01, respectively). Higher SES was also associated with greater regional size in all subcortical volumes (median β = 0.07) and 90% of cortical surface areas (61/68, median β = 0.06). For mean thicknesses, greater SES was associated with a thicker cortex in only 9/68 regions (median β = 0.05) and a thinner cortex in thickness of the left isthmus of the cingulate gyrus (β = -0.04, SE = 0.02; **Figure 1**).

As observed for the EA PGI-cortical associations, the associations of SES with regional brain structure metrics were greater for mean thicknesses and smaller for surface areas in lower-order cortices and varied across cytoarchitectonic classes for mean thicknesses but not surface areas (**Supplementary Material**).

As observed for the EA PGI-cortical associations, correlations between cortical sensorimotor-axis ranks (Syndor et al., 2021) and SES beta coefficients indicated that the association with SES was greater in mean thicknesses from lower-order cortices (ρ = -0.24) and greater in surface areas from higher-order cortices (ρ = 0.24). The SES-brain association also only varied across different cytoarchitectonic classes for mean thicknesses ($p < 0.01$; **Supplementary Material)**, but not surface areas.

As for global measures, higher parental SES was associated with greater TBV (β = 0. 09, SE = 0.01) and TSA (β = 0. 08, SE = 0.01) but not with total MCT (**Supplemental Table 5**). Of the 94 brain measures with significant SES associations, about a quarter (23%, 22/94) were still significant after adjusting for their respective global measure (**Supplemental Table 6)**.

The EA PGI and SES were modestly correlated with each other (r = 0.25) and including both variables as simultaneous predictors did not substantially change the estimated regression coefficients. In models that included both SES and the EA PGI as covariates, associations with SES were generally consistent across phenotypes: SES still was associated with 86% (84/98) of the regions that were significantly associated with SES before adjusting for the EA PGI, and decreases in effect size were small (median |Δβ| = 0.01). SES was no longer associated with the right caudate volume, the left isthmus cingulate thickness, and 20% (12/61) of surface areas. Of the 81 brain measures with significant associations with SES after adjusting for the EA PGI, less than a quarter (25%, 20/81) were still significant after adjusting for their respective global measure (**Supplementary Table 6; Supplementary Material**).

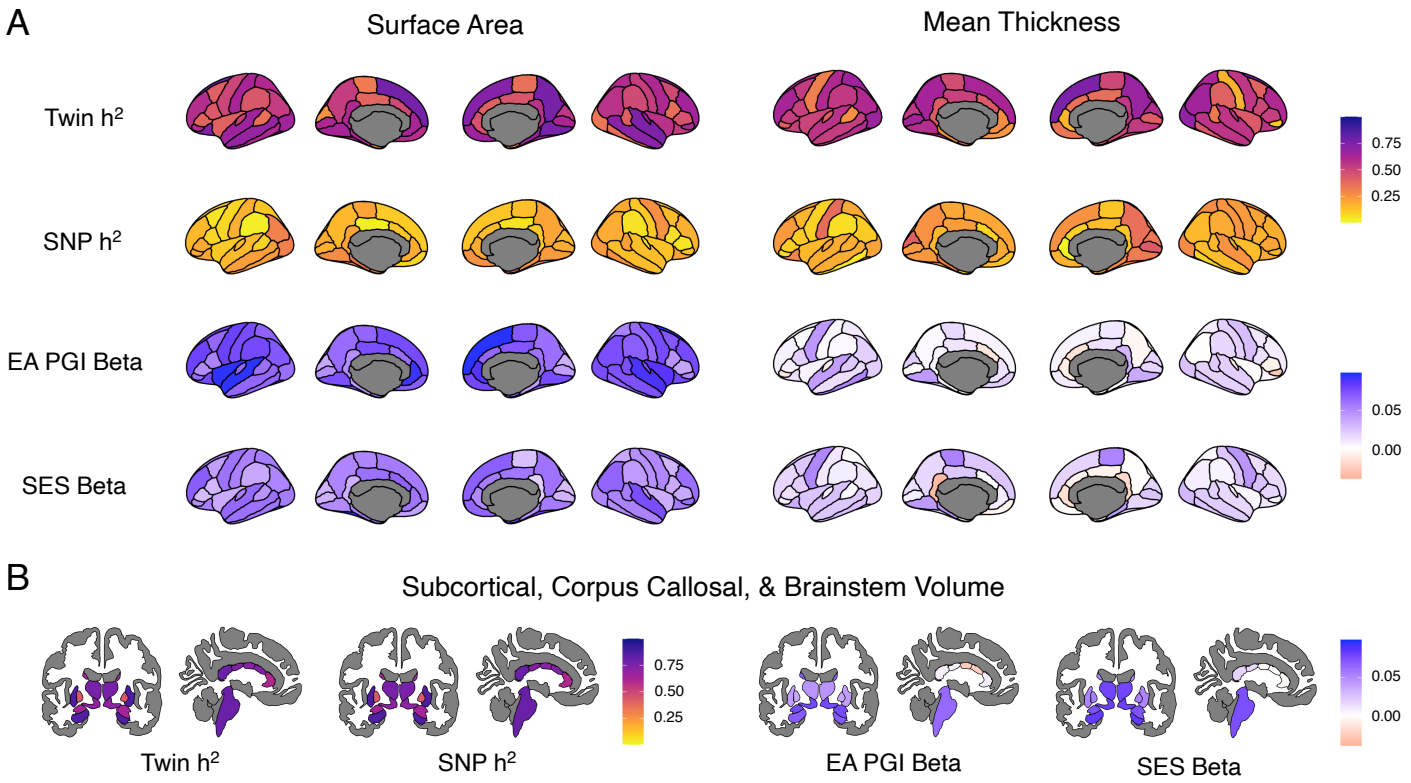

Figure 1. Distribution of heritabilities, genetic associations, and socioeconomic associations across (A) cortical surface areas and mean thicknesses and (B) volumes. Heritability (h^2) was estimated using twins and single nucleotide polymorphisms (SNPs) estimates. Beta corresponds to the standardized beta from regressions on socioeconomic status (SES) and the educational attainment polygenic index (EA PGI). Associations not adjusted for global brain size.

3.4. State-level economic contexts and policies moderated the association of SES with select volumes and surface areas

Among the phenotypes with a significant association with SES, that association varied by study site in 10 volumes, 6 surface areas, and one mean thickness (random slope median $\beta = 0.003$; **Supplemental Table 7**). In the next models, which estimated moderation by state-level economic policies and context, we only evaluated these 16 phenotypes.

In the models with mean cash assistance as the state's economic policy, there was a significant 2-way interaction between the state's cost of living and SES for the left and right cerebellar grey matter volumes (**Table 1**). The association of SES with regional size was greater in high compared to low cost of living states for the left and right cerebellar grey matter volumes ($\beta = 0.04$, SE = 0.02, and $\beta = 0.05$, SE = 0.02, respectively). After adjusting for the EA PGI and global brain size, the interaction was no longer significant for the left cerebellar grey matter volume and the magnitude of the interaction of both volumes decreased by 10% (median $|\Delta\beta| = 0.002$), suggesting that the interaction was not driven by gross neuroanatomical variation (**Supplemental Table 8-9**).

In regression analyses including Medicaid expansion as the state's economic policy, we observed 2-way interactions between the state's cost of living and SES and between SES and Medicaid expansion, as well as 3-way interactions between SES, the state's cost of living, and Medicaid expansion (**Table 1**). In regions with a significant 2-way interaction between SES and Medicaid (**Figure 2A**), the association of SES with regional brain size was attenuated in states that expanded Medicaid. In regions with a significant 2-way interaction between SES and cost of living (**Figure 2B**), the association between SES and regional size was greater in high-cost-of-living states than in low-cost-of-living states. However, for a subset of these regions, including the left thalamus and left and right cerebral white matter volumes, the SES-brain association in high cost-of-living states was attenuated in states that expanded Medicaid (**Figure 2C, Supplemental Table 8-9**).

Table 1. Significant moderation of the SES association with brain phenotypes by state-level economic context and policies

Economic Policy	Region	Coefficient	β	SE	FDR p
Mean cash assistance	left cerebellar grey matter volume	SES x cost of living	0.038	0.018	4.095E-02
	right cerebellar grey matter volume *	SES x cost of living	0.045	0.018	1.269E-02
Medicaid expansion	left cerebral white matter volume	SES x cost of living	0.080	0.028	4.829E-03
		SES x Medicaid expansion x cost of living	-0.084	0.034	1.325E-02
	right cerebral white matter volume	SES x cost of living	0.085	0.028	2.712E-03
		SES x Medicaid expansion x cost of living	-0.079	0.034	1.942E-02
	left thalamus volume	SES x cost of living	0.078	0.029	8.588E-03
		SES x Medicaid expansion x cost of living	-0.098	0.035	5.183E-03
	right ventral diencephalon volume	SES x cost of living	0.060	0.029	4.526E-02
	left cuneus surface area	SES x Medicaid expansion	-0.088	0.035	1.246E-02
	lingual right surface area	SES x Medicaid expansion	-0.087	0.035	1.344E-02
	left pericalcarine surface area	SES x Medicaid expansion	-0.088	0.036	1.516E-02
	right precentral surface area	SES x cost of living	0.068	0.029	1.967E-02
		SES x Medicaid expansion x cost of living	-0.086	0.034	1.311E-02
	right superior frontal surface area	SES x cost of living	0.086	0.030	3.765E-03
		SES x Medicaid expansion	-0.069	0.033	4.149E-02
		SES x Medicaid expansion x cost of living	-0.085	0.035	1.715E-02

N.B. Results from equation 4 (see main text). * also significant after adjusting for global brain size. Socioeconomic status (SES). State cost of living. Standardized beta (β).

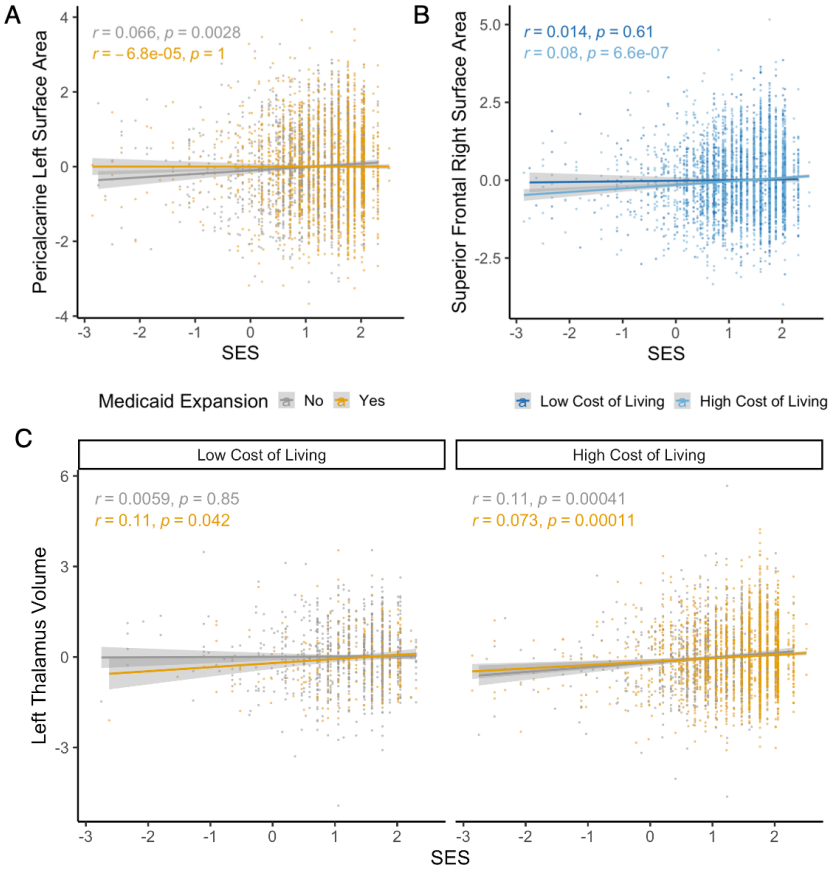

Figure 2. Largest moderation of socioeconomic status (SES) on brain phenotypes by (A) the state's choice of expanding Medicaid, (B) the state's cost of living, and (C) the state's cost of living and choice of expanding Medicaid. Each point corresponds to an individual. Phenotypes are adjusted for age, sex, age*sex, and the MRI manufacturer, and the random intercepts of the study site and family ID. In panel A, phenotypes are also adjusted for Medicaid expansion, and in panel B for the state's cost of living. Parental socioeconomic status is measured as the log of the income-to-needs ratio (SES).

3.5. Genetic and environmental associations did not correlate across volumes, surface areas, and mean thicknesses

Prior to correcting for global brain size, volumes and mean thicknesses that were more heritable did not show a significantly smaller association with SES, but there was a positive relationship between twin heritability and the SES beta for surface areas (r = .31). There was also a positive association between the SES beta and the EA PGI beta for volumes (r = 0.88) and mean thicknesses (r = 0.43) (**Supplemental Material; Table 2**).

After adjusting for global brain size, the relationship between the EA PGI beta and the SES beta was attenuated but remained significant and positive for mean thicknesses (r = 0.37) and became significant for surface areas (r = 0.36) but was no longer observed for volumes. Additionally, there was no significant relationship between heritabilities and the magnitude of the SES association after adjusting for global measures, except for a slightly positive relationship between the SES beta and SNP heritability for mean thicknesses (r = .17). (Recall that few mean thicknesses were significantly associated with SES). Overall, brain phenotypes that were more heritable or more strongly associated with the EA PGI were not less associated with SES. Instead, most correlations between genetic associations and SES associations across brain measures were null; the few that were reliably different than zero were positive and substantially driven by global brain size.

Similarly, brain phenotypes that showed stronger policy interactions showed no consistent pattern with respect to heritability or EA PGI associations (**Table 2**; **Supplementary Material**). Correlations were only apparent after correcting for global brain size: the two-way interaction between family SES and state cost-of-living was generally closer to zero for more heritable volumes (r ranging from -.51 to -0.53). The three-way interaction with Medicaid expansion was also closer to zero for more heritable volumes (r = 0.54). For mean thicknesses, the opposite pattern was detected, but only for SNP-heritability: More heritable regions showed a stronger two-way interaction between family SES and state economic context. Generally, genetic associations with a phenotype were not consistently correlated with the extent to which the state-level economic context and policies moderated the SES-brain association in the adolescent brain.

Table 2. Correlation between a phenotype's genetic associations and the beta of socio-economic status or the interaction beta of socioeconomic status with the state's economic context and/or policy of a phenotype across models with and without adjusting for global brain size.

			Volumes		***Surfaces****		***Mean Thicknesses****	
Equation	***Genetic Measure***	***Coefficient***	*Not Adj.*	*Adj.*	*Not Adj.*	*Adj.*	*Not Adj.*	*Adj.*
Equation 2	Twin h^2	SES	0.16	0.04	**0.31**	-0.04	0.20	-0.01
	SNP h^2	SES	-0.05	0.09	0.38	0.29	0.28	**0.17**
	EA PGI	SES	**0.88**	0.19	0.45	**0.36**	**0.43**	**0.37**
Equation 4 Mean Cash Assistance	Twin h^2	SES x COL	0.25	**-0.51**	0.16	-0.09	**0.38**	0.21
	SNP h^2	SES x COL	-0.29	**-0.53**	**-0.22**	-0.12	0.12	0.11
	EA PGI	SES x COL	-0.35	0.03	0.03	-0.12	0.16	0.05
Equation 4 Medicaid Expansion	Twin h^2	SES x COL	0.11	**-0.52**	0.14	-0.02	**0.20**	**0.18**
		SES x Medicaid	-0.26	0.16	**-0.27**	-0.21	0.02	-0.18
		SES x COL x Medicaid	-0.22	0.27	-0.08	0.06	-0.22	-0.19
	SNP h^2	SES x COL	**-0.46**	**-0.53**	-0.05	-0.20	0.22	0.17
		SES x Medicaid	0.30	0.28	0.02	0.05	-0.30	-0.16
		SES x COL x Medicaid	0.32	0.27	0.01	0.20	-0.33	-0.26
	EA PGI	SES x COL	-0.14	-0.44	0.13	0.03	0.11	0.10
		SES x Medicaid	0.11	0.37	0.07	0.06	0.10	0.00
		SES x COL x Medicaid	0.09	**0.54**	-0.14	-0.13	-0.13	-0.11

N.B. Equations are described in the main text. The mean cash assistance model includes mean cash assistance as the state's policy and the Medicaid expansion model includes Medicaid expansion as the state's policy. For SES x COL, a more positive correlation coefficient suggests a stronger moderating effect by the state's cost of living. For SES x Medicaid and SES x COL x Medicaid, a more negative correlation coefficient suggests a stronger moderating effect by Medicaid expansion. Bolded values, significant at $p < 0.05$. * p values from spin permutation test (**Supplemental Material**). Socioeconomic status (SES). State's cost of living (COL). Medicaid (Medicaid expansion). Heritability (h^2). Single-nucleotide polymorphism (SNP). Educational attainment polygenic index (EA PGI).

4. Discussion

In the present study, we investigated whether adolescent brain phenotypes more strongly associated with genetic differences, as estimated from twin heritability, SNP heritability, and PGI analyses, were less related to variation in family- and state-level economic contexts. Contrary to the widespread belief that more genetically associated phenotypes are less plastic in response to environmental differences (Haslam & Kvaale, 2015; Jensen, 1969; Tonsor et al., 2013), we found that phenotypes that showed a more pronounced SES gradient, or that showed greater moderation of the SES gradient by macroeconomic context and policy, had no consistent pattern with respect to their heritability estimates or PGI associations. These findings contribute to a small literature that provides empirical evidence against the use of heritability estimates or polygenic index associations as the basis for identifying promising targets for intervention (Burgoyne et al., 2020; Haworth & Davis, 2014; Raffington et al., 2022).

We found that family SES was broadly associated with cognition and psychopathology, and with brain volumes and surface areas, whereas associations with mean thicknesses were sparser. Nearly all these SES associations were still observed after controlling for the EA PGI, but only a fraction were observed after controlling for global brain size. Moreover, SES-related differences in the adolescent brain were remarkably consistent across US states; there was significant geographical variation in SES associations in only a select number of brain volumes and surface areas. These moderated regions have previously been associated with SES (Farah, 2017; Rakesh & Whittle, 2021; Rosen et al., 2019; Yaple & Yu, 2020) and are typically involved in physiological regulation and sensory processing, such as the brainstem and thalamus (Monge Argilés et al., 2000) (Sherman, 2007), as well as higher-level functions related to memory and cognition (e.g., hippocampus volume, superior frontal surface areas, cerebral white matter volume) (Anand & Dhikav, 2012; du Boisgueheneuc et al., 2006; Stephens et al., 2020).

For some of these regions, the SES-brain association was greater in high- compared to low-cost-of-living states, and in some cases, this association was attenuated in states that expanded Medicaid. In contrast to a previous ABCD study (Weissman et al., 2023) that reported similar moderation effects for internalizing scores and hippocampal volume after adjusting for global brain size, we found that, for most SES-brain associations, moderation effects were substantially attenuated and no longer significant after adjusting for global brain size. However, unlike Weissman et al. (2023), who considered sample diversity by adjusting for the study site ethnicity, our analytic sample was, unfortunately, limited to participants of European ancestries, whose genotypes were most like individuals who participated in previous large-

scale GWAS. Therefore, we decreased our study's power to detect two- and three-way interactions and excluded many minoritized individuals who are disproportionately from lower socio-economic backgrounds and who might benefit most from social welfare policies. The exclusion of individuals and groups who do not have European genetic ancestries continues to be one of the most severe limitations of social science genomics research.

In line with previous studies (Judd et al., 2020; Kweon et al., 2022), SES and the EA PGI generally had additive associations across brain phenotypes. Even after adjusting for global brain size, several aspects of adolescent neurobiology were significantly associated with SES. These regions were related to memory consolidation, recollection, and integration (hippocampal volume and the parahippocampus, entorhinal, isthmus cingulate, and superior parietal surface areas) or are highly connected with these regions (amygdala, fusiform gyrus) (Anand & Dhikav, 2012; Nielsen et al., 2005; Takehara-Nishiuchi, 2014; J. Wang et al., 2014). Our findings are consistent with previous structural and functional studies that generally report smaller regions and less activation in memory-related regions of children from lower SES (Assari et al., 2020; Noble & Giebler, 2020; Rakesh & Whittle, 2021).

The present study is not without limitations. First, and most importantly, we cannot make causal claims about the effects of investigated policies on individual differences in brain structure given that other state-level factors may be driving the moderation associations. Generally, longitudinal designs, natural experiments, and randomized control trials are necessary to make causal claims on the effects of state-level economic context and policies (Emilio Gianicolo et al., 2020). Second, given that population-specific genetic variations and allele frequencies influence identified genetic associations, our analyses are not generalizable to individuals that do not have similar genotypes to the 1KG-EUR-like individuals included in this study. Our analyses were restricted to individuals of European ancestries due to insufficiently large GWAS results in samples from other genetic ancestries (Wang et al., 2022). Third, heritability estimates of brain phenotypes appear to vary across the lifespan: for instance, whereas heritability estimates of white matter tend to be constant from birth onwards, heritability estimates of cortical surface areas, thicknesses, and volumes increase between childhood and adulthood (Jansen et al., 2015; Lenroot et al., 2009). Therefore, correlations between heritability estimates and economic context may vary across the lifespan and should be further investigated.

The present study contributes to a long-standing theoretical debate with public interest that has receive little empirical investigation. We show that the strength of genetic associations across brain regions is unrelated to their associations with macroeconomic contexts and

Commented [TM1]: This is my attempt to re-write your prior statement about "reducing disparities in brain size" - a statement that I find to be problematic. Please feel free to edit it further, but note that discussion of "disparities" in the context of neuroimaging variables attaches a value judgement to neuroanatomical variation in a way that is unwanted and unjustified. We go to great lengths to talk carefully about genetic variation in the population (i.e., using "polygenic indices" terminology instead of "polygenic scores"), and we should make the same efforts when describing neuroanatomical variation.

Global and regional morphometric indices of brain structure are, at best, a vague biological proxy of the actual thing we care about - neurodevelopment and its associated outcomes (cognition, psychopathology, etc.). These things have interesting relationships with the actual manifest outcomes that we care about, but statistical associations are modest in magnitude and we don't have a firm grasp of what they mean with respect to biology or mechanism. Accordingly, it's my position that we should at no point be talking about brain structure metrics as if they are outcomes to be intervened on in the name of addressing inequalities or disparities.

policies in adolescents in the US. As both genetic factors, home contexts, and macroeconomic policies are concurrently associated with brain, cognition, and psychopathology in adolescents, integrative designs that jointly consider factors ranging from the genome to home to the legislature will be necessary to understand brain and psychological development during this critical period of the human lifespan.

5. References

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA school-age forms & profiles: An integrated system of multi-informant assessment* (Vol. 1617). University of Vermont.

Anand, K. S., & Dhikav, V. (2012). Hippocampus in health and disease: An overview. *Annals of Indian Academy of Neurology*, *15*(4), 239–246. https://doi.org/10.4103/0972-2327.104323

Assari, S., Boyce, S., Bazargan, M., & Caldwell, C. H. (2020). Family Income Mediates the Effect of Parental Education on Adolescents' Hippocampus Activation During an N-Back Memory Task. *Brain Sciences*, *10*(8), Article 8. https://doi.org/10.3390/brainsci10080520

Bates, T. C., Neale, M. C., & Maes, H. H. (2019). umx: A library for Structural Equation and Twin Modelling in R. *Twin Research and Human Genetics*, *22*, 27–41. https://doi.org/10.1017/thg.2019.2

Bitler, M., Hoynes, H., & Kuka, E. (2017). Child Poverty, the Great Recession, and the Social Safety Net in the United States. *Journal of Policy Analysis and Management*, *36*(2), 358–389. https://doi.org/10.1002/pam.21963

Blokland, G. A. M., Zubicaray, G. I. de, McMahon, K. L., & Wright, M. J. (2012). Genetic and Environmental Influences on Neuroimaging Phenotypes: A Meta-Analytical Perspective on Twin Imaging Studies. *Twin Research and Human Genetics*, *15*(3), 351–371. https://doi.org/10.1017/thg.2012.11

Burgoyne, A. P., Carroll, S., Clark, D. A., Hambrick, D. Z., Plaisance, K. S., Klump, K. L., & Burt, S. A. (2020). Can a brief intervention alter genetic and environmental influences on psychological traits? An experimental behavioral genetics approach. *Learning and Motivation*, *72*, 101683-. https://doi.org/10.1016/j.lmot.2020.101683

Burt, S. A., Plaisance, K. S., & Hambrick, D. Z. (2019). Understanding 'What Could Be': A Call for "Experimental Behavioral Genetics". *Behavior Genetics*, *49*(2), 235–243. https://doi.org/10.1007/s10519-018-9918-y

Casey, B. J., Cannonier, T., Conley, M. I., Cohen, A. O., Barch, D. M., Heitzeg, M. M., Soules, M. E., Teslovich, T., Dellarco, D. V., Garavan, H., Orr, C. A., Wager, T. D., Banich, M. T., Speer, N. K., Sutherland, M. T., Riedel, M. C., Dick, A. S., Bjork, J. M., Thomas, K. M., … Dale, A. M. (2018). The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. *Developmental Cognitive Neuroscience*, *32*, 43–54. https://doi.org/10.1016/j.dcn.2018.03.001

Choi, S. W., Mak, T. S. H., & O'Reilly, P. F. (2020). A guide to performing Polygenic Risk Score analyses. *Nature Protocols*, *15*(9), 2759–2772. https://doi.org/10.1038/s41596-020-0353-1

de la Fuente, J., Davies, G., Grotzinger, A. D., Tucker-Drob, E. M., & Deary, I. J. (2021). A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data. *Nature Human Behaviour*, *5*(1), Article 1. https://doi.org/10.1038/s41562-020-00936-2

Dennis, E., Manza, P., & Volkow, N. D. (2022). Socioeconomic status, BMI, and brain development in children. *Translational Psychiatry*, *12*(1), Article 1. https://doi.org/10.1038/s41398-022-01779-3

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

du Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., Samson, Y., Zhang, S., & Dubois, B. (2006). Functions of the left superior frontal gyrus in humans: A lesion study. *Brain: A Journal of Neurology*, *129*(Pt 12), 3315–3328. https://doi.org/10.1093/brain/awl244

Economo, C. F. von, & Koskinas, G. N. (1925). *Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen*. J. Springer.

Emilio Gianicolo, Eichler, M., Muensterer, O., Strauch, K., & Blettner, M. (2020). Methods for Evaluating Causality in Observational Studies. *Deutsches Ärzteblatt International*, *117*(7), 101–107. https://doi.org/10.3238/arztebl.2020.0101

Farah, M. J. (2017). The Neuroscience of Socioeconomic Status: Correlates, Causes, and Consequences. *Neuron*, *96*(1), 56–71. https://doi.org/10.1016/j.neuron.2017.08.034

Fischl, B. (2012). FreeSurfer. *NeuroImage*, *62*(2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021

Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R. Z., Heeringa, S., Jernigan, T., Potter, A., Thompson, W., & Zahs, D. (2018). Recruiting the ABCD sample: Design considerations and procedures. *Developmental Cognitive Neuroscience*, *32*, 16–22. https://doi.org/10.1016/j.dcn.2018.04.004

Ge, T., Chen, C.-Y., Ni, Y., Feng, Y.-C. A., & Smoller, J. W. (2019). Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nature Communications*, *10*(1), Article 1. https://doi.org/10.1038/s41467-019-09718-5

Goldberger, A. S. (1979). Heritability. *Economica*, *46*(184), 327–347. JSTOR. https://doi.org/10.2307/2553675

Grotzinger, A. D., Mallard, T. T., Liu, Z., Seidlitz, J., Ge, T., & Smoller, J. W. (2023). Multivariate genomic architecture of cortical thickness and surface area at multiple

levels of analysis. *Nature Communications*, *14*(1), Article 1. https://doi.org/10.1038/s41467-023-36605-x

Hagler, D. J., Hatton, S. N., Cornejo, M. D., Makowski, C., Fair, D. A., Dick, A. S., Sutherland, M. T., Casey, B., Barch, D. M., Harms, M. P., Watts, R., Bjork, J. M., Garavan, H. P., Hilmer, L., Pung, C. J., Sicat, C. S., Kuperman, J., Bartsch, H., Xue, F., … Dale, A. M. (2019). Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. *NeuroImage*, *202*, 116091. https://doi.org/10.1016/j.neuroimage.2019.116091

Harden, K. P. (2021). *The Genetic Lottery*. https://press.princeton.edu/books/hardcover/9780691190808/the-genetic-lottery

Haslam, N., & Kvaale, E. P. (2015). Biogenetic Explanations of Mental Disorder: The Mixed-Blessings Model. *Current Directions in Psychological Science*, *24*(5), 399–404. https://doi.org/10.1177/0963721415588082

Haworth, C. M. A., & Davis, O. S. P. (2014). From observational to dynamic genetics. *Frontiers in Genetics*, *5*, 6. https://doi.org/10.3389/fgene.2014.00006

Isungset, M. A., Conley, D., Zachrisson, H. D., Ystrom, E., Havdahl, A., Njølstad, P. R., & Lyngstad, T. H. (2022). Social and genetic associations with educational performance in a Scandinavian welfare state. *Proceedings of the National Academy of Sciences*, *119*(25), e2201869119. https://doi.org/10.1073/pnas.2201869119

Jansen, A. G., Mous, S. E., White, T., Posthuma, D., & Polderman, T. J. C. (2015). What Twin Studies Tell Us About the Heritability of Brain Development, Morphology, and Function: A Review. *Neuropsychology Review*, *25*(1), 27–46. https://doi.org/10.1007/s11065-015-9278-9

Jensen, A. R. (1969). How much can we boost IQ and scholastic achievement? *Harvard Educational Review*, *39*(1), 1–123. https://doi.org/10.17763/haer.39.1.l3u15956627424k7

Judd, N., Sauce, B., Wiedenhoeft, J., Tromp, J., Chaarani, B., Schliep, A., van Noort, B., Penttilä, J., Grimmer, Y., Insensee, C., Becker, A., Banaschewski, T., Bokde, A. L. W., Quinlan, E. B., Desrivières, S., Flor, H., Grigis, A., Gowland, P., Heinz, A., … Klingberg, T. (2020). Cognitive and brain development is independently influenced by socioeconomic status and polygenic scores for educational attainment. *Proceedings of the National Academy of Sciences*, *117*(22), 12411–12418. https://doi.org/10.1073/pnas.2001228117

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*, *82*(13), 1–26. https://doi.org/10.18637/jss.v082.i13

Kweon, H., Aydogan, G., Dagher, A., Bzdok, D., Ruff, C. C., Nave, G., Farah, M. J., & Koellinger, P. D. (2022). Human brain anatomy reflects separable genetic and environmental components of socioeconomic status. *Science Advances*, *8*(20), eabm2923. https://doi.org/10.1126/sciadv.abm2923

Lebowitz, M. S., & Appelbaum, P. S. (2019). Biomedical Explanations of Psychopathology and Their Implications for Attitudes and Beliefs About Mental Disorders. *Annual Review of Clinical Psychology*, *15*(1), 555–577. https://doi.org/10.1146/annurev-clinpsy-050718-095416

Lenroot, R. K., Schmitt, J. E., Ordaz, S. J., Wallace, G. L., Neale, M. C., Lerch, J. P., Kendler, K. S., Evans, A. C., & Giedd, J. N. (2009). Differences in genetic and environmental influences on the human cerebral cortex associated with development

during childhood and adolescence. *Human Brain Mapping*, *30*(1), 163–174. https://doi.org/10.1002/hbm.20494

Merz, E. C., Strack, J., Hurtado, H., Vainik, U., Thomas, M., Evans, A., & Khundrakpam, B. (2022). Educational attainment polygenic scores, socioeconomic factors, and cortical structure in children and adolescents. *Human Brain Mapping*, *43*(16), 4886–4900. https://doi.org/10.1002/hbm.26034

Monge Argilés, J. A., Palacios Ortega, F., Vila Sobrino, J. A., Bautista Prados, J., Pérez Vicente, J. A., Morales Ortiz, A., & Palao Sánchez, A. (2000). Brainstem lesions decrease heart rate variability. *Neurologia (Barcelona, Spain)*, *15*(4), 158–163.

Murray, C. (2020). *Human Diversity: The Biology of Gender, Race, and Class*. Twelve.

Nielsen, F. Å., Balslev, D., & Hansen, L. K. (2005). Mining the posterior cingulate: Segregation between memory and pain components. *NeuroImage*, *27*(3), 520–532. https://doi.org/10.1016/j.neuroimage.2005.04.034

Noble, K. G., & Giebler, M. A. (2020). The neuroscience of socioeconomic inequality. *Current Opinion in Behavioral Sciences*, *36*, 23–28. https://doi.org/10.1016/j.cobeha.2020.05.007

Okbay, A., Wu, Y., Wang, N., Jayashankar, H., Bennett, M., Nehzati, S. M., Sidorenko, J., Kweon, H., Goldman, G., Gjorgjieva, T., Jiang, Y., Hicks, B., Tian, C., Hinds, D. A., Ahlskog, R., Magnusson, P. K. E., Oskarsson, S., Hayward, C., Campbell, A., … Young, A. I. (2022). Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. *Nature Genetics*, *54*(4), Article 4. https://doi.org/10.1038/s41588-022-01016-z

Polderman, T. J. C., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M., & Posthuma, D. (2015). Meta-analysis of the heritability of human

traits based on fifty years of twin studies. *Nature Genetics*, *47*(7), 702–709. https://doi.org/10.1038/ng.3285

R Core Team. (2022). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. https://www.R-project.org/

Raffington, L., Malanchini, M., Grotzinger, A. D., Madole, J. W., Engelhardt, L. E., Sabhlok, A., Youn, C., Patterson, M. W., Harden, K. P., & Tucker-Drob, E. M. (2022). An in-laboratory stressor reveals unique genetic variation in child cortisol output. *Developmental Psychology*. https://doi.org/10.1037/dev0001393

Rakesh, D., & Whittle, S. (2021). Socioeconomic status and the developing brain – A systematic review of neuroimaging findings in youth. *Neuroscience & Biobehavioral Reviews*, *130*, 379–407. https://doi.org/10.1016/j.neubiorev.2021.08.027

Rosen, M. L., Amso, D., & McLaughlin, K. A. (2019). The role of the visual association cortex in scaffolding prefrontal cortex development: A novel mechanism linking socioeconomic status and executive function. *Developmental Cognitive Neuroscience*, *39*, 100699. https://doi.org/10.1016/j.dcn.2019.100699

Sherman, S. M. (2007). The thalamus is more than just a relay. *Current Opinion in Neurobiology*, *17*(4), 417–422. https://doi.org/10.1016/j.conb.2007.07.003

Stephens, R. L., Langworthy, B. W., Short, S. J., Girault, J. B., Styner, M. A., & Gilmore, J. H. (2020). White Matter Development from Birth to 6 Years of Age: A Longitudinal Study. *Cerebral Cortex (New York, NY)*, *30*(12), 6152–6168. https://doi.org/10.1093/cercor/bhaa170

Sydnor, V. J., Larsen, B., Bassett, D. S., Alexander-Bloch, A., Fair, D. A., Liston, C., Mackey, A. P., Milham, M. P., Pines, A., Roalf, D. R., Seidlitz, J., Xu, T., Raznahan, A., & Satterthwaite, T. D. (2021). Neurodevelopment of the association cortices:

Patterns, mechanisms, and implications for psychopathology. *Neuron*, *109*(18), 2820–2846. https://doi.org/10.1016/j.neuron.2021.06.016

Takehara-Nishiuchi, K. (2014). Entorhinal cortex and consolidated memory. *Neuroscience Research*, *84*, 27–33. https://doi.org/10.1016/j.neures.2014.02.012

Taylor, R. L., Cooper, S. R., Jackson, J. J., & Barch, D. M. (2020). Assessment of Neighborhood Poverty, Cognitive Function, and Prefrontal and Hippocampal Volumes in Children. *JAMA Network Open*, *3*(11), e2023774. https://doi.org/10.1001/jamanetworkopen.2020.23774

Tesser, A., Whitaker, D., Martin, L., & Ward, D. (1998). Attitude heritability, attitude change and physiological responsivity. *Personality and Individual Differences*, *24*(1), 89–96. https://doi.org/10.1016/S0191-8869(97)00137-2

Tonsor, S., Elnaccash, T., & Scheiner, S. (2013). Developmental instability is genetically correlated with phenotypic plasticity, constraining heritability, and fitness. *Evolution; International Journal of Organic Evolution*, *67*, 2923–2935. https://doi.org/10.1111/evo.12175

Volkow, N. D., Koob, G. F., Croyle, R. T., Bianchi, D. W., Gordon, J. A., Koroshetz, W. J., Pérez-Stable, E. J., Riley, W. T., Bloch, M. H., Conway, K., Deeds, B. G., Dowling, G. J., Grant, S., Howlett, K. D., Matochik, J. A., Morgan, G. D., Murray, M. M., Noronha, A., Spong, C. Y., … Weiss, S. R. B. (2018). The conception of the ABCD study: From substance use to a broad NIH collaboration. *Developmental Cognitive Neuroscience*, *32*, 4–7. https://doi.org/10.1016/j.dcn.2017.10.002

Wang, J., Yang, Y., Fan, L., Xu, J., Li, C., Liu, Y., Fox, P. T., Eickhoff, S. B., Yu, C., & Jiang, T. (2014). Convergent functional architecture of the superior parietal lobule unraveled with multimodal neuroimaging approaches. *Human Brain Mapping*, *36*(1), 238–257. https://doi.org/10.1002/hbm.22626

Wang, Y., Tsuo, K., Kanai, M., Neale, B. M., & Martin, A. R. (2022). Challenges and Opportunities for Developing More Generalizable Polygenic Risk Scores. *Annual Review of Biomedical Data Science*, *5*(1), 293–320. https://doi.org/10.1146/annurev-biodatasci-111721-074830

Weissman, D. G., Hatzenbuehler, M. L., Cikara, M., Barch, D. M., & McLaughlin, K. A. (2023). State-level macro-economic factors moderate the association of low income with brain structure and mental health in U.S. children. *Nature Communications*, *14*(1), Article 1. https://doi.org/10.1038/s41467-023-37778-1

Yaple, Z. A., & Yu, R. (2020). Functional and Structural Brain Correlates of Socioeconomic Status. *Cerebral Cortex*, *30*(1), 181–196. https://doi.org/10.1093/cercor/bhz080

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011

Young, A. I. (2019). Solving the missing heritability problem. *PLOS Genetics*, *15*(6), e1008222. https://doi.org/10.1371/journal.pgen.1008222