Independent effects of socioeconomic status and genetics on adolescent cognition and brain development

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Abstract

Genetic factors and socioeconomic (SES) inequalities play a large role in educational attainment, and both have been associated with variations in brain structure and cognition. However, genetics and SES are correlated, and no prior study has assessed their neural effects independently. Here we used polygenic score for educational attainment (EduYears-PGS) as well as SES, in a longitudinal study of 551 adolescents, to tease apart genetic and environmental effects on brain development and cognition. Subjects received a structural MRI scan at ages 14 and 19. At both time-points, they performed three working memory (WM) tasks. SES and EduYears-PGS were correlated ($r = 0.27$) and had both common and independent effects on brain structure and cognition. Specifically, lower SES was related to less total cortical surface area and lower WM. EduYears-PGS was also related to total cortical surface area, but in addition had a regional effect on surface area in the right parietal lobe, a region related to non-verbal cognitive functions, including mathematics, problem solving and WM. SES, but not EduYears-PGS, affected the change in total cortical surface area from age 14 to 19. This is the first study demonstrating the regional effects of EduYears-PGS and the independent role of SES on cognitive function and brain development. It suggests that the SES effects are substantial, affect global aspects of cortical development, and exert a persistent influence on brain development during adolescence.

Introduction

Adolescence is a critical phase in neural and cognitive development during which much of adult trajectories are shaped, yet there is still much we don't know about the environmental and genetic influences on this developmental period [1–3]. Socioeconomic status (SES) inequalities have been associated with differences in executive function, memory, emotional regulation and educational attainment [4–6]. SES is also associated with functional and structural neural differences in a wide range of cortical areas, including those underlying higher cognitive functions [7–11].

Although SES is commonly assumed to represent a purely environmental factor, large portions of variability in SES can be explained by additive genetic factors [12]. Genetic differences are thus a confound that has not been adequately addressed by prior studies of SES and neural development [13,14].

Recent advances in behavioral genetics have identified substantial genetic associations with educational attainment. In a genome wide association study with 1.1 million individuals, Lee and colleagues [15] described a polygenetic score (EduYears-PGS) which explained up to 13% of the variance in educational attainment. A large proportion of the genetic variants identified are relevant for brain development and show tissue-specific expression in the cerebral cortex. Therefore, while SES is a strong environmental predictor for educational attainment, EduYears-PGS represents a powerful genetic predictor.

Here we evaluated the independent effects of SES and EduYears-PGS in a longitudinal study of brain development and cognitive function in 551 adolescents. A major strength of our sample is that it was specifically designed to include poor communities for an accurate range of SES inequalities [16]. Adolescent age at the first timepoint was 14, and at the second time point was 19, which represents an important developmental window which includes high school education. Indeed, an impact on cognition is one likely pathway by which both SES and genetics could influence educational attainment. We chose working memory (WM) as a measure of cognitive function, since it is highly correlated with academic ability and was available at both timepoints [17].

Genetics and environment effects could either be manifested in local cortical regions, such as a specific prefrontal area, or they could have global effects, for example via a molecular mechanism that involves most cortical neurons. The distinction is important because it tells us about the potential mechanisms in play, has functional consequences for the individual and could have implications for remedial interventions. Therefore, we tested for distinct global and regional effects, commonly ignored in the previously literature [7,8,11], with the exception of only one known study to date [18]. The latter, however, did not control for any genetic component of SES.

We used a bivariate latent change score model (bLCS) to analyze the independent effect of EduYears-PGS and SES on cognition and global measures of cortical thickness and surface area at age 14 and on the amount of change until 19, while controlling for age, gender, and scan site. Second, to examine regional effects in the cortex, we used cluster corrected vertex-wise analyses to isolate the independent effects of SES and EduYears-PGS, while controlling for respective global values.

Results

Cognitive effects in Early Adolescence

Data from 551 adolescents recruited by the IMAGEN consortium (https://imagen-europe.com/) were included. First, global measures of cortical surface area and scores from three WM tasks were entered into a bLCS model.

A strict measurement invariant, bivariate-LCS model (Fig. 1), with SES and EduYears-PGS as covariates of interest, fit the data well, RMSEA = .031, CFI = .997. We found that SES and EduYears-PGS were significantly and positively correlated ($r = .27$, $p < .001$). SES had a positive and significant association to WM, even when correcting for EduYears-PGS ($\beta = .23$, $p < .001$). EduYears-PGS also had a positive, independent, although weaker effect, on WM at 14 ($\beta = .11$, $p < .05$).

Two subtests of an IQ test (WISC, perceptual reasoning and verbal comprehension) were available when participants were 14 years old, but not at 19. The results from both subtests mirrored the results from WM with significant, independent effects of both SES and EduYears-PGS (SI Table 1 and 2).

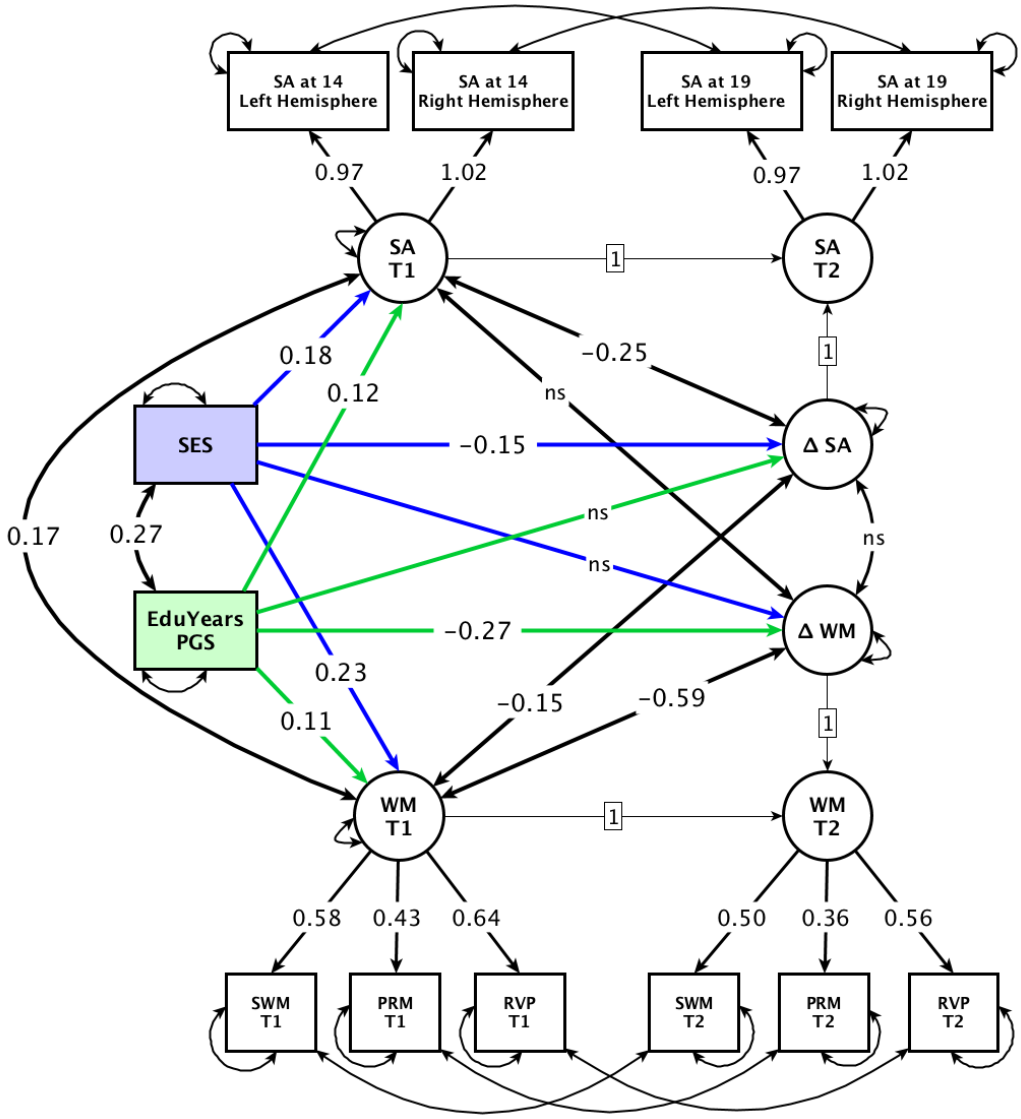

Figure 1 Path diagram of a strict measurement invariant bLCS model with the change of surface area (SA) and working memory (WM) from 14 to 19. SES and EduYears-PGS are our exogenous variables of interest, all variables are standardized.

Following convention, squares represent observed variables and circles represent latent variables. Single headed arrows denote regressions while double headed arrows represent variances, co-variances or error. See SI Fig. 2 for a specification without SES and EduYears-PGS and with SA and WM at 14 as exogenous variables on change.

Global Surface Area in Early Adolescence

Global surface area in 14-year-olds was significantly associated with both SES (β = .18, $p < .001$) and EduYears-PGS (β = .12, $p < .01$), each contributing unique variance. Both effects were positive with a slightly stronger effect of SES (Fig. 2). As expected, surface area and WM were both correlated at age 14 ($r = .17$, $p < .01$). A linear model showed a relationship between surface area and gender, yet there was no interaction between gender and SES (see SI Table 3).

An important question on SES and brain development is whether there is a threshold effect (such that only subjects below a certain SES level are affected), or whether the effects are gradual for all levels of SES. To evaluate this, we fitted models with the natural logarithmic and a 3rd degree polynomial for SES. In comparison to the linear model (AIC = -1161), neither the logarithmic (AIC = -1161) nor the polynomial model (AIC = -1157) showed improved model fits. There was thus no evidence of a threshold effect in our sample.

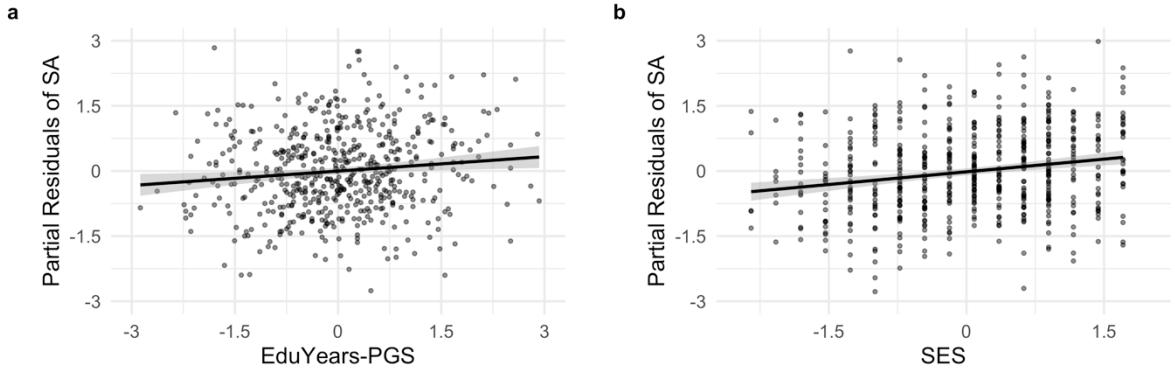

Figure 2 Partial residual plots of a) EduYears-PGS and b) SES on global surface area (SA) at age 14.

Regional cortical effects in Early Adolescence

Next, we investigated regional cortical effects of SES and EduYears-PGS on surface area at age 14. In this analysis, we corrected for average surface area, age, sex and scanning site. A vertex-wise analysis (CFT < .001, CWP < .05) identified one cluster, uniquely related to EduYears-PGS, located in the right intraparietal sulcus, partly covering the top of the supramarginal gyrus (309 mm^2, [x = 49, y = -42, z = 39], $p < .05$) (Fig. 3).

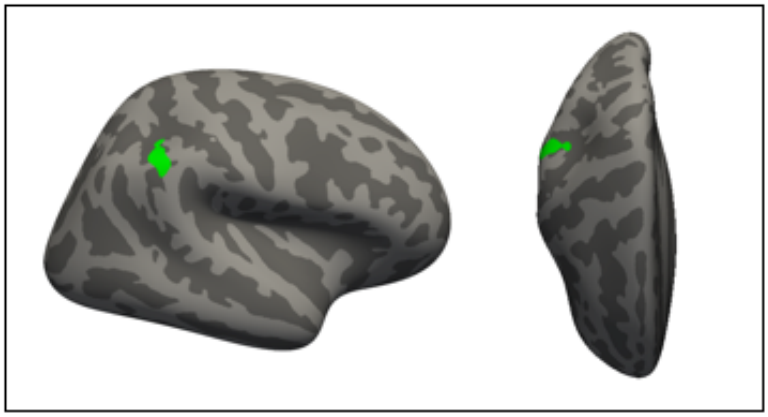

Figure 3: The right IPS in which surface area at 14 relates to EduYears-PGS while controlling for SES and global effects.

SES did not have any regional effects at age 14 when covarying for average surface area. Figure 4 illustrates this finding by showing uncorrected, vertex-wise, surface maps in which the mean image of all subjects 1 SD above the means for SES and EduYears-PGS (analyses are done separately for the two measures) are subtracted from the mean image of all subjects 1 SD below the mean (SES-low n=83, SES-high n=86, PGS-low n=79, PGS-high n=80). To obtain representative mean and standard deviations of random data, this procedure was repeated 10,000 times on randomly sampled data without replacement (groups n = 85). Consistent with the statistical analyses, these maps and histograms suggest that almost all the cortex was affected by SES. Firstly, this effect is clearly shown by the density histogram of SES, in which almost every vertex value is above zero (i.e., the mean of randomly sampled data) (Fig. 4a). To further illustrate this widespread cortical effect, we took all vertex values from one hemisphere to produce a square, 2-dimensional flat-map which contained all data from the hemisphere in one matrix (Fig. 4b). We thereby reduced topographical information (i.e., localization to brain regions) in order to only focus on size and distribution of relative increases and decreases in surface areas. This resulted in 3 flat maps (random, EduYears-PGS and SES), the color bar was constrained to the minimum and maximum values of random data.

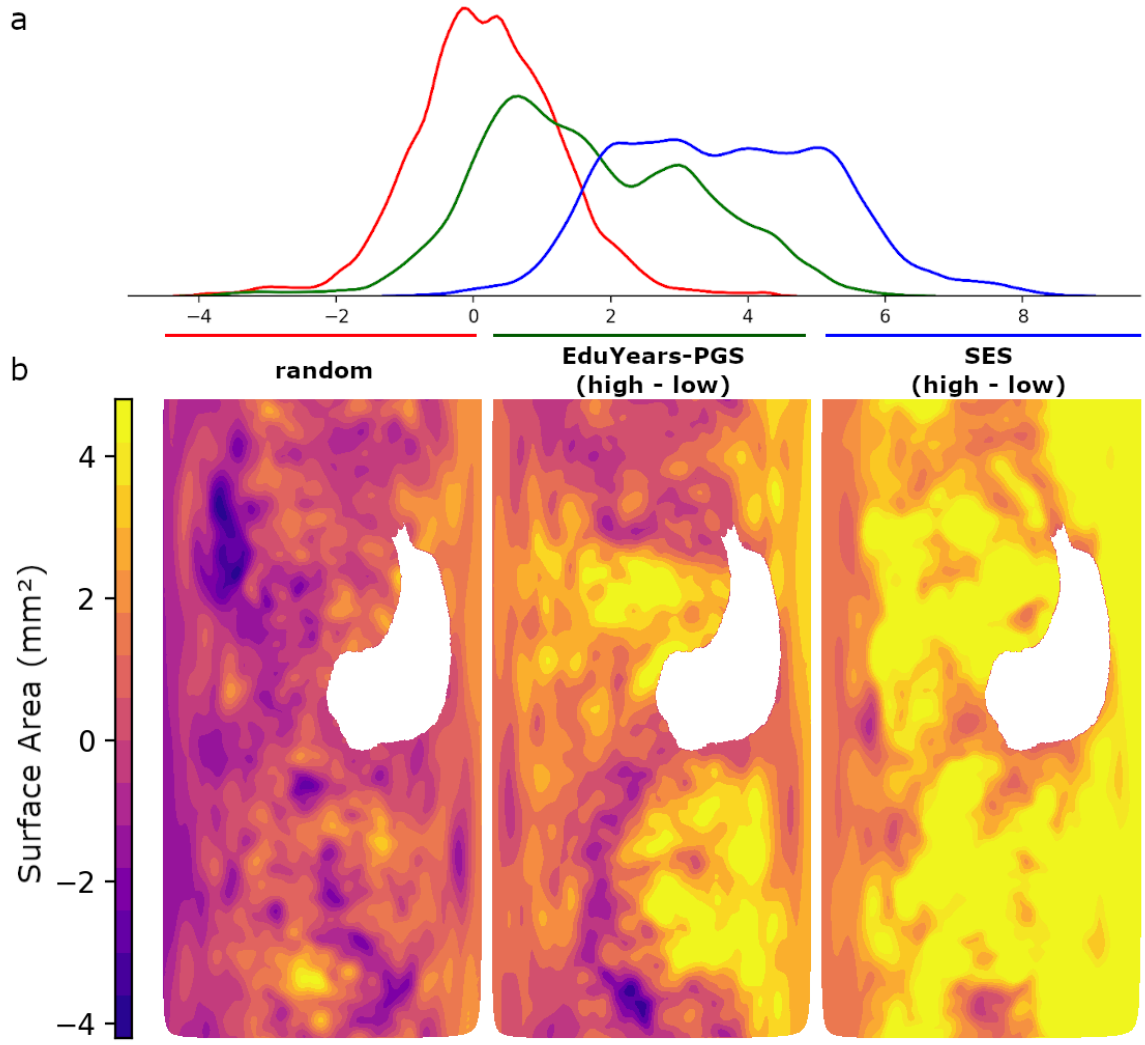

*Figure 4: Global surface area effects of the left hemisphere displayed with **(a)** density histogram and, (**b**) flat maps. White area corresponds to missing values from the cerebellum. Data for EduYears-PGS (middle figure) and SES (right most) were calculated by vertex-wise averaging of subjects 1 SD above the mean subtracted from those 1 SD below. Random data were selected by random sampling without replacement (n = 85 for each group). The two groups were then separately averaged vertex-wise and subtracted from each other. This was repeated 10,000 times to calculate an average random mean and standard deviation. To produce plots for random data the first representative sample was chosen.*

Adolescent Development in Cognition

There was significant improvement in WM from age 14 to 19 ($\beta = 2.31$, $p < .001$) and this was more pronounced in the subjects with lower WM scores at age 14 ($r = -0.59$, $p < .01$). However, inspection of the distributions and variation of performance on the WM tasks at the second timepoint suggested that there were ceiling effects, which could artificially lead to subjects who performed well at age 14 having less room for improvement. SES was not related to change in WM ($p > .05$), but EduYears-PGS was ($\beta = -.27$, $p < .05$).

Adolescent Development in Surface Area

Next, we investigated global changes in surface area over the course of five years. Correlation in global surface area between the ages of 14 (Mean = 181682mm^2, SD = 16130mm^2) and 19 (Mean = 177625mm^2, SD = 15860mm^2) was very high ($r = .99$, $p < .001$). On average, there was a significant decrease in total surface area over five years (-4057mm^2,

β = -2.57, $p < .001$; SI fig. 6a). SES, but not EduYears-PGS, was significantly related to change in surface area (β = -.15, $p < .01$).

Subtracting each individual's surface area at age 14 from their surface area at age 19 removes inter-individual differences in total surface area. However, prior studies have shown that change is dependent on point of departure, as subjects with higher initial surface area show larger change [19]. Therefore, we performed regional analyses both with and without correction for average surface area at 14. Using vertex-wise subtracted images, we found a cluster in left caudal superior frontal sulcus (138 mm^2, [x = -28, y = 10, z = 48], $p < .05$) significantly associated with SES (SI Fig. 4). This cluster was no longer significant when covarying for global surface area at 14. Furthermore, in a post hoc analysis we found no significant association of change in this region to the change of WM. No clusters were found for the effect of EduYears-PGS on change in cortical surface area.

Cortical thickness

Global cortical thickness decreased from age 14 to 19 (-.25mm, $p < .001$; SI fig. 6b). A strict measurement invariant, bivariate-LCS model for global cortical thickness (Sup Fig. 1b), with SES and EduYears-PGS as covariates of interest, fit the data well, RMSEA = .037, CFI = .988. Neither SES nor EduYears-PGS were significantly related to average cortical thickness at age 14 or to the thinning over adolescence. Furthermore, there was no significant regional effect (at 14 or from 14-19) on cortical thickness from either SES or EduYears-PGS, regardless of global correction.

Discussion

Here we have shown that both environmental (SES) and genetic (EduYears-PGS) factors, each of which influence educational attainment, play an important role in cognitive and brain development during adolescence. This is the first study to test for and confirm independent, non-overlapping effects of SES and EduYears-PGS. We found that although genetic and environmental determinants of educational attainment are correlated, they carry independent influences on cognition and brain development. Both SES and EduYears-PGS affected total cortical surface area at age 14, with SES having only a global effect, while EduYears-PGS also had a regional effect in the right intraparietal sulcus. In analyzing developmental changes, we found that SES, but not EduYears-PGS, continued to be relevant for surface area change from 14 to 19 years.

Cognition in early adolescence

Both SES and EduYears-PGS independently correlated with working memory (WM) in early adolescence, with SES having about twice as strong of an influence. The IQ-subtests displayed the same pattern, showing that the associations were not specific for WM, but likely reflect a general effect on cognition. This is consistent with the well-known correlation between educational attainment and IQ [20,21] and underscore the value of WM as a suitable and meaningful measure of adolescent cognition and cognitive development.

Morphometry in early adolescence

The strong relationship observed between SES and global surface area at age 14 is consistent with prior findings [7,11]. There are multiple potential mechanisms mediating an

effect of SES on brain development, including stress and glucocorticoids during pregnancy, toxins, premature delivery, maternal care, lack of cognitive stimulation and chronic stress during childhood and adolescence [9,22]. The global effect we observed could come from one or several factors with a global impact or be the result of several regional effects that together affect most of the cortex with wide-ranging behavioral effects [23].

After correcting for global surface area, there were no regional effects of SES. Similarly, no clusters were significant when total intracranial volume was corrected for instead of global surface area. Although several studies report regional effects of SES on surface area and cortical thickness [7,11], these studies did not correct for global effects. A post-hoc analysis of our data showed that if the global differences are not controlled for, several clusters reach significance, in agreement with prior studies (SI, Fig. 5).

Contrasting the average surface area in high vs low SES subjects (Fig. 4), it is clear that almost the entire cortex is affected. Without total surface area correction the regional effects can give a false sense of localization [24,25]. We view it as more accurate to describe the effect of SES on surface area as a global effect, where regional effects over-and-above this global effect cannot be statistically distinguished from noise.

EduYears-PGS affected global surface area, consistent with prior findings showing a relationship between EduYears-PGS and intracranial volume [26,27]. That was expected for our polygenic score for educational attainment, given that both intracranial volume and total surface area were also shown in the past to be correlated with IQ [19,28]. In addition, here we found that EduYears-PGS was associated with regional surface area in the intraparietal sulcus.

Regional effects are consistent with the fact that some of the genetic markers from the EduYears-PGS are associated with regional gene expression [15]. The intraparietal sulcus is a region typically associated with a range of non-verbal cognitive abilities, including nonverbal reasoning, visuospatial WM and mathematics [29–31]. Gray matter volume [32,33] and brain activity [34–36] of the intraparietal sulcus predicts current and future mathematical skills in children and adolescents.

A study spanning 6-18 year-old's found that the right anterior intraparietal sulcus was first associated with visuo-spatial WM, and later during development associated with mathematics, suggesting a functional plasticity of this region [37]. Given that both non-verbal reasoning, WM and mathematics are predictors of future educational attainment, it is of particular note that our data show the intraparietal sulcus to be specifically affected by EduYears-PGS above and beyond the polygeneic influences on global cortical surface area.

We found no association between EduYears-PGS or SES with cortical thickness, in agreement with some previous studies on SES [7], but not others [8,11]. It is important to emphasize that our quality control procedure were very strict and previous literature has shown cortical thickness results to change based upon strictness [38–40]. This reasoning, combined with our large sample size and the presence of effects found for surface area, lead us to interpret this as an important null result.

Adolescent Development

Over the course of 5 years, we found a global decrease in surface area. The amount of decrease was related to SES, but not EduYears-PGS, showing a continuing effect of SES on brain development during adolescence. Although the effect of SES at age 14 was positive, the effect on change was negative (Fig. 1). This is likely related to the non-linear developmental trajectories of surface area during childhood and adolescence with an inverted u-form (typically a loss of surface area starting in adolescence) where height and delay of the peak can differ between individuals as well as between brain region [1,2,23].

There was an association between SES and regional change in the left caudal middle frontal gyrus, but this did not survive correction for global surface area at age 14. The interpretation of this regional finding is therefore unclear.

One of the benefits of using a bLCS model is that it allows us to examine the influence of baseline measures (e.g., surface area and WM at 14) on the change of those measures. Interestingly, higher WM independent of surface area at 14, and after correction for SES and EduYears-PGS, affected the amount of global surface area decrease during adolescence. Recent research has shown intra-individual change in cognition affecting later change in surface area [41]. An accelerated reduction of surface area during development has previously been observed in higher IQ subjects [19]. In summary, SA typically decreases during adolescence. Higher WM enhances this decrease, suggesting that it is a beneficial developmental process blunted by low SES.

WM at age 14 also negatively predicted the amount of WM change over adolescence. However, due to some ceiling in our WM tasks at the second time-point (an inherent problem in longitudinal studies), we interpret this result with caution. If this result reflects a true effect, it could represent a catch-up – subjects with lower WM show greater gains in WM during adolescence. However, a previous study of PGS and SES on IQ showed a widening gap between subjects with low and high EduYears-PGS [42]. At least in part, our results here could alternatively be explained by ceiling effects, which could artificially lead to high performing subjects having less room to improve.

Limitations

A major caveat of current PGS studies is that they are often limited to subjects with European ancestry, which limits generalizability. The neural measures of this study were cortical surface area and cortical thickness. Of these, only surface area correlated with genetics, environmental factors and cognitive measures, which suggests that this is the more important measure for the present investigation. However, these surface area methods are limited to cortical structures thereby excluding subcortical regions such as the hippocampus. Finally, our aim was to use environmental and genetic predictors of educational attainment. If the sole goal were to isolate a “pure” measure of SES as an environmental factor, then this would have been better accomplished by using a PGS for SES.

Conclusions

Here we report, for the first time, distinct effects of EduYears-PGS and SES on cognition, brain structure, and brain development. These findings imply that behavioral and psychological consequences of SES are likely wide ranging, and less targeted towards a specific cognitive function or behavioral deficit. Importantly, SES has a significant effect on cognition, even after removing genetic variance. Future analyses should aim to disentangle the many aspects of SES. A continued greater insight into the genetics of cognitive development will help inform policy decision to tackle environmental influences.

Methods

Study description

IMAGEN is a European multi-site longitudinal genetic and neuroimaging study. All procedures were approved by each of the sites' (Berlin, Dresden, Dublin, Hamburg, London, Mannheim, Nottingham, Paris) ethics committees. Written informed consent was obtained from the adolescents and parents involved in the study. Our study uses data from the first two neuroimaging waves, at ages fourteen (14.44, SD = 0.38) and nineteen (19.01, SD = 0.72). See Schumann and colleagues[16] for more information on IMAGEN protocols and inclusion/exclusion criteria.

For subjects to be included in our study, they had to be of European ancestry (due to limitations of the imputations and possible inferences for creating the EduYears-PGS) and have no siblings included in the study. Importantly, subjects also had to have all of the relevant data available; structural MRI's at both timepoints, genetics, relevant demographics (e.g., gender and age) and three behavioral WM tasks at the first timepoint. Lastly, genetic and neuroimaging data had to pass their respective quality controls (criterion discussed in depth below). This resulted in a final sample of 551 subjects (321 females).

Behavioral measures

We estimated working memory (WM) based on three cognitive tasks from the CANTAB battery available in IMAGEN. We combined these into a latent factor that explained around 40% of the common variance. The tasks were: 1) Spatial WM task (SWM), in which participants must search for a token hidden in one of many boxes. The token does not repeat location, and the measure consisted of the number of times participants returned to search a box that had a token. 2) Pattern Recognition Memory task (PRM), in which participants must remember 12 abstract patterns shown in a sequence. The measure consisted of correct choices on a two alternative forced choice task immediately after encoding. 3) Rapid Visual Information Processing task (RVP), in which participants must monitor for a 3-digit target sequence from a stream of 100 digits per minute. The measure used was correct responses.

Socioeconomic status

The socioeconomic status (SES) score was comprised of the sum of the following variables: Mother's Education Score, Father's Education Score, Family Stress Unemployment Score, Financial Difficulties Score, Home Inadequacy Score, Neighborhood Score, Financial Crisis Score, Mother Employed Score, Father Employed Score.

EduYears Polygenic Score

All participants in IMAGEN had DNA extracted from blood samples and were genotyped with the Illumina Human610-Quad Beadchip or the Illumina Human660-Quad Beadchip. A PCA approach was used to identify and exclude individuals with non-European ancestry. The quality control procedures excluded SNPs with call rates >95%, minor allele frequencies less than 5%, and SNPs that did not pass an exact test of Hardy-Weinberg equilibrium at $P < 5x10^{-4}$. After quality control, around 480,000 SNPs were then used for imputations via a reference file created by the ENIGMA2 Genetics Support Team. Haplotype phasing and imputation was performed using, respectively, Mach1 and Minimac codes from the MaCH

software suit [43], as specified in the ENIGMA2 protocol (http://enigma.ini.usc.edu/wpcontent/uploads/2012/07/ENIGMA2_1KGP_cookbook_v3.pdf).

We then used this genotype data to estimate EduYears-PGS in each participant based on the effect sizes of thousands of SNPs discovered by the most recent GWAS on educational attainment [15]. We first obtained the summary statistics of the GWAS from the Social Science Genetic Association Consortium (https://www.thessgac.org/data). We decided which significance threshold to use in our sample by performing high resolution scoring in PRSice-2 [44] based on the phenotype of WM (from the latent factor of our three cognitive tasks). The threshold that optimally explains the variance in WM resulted in an EduYears PGS containing 5709 SNPs. To guard against overfitting, we performed 1 million permutations and obtained a significant empirical p-value of our estimate (empirical p = 0.009). EduYears-PGS in our sample was standardized to have a mean of zero and a standard deviation of one for the population. All steps for creating the EduYears-PGS were performed using the R package PRSice-2 [44] and PLINK version 1.90 [45].

Structural Imaging

Image Acquisition and Preprocessing

Structural imaging data were acquired using numerous 3T MRI scanners (Philips Medical Systems Achieva, Bruker, Siemens TrioTim, Siemens Verio, Bruker/GE Medical Systems Signa Excite, GE Medical Systems Signa HDx) with a T1-weighted gradient echo sequence (isotropic 1.1mm) based on the ADNI protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/) [46]. Freesurfer (v6.0.0; http://surfer.nmr.mgh. harvard.edu/) was used for image preprocessing and SA/CT estimation, previously reported in depth [47]. Specifically, the longitudinal pipeline was used as it is optimized for longitudinal data by registering the differing timepoints to a median image thereby reducing within-subject variability and avoiding registration bias [48]. All processing was run using the high-performance computing (Bianca cluster) resources provided by SNIC through Uppsala's Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project sens2018615 using gnuparallel [49]. Since IMAGEN is a multi-center study we used ComBat at the vertex-wise level to remove unwanted site-based variability [50]. Variables of interest (baseline age, EduYears-PGS, SES, scan interval, gender) also showed site specific variability, therefore we entered these in ComBat to retain these true site-specific differences. Mean CT and SA were calculated by averaging all of the vertices. For vertex-wise analysis we smoothed the data with a gaussian smoothing kernel of 10mm FWHM.

Quality Control

The IMAGEN team provided anatomical quality control for the second time-point and partially for the first time-point. Following longitudinal preprocessing, two raters graded the Desikan–Killiany parcellated atlas and the white matter/pial boundary overlaid on the T1 (norm.mgz) in a coronal view separately for both the final longitudinal timepoints and the base (median) image on a 3-point scale (pass, doubtful, fail). Any scan that was marked 'doubtful' was reviewed by the other rater, and a consensus decision to include (pass) or exclude (fail) was made. A large number of scans were determined to have skull strip errors (via the pial boundary). As previous research on cortical thickness has shown that quality control can impact the conclusions drawn [38], we reran recon-all on a subset of subjects

showing skull strip errors with 'gcut'. If the error persisted in either timepoint the subject was excluded. From 1963 subjects, 1168 had structural scans at both timepoints, from these 748 passed quality control (pass rate 64%). In a similar fashion to previous research with large sample sizes quality control was not entirely overlapping between the two raters [51]. In the overlap sample of 101 subjects we found a high inter-rater agreement (kappa = 0.88).

Statistical analysis

Global measures

We choose to use a bivariate latent change score (bLCS) model as it allowed us to examine the development of neural and behavioral measures simultaneously without the constraints of measurement error [52,53]. A latent change score model can be conceptualized as a reparameterization of a paired t-test and has recently been highlighted for its usefulness in teasing apart the complex processes involved in longitudinal developmental research [54,55]. bLCS models were estimated for average cortical thickness and average surface area. For model estimation we used full information maximum likelihood and a robust maximum likelihood estimator with a Yuan-Bentler scaled test statistic from the R (v. 3.6.0) package Lavaan (v. 0.6-3) [56,57]. Missing follow-up behavioral data was imputed under the assumption of missing at random (see SI Fig. 3) [58]. We assessed model fit using the comparative fit index (CFI; fit > 0.95) and the root mean square error of approximation (RMSEA; fit < .08)[59]. The subjects' age and gender were regressed from all observed behavioral and neural measures in both timepoints before model fitting. All models have strict measurement invariance; intercepts, loadings and error variance were constrained to be equal across time. Prior to fitting a bLCS model we assessed fit on respective measurement models. If estimates present Heywood cases (negative error variances) we left them unconstrained as long as the null hypothesis could not be rejected with the use of confidence intervals [60]. Any model presented will have a positive upper bound confidence interval; we chose this approach since constraining variance can lead to unintended consequences [60,61].

Vertex-wise exploratory analysis

An inherent goal in vertex-wise exploratory analysis is anatomical localization therefore we corrected for average values of surface area and cortical thickness. Correcting for global values in the analysis at age 14 allowed us to detect regional areas that are unrelated to the overall global effects (see discussion for further elaboration). Linear models were fit for each vertex in Freesurfer using Monte Carlo based cluster-wise correction with a cluster-forming threshold of .001, a cluster-wise alpha of .05 and Bonferroni correction for making two independent tests for the two hemispheres [62,63].

We used two linear models to probe regional specificity of SES and EduYears-PGS, one for subjects at 14 and another on the vertex-wise subtracted images (age 19 subtracted from age 14). Both models were fit for SA and CT separately, resulting in a total of 4 analyses. In the model at age 14 vertices were predicted by the EduYears-PGS and SES while being controlled for mean value of the modality analyzed, gender, age at the first scan and gcut. Gcut is a dummy variable coding for subjects who needed stricter skull strip processing to pass quality control. Subtracted vertices were predicted by SES and EduYears-PGS while being controlled for gender, between scan interval and gcut.

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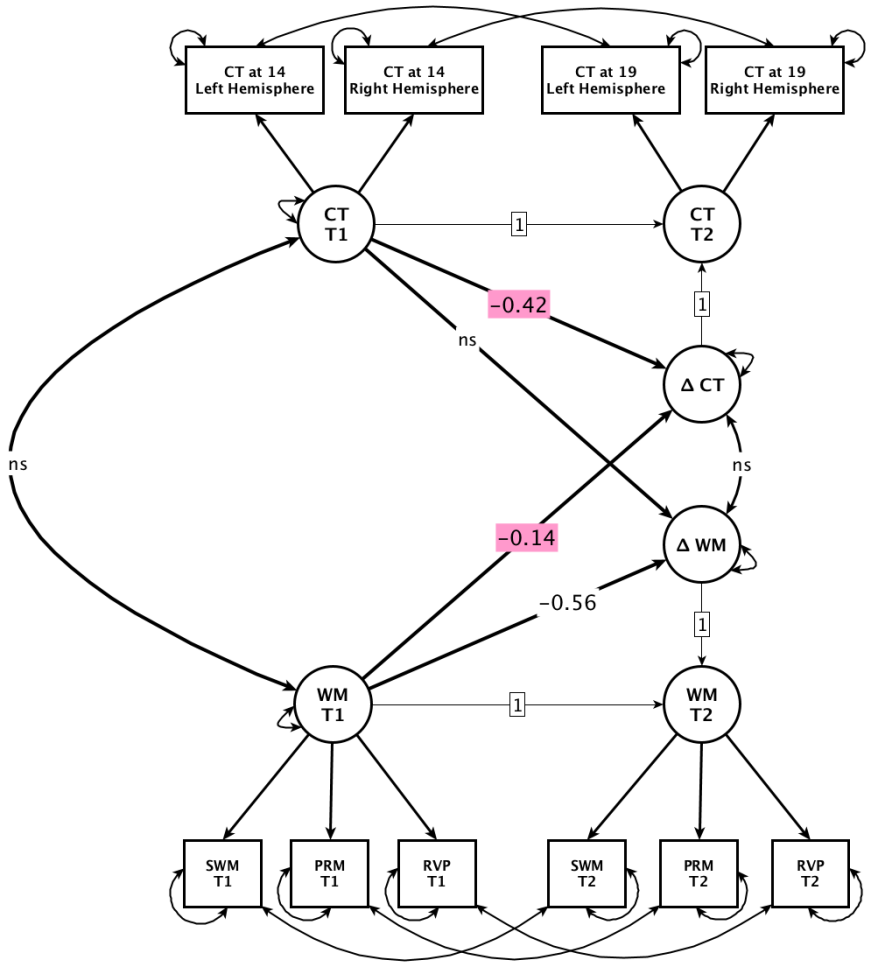
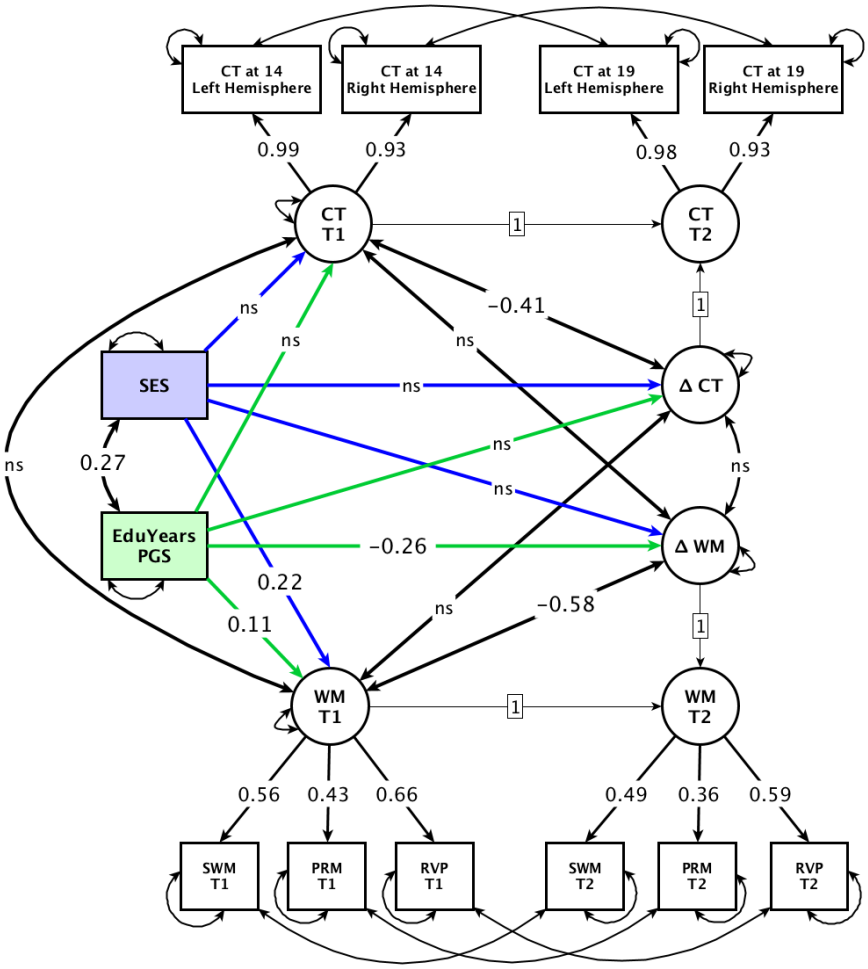
Supplementary:

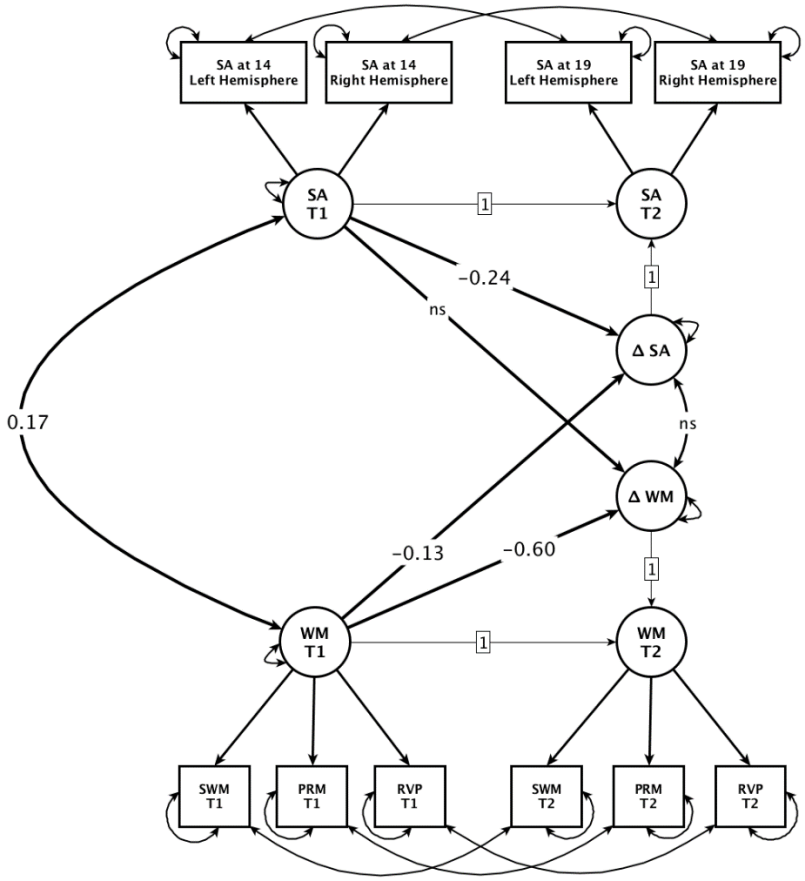
Supplementary Figures:



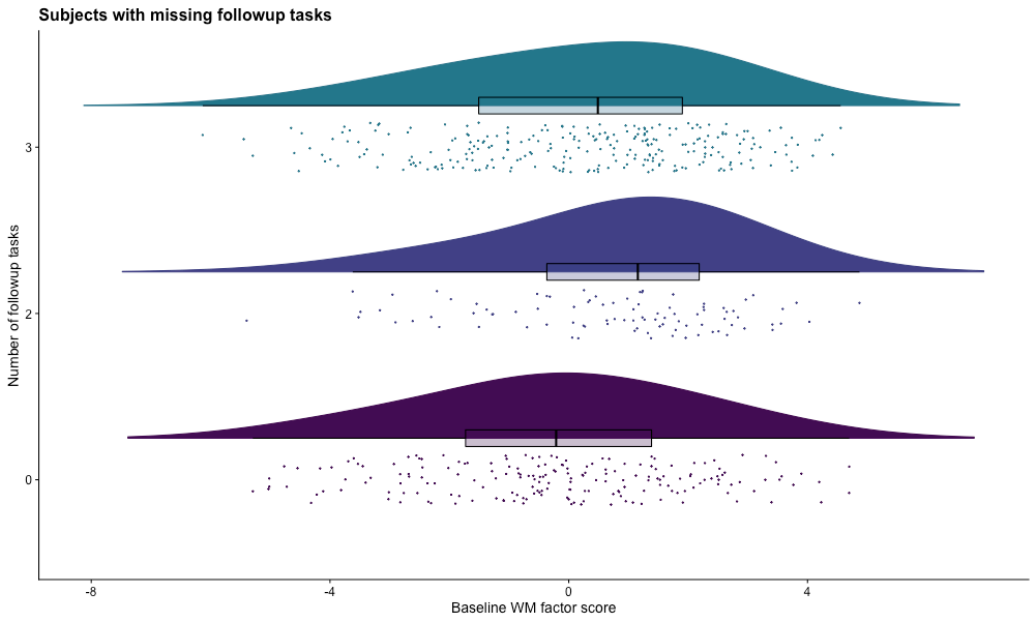
Supplementary Figure 1a: A bLCS model with strict measurement invariance (CFI = .88, RMSEA = .04) showing the relationship of WM at 14 with the amount of cortical thickness change when covarying for cortical thickness at 14.



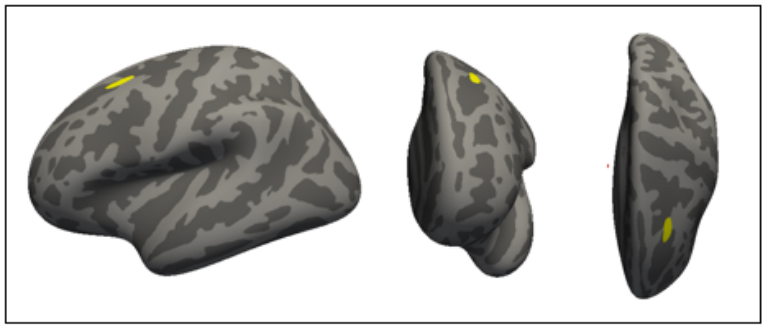
Supplementary Figure 1b: A bLCS model with strict measurement invariance for cortical thickness.



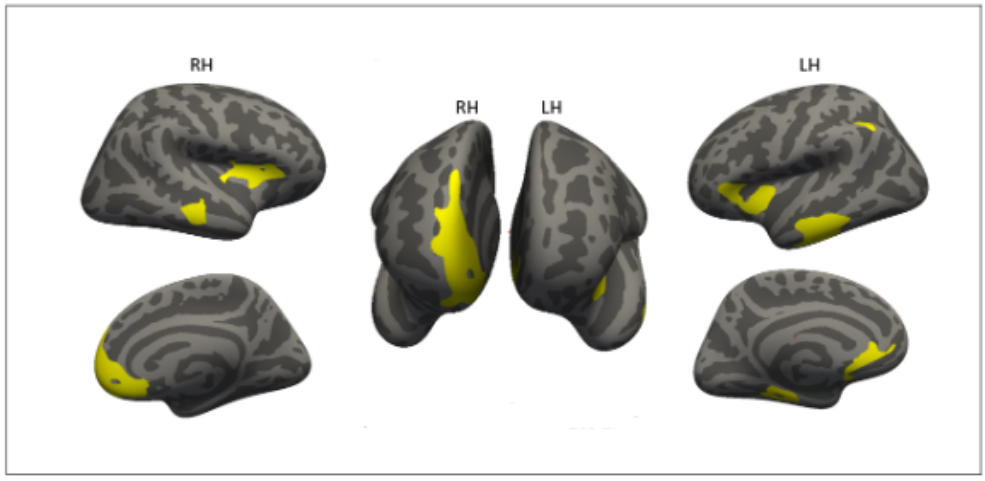
Supplementary Figure 2: A bLCS model with strict measurement invariance (CFI = .997, RMSEA = .048) showing cross & self-feedbacks as regressions, the results do not change much from a covariance model (in text Fig. 1).



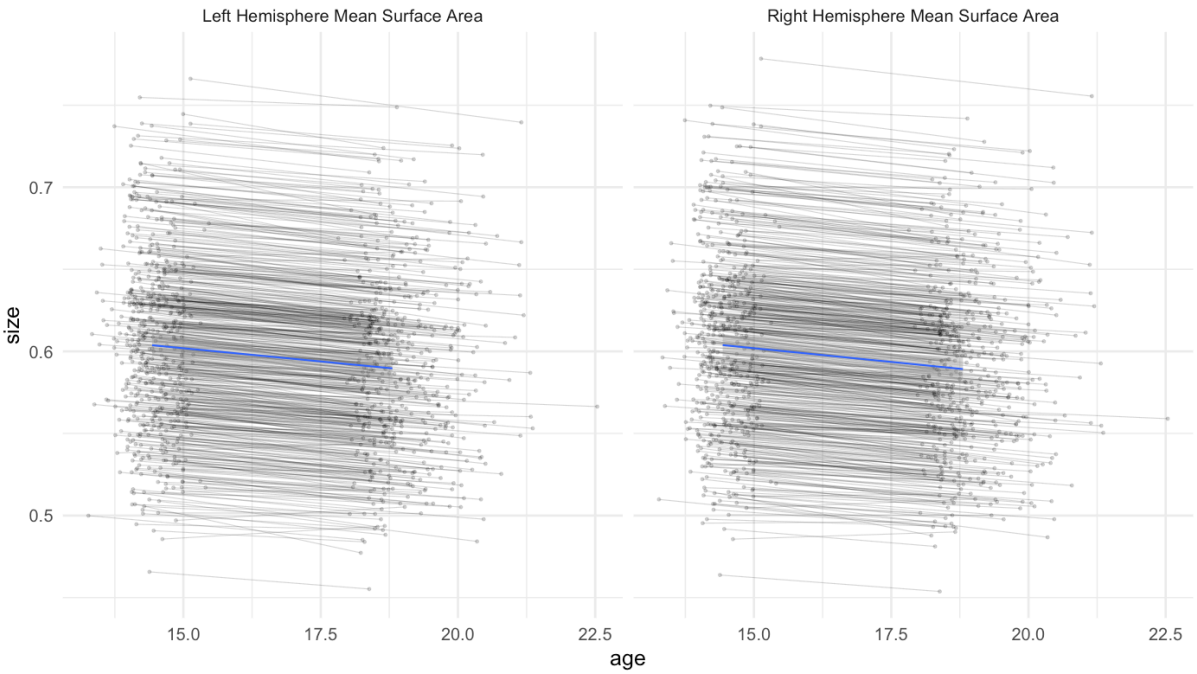
Supplementary Figure 3: Rain cloud showing the assumption of missing at random, for the imputed follow-up working memory tasks.



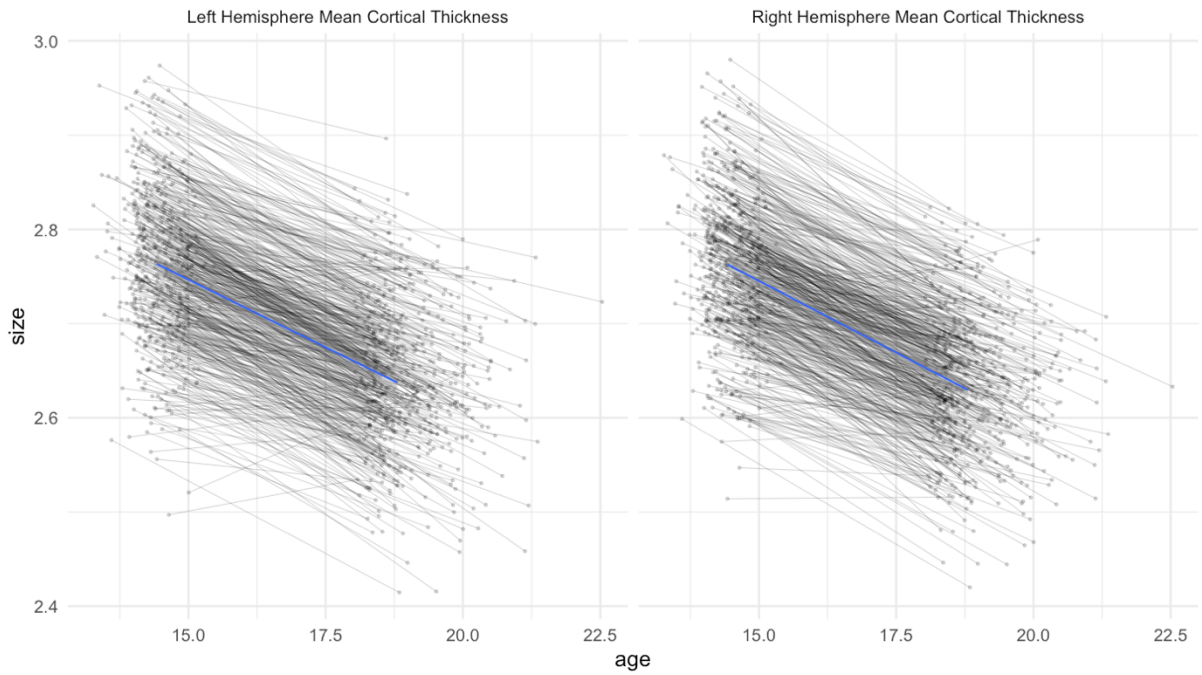
Supplementary Figure 4 The left caudal middle frontal in which change of surface area is related to SES. This cluster did not survive if we covaried for average surface area at 14.



Supplementary Figure 5: Surface area clusters at age 14 related to SES while controlling for EduYears-PGS. Interpretation should be limited as they are not covaried for total intercranial volume or average surface area.



Supplementary Figure 6a: Mean surface area change per hemisphere



Supplementary Figure 6b: Mean cortical thickness change per hemisphere

Supplementary Tables:

Table 1

Regression results using WISC subtest perceptual reasoning as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
(Intercept)	73.89**	[28.36, 119.42]			
all_SES	1.05**	[0.71, 1.38]	.07	[.03, .11]	
PGS	0.47**	[0.16, 0.77]	.02	[-.00, .04]	
BL_MPRAGE_AGE	0.00	[-0.01, 0.01]	.00	[-.00, .00]	
all_sexMale	-2.22	[-4.66, 0.21]	.01	[-.01, .02]	
					R^2 = .118**

Note. A significant *b*-weight indicates the semi-partial correlation is also significant. *b* represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. * indicates p < .05. ** indicates p < .01.

Table 2

Regression results using WISC subtest verbal comprehension as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
(Intercept)	94.67**	[52.12, 137.23]			
all_SES	1.22**	[0.90, 1.53]	.10	[.05, .15]	
PGS	0.30*	[0.01, 0.59]	.01	[-.01, .02]	
BL_MPRAGE_AGE	-0.00	[-0.01, 0.00]	.00	[-.00, .01]	
all_sexMale	2.86*	[0.58, 5.13]	.01	[-.01, .03]	
					R^2 = .141**

Note. A significant *b*-weight indicates the semi-partial correlation is also significant. *b* represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. * indicates p < .05. ** indicates p < .01.

Table 3

Regression results using total_SA_MRI1 as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
(Intercept)	1.17**	[0.90, 1.43]			
all_SES	0.01**	[0.00, 0.01]	.03	[.01, .06]	
all_sexMale	0.13**	[0.12, 0.15]	.36	[.30, .43]	
BL_MPRAGE_AGE	-0.00	[-0.00, 0.00]	.00	[-.00, .00]	
					R^2 = .390**

Note. A significant *b*-weight indicates the semi-partial correlation is also significant. *b* represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. * indicates p < .05. ** indicates p < .01.