Cognitive and brain development is independently influenced by socioeconomic status and polygenic scores for educational attainment

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Genetic factors and socioeconomic status (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 associations independently. Here we used a polygenic score for educational attainment (EduYears-PGS), as well as SES, in a longitudinal study of 551 adolescents to tease apart genetic and environmental associations with 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 associations with 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 association with surface area in the right parietal lobe, a region related to nonverbal cognitive functions, including mathematics, spatial cognition, and WM. SES, but not EduYears-PGS, was related to a change in total cortical surface area from age 14 to 19. This study demonstrates a regional association of EduYears-PGS and the independent prediction of SES with cognitive function and brain development. It suggests that the SES inequalities, in particular parental education, are related to global aspects of cortical development, and exert a persistent influence on brain development during adolescence.

structural MRI | development | working memory | polygenic scores | socioeconomic status

Significance

The influence of socioeconomic status (SES) inequalities on brain and cognitive development is a hotly debated topic. However, previous studies have not considered that genetic factors overlap with SES. Here we show that SES and EduYears-PGS (a score from thousands of genetic markers for educational attainment) have independent associations with both cognition and global cortical surface area in adolescents. EduYears-PGS also had a localized association in the brain: the intraparietal sulcus, a region related to nonverbal intelligence. In contrast, SES had global, but not regional, associations, and these persisted throughout adolescence. This suggests that the influence of SES inequalities is widespread—a result that opposes the current paradigm and can help inform policies in education.

Adolescence is a critical phase in neural and cognitive development during which much of adult trajectories are shaped,

yet there is still much we do not know about the environmental and genetic influences during this period (1–3).

Socioeconomic status (SES) inequalities have been associated with differences in executive function, memory, emotional regulation, and educational attainment (1–3). SES is also associated with functional and structural neural differences in a wide range of cortical areas, including those underlying higher cognitive functions (4–8). Although SES is commonly assumed to represent a purely environmental factor, large portions of variability in SES can be explained by additive genetic factors (9). SES explains 9 to 25% of educational achievement, half of which is suggested to be genetically mediated (10, 11). Genetic differences are thus a confound not adequately addressed by prior studies of SES and neural development (12).

Recent advances in behavioral genetics have identified substantial genetic associations with educational attainment. In a genome-wide association study (GWAS) with 1.1 million individuals, Lee and colleagues (13) described a polygenic score (PGS) which explained up to 13% of the variance in educational attainment. That represents the best composite of genetic variants currently known for educational attainment (henceforth EduYears-PGS), and many of these variants 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 is a powerful genetic predictor, and at least some of the impact from these two predictors is likely to overlap and to be via cognition.

Here we evaluated the independent associations 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 (14). Adolescent age was around 14 at the first time point and 19 at the second time point, a time span that captures secondary education. We chose working memory (WM) as a measure of cognitive function since it is highly correlated with academic ability and was available at both time points (15).

Genetics and environmental 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 associations—a practice still ignored in the literature (4, 5, 8), with the exception of only one known study to date (16). The latter, however, did not control for any genetic component of SES.

We defined SES as a combination of income, education, and neighborhood quality. A single, combined SES component allowed for better comparison with EduYears-PGS (itself a single, genetic composite) and was hypothesized to increase power to detect associations in the case of additive influences from each SES-related factor. A combined measure also makes our results more interpretable in light of the broader SES literature (most of it also uses composite scores). Yet, recent research has highlighted issues and limitations arising from using SES as a composite measure (17). Therefore, in a post hoc analysis, we split our SES composite into parental education, income-related stresses, and neighborhood quality to evaluate how these components contributed to our main findings from the analysis of the combined SES measure.

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

Results

Cognitive Associations 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 bLCS model (Fig. 1), with SES and EduYears-PGS as covariates of interest, fit the data well: root-mean-square error of approximation (RMSEA) = 0.031, comparative fit index (CFI) = 0.997. We found that SES and EduYears-PGS were significantly and positively correlated ($r = 0.27$, $P < 0.001$). SES had a positive and significant association with WM, even when correcting for EduYears-PGS ($\beta = 0.23$, $P < 0.001$). Splitting SES into subcomponents revealed that only parental education was significantly associated with WM. EduYears-PGS also had a positive, independent, although weaker relationship with WM at age 14 ($\beta = 0.11$, $P < 0.05$).

Two subtests of an IQ test (Wechsler Intelligence Scale for Children [WISC], perceptual reasoning, and verbal comprehension) were available when participants were 14 y old, but not at 19. The results from both subtests mirrored the results from WM with significant, independent relationships for both SES and EduYears-PGS (*SI Appendix*, Tables S1 and S2).

Global Surface Area in Early Adolescence. Global surface area in 14 y olds was significantly associated with both SES ($\beta = 0.18$, $P < 0.001$) and EduYears-PGS ($\beta = 0.12$, $P < 0.01$), each contributing unique variance. Both associations were positive with a
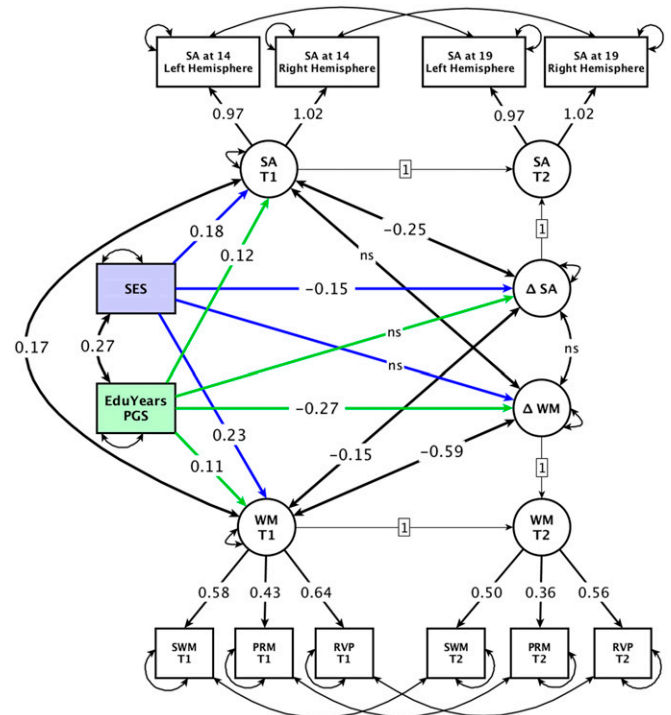
Fig. 1. Path diagram of a strict measurement invariant bLCS model with the change of surface area and working memory from 14 to 19. SES and EduYears-PGS are our exogenous variables of interest; all variables are standardized. Following convention, squares represent observed variables and circles represent latent variables. Single-headed arrows denote regressions while double-headed arrows represent variances, covariances, or errors. See *SI Appendix*, Fig. S2 for a specification without SES and EduYears-PGS and with SA and WM at 14 as exogenous variables on change.
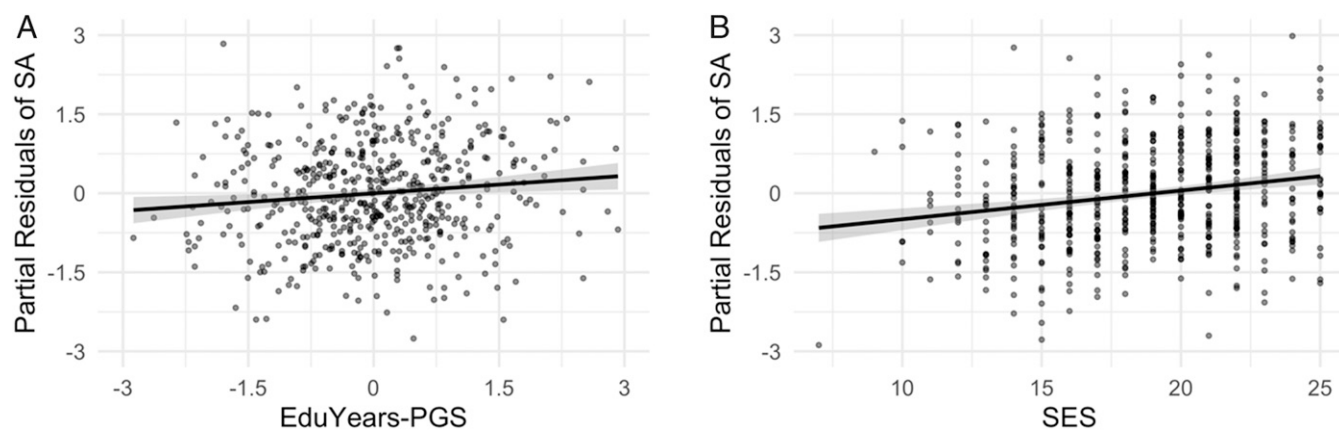
Fig. 2. Partial residual plots of (*A*) EduYears-PGS and (*B*) SES on global SA at age 14.

stronger association for SES (Fig. 2). As expected, surface area and WM were both correlated at age 14 ($r = 0.17$, $P < 0.01$). A linear model showed a relationship between surface area and gender, yet there was no interaction between gender and SES (*SI Appendix*, Table S3).

An important question on SES and brain development is whether results only hold for certain SES levels or whether it is linear for all ranges of SES. To evaluate this, we fitted models with the natural logarithmic and a third-degree polynomial for SES. In comparison with the linear model (Akaike information criterion [AIC] = −1,161), neither the logarithmic (AIC = −1,161) nor the polynomial model (AIC = −1,157) showed improved model fits. There was thus no evidence of nonlinearity in our sample.

Regional Cortical Associations in Early Adolescence. Next, we investigated regional cortical associations of SES and EduYears-PGS with surface area at age 14. In this analysis, we corrected for total surface area, age, gender, and scanning site. A vertex-wise analysis (cluster-forming threshold [CFT], < 0.001, cluster-wise p-value [CWP] < 0.05) identified one cluster, uniquely related to EduYears-PGS, located in the right intraparietal sulcus, partly covering the top of the supramarginal gyrus (309 mm², [$x = 49$, $y = −42$, $z = 39$], $P < 0.05$) (Fig. 3).

SES did not have any regional associations at age 14 when covarying for total surface area. Fig. 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) is 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 a representative mean and SDs 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 of the cortex was related to SES inequalities. First, this finding is clearly shown by the density histogram of SES, in which almost every vertex value is above 0 (i.e., the mean of randomly sampled data) (Fig. 4*A*). To further illustrate this widespread cortical association, we took all vertex values from one hemisphere to produce a square, two-dimensional flat map which contained all data from the hemisphere in one matrix (Fig. 4*B*). 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 three flat maps (random, EduYears-PGS, and SES); the color bar was constrained to the minimum and maximum values of random data.

Adolescent Development in Cognition. There was significant improvement in WM from age 14 to 19 ($\beta = 2.31$, $P < 0.001$) and this was more pronounced in the subjects with lower WM scores at age 14 ($r = −0.59$, $P < 0.01$). However, inspection of the distributions and variation of performance on the WM tasks at the second time point 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 ($P > 0.05$), but EduYears-PGS was ($\beta = −0.27$, $P < 0.05$).

Adolescent Development in Surface Area. Next, we investigated global changes in surface area over the course of 5 y. Correlation in global surface area between the ages of 14 (mean = 181,682 mm², SD = 16,130 mm²) and 19 (mean = 177,625 mm², SD = 15,860 mm²) was very high ($r = 0.99$, $P < 0.001$). On average, there was a significant decrease in total surface area over 5 y (−4,057 mm², $P < 0.001$, paired *t* test; *SI Appendix*, Fig. S6*A*). SES, but not EduYears-PGS, was significantly related to change in surface area ($\beta = −0.15$, $P < 0.01$).

Subtracting each individual's surface area at age 14 from their surface area at age 19 removes interindividual 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 (18). Therefore, we performed regional analyses both with and without correction for total surface area at 14. Using vertex-wise subtracted images, we found a cluster in the left caudal superior frontal sulcus (138 mm², [$x = −28$, $y = 10$, $z = 48$], $P < 0.05$) significantly associated with SES (*SI Appendix*, Fig. S4). This cluster was no longer significant
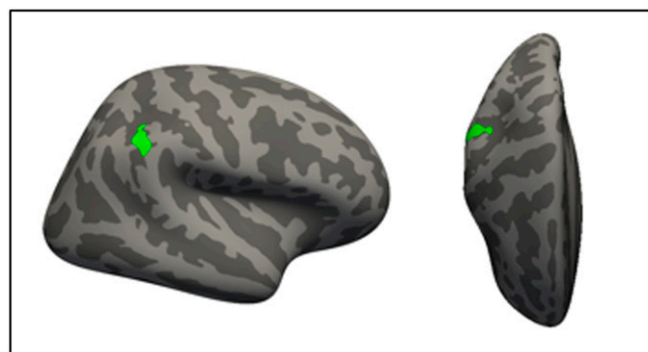

Fig. 3. Right intraparietal sulcus in which surface area at 14 relates to EduYears-PGS while controlling for SES and global effects.
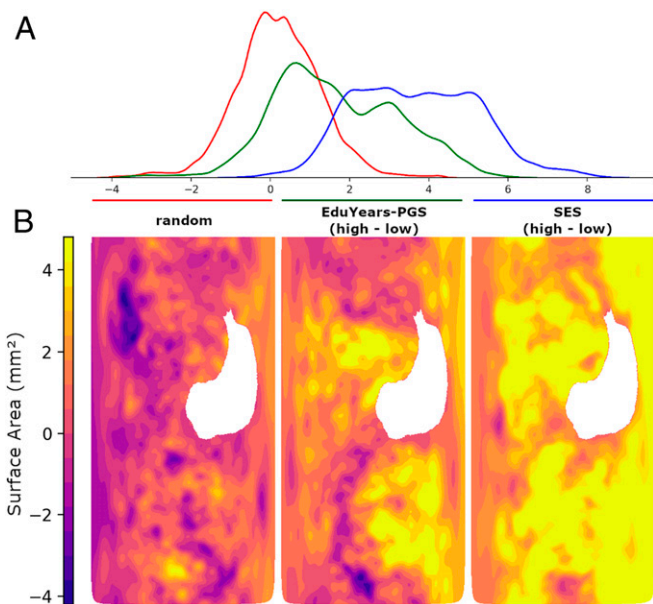
Fig. 4. Global surface area of the left hemisphere displayed with (*A*) a density histogram and (*B*) flat maps. White area corresponds to missing values from the corpus callosum. Data for EduYears-PGS (*Middle*) and SES (*Right*) were calculated by vertex-wise averaging of subjects 1 SD above the mean 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 SD. To produce plots for random data the first representative sample was chosen.

when covarying for global surface area at 14. Furthermore, in a post hoc analysis, we found no significant association of change in this region with the change of WM. No clusters were found for the relationship of EduYears-PGS on change in cortical surface area.

Cortical Thickness. Global cortical thickness (CT) decreased from age 14 to 19 (−0.12 mm, *P* < 0.001, paired *t* test; *SI Appendix*, Fig. S6*B*). A strict measurement invariant bLCS model for global cortical thickness (*SI Appendix*, Fig. S1*B*), with SES and EduYears-PGS as covariates of interest, fit the data well: RMSEA = 0.037, CFI = 0.988. Neither SES nor EduYears-PGS was significantly related to average cortical thickness at age 14 or to the thinning over adolescence. Furthermore, there were no significant regional associations (at 14 or from 14 to 19) for cortical thickness from either SES or EduYears-PGS, regardless of global correction.

Amygdala and Hippocampal Volume. The main focus of this study was neocortical development, with a specific focus on distinguishing between cortical thickness and cortical surface area. Although our method did not allow us to separate thickness and area for the amygdala and hippocampus, we analyzed the volume of these structures to tie into the wider body of SES literature.

The volume of the amygdala did not change from age 14 to 19 (13.6 mm³, *P* > 0.05, paired *t* test; *SI Appendix*, Fig. S6*C*). A bLCS model for the amygdala with SES and EduYears-PGS fit the data well: RMSEA = 0.025, CFI = 0.994. Neither SES nor EduYears-PGS was significantly related to amygdala volume at age 14 or to the change in volume over adolescence.

The hippocampus also did not show a significant change in volume over adolescence (−9.3 mm³, *P* > 0.05, paired *t* test; *SI Appendix*, Fig. S6*D*). A bLCS model (RMSEA = 0.035, CFI = 0.991) found hippocampal volume at age 14 to be related to SES (β = 0.12,

P < 0.01), yet not EduYears-PGS. Hippocampal volume change over adolescence was not related to SES or EduYears-PGS.

SES Subcomponent Analysis. As described in the Introduction, our main analysis used an SES composite, which has advantages and limitations. Therefore, we post hoc split our SES composite into parental education, income-related stresses, and neighborhood quality. Each SES subcomponent was added individually in bLCS models with surface area, cortical thickness, amygdala volume, and hippocampal volume. All models fit the data well (RMSEA < 0.08, CFI > 0.95). All cortical and cognitive results that were significant for the SES composite were also significant when only using parental education as a covariate, while income and neighborhood were not significant (*SI Appendix*, Table S5). The only discrepancy between the findings for parental education and the SES composite was regarding the relationship of parental education to hippocampal volume at age 14, which did not survive multiple-comparison correction.

Discussion

Here we showed that both environmental (SES) and genetic (EduYears-PGS) factors, each of which influences educational attainment, play an important role in cognitive and brain development during adolescence. This study tested for and confirmed independent, nonoverlapping associations for 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 were related to total cortical surface area at age 14, with SES having only a global association, while EduYears-PGS also had a regional association with cortical surface area 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 y.

Cognition in Early Adolescence. Both SES and EduYears-PGS independently correlated with WM in early adolescence, with SES having about twice as strong of an influence. This independent SES result is similar to one found by a meta-analysis for educational achievement (*r* = 0.3) (11). 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 (19, 20) and underscores the value of WM as a suitable and meaningful measure of adolescent cognition and cognitive development.

Brain Structure in Early Adolescence. The strong relationship observed between SES and global surface area at age 14 is consistent with prior findings (4, 8). 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 (6, 21). Those factors might exert their influence via brain functioning and possible epigenetic mechanisms. Reward signals and selected epigenetic markers have indeed been discussed as possible malleable neurobiological markers being associated with cognitive capacity in adolescents (22). However, to date, one epigenome-wide analysis for educational attainment casts doubt on possible epigenetic markers for educational attainment (23). The global result we observed could come from one or several factors with a global impact or be the result of several regional effects that together impact most of the cortex with wide-ranging behavioral outcomes (24).

After correcting for global surface area, there were no regional associations with SES. Similarly, no clusters were significant when

total intracranial volume was corrected for instead of global surface area. Although several studies report regional findings of SES with surface area and cortical thickness (4, 8), these studies did not correct for global associations. 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 Appendix*, Fig. S5).

Contrasting the surface area in high- vs. low-SES subjects (Fig. 4), it is clear that almost the entire cortex is related to SES inequalities. Without total surface area correction the regional associations can give a false sense of localization (25, 26). We view it as more accurate to describe the association of SES with surface area as global in nature, where regional effects over and above this global effect cannot be statistically distinguished from noise.

EduYears-PGS was associated with global surface area, consistent with prior findings showing a relationship between EduYears-PGS and intracranial volume (27, 28). This 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 correlate with IQ (18, 29). In addition, here we found that EduYears-PGS was related to regional surface area in the intraparietal sulcus.

Regional cortical findings are consistent with the fact that some of the genetic markers from EduYears-PGS are associated with regional gene expression (13). The intraparietal sulcus is a region typically associated with nonverbal reasoning, visuospatial WM, and mathematics (30–32). Gray matter volume (33, 34) and brain activity (35–37) of the intraparietal sulcus predict current and future mathematical skills in children and adolescents.

A study spanning 6 to 18 y olds found that the right anterior intraparietal sulcus was associated with visuospatial WM at younger ages and later during development associated with mathematics, suggesting a functional plasticity of this region (38). Given that nonverbal 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 associated with EduYears-PGS above and beyond the polygenic influences on global cortical surface area.

We found no association between EduYears-PGS or SES and cortical thickness, in agreement with some previous studies on SES (4), but not others (5, 8). It is important to emphasize that our quality control procedure was very strict and previous literature has shown cortical thickness results to change based upon strictness (39–41). This reasoning, combined with our large sample size and our findings for surface area, lead us to interpret this as an important null result.

Adolescent Development. Over the course of 5 y, we found a global decrease in surface area. The amount of decrease was related to SES, but not EduYears-PGS, showing a continuing relationship of SES with brain development during adolescence. Although SES's association with surface area at age 14 was positive, this relationship flipped (i.e., became negative) for the change over 5 y (Fig. 1). This is likely related to the nonlinear developmental trajectories of surface area during childhood and adolescence with an inverted U shape (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 regions (24, 42, 43).

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, was related to a decrease in global surface area during adolescence. Recent research has shown intraindividual change in cognition associated with later change in surface area (44). An accelerated reduction of surface area during development has previously been observed in higher-IQ subjects (18). In summary, surface area (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 with IQ showed a widening gap between subjects with low and high EduYears-PGS (45). 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 and SES Subcomponents. As in most studies that use PGS, we were technically restricted to analyzing only subjects of European ancestry, so our results here cannot generalize to other ethnicities. Additionally, our study focused on environmental and genetic predictors of the trait educational attainment. Therefore, our SES measure is "pure" in the sense that we removed some of the genetic variation associated with educational attainment present in teenagers (and that other studies typically confound). Importantly, however, this controlling does not mean that our SES measure is environmentally pure—there are other potential genetic factors associated with SES, such as genes modulating other traits correlated with SES, as well as parental genes for educational attainment that were not passed down to the teenagers but that helped in shaping the environment where they grew up (46).

It is also worth noting that the SES composite we used here is a combination of many distinct SES-related components. When splitting this into education, income, and neighborhood components, we found that most of the SES findings in our sample are driven by the level of education of the parents. We were surprised that even after controlling for the best composite of genetic variants currently known for educational attainment (EduYears-PGS from the largest GWAS to date), the education of the parents was still associated with WM and brain structures in our models. Possible environmental factors might be study habits, cognitively stimulating environments, or books in a household but might also be diet and stress, all of which are related to higher education. It would be of interest to further study the specific environmental and nontransmitted genetic factors related to cognitive and brain development.

Conclusions

Here we report distinct associations of EduYears-PGS and SES with cognition, brain structure, and adolescent brain development. These findings imply that behavioral and psychological consequences of SES are likely wide-ranging, and less targeted toward a specific cognitive function or behavioral deficit. Importantly, SES has a significant relationship with cognition, even after removing genetic variance. A continued greater insight into the genetics of cognitive development will help inform policy decisions to tackle environmental influences.

Methods

Study Description. IMAGEN is a European multisite longitudinal genetic and neuroimaging study. All procedures were approved by each of the sites' (Berlin, Dresden, Dublin, Hamburg, London, Mannheim, Nottingham, and Paris) IRB/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 14 (14.44, SD = 0.38) and 19 (19.01, SD = 0.72).

See Schumann and colleagues (14) 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 (the few sibling pairs were only present due to mistakes in data collection). Importantly, subjects also had to have all of the relevant data available: structural MRI at both time points, genetics, relevant demographics (e.g., gender and age), and three behavioral WM tasks at the first time point. 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 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 as follows. 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 three-digit target sequence from a stream of 100 digits per minute. The measure used was correct responses.

Socioeconomic Status. The socioeconomic status score was composed 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, and father employed score (*SI Appendix,* Table S4). To further disentangle SES-related variation, post hoc we divided our measure into three summed subcomponents: parental education (composed of mother's and father's education score), neighborhood-related factors (composed of neighborhood score and home inadequacy score), and income-related variables (composed of financial difficulties score, financial crisis score, and family stress unemployment 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 principal-component analysis approach was used to identify and exclude individuals with non-European ancestry. The quality control procedures excluded single-nucleotide polymorphisms (SNPs) with call rates >95%, minor allele frequencies of less than 5%, and SNPs that did not pass an exact test of the Hardy–Weinberg equilibrium at $P < 5 \times 10^{-4}$. 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 were performed using, respectively, Mach1 and Minimac codes from the MaCH software suite (47), as specified in the ENIGMA2 protocol (http://enigma.ini.usc.edu/wpcontent/uploads/2012/07/ENIGMA2_1KGP_cookbook_v3.pdf).

We then used these 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 (13). 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 (48) 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 5,709 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 0 and an SD of 1 for the population. All steps for creating the EduYears-PGS were performed using the R package PRSice-2 (48) and PLINK version 1.90 (49).

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, and GE Medical Systems Signa HDx) with a T1-weighted gradient echo sequence (isotropic 1.1 mm) based on the ADNI protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols) (50). FreeSurfer (version 6.0.0; https://surfer.nmr.mgh.harvard.edu/) was used for image preprocessing and SA/CT estimation, previously reported in-depth (51). Specifically, the longitudinal

pipeline was used, as it is optimized for longitudinal data by registering the differing time points to a median image, thereby reducing within-subject variability and avoiding registration bias (52). All processing was run using the high-performance computing (Bianca cluster) resources provided by Swedish National Infrastructure for Computing (SNIC) through Uppsala's Multidisciplinary Center for Advanced Computational Science under Project sens2018615 using gnuparallel (53). Since IMAGEN is a multicenter study, we used ComBat at the vertex-wise level to remove unwanted site-based variability (54). Variables of interest (baseline age, EduYears-PGS, SES, scan interval, and gender) also showed site-specific variability, and 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 10-mm full width at half maximum.

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 time points and the base (median) image on a three-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 (41), we reran recon-all on a subset of subjects showing skull strip errors with gcut. If the error persisted in either time point the subject was excluded. From 1,963 subjects, 1,168 had structural scans at both time points, and 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 (55). In the overlap sample of 101 subjects, we found a high interrater agreement (kappa = 0.88).

Statistical Analysis.
Surface area, cortical thickness, hippocampus, and amygdala. We chose to use a bivariate latent change score model as it allowed us to examine the development of neural and behavioral measures simultaneously without the constraints of measurement error (56, 57). 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 (58, 59). bLCS models were estimated for average cortical thickness and total surface area. For scaling purposes, we defined total surface area as the sum of all vertices divided by the amount in standard space. 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 (version 3.6.0) package Lavaan (version 0.6-3) (60, 61). Missing follow-up behavioral data were imputed under the assumption of missing at random (*SI Appendix,* Fig. S3) (62). We assessed model fit using the comparative fit index (fit > 0.95) and the root-mean-square error of approximation (fit < 0.08) (63). The subjects' age and gender were regressed from all observed behavioral and neural measures at both time points before model fitting. For the hippocampus and amygdala analyses, total intercranial volume was also corrected for. 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 presented Heywood cases (negative error variances), we left them unconstrained as long as the null hypothesis could not be rejected with the use of CIs (64). Any model presented will have a positive upper-bound CI; we chose this approach since constraining variance can lead to unintended consequences (64, 65). Each SES subcomponent was individually substituted for the SES composite in all models; P values were false discovery rate, corrected for the number of tests (*SI Appendix,* Table S5).

Vertex-wise exploratory analysis. An inherent goal in vertex-wise exploratory analysis is anatomical localization, and therefore we corrected for global values (i.e., total surface area and average 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 0.001, a cluster-wise alpha of 0.05, and Bonferroni correction for making two independent tests for the two hemispheres (66, 67).

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 four analyses. In the model at age 14, vertices were predicted by EduYears-PGS and SES while being controlled for the mean value of the modality analyzed, gender, age at 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.

Data Availability. It was not part of the written consent of the participants for the data to be publicly shared. Researchers may access the dataset through a request to the IMAGEN consortium: https://imagen-europe.com/resources/imagen-project-proposal/. Data and code newly created for this study is made available by request to the corresponding author following approval by the IMAGEN consortium.

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