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Educational attainment polygenic scores are associated with cortical total surface area and regions important for language and memory

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ABSTRACT

It is well established that higher cognitive ability is associated with larger brain size. However, individual variation in intelligence exists despite brain size and recent studies have shown that a simple unifactorial view of the neurobiology underpinning cognitive ability is probably unrealistic. Educational attainment (EA) is often used as a proxy for cognitive ability since it is easily measured, resulting in large sample sizes and, consequently, sufficient statistical power to detect small associations. This study investigates the association between three global (total surface area (TSA), intra-cranial volume (ICV) and average cortical thickness) and 34 regional cortical measures with educational attainment using a polygenic scoring (PGS) approach. Analyses were conducted on two independent target samples of young twin adults with neuroimaging data, from Australia (N = 1097) and the USA (N = 723), and found that higher EA-PGS were significantly associated with larger global brain size measures, ICV and TSA (R^2 = 0.006 and 0.016 respectively, $p < 0.001$) but not average thickness. At the regional level, we identified seven cortical regions—in the frontal and temporal lobes—that showed variation in surface area and average cortical thickness over-and-above the global effect. These regions have been robustly implicated in language, memory, visual recognition and cognitive processing. Additionally, we demonstrate that these identified brain regions partly mediate the association between EA-PGS and cognitive test performance. Altogether, these findings advance our understanding of the neurobiology that underpins educational attainment and cognitive ability, providing focus points for future research.

1. Introduction

It's widely understood that significant differences in cognitive ability exist between human beings. However, the biological aetiology behind this variation remains somewhat elusive. The advent of brain imaging has enabled the investigation of neural substrates for human cognitive ability *in vivo,* leading to the identification of several anatomical and functional correlates of cognitive ability (Jansen et al., 2019; Knol et al., 2019; Schmitt et al., 2019).

Previous evidence has suggested that healthy individuals with higher intelligence tend to have larger brains. The first published study examining intelligence and brain size reported a correlation of 0.5 in a group of college students (Willerman et al., 1991). However, these estimates lessened as sample sizes grew and associated variables, such as height and socio-economic status (SES) were included in analyses. Several recent studies have estimated the correlation between intelligence and intra-cranial volume (ICV) to be between 0.2 and 0.4 (Cox, Ritchie, Fawns-Ritchie, Tucker-Drob and Deary, 2019; MacLullich et al., 2002;

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McDaniel, 2005; Pietschnig et al., 2015; Rushton and Ankney, 2009), with the two largest studies to date (N = 13,600 and N = 8000) reporting a correlation of 0.19 (Nave et al., 2019) and 0.24 (Pietschnig et al., 2015) respectively. Although these correlation estimates are modest, the association between brain size and intelligence appears to be almost entirely due to genetics (Koenis et al., 2018; Posthuma et al., 2002).

Twin studies leverage the shared genes between twin siblings to disentangle the genetic and environmental influences behind phenotypic variability, and have contributed substantially to the current understanding of cognitive neurobiology. Twin analyses have found that general cognitive ability positively correlated both phenotypically and genetically with total surface area (TSA) however, no correlation was observed with average cortical thickness (Vuoksimaa et al., 2014; Walhovd et al., 2016). Additionally, the positive association between cognitive ability and TSA remained significant throughout the lifespan (Walhovd et al., 2016). Though reportedly uncorrelated at a global level, some studies have found regional variability in the correlations between average cortical thickness and cognitive ability, reporting both positive and negative correlations (Panizzon et al., 2009; Winkler et al., 2010).

Several neuroimaging studies suggest that general intelligence, termed '*g*', is most strongly associated with grey matter volume measures from the pre-frontal cortex, language centres in the fronto-parietal network and specific regions in the temporal and occipital lobes (Basten et al., 2015; Gläscher et al., 2010; Jung and Haier, 2007). The morphometry of these regions is also highly heritable in both children (Lenroot et al., 2009) and adults (Rimol et al., 2010; Thompson et al., 2001). In addition, twin studies have reported that a high-expanded surface area (SA) in prefrontal, lateral temporal and inferior parietal regions was positively associated with general cognitive ability (Vuoksimaa et al., 2016; Walhovd et al., 2016) and that these regions exhibit cortical stretching, where increased SA is accompanied by a thinner cortex. Other cerebral features, such as structural and resting-state connectivity (Dubois et al., 2018), white matter microstructure (Chiang et al., 2009), the magnitude of local coherence (synchronized functional activity between regions) (Fjell et al., 2015; Wang et al., 2011) and neural network efficiency (Neubauer and Fink, 2009; Santarnecchi et al., 2014; Van Den Heuvel et al., 2009) have also been associated with general intelligence, highlighting potential functional mechanisms underlying individual variability in intelligence (Santarnecchi and Rossi, 2016). To add further complexity, the regional association of brain structure with intelligence may change across the lifespan (Fjell et al., 2015). For instance, the surface area of the prefrontal and anterior cingulate cortices are most strongly associated with intelligence in children (Reiss et al., 1996; Schnack et al., 2014; Wilke et al., 2003), while the orbitofrontal and middle frontal cortices are most strongly associated with intelligence in adolescents (Frangou et al., 2004). For cortical thickness, the association with intelligence changes with age, with the strength of these associations appearing to peak around age 12 (Schmitt et al., 2019; Shaw et al., 2006). These findings point to specific age-mediated structural and functional anatomical events associated with cognitive ability (Fjell et al., 2015). Together these findings indicate that a simple unifactorial view of the neurobiology underpinning cognitive ability is unrealistic, and that the relationship is far more dynamic and nuanced.

Intelligence is somewhat malleable through interventional strategies that include education, improved diet and positive home environments (Brinch and Galloway, 2012; Protzko, 2016). These correlates may be important mediators of the association between cognitive ability and neurobiology. For example, children from lower income families showed greater variation in cortical surface area and thickness than those from higher income families (Noble et al., 2015). These relationships were most prominent in regions supporting language, reading, executive functions and spatial skills. Variables such as these, which are themselves influenced by genetics (Lee et al., 2018; Lemery-Chalfant et al., 2013; Liu, 2019), add to the complexity of unravelling observed relationships between cognition and brain phenotypes.

Due to the recent availability of large genome-wide association studies (GWAS) of cognitive-related phenotypes, the relationship between intelligence and its neurobiological correlates can now be examined at the molecular level. Recent studies have given weight to previous twin research and found shared genetic factors between cognitive traits and brain imaging phenotypes, such as total brain size and cortical thickness (Elliott et al., 2018; Ge et al., 2018; Schmitt et al., 2019). In fact, post-GWA studies of intelligence and brain volume found a genetic correlation (r_g) of 0.23, which mapped to 67 shared genes (Jansen et al., 2019), and indicated that brain volume accounted for approximately 2% of the variance observed in IQ and 1% in educational attainment (Nave et al., 2019). These studies have predominantly examined this relationship with global anatomical measures yielding insights into the shared genetic aetiology between neuroanatomy and cognitive ability (Santarnecchi and Rossi, 2016). Even so, the phenotypic and genetic correlations between regional cortical areas and cognitive ability have not been thoroughly explored (Grasby et al., 2020). Thus, further fine-scale analysis is required to ascertain the extent to which the genetics influencing cognitive ability affects the structure of individual cortical regions.

Educational attainment (EA), defined as the number of full-time years of education an individual receives, is a useful proxy trait for cognitive ability and is associated with important health-related and life outcomes such as occupational success, social and geographic mobility, mate choice and even the age an individual acquires reading and writing skills (Belsky et al., 2016; Plomin and von Stumm, 2018). EA is correlated both phenotypically (0.50) and genetically (0.65) with intelligence (Plomin and von Stumm, 2018; Rietveld et al., 2014) but is regarded as a combination of both cognitive and non-cognitive skills, and is influenced by both genes and the environment (Belsky et al., 2018; Krapohl and Plomin, 2016). For instance, parents' polygenic scores for educational attainment (EA-PGS)[1] were shown to still predict their children's EA even after adjusting for the child's own EA-PGS, substantiating an effect of parental environment on children's EA (Belsky et al., 2018). Additionally, children with higher EA-PGS often display more social mobility and surpass their parents' occupational success (Belsky et al., 2018). As 'years of education' is a commonly obtained demographic marker collected in almost every population or clinical GWAS study, a recent educational attainment meta-analysis (termed EA3) was able to aggregate a sample size of 1.1 million people, giving unparalleled statistical power (Cesarini and Visscher, 2017; Lee et al., 2018).

While the current literature suggests that genetics, neuroanatomic specificity, and age are all critical to understanding the neural substrates of intelligence, few studies have addressed this using large-scale genetic data. Studies of the shared genetic aetiology between neuroanatomy and intelligence have predominantly focused on global measures, perhaps due to the limited statistical power of the GWAS of intelligence-related phenotypes available at the time. Although this is one of the first studies investigating the associations between the genes for education and brain anatomy using a polygenic scoring approach, a few recent studies have used a similar approach of examining the association between PGS for behavioural/cognitive traits and neuroanatomy (Aydogan et al., 2019; Foley et al., 2017; French et al., 2015; Matloff et al., 2019). This study aimed to assess the association between the genes related to education (as a proxy for general cognitive ability) and the morphometry of specific cortical regions (3 global and 34 regional). Secondly, we assessed whether the established association between an EA-PGS and IQ scores is mediated by identified brain structures.

[1] A polygenic score (PGS) is an individual's cumulative genetic score for a complex trait. PGS are derived from aggregating the contributions of all known trait-associated genetic variants (Sugrue and Desikan, 2019).

2. Materials and methods

2.1. Participants

Two cohorts were examined in this study. The first cohort was the *Queensland Twin Imaging Study* (QTIM) (Blokland et al., 2014) consisting of 1165 Australian twins and siblings. As it has previously been shown that the EA-PGS (calculated from European ancestry GWAS), has poor predictive ability in non-European samples (Lee et al., 2018), the cohort was filtered by genetic ancestry, determined using principal component analysis, resulting in a final sample of 1097 participants included in this study. Principal component analysis was performed to identify ancestry outliers[2] using SmartPCA 1600 in EIGENSOFT 7.2.1 (https://www.hsph.harvard.edu/alkes-price/software/). This ensured that individuals in the analysis were of European descent by excluding those individuals who were more than 6 s.d. from the principal component 1 and 2 centroid from the 1000 Genomes European population (68 individuals excluded). Thus, the final sample included 176 MZ pairs, 228 DZ pairs, 212 unpaired twins and 77 siblings, with a mean age of 22.3 years (s.d. = 3.3, range 16–30). Written informed consent was obtained from each participant and from a parent or legal guardian for participants under the age of 18. All of these individuals had previously participated in the Brisbane Twin Memory and Cognition study at age 16 (Wright and Martin, 2004). Thus, additional information was available on general cognitive ability (full-scale intelligence quotient; FIQ), as well as Verbal and Performance IQ (VIQ and PIQ). The mean interval between cognitive testing and magnetic resonance imaging (MRI) scanning was 4.4 years (range 0–14 years). Gestational duration, birth weight, and parental socioeconomic status were also obtained from parental reports. Individuals with significant medical, psychiatric, or neurological conditions—including head injuries, a current or past diagnosis of substance abuse, or current use of medication that could affect cognition—were excluded from participating in the study. Zygosity was determined using genome-wide single nucleotide polymorphism (SNP) genotyping chips (Illumina 610 K).

The second cohort was from the *Human Connectome Project* (HCP) (Van Essen et al., 2013), which consists of 1113 ethnically-diverse adults primarily from Missouri, USA (mean age 28.8, s.d. = 3.7, range 22–37 years) with imaging data available. Individuals of non-European ancestry were filtered according to i) their self-reported race (white) and ethnicity (not Hispanic/Latino) and ii) genetic ancestry determined using principal components analysis (as described for the QTIM cohort). Thus, the final HCP sample analysed in this study consisted of 723 white, non-Hispanic/Latino individuals, mean age 29.1 s.d. = 3.5, range 22–36 years, consisting of 119 MZ and 64 DZ pairs, 96 singletons, and 261 siblings (390 individuals excluded). All subjects were scanned on a customized 3 T scanner at Washington University in St Louis (WashU). Genotyping was performed on the Illumina Infinium HD beadchip. Demographic and behavioural information, including fluid and crystallized IQ scores, was also collected. Demographic information for both QTIM and HCP cohorts are shown in Table 1.

2.2. Ethics statement

The QTIM study was approved by the Human Research Ethics Committees of the QIMR Berghofer Medical Research Institute, the University of Queensland, and Uniting Health Care at Wesley Hospital. The HCP study was approved by the internal review board of Washington University (IRB # 201204036).

[2] Systematic differences in genetic variant frequencies can occur in samples that contain individuals from different ancestry populations, which can confound results of GWAS. Genetic principal component analysis (PCA) can be used to identify individuals in different ancestry groups so they can be excluded from analyses. For more information see (Abegaz et al., 2019; Price et al., 2006; Price et al., 2010).

2.3. MRI acquisition and processing

2.3.1. QTIM cohort

Imaging was conducted on a 4 T Bruker Medspec whole body scanner (Bruker, Germany) with a transverse electromagnetic (TEM) head coil in Brisbane, Australia. Structural T1-weighted 3D images were acquired (TR = 1500 ms, TE = 3.35 ms, TI = 700 ms, 230 mm FOV, 0.9 mm slice thickness, 256 or 240 slices depending on acquisition orientation (86% coronal [256 slices], 14% sagittal [240 slices]). Surface area and cortical thickness were measured using FreeSurfer (v5.3; http://surfer.nmr.mgh.harvard.edu/) as previously described (Fischl and Dale, 2000). Prior to FreeSurfer analysis, the raw T1-weighted images were corrected for intensity inhomogeneity with SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Total surface area and average cortical thickness were extracted for 34 regions of interest (ROI) per hemisphere from the Desikan-Killiany atlas (Desikan et al., 2006) contained within FreeSurfer. Three global measures, intra-cranial volume, total surface area, average cortical thickness, were also extracted. Cortical reconstructions and ROI labelling were checked using the standardised procedures of the ENIGMA consortium (enigma.ini.usc.edu) (Thompson et al., 2014), with any incorrectly delineated cortical structures also being excluded from the analysis.

2.3.2. HCP cohort

Details of the specific processing procedures used for the HCP dataset can be found in previous articles (Glasser et al., 2013; Van Essen et al., 2013). Briefly, for each subject in the HCP a pair of T1-weighted scans and a pair of T2-weighted (T2w) scans were acquired, both with a spatial resolution of 0.7 mm (isotropic voxels). All scans were quality-rated based on visual inspection before processing, and only those of excellent quality in both categories entered the processing pipeline. The HCP structural pipelines used a specialized version of FreeSurfer 'FreeSurfer 5.3-HCP' software. Registration to atlas space included an initial volumetric registration to MNI152 space using FreeSurfer's linear FLIRT tool, followed by the nonlinear FNIRT algorithm to align subcortical structures. Cortical surfaces were aligned further to population-average surfaces using FreeSurfer to register each hemisphere to a separate left and right hemisphere surfaces based on the matching of cortical folding patterns (Fischl et al., 1999) and landmark assisted registration using the Conte69 atlas (Van Essen et al., 2012).

Left and right hemispheres were averaged for each of the 68 regions of the Desikan-Killiany atlas (Desikan et al., 2006) in both cohorts resulting in a final 34 cortical ROI. This atlas was chosen as it is a common output from Freesurfer and yields larger regions based on common cortical folding patterns resulting in regions that have clear boundaries and are largely consistent between cohorts (Grasby et al., 2020). Averaging the ROIs across hemispheres was done primarily due to the high genetic correlation between corresponding ROI in each hemisphere (Strike et al., 2018; Wen et al., 2016), indicating that variation between corresponding ROI may be more environmental in nature and thus, not within the scope of this study. Additionally, averaging across hemispheres effectively halves the multiple testing burden, an important consideration in genetic studies with relatively small associations - especially in cohorts with smaller sample sizes. Lastly, averaging regions combats laterality issues such as possible switching of left and right MRI scans and the need to account for other confounding variables such as handedness.

2.4. Computation of polygenic scores for educational attainment (EA-PGS)

Standard genotyping, imputation and quality control procedures for the QTIM sample have been described previously (Colodro-Conde et al., 2018). Briefly, quality-control, conducted using PLINK 1.9 (Purcell et al., 2007), included removing SNPs with a minor allele frequency (MAF) <0.005, SNP call rate (>95%), ancestral outliers and Hardy-Weinberg equilibrium deviation ($p < 1x10^{-6}$) before imputation using the

Table 1
Demographic information for QTIM and HCP samples.

	QTIM Sample			HCP Sample		
	Females	Males	Total	Females	Males	Total
Full sample (N)	683	414	1097	384	339	723
Twins (N)	631	389	1020	234	228	462
MZ pairs (N)	106	70	176	62	57	119
DZ pairs (N)	125	103	228	35	29	64
Age (s.d.)	22.2 (3.3)	22.4 (3.4)	22.3 (3.3)	29.9 (3.3)	28.1 (3.5)	29.1 (3.5)
FIQ/Fluid Intelligence[a]	111.8 (12.1)	116.8 (13.1)	113.6 (12.7)	115.2 (10.6)	117.1 (11.3)	116.0 (11)
Height (cm)	166 (6.9)	180.7 (7.3)	171.5 (10)	167 (6.6)	181.5 (7.4)	173.7 (10.1)
BMI (kg/m^2)	22.8 (3.9)	23.9 (3.7)	23.2 (3.9)	25.6 (5.4)	27.0 (4.3)	26.8 (5.6)
Socio-Economic Status[b]	53.3 (20.9)	56.6 (21.2)	54.6 (21.1)	5.3 (2.1)	5.5 (1.9)	5.4 (2.0)
Total Surface Area (mm^2)	164049 (13046)	184379 (14713)	171229 (16759)	165203 (12741)	187667 (14511)	175736 (17622)
Average Thickness (mm)	2.5 (0.09)	2.5 (0.08)	2.5 (0.09)	2.7 (0.07)	2.7 (0.09)	2.7 (0.08)

Parentheses indicate standard deviation.

[a] Full-Scale Intelligence quotient (FIQ) measured in QTIM sample an average of 4 years prior to scanning; Fluid Intelligence measured in HCP sample at time of scanning.

[b] Socioeconomic status (SES) is calculated on the Australian Socioeconomic Index occupational status scale in QTIM (scale 0–100) while SES in HCP was computed using income-to-poverty ratio based on self-reported family income relative to poverty thresholds in the United States (scale 0–10).

Haplotype Reference Consortium 1.1 reference panel. After imputation, prior to EA-PGS calculation, insertions and deletions, ambiguous strands, and low-quality imputation variants ($R^2 < 0.6$) were excluded. For the HCP cohort, imputed genotypes in dosage format from the HCP (dbgap: phg000988.v1) were transformed to best guess using *gtool* (https://www.well.ox.ac.uk/~cfreeman/software/gwas/gtool.html). QC procedures were conducted as described for QTIM.

Summary statistics from the most recent EA GWAS (EA3) (Lee et al., 2018) were used to calculate the EA-PGS for all individuals in the QTIM (N = 1097) and HCP (N = 723) cohorts. The EA3 GWAS comprised data from over a million individuals (N = 1,131,881) of European ancestry from 71 independent cohorts across the world. As the QTIM cohort was included in the EA GWAS, 'leave-one-out' summary statistics for EA were required to avoid sample overlap. Leave-one-out summary statistics were generated by removing all individuals from the Queensland Twin Registry (which includes the QTIM cohort) from the original dataset and re-conducting the GWAS.

Using the leave-one-out summary statistics, EA-PGS were calculated using PLINK 1.9. SNPs were clumped according to Purcell et al., (2007) guidelines ($r^2 < 0.1$, kb = 10000) to account for linkage disequilibrium (Purcell et al., 2007). Eight EA-PGSs were calculated using different SNP *p*-value significance thresholds: $p < 5 \times 10^{-8}$, $p < 1 \times 10^{-5}$, $p < 0.001$, $p < 0.01$, $p < 0.05$, $p < 0.1$, $p < 0.5$, $p < 1$. For each individual, at each threshold, an EA-PGS was calculated by multiplying the dosage and effect size for each SNP, and then these values were summed across all loci. For the number of SNPs included at each *p*-value threshold, see Supplementary Table 1.

2.5. Correlations between EA-PGS and examined phenotypes

Partial correlations between all EA-PGS thresholds, the three global brain measures, IQ, and educational attainment (available only in HCP cohort) were assessed in SPSS 22.0 (SPSS Inc., Chicago, IL, USA). One member from each family was selected to ensure individuals were unrelated to avoid dependency among residuals within family. Significance values were calculated using a two-tailed Students *t*-test (DF = 979 in QTIM and DF = 718 in HCP). All correlations were corrected for sex and age and significance values were Bonferroni corrected for multiple testing ($p < 0.05$/effective number of independent observations).

2.6. Polygenic score association analysis

The association between the genetic influences on educational attainment and neuroimaging phenotypes was assessed by estimating how much of the variance in brain phenotypes was accounted for by the EA-PGS in each cohort. The initial neuroimaging phenotypes of interest were ICV, TSA and average cortical thickness. This was done using a linear mixed model regression with the EA-PGS as a predictor variable while accounting for sex, age, age,[2] sex*age, sex*age,[2] the first ten genetic principal components (to account for residual population stratification), and imputation run as fixed effects; relatedness among individuals was accounted for as a random effect with a genetic relatedness matrix, implemented in GCTA 1.91.7 (Yang et al., 2011; Yang et al., 2014). A partial R^2 was used to estimate the variance explained by the polygenic risk score. Significance values were calculated using a two-tailed Student's *t*-test. To correct for multiple testing error, the effective number of independent observations (calculated from a correlation matrix of 8 PGS thresholds x 3 ROIs) was estimated using Matrix Spectral Decomposition (MatSpD) (Nyholt, 2004) before undergoing Bonferroni correction.

After assessing the association with global brain measures, EA-PGS were then tested for association with surface area and average cortical thickness for each of the 34 cortical regions of interest. For these analyses, TSA or average thickness were added as covariates to the linear mixed model regression in GCTA to test whether the EA-PGS predicted variance that was specific to the cortical region. Resulting p-values were corrected for multiple testing error as described above. The ROI analyses were conducted separately from those of the global measures as they included either TSA or average thickness as covariates. Thus, multiple testing correction was conducted separately for the global measure analysis and the regional analyses.

We next tested the robustness of observed associations between EA-PGS and cortical measures when controlling for height, body mass index (BMI) and socio-economic (SES). In both cohorts, both height and body weight were collected at the time of MRI scanning. The closest available approximation for family SES was calculated as a product of parental income and occupation status at the time of IQ testing (an average of 4 years prior to scanning) using the Australian Socioeconomic Index 2006 (AUSEI06) occupational status scale for the QTIM cohort as previously described (McMillan et al., 2009) (scale 0–100). For the HCP cohort, SES was computed using income-to-poverty ratio based on self-reported family income relative to poverty thresholds in the United States and is adjusted by family size (Diemer et al., 2013; Somerville et al., 2018) (scale 0–10).

2.7. Testing the association between EA-PGS and cognitive ability

Similar to the analyses described above, the proportion of individual variance in general cognitive ability that could be predicted by the EA-PGS was examined. Three measures of IQ were used in the QTIM cohort: Full IQ, Performance IQ and Verbal IQ (FIQ, PIQ and VIQ) (Jackson, 1998) and two in the HCP cohort (Crystallized and Fluid IQ)

(Weintraub et al., 2014). The GCTA analysis was conducted using the same covariates as above. Next, PGS-based regressions were conducted to assess the association between EA-PGS, neuroanatomical correlates and IQ scores. TSA and the identified cortical regions of interest were used as covariates (both independently and simultaneously) to ascertain the amount of variance in the association between EA-PGS and IQ scores that these regions account for. To test the significance of each regional cortical measure as a covariate on the EA-PGS association with FIQ score, the standardized fixed effect (β) and s.e. for each covariate were used in a Wald test to calculate their associated *p*-value.

2.8. Mediation analysis

A mediation analysis was conducted to test if the regional cortical ROIs *mediated* the relationship between EA-PGS and FIQ (using the EA-PGS calculated at $p < 1$ threshold). FIQ was chosen as the best representative of general cognitive ability (as it is calculated as a function of both PIQ and VIQ) (Jackson, 1998). A series of linear mixed models were fitted in GCTA using sex, age, height, 10 PCs as covariates and the genetic relationship matrix as a random effect. First, EA-PGS was used as a predictor of FIQ (path C). Secondly, EA-PGS was used as a predictor of the mediator variable (the relevant ROI) (path A). Thirdly, both EA-PGS (path C') and the moderator ROI (path B) were included as predictors of FIQ (see Fig. 1). Ideally a bias-corrected bootstrap CI would be used to assess the significance of the indirect path (Hayes and Scharkow, 2013); however, this was not a computation option using GCTA. A Sobel test was conducted to test the significance of the indirect path (AB) so as to establish whether mediation was occurring (Sobel, 1982). Although the Sobel test is considered conservative, given that our sample size was >500 this ought not to impede the decision accuracy in these data (Hayes and Scharkow, 2013). In addition to testing the regional ROIs independently, all ROIs, as well as a model with all ROIs and TSA were included in multiple mediation models. The effective number of independent observations was calculated between all ROI and TSA using MatSpD as described for previous analysis. All comparisons were corrected for multiple testing using the Bonferroni multiple testing correction as described.

3. Results

3.1. Correlation between EA-PGS, IQ and brain measures

All EA-PGS thresholds had a significant, positive correlation with TSA in both samples after correcting for the effects of age and sex (See Fig. 2). ICV was also significantly correlated with EA-PGSs at most *p*-value thresholds in QTIM; however, the association did not survive multiple testing correction in the HCP sample. Average cortical thickness was negatively correlated with TSA in both samples. Full-Scale IQ and Fluid IQ showed significantly positive correlations with TSA, ICV and all EA-PGS thresholds in both the QTIM and HCP cohorts respectively. Similarly, educational attainment was significantly correlated with all measures except average thickness in the HCP cohort (EA data not collected in QTIM) (see Fig. 2). Notably, given the age range in the HCP cohort, it is possible that individuals are still studying and that this measure of EA may not reflect their final education level. Further, the EA-PGS explains a maximum of 1.6% of variance in TSA in the QTIM cohort and 1.2% of the variance in the HCP cohort ($p < 0.005$) (Fig. 3, Supplementary Fig. 1). Similarly, EA-PGS explains up to 0.5% of the variance in ICV in both cohorts ($p < 0.005$). The amount of variance explained in cortical thickness by the EA-PGS did not reach statistical significance at any EA-PGS threshold in either cohort.

3.2. Secondary analysis controlling for height, BMI and SES

Further examinations were made to assess whether the associations between EA-PGS and the three global measures were influenced by height, BMI and SES; all of which have been associated with differences in both EA and brain structure. The only variable with a significant effect on all three global measures in both samples was height (see Table 2), which was negatively associated with average thickness, though the association was small.

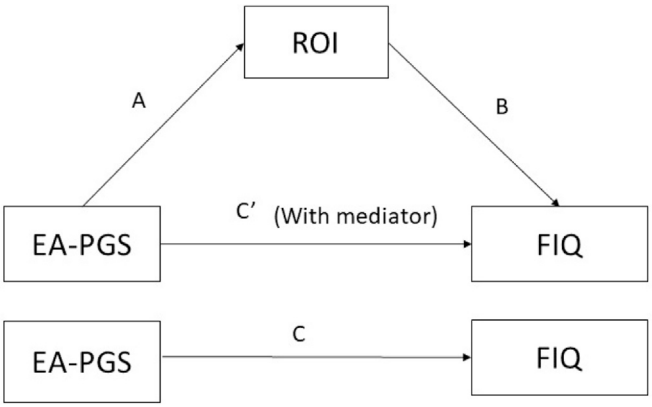

Fig. 1. Schematic of mediation model (based on Hayes, 2017) where EA-PGS represents the independent variable, FIQ the dependent variable and ROI the mediator.

Socio-economic status had a small but nominally significant ($p < 0.05$) effect on TSA (std β: 0.04 [0.00–0.08]) and ICV (std β: 0.05 [0.01–0.09]) but not average thickness in the HCP cohort. The effect of SES was not significant for all three variables in the QTIM cohort. Adjusting for all three covariates produced very similar results in the variance explained of global measures and had no significant effect on regional analysis. Nonetheless, height was included as a covariate in all subsequent analyses. It is important to note that height, BMI and SES all

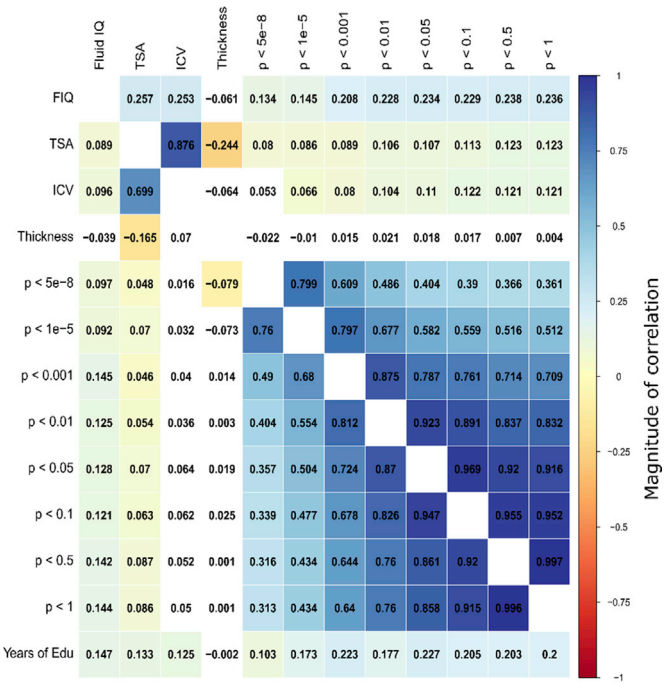

Fig. 2. Partial correlations between global cortical measures, IQ, educational attainment and EA-PGS *p*-value thresholds in both the QTIM and HCP cohorts. Correlations control for sex and age using only unrelated individuals. Correlations above the diagonal are for the QTIM cohort and below the diagonal are for the HCP cohort. Magnitude of correlations are colour coded as indicated by colour bar. White squares indicate correlations that did not meet significance after correction for multiple testing ($p < 0.05$). Educational attainment (Years of Edu) was only available for HCP cohort.

share a substantial genetic correlation with EA (see Lee et al., 2018) so adding these as covariates may diminish legitimate effects produced from pleiotropic genes.

3.3. Cortical surface area ROI analysis

Further analysis of the association between regional surface area and EA-PGS was conducted. Cortical regions were divided into 5 groups based on their anatomical location (frontal, parietal, temporal and occipital lobes and the cingulate) and averaged across hemispheres. The regions that comprise each area were designated according to the Desikan-Killiany atlas (Desikan et al., 2006). In the QTIM sample, the EA-PGS explained some of the variance in seven cortical regions, three in the temporal lobes and four in the frontal lobes over and above the effect of TSA – an effect that remained significant after Bonferroni multiple testing correction (Fig. 3). EA-PGS significantly predicted up to 0.6% of variance in the surface area of these cortical structures at most *p*-value thresholds. These regions were the *fusiform gyrus*, *entorhinal cortex*, *banks of the superior temporal sulcus* (*bankssts*) in the temporal lobes, all three parts of the inferior frontal gyrus (*pars orbitalis, pars opercularis* and *pars triangularis*) and the *medial orbitalfrontal gyrus* (Fig. 4). In the HCP replication sample, five of the same regions (up to 0.6% of variance explained) were also significantly predicted by the EA-PGS, with the exception of *bankssts* and *medial orbital frontal gyrus* (that did not survive multiple testing correction) (Fig. 4). Most regions were positively associated with EA-PGS, indicating that higher EA genetic scores were correlated with larger SA, except for the *medial orbital frontal gyrus* that was in the opposite direction (higher genetic scores associated with smaller SA). No regions were significantly predicted in either cohort in any of the remaining lobes or the cingulate after multiple testing correction (Supplementary Fig. 2). Supplementary Table 2 contains the standardized effect sizes of all 34 examined ROI SA and EA-PGS associations.

3.4. Cortical thickness ROI analysis

Based on the findings of SA ROIs that covary with EA-PGS over-and-above the effect of TSA, and the knowledge that cortical thickness varies substantially between brain regions (Jha et al., 2018; Schmitt et al., 2019; Shaw et al., 2006), the associations between EA-PGS and the average thickness of all 34 cortical ROIs were examined, despite the lack of a global association. Thickness ROIs showed substantially more differentiation between cohorts than was observed in SA ROIs (Fig. 5, Supplementary Fig. 3). Most of the identified ROIs from the SA analysis were also significantly associated with EA-PGS (explaining up to 1.5% of variance), with the exception of *bankssts*. The *pars triangularis* association did not survive multiple testing correction in the HCP cohort (Fig. 5). Several novel ROIs were also identified. These included the *cuneus, supramarginal, post central* and *inferior parietal* thickness. Most of these associations did not survive multiple testing correction or were only observed in one cohort with the exception of *inferior parietal* thickness which remained significant in both cohorts (Supplementary Fig. 3). Most thickness associations with EA-PGS were negative, indicating that individuals with higher EA-PGS have thinner cortices in these regions. Supplementary Table 3 contains the standardized effect sizes of all examined ROI thickness and EA-PGS associations.

3.5. Estimating the effects of cortical surface area on cognitive ability

EA-PGS (at $p < 1$ threshold) was significantly positively correlated with IQ scores ($r = 0.23, p < 0.001$) and TSA ($r = 0.13, p < 0.001$) (Fig. 6) in the QTIM cohort. This threshold for the EA-PGS was chosen as it generally accounted for the most variance explained in previous global brain measures and it predicted the largest amount of variance in the original EA3 GWAS (Lee et al., 2018). Additionally, EA-PGS explained approximately ~5.7% percent of variance (std $\beta = 0.2, p < 0.001$) in FIQ scores in the QTIM cohort (Fig. 7). When examining IQ sub-types, EA-PGS accounted for significantly greater variance in VIQ (~7.2%, std $\beta = 0.23$, $p < 0.001$) than PIQ (~3.6%, std $\beta = 0.15$, $p < 0.001$) (difference = $p = 0.006$, two-tailed Students *t*-test, DF = 979). In the HCP cohort, EA-PGS predicted up to 2.5% of the variance in crystallized IQ (std $\beta = 0.10$, $p < 0.001$) but did not significantly predict fluid IQ (Supplementary Fig. 4).

When accounting for the effect of TSA, the EA-PGS explained ~4.5% of variance in FIQ scores (a 25% reduction) and a maximum of 5.8% and 2.9% in VIQ and PIQ respectively (a 20% reduction; $p = 0.25$, $p = 0.28$ and $p = 0.6$ respectively; Fig. 7). The reduction in variance explained is attributable to the effect of TSA on the association between EA-PGS and

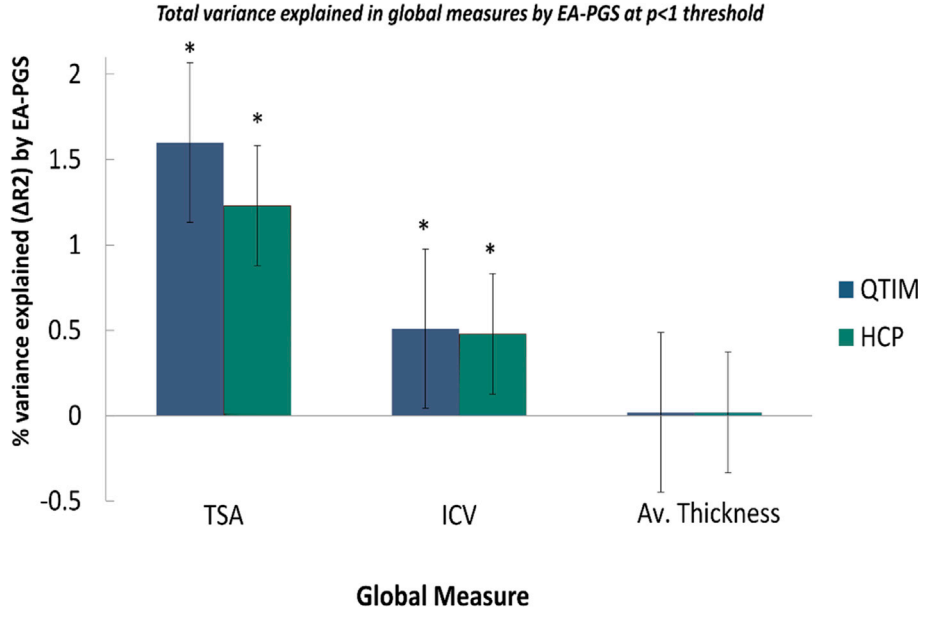

Fig. 3. EA-PGS ($p < 1$) predicts a maximum of 1.6% of variance in total surface area and 0.5% of variance in ICV but does not predict average cortical thickness in both cohorts of young adults. Results presented are from $p < 1$ EA-PGS threshold as it generally represented the greatest amount of variance explained in global brain measures. Error bars represent 95% confidence intervals, Significance is indicated by *; calculated as $p < 0.05$ (after Bonferroni correction for multiple testing).

Table 2
Standardized effect sizes, 95% Confidence Intervals (CI) and *p*-values of height, BMI and SES on the association between EA-PGS ($p < 1$ threshold) and global brain measures.

		QTIM			HCP		
		Std β	95% CI	Pval	Std β	95% CI	Pval
TSA	**EA-PGS**	0.231	0.13–0.33	1.08E-05	0.393	0.191–0.582	1.05E-04
	Height	0.120	0.077–0.163	2.05E-08	0.308	0.224–0.392	6.21E-13
	BMI	0.021	−0.008–0.049	0.153	0.017	−0.031–0.064	0.489
	SES	0.033	−0.005–0.070	0.875	0.044	0.003–0.086	0.035
ICV	**EA-PGS**	0.143	0.074–0.203	7.06E-06	0.203	0.07 4–0.321	3.94E-06
	Height	0.090	0.051–0.129	2.58E-06	0.167	0.084–0.249	4.29E-10
	BMI	0.003	−0.024–0.030	0.883	0.060	0.012–0.108	0.015
	SES	0.015	– 0.017–0.047	0.349	0.051	0.006–0.095	0.026
Av. Thickness	**EA-PGS**	1.34E-03	−1.23E-03– 0.001	0.614	−0.024	−0.094–0.042	0.50
	Height	−0.004	−0.007–−0.001	8.20E-04	−0.060	−0.072–−0.048	1.83E-14
	BMI	−0.003	−0.004–−0.001	0.799	0.034	−0.038–0.105	0.348
	SES	9.60E-05	−0.002–0.002	0.924	−0.014	−0.082–0.054	0.687

Note: Standardized betas for EA-PGS ($p < 1$) are for the association with the three global measures after accounting for the effects of height, BMI and SES (as well as other standard covariates).

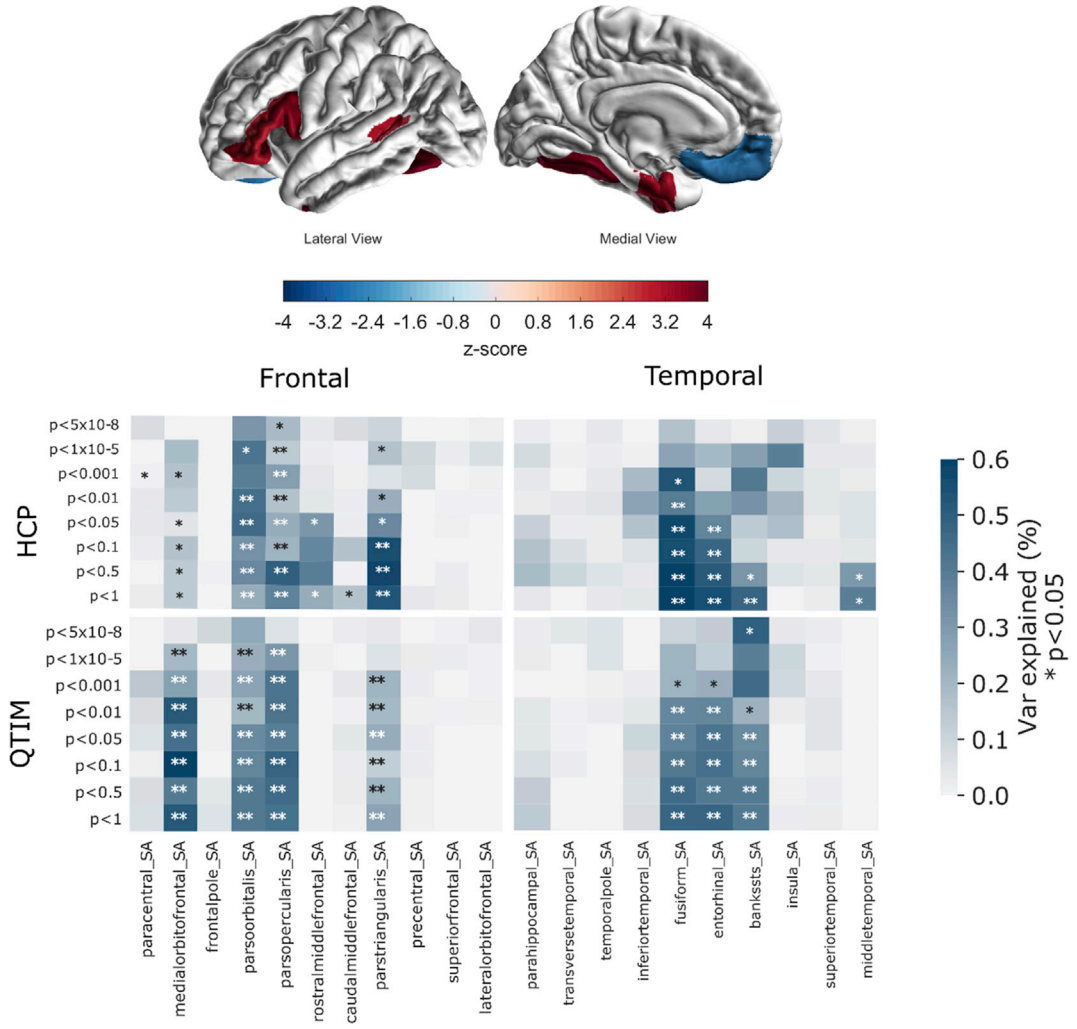

Fig. 4. Surface area: PGS for educational attainment (EA3) predict four frontal cortical surface areas (left) and three temporal (right) in both the QTIM (lower) and HCP (upper) cohorts. Brain plots show the location, as well as direction of association (z-scores), for identified regions with blue regions depicting negative associations and red scores depicting positive associations. The *y*-axes of the heatmaps represent the *p*-value cut-off thresholds for EA-associated SNPs used to calculate the PGS. The heatmap colour shading represents the amount of variance explained by the PGS. The double asterisk represents significant predictions after Bonferroni correction for multiple testing. $^{**}p < 0.0001$, * indicates associations that did not survive multiple testing correction. Only the medial orbitofrontal gyrus showed a negative association with EA-PGS.

the IQ measures. Next, we tested both the individual and combined effect of the ROI identified from the EA-PGS prediction in the QTIM cohort by adding them as covariates (without TSA) to the analysis. The significance of adding each cortical region as a covariate (over and above the effect of

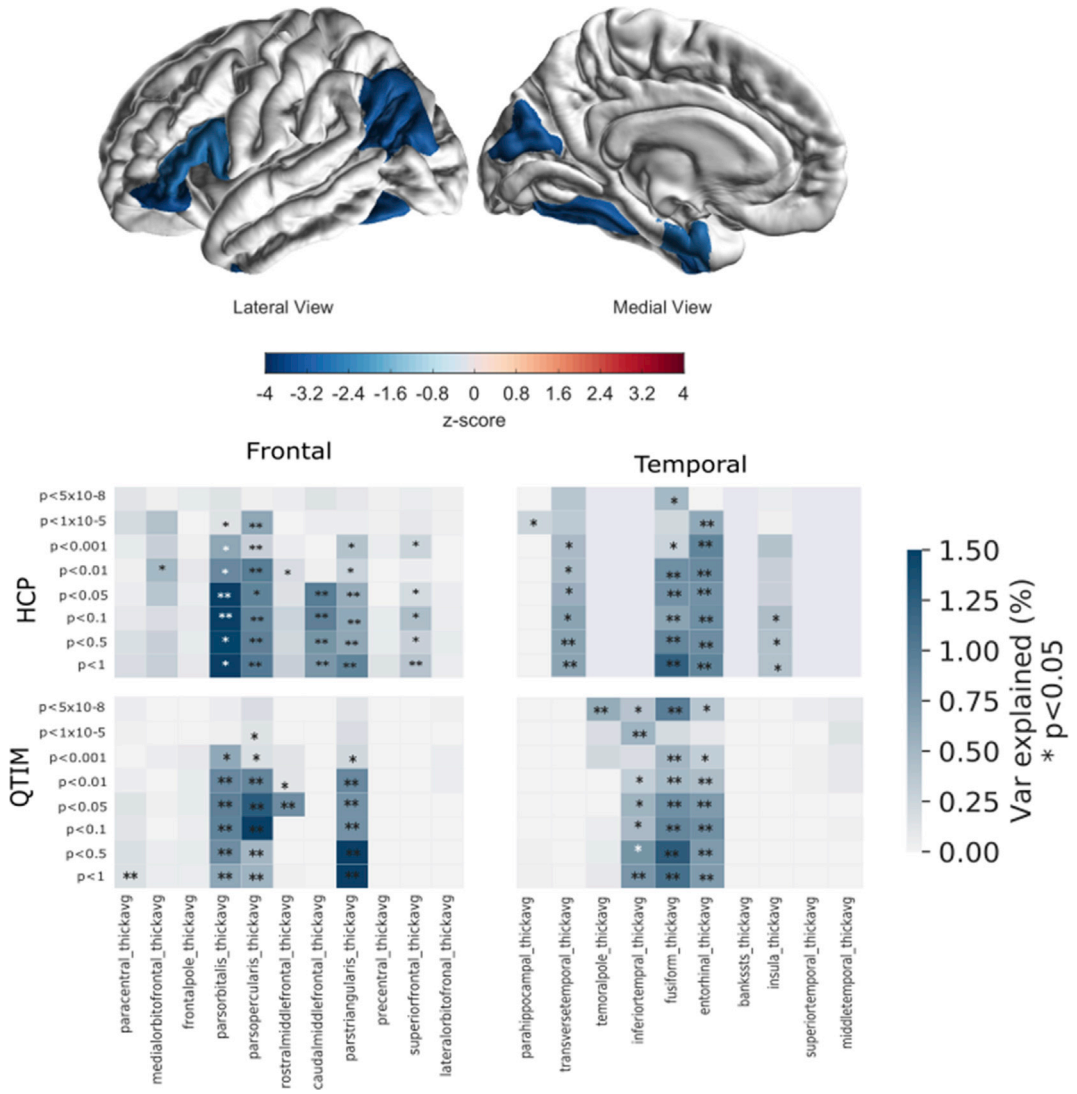

Fig. 5. Thickness: PGS for educational attainment (EA3) significantly associate with the cortical thickness in four frontal regions (left) in at least one cohort and two temporal (right). Brain plots show the location, as well as direction of association (z-scores), for identified regions with blue regions depicting negative associations and red scores depicting positive associations. The *y*-axes of the heat maps represent the *p*-value cut-off thresholds for EA-associated SNPs used to calculate the PGS. The heatmap colour shading represents the amount of variance explained by the PGS. The double asterisk represents significant predictions after Bonferroni correction for multiple testing. $^{**}p < 0.0001$, * indicates associations that did not survive multiple testing correction. All regions showed a negative association with EA-PGS.

TSA) was tested using a two-tailed Student's *t*-test. All ROIs in the QTIM sample had a significant effect on the association, except for the *entorhinal* region that was only nominally so. Additionally, the *fusiform* and *pars orbitalis* had the greatest effect on the association with FIQ (Supplementary Table 4). When examining the effect of all ROI as a group, the percentage of variance in FIQ explained by the PGS scores dropped even further to ~3.8% ($p = 0.12$; Fig. 7). A similar decrease in variance explained for VIQ and PIQ (~4.8% and 2.5%; $p = 0.06$ and $p = 0.8$) was observed. When assessing the six ROIs and TSA simultaneously as covariates, the variance explained was significantly different from the original analysis, indicating that these regions capture a significant amount of the variance in IQ measures that is explained by the EA-PGS (Fig. 7). Similar results were seen in the crystallized IQ measures from the HCP cohort (Supplementary Fig. 5).

3.6. Mediation analysis

As established, FIQ is significantly predicted by EA-PGS (β [95% CI] = 0.25 [0.192–0.310], $p < 0.001$) (path C). All paths and indirect paths were significant for all ROI associations remained significant after Bonferroni multiple testing correction ($\alpha = 0.013$). The Sobel test established partial but significant mediation by all ROI, with *fusiform* having the largest mediation effect (percentage mediation) and the *medial oribtofrontal gyrus* having the smallest mediatory effect (See Table 3). As a group, all ROIs were still significant mediators as well as when all ROIs and TSA were added simultaneously as multilevel mediators. The combination of all ROI as multiple mediators had the largest mediatory effect (3.2%) (see Table 3).

4. Discussion

In this study, the association between the genetic influences on educational attainment and cortical morphology was examined. Using two large twin cohorts, robust, positive association was established between EA-PGS, total surface area and intra-cranial volume but not average cortical thickness – lending weight to similar results from previous twin studies (Brouwer et al., 2014; Vuoksimaa et al., 2014, 2016). These results also suggest that cortical surface area and average thickness share a small correlation ($r = 0.08$) at both global and regional levels, despite both phenotypes being significantly heritable ($h^2 = 0.8$ and

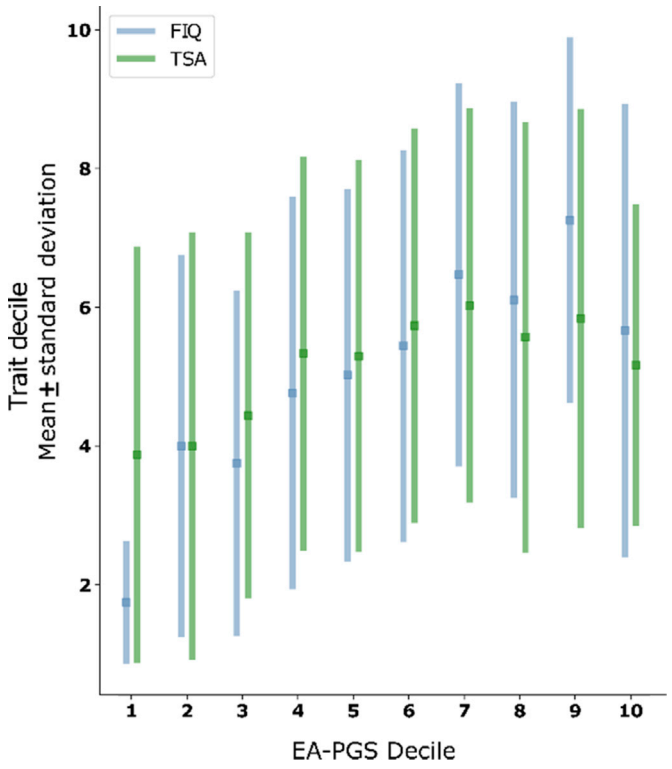

Fig. 6. EA-PGS ($p < 1$ threshold) is positively correlated with FIQ (blue; r = 0.23) and TSA (green; r = 0.13) in QTIM. The *x*-axis represents the deciles of EA-PGS scores, *y*-axis represents the mean ± standard deviation of TSA and FIQ by decile.

above; narrow sense) (Panizzon et al., 2009; Reiss et al., 1996; Schnack et al., 2014; Wilke et al., 2003; Winkler et al., 2010). These results also support recent studies utilizing large-cohort GWAS. For example, a strong (~0.8), positive genetic correlation (r_g) between TSA and ICV, while a negative r_g between TSA and average cortical thickness was seen in a recent, exceptionally large (35 k individuals), neuroimaging meta-analysis (Grasby et al., 2020), as well as smaller studies (Strike et al., 2018). Significant, positive r_g between TSA and EA (~0.2) and general cognitive ability (~0.2) has also been reported in the ENGIMA consortium study (Grasby et al., 2020). Similarly, a GWAS of brain volume (N = 54,407) reported a r_g of 0.23 between brain volume and intelligence and were able to identify 67 overlapping genes, which are predominantly involved in cell growth pathways (Jansen et al., 2019). This is in line with other studies that suggest that the phenotypic relationship between brain size and intelligence may be driven by TSA rather than cortical thickness (Brouwer et al., 2014; Cox et al., 2019; Cox et al., 2018; Nave et al., 2019; Panizzon et al., 2009; Vuoksimaa et al., 2014; Vuoksimaa et al., 2016). Additionally, a study by Cox et al. (2019) found that global measures account for double the variation in general cognitive ability in older adults compared to middle-aged adults (S. Cox et al., 2019), suggesting that age may moderate this relationship.

This study found a significant effect of height on our associations, but not of BMI as was seen in other studies (Pietschnig et al., 2015; Vuoksimaa et al., 2018). However, our associations still held even when correcting for all three covariates, as was also seen in other studies (Pietschnig et al., 2015; Rushton and Ankney, 2009). SES was a nominally significant covariate only in the HCP cohort, possibly due to the active recruitment of individuals from diverse social backgrounds in this study. Studies have shown that both genes and environment play substantial roles in the EA phenotype. In fact, individuals with higher EA-PGS have been shown to be born in to homes of higher socio-economic standing and be both socially and geographically mobile (Belsky et al., 2016, 2018; Walhovd et al., 2016). Additionally, the association between EA-PGS and educational attainment has been shown to be mediated through personality traits such as self-control and neuroticism (Belsky et al., 2016). It is thus understandable that both cognitive and non-cognitive domains may play a role in the association between EA and brain morphology. Despite these associations, it is important to note that EA shares substantial genetic correlation with all three examined variables and thus, by adding them as covariates, it may diminish legitimate associations that are driven by pleiotropic genes (Vuoksimaa et al., 2018).

Significant regional heterogeneity and individual variation exist in the associations among cortical ROI and cognitive phenotypes (Panizzon et al., 2009; Vuoksimaa et al., 2016; Winkler et al., 2010). This study identified seven specific cortical regions associated with EA-PGS over--and-above the effect of global surface area, four in the frontal lobe and three in the temporal lobe, which showed replicable association with EA-PGS in both independent samples. These regions were the *medial orbitofrontal gyrus* (part of the prefrontal cortex, responsible for cognitive process and decision-making) and all three parts of the *inferior frontal gyrus* (Broca's area). Broca's area is responsible for speech production (Flinker et al., 2015), perception (Imada et al., 2006; Watkins and Paus,

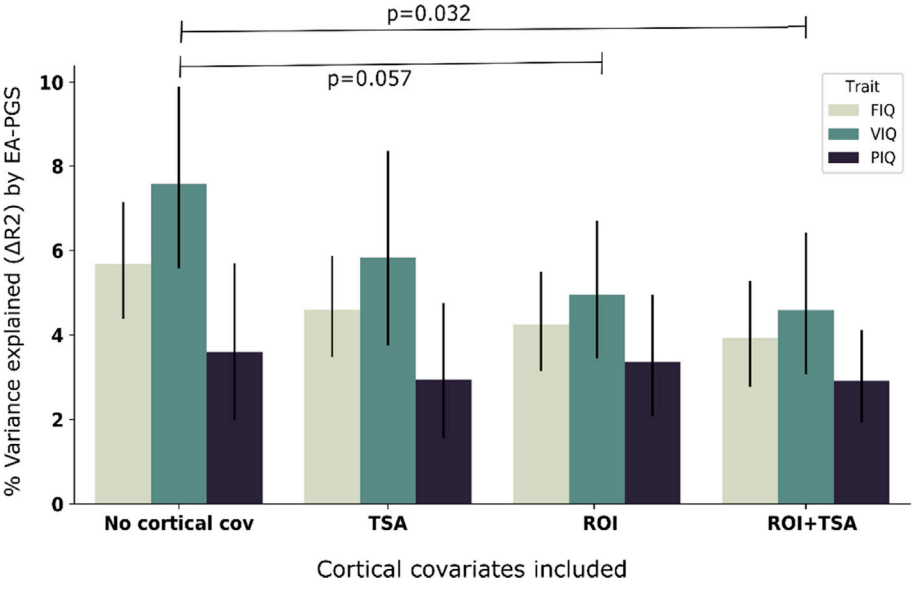

Fig. 7. EA-PGS predicts up to 7.5% of variance in VIQ, 5.8% FIQ and 3.6% in PIQ scores in the QTIM cohort. This decreases to approximately 5.8%, 4.5% and 2.9% when TSA is added as an additional covariate for VIQ, FIQ and PIQ respectively. A further reduction (approximately 15%) is observed in all three IQ scores when all ROIs are added as covariates simultaneously (4.8%, 3.8% and 2.5% respectively). Only the ROI and TSA analysis was significantly different from the original analysis. Error bars represent 95% confidence intervals.

Table 3
Mediation model testing the significance of identified ROIs SA as mediators of the EA-PGS and FIQ association.

ROI	Model	Std β	95% CI	P-value	% Mediation	Sobel	P sobel
	C	0.251	0.192–0.310	<2e-16			
	A	0.113	0.050–0.176	5.54E-04			
Fusiform	B	0.197	0.140–0.254	9.29E-12			
	C′	0.225	0.168–0.282	3.29E-14	2.6%	3.100	0.002
	A	0.121	0.056–0.186	2.15E-04			
Bankssts	B	0.151	0.098–0.204	5.49E-08			
	C′	0.228	0.169–0.287	2.86E-14	2.3%	3.089	0.002
	A	0.113	0.048–0.178	5.87E-04			
Entorhinal	B	0.100	0.047–0.153	2.28E-04			
	C′	0.240	0.181–0.299	2.12E-15	1.1%	2.423	0.015
	A	0.126	0.061–0.191	1.49E-04			
Pars Opercularis	B	0.156	0.101–0.211	3.97E-08			
	C′	0.230	0.171–0.289	1.60E-14	2.1%	3.276	0.001
	A	0.080	0.017–0.143	1.23E-02			
Pars Orbitalis	B	0.130	0.077–0.183	1.88E-06			
	C′	0.236	0.177–0.295	3.49E-15	1.3%	2.360	0.018
	A	0.088	0.023–0.153	8.06E-03			
Pars Triangularis	B	0.165	0.112–0.218	1.00E-09			
	C′	0.238	0.181–0.295	1.04E-15	1.3%	2.432	0.015
	A	0.068	−0.016–0.152	1.06E-03			
Medial Orbitofrontal	B	0.123	0.072–0.174	1.00E-09			
	C′	0.243	0.200–0.286	1.04E-15	0.8%	3.240	0.012
	A	0.110	0.049–0.171	4.58E-04			
TSA	B	0.257	0.198–0.316	<2e-16			
	C′	0.226	0.169–0.283	1.66E-14	2.5%	3.252	0.001
All ROI	C′	0.217	0.160–0.274	3.26E-13	3.4%		
All ROI + TSA	C′	0.219	0.162–0.276	1.90E-13	3.2%		

* Mediation models including sex, age, height, 10 PCs and a genetic relationship matrix as covariates.
Note: β = Beta, CI = Confidence Intervals, % = percentage.

2004) and language comprehension (Musso et al., 2003) and has been linked to semantic processing (Belyk et al., 2017; Sabb et al., 2007) and working memory (Sabb et al., 2007). The surface area of three regions in the temporal lobe were significantly predicted by EA-PGS, including the *fusiform gyrus* implicated in semantic processing (Balsamo et al., 2006), reading (McCandliss et al., 2003), face perception (Kanwisher and Yovel, 2006) and the learning of languages (Mei et al., 2015; Tan et al., 2011); the *entorhinal cortex* involved in memory, navigation, and perception, and the *banks of the superior temporal sulcus* which has been linked to multi-sensory processing (Hein and Knight, 2008). EA-PGS also showed a significant negative association with the thickness of several of these regions, which aligns with previous twin studies that identified cortical stretching in regions associated with cognitive ability (Vuoksimaa et al., 2016). In addition, EA-PGS was negatively associated with the thickness of the *cuneus* and the *inferior parietal* cortex. Our findings substantiate previous studies that show an expanded SA (and cortical thinning) in prefrontal, lateral temporal and inferior parietal regions was positively associated with general cognitive ability (Nave et al., 2019; Vuoksimaa et al., 2014, 2016).

We hence examined if the surface area of the identified regions mediated the relationship between EA-PGS and IQ scores. EA-PGS explained a significantly greater amount of variance in VIQ than in QTIM. Verbal IQ is a measure of acquired knowledge and verbal reasoning (Kaufman, 1976), while PIQ assesses non-verbal cognitive ability such as perceptual organization and processing speed. Previous studies have found a phenotypic correlation of 0.16 with Fluid IQ (Ritchie et al., 2018) while another study reported a similar correlation of 0.19 with VIQ on a large sample of over 13,000 individuals (Nave et al., 2019). The increased prediction of EA-PGS into VIQ indicates that the variants captured by the EA-PGS probably relate more strongly to verbal cognitive processing, which also supports the finding that the EA-PGS were associated with cerebral regions important for memory and language. In addition, using a Sobel test we also found significant evidence that all identified ROIs partially mediate the relationship between EA-PGS and FIQ.

Although the results of this study provide evidence of the association between EA-PGS and cortical brain regions, there is debate behind the meaning of cognitive neuroanatomical correlations and how well results would generalize across populations or individuals at either end of the cognitive ability spectrum. For example, Pietschnig et al. (2015) and Richie et al. (2018) discuss whether brain size is a proxy for neuron number and what compensatory mechanisms may be responsible for individual differences in intellectual ability (S. Cox et al., 2019; Deary et al., 2007). The identification of regional heterogeneity associated with EA in this study adds weight to the hypothesis of compensatory mechanisms accounting for individual variation in intellectual ability over-and-above the effect of total brain size. Another consideration regarding the generalizability of our findings is the demographics represented in our cohorts. The cohorts in this study were filtered to represent homogenous European populations due to the poor predictive power of current PGSs in non-European populations. These samples were also over-representative of people of higher SES and educational attainment and therefore our results may not extend to individuals of different ethnic backgrounds, as well as in population with increased rates of inequality. Lastly, as discussed by Nave et al. (2019), the positive relationship between brain size and intelligence becomes substantially weaker when examining individuals at either end of the cognitive ability spectrum. Thus, the results found in this study reflect associations for individuals within the normal range of cognitive ability and may not generalize to individuals with cognitive impairment or neurodegenerative diseases or those of extremely high-functioning cognitive ability.

Together, these findings expand on several previous twin and genomic studies that have identified a significant association between general cognitive ability and increased TSA. Additionally, these findings robustly replicate the positive association between EA-PGS and increased surface area, and a negative association with average thickness, in cortical regions related to memory and language in two independent cohorts. However, some limitations must be acknowledged. First, these results do not give any indication of the causality of the relationship. Individuals with a genetic predisposition for higher cognitive ability may have larger cortical regions; however, the causal direction may operate in reverse—whereby the (genetically influenced) larger brain regions may allow individuals to achieve higher educational attainment. Secondly,

the use of two geographically diverse cohorts provides confidence in the robustness of the observed associations, but also resulted in some measures being either quantified or temporally assessed differently between cohorts. For instance, in the QTIM cohort, the IQ and SES scores were obtained from an earlier wave of data collection that was conducted 0–14 (mean 4.4) years prior to MRI scanning. Although IQ is a relatively stable measure from the age of 16 onwards, giving the growth trajectories during this age period, it is possible that these measures may not be entirely representative of an individual's current cognitive ability at the time of MRI. Additionally, the measures of SES between cohorts were calculated according to different indices that may also contribute to additional variation between cohorts. Thirdly, in this study regions were averaged across hemispheres using the Desikan-Killiany atlas for ROI delineation because it results in large regions with consistent borders between studies. Thus we are unable to test for differences in laterality between hemispheres (specifically in the language regions). It would be interesting to conduct similar analyses using vertex-wide measures or genetically informative parcellations examining differences in laterality with larger cohorts that can handle the increase in testing burden. Another important factor to be cognisant of is that EA has a correlation of 0.6 with IQ, and that as a proxy measure this indicates a portion of variance in this phenotype that is also distinct from intelligence. Given the small effect sizes of genetic variants known to influence IQ (Savage et al., 2018), we need much larger sample sizes to be have comparable power to the EA results in order to conduct a reliable comparison between EA-PRS and IQ-PRS. Future studies would benefit from the comparison of the prediction between EA- and IQ- PGS as sample sizes grow. Lastly, further statistical, molecular and functional studies are needed to uncover the specific genes and pathways that underlie both these traits and dissect the observed genetic overlap.

5. Conclusions

In this study, a significant, positive association was identified between the genetic influences on educational attainment and total cortical surface area. Additionally, this study is the first to extend the focus beyond the established proxy of global brain volume to regional-specific associations with the genetics of general cognitive ability. Several identified regions showed a positive association between EA-PGS and SA, while average thickness was negatively associated in these areas. These regions, which include Broca's area, have been implicated in language, memory, visual recognition and cognitive processing. We also provide evidence that these brain regions may partially mediate the association between the genetic predisposition to educational attainment and IQ scores. However, much research is still required to understand the combined relationship between structure and function. This study provides focus points for future research to examine causal links between brain characteristics and cognitive performance.

Author contributions

B.L.M. and M.E.R. designed and conceived the study. M.J.W., P.M.T. and N.G.M. were responsible for the QTIM cohort design and genotyping. L.T.S., G.C.P., A.I.C. were involved in the data processing, quality control and preparation while B.L.M, M.E.R. and G.C.P. were responsible for the data analysis. A.O. provided the EA3 'leave-one-out' summary statistics. K.L.G, M.E.R. and S.E.M. provided guidance and aided in interpreting the data. B.L.M. wrote the manuscript. All authors assisted in the preparation and editing of the manuscript.

Declaration of competing interest

All authors report no conflicts of interest in relation with this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116691.

References

Abegaz, F., Chaichoompu, K., Génin, E., Fardo, D.W., König, I.R., Mahachie John, J.M., Van Steen, K., 2019. Principals about principal components in statistical genetics. Briefings Bioinf. 20 (6), 2200–2216.

Aydogan, G., Daviet, R., Linner, R.K., Hare, T.A., Kable, J.W., Kranzler, H.R., et al., 2019. Genetic underpinnings of risky behavior relate to altered neuroanatomy. bioRxiv, 862417.

Balsamo, L.M., Xu, B., Gaillard, W.D., 2006. Language lateralization and the role of the fusiform gyrus in semantic processing in young children. Neuroimage 31 (3), 1306–1314.

Basten, U., Hilger, K., Fiebach, C.J., 2015. Where smart brains are different: a quantitative meta-analysis of functional and structural brain imaging studies on intelligence. Intelligence 51, 10–27.

Belsky, D.W., Domingue, B.W., Wedow, R., Arseneault, L., Boardman, J.D., Caspi, A., et al., 2018. Genetic analysis of social-class mobility in five longitudinal studies. Proc. Natl. Acad. Sci. Unit. States Am. 115 (31), E7275–E7284.

Belsky, D.W., Moffitt, T.E., Corcoran, D.L., Domingue, B., Harrington, H., Hogan, S., et al., 2016. The genetics of success: how single-nucleotide polymorphisms associated with educational attainment relate to life-course development. Psychol. Sci. 27 (7), 957–972.

Belyk, M., Brown, S., Lim, J., Kotz, S.A., 2017. Convergence of semantics and emotional expression within the IFG pars orbitalis. Neuroimage 156, 240–248.

Blokland, G.A., McMahon, K.L., Thompson, P.M., Hickie, I.B., Martin, N.G., de Zubicaray, G.I., Wright, M.J., 2014. Genetic effects on the cerebellar role in working memory: same brain, different genes? Neuroimage 86, 392–403.

Brinch, C.N., Galloway, T.A., 2012. Schooling in adolescence raises IQ scores. Proc. Natl. Acad. Sci. Unit. States Am. 109 (2), 425–430.

Brouwer, R.M., van Soelen, I.L., Swagerman, S.C., Schnack, H.G., Ehli, E.A., Kahn, R.S., et al., 2014. Genetic associations between intelligence and cortical thickness emerge at the start of puberty. Hum. Brain Mapp. 35 (8), 3760–3773.

Cesarini, D., Visscher, P.M., 2017. Genetics and educational attainment. npj Science of Learning 2 (1), 4.

Chiang, M.-C., Barysheva, M., Shattuck, D.W., Lee, A.D., Madsen, S.K., Avedissian, C., De Zubicaray, G.I., 2009. Genetics of brain fiber architecture and intellectual performance. J. Neurosci. 29 (7), 2212–2224.

Colodro-Conde, L., Couvy-Duchesne, B., Zhu, G., Coventry, W.L., Byrne, E.M., Gordon, S., et al., 2018. A direct test of the diathesis–stress model for depression. Mol. Psychiatr. 23 (7), 1590.

Cox, S., Ritchie, S., Fawns-Ritchie, C., Tucker-Drob, E., Deary, I., 2019. Structural brain imaging correlates of general intelligence in UK Biobank. Intelligence 76, 101376.

Cox, S.R., Bastin, M.E., Ritchie, S.J., Dickie, D.A., Liewald, D.C., Maniega, S.M., et al., 2018. Brain cortical characteristics of lifetime cognitive ageing. Brain Struct. Funct. 223 (1), 509–518.

Deary, I.J., Irwing, P., Der, G., Bates, T.C., 2007. Brother–sister differences in the g factor in intelligence: analysis of full, opposite-sex siblings from the NLSY1979. Intelligence 35 (5), 451–456.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., et al., 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.

Diemer, M.A., Mistry, R.S., Wadsworth, M.E., López, I., Reimers, F., 2013. Best practices in conceptualizing and measuring social class in psychological research. Anal. Soc. Issues Public Policy 13 (1), 77–113.
Dubois, J., Galdi, P., Paul, L.K., Adolphs, R., 2018. A distributed brain network predicts general intelligence from resting-state human neuroimaging data. Phil. Trans. Biol. Sci. 373 (1756), 20170284.
Elliott, M.L., Belsky, D.W., Anderson, K., Corcoran, D.L., Ge, T., Knodt, A., et al., 2018. A polygenic score for higher educational attainment is associated with larger brains. Cerebr. Cortex, 287490.
Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. Unit. States Am. 97 (20), 11050–11055.
Fischl, B., Sereno, M., Tootell, R., Dale, A., 1999. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum. Brain Mapp. 8 (4), 272–284.
Fjell, A.M., Sneve, M.H., Storsve, A.B., Grydeland, H., Yendiki, A., Walhovd, K.B., 2015. Brain events underlying episodic memory changes in aging: a longitudinal investigation of structural and functional connectivity. Cerebr. Cortex 26 (3), 1272–1286.
Flinker, A., Korzeniewska, A., Shestyuk, A.Y., Franaszczuk, P.J., Dronkers, N.F., Knight, R.T., Crone, N.E., 2015. Redefining the role of Broca's area in speech. Proc. Natl. Acad. Sci. Unit. States Am. 112 (9), 2871–2875.
Foley, S.F., Tansey, K.E., Caseras, X., Lancaster, T., Bracht, T., Parker, G., et al., 2017. Multimodal brain imaging reveals structural differences in Alzheimer's disease polygenic risk carriers: a study in healthy young adults. Biol. Psychiatr. 81 (2), 154–161.
Frangou, S., Chitins, X., Williams, S.C., 2004. Mapping IQ and gray matter density in healthy young people. Neuroimage 23 (3), 800–805.
French, L., Gray, C., Leonard, G., Perron, M., Pike, G.B., Richer, L., et al., 2015. Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence. JAMA Psychiat 72 (10), 1002–1011.
Ge, T., Chen, C.-Y., Doyle, A.E., Vettermann, R., Tuominen, L.J., Holt, D.J., et al., 2018. The shared genetic basis of educational attainment and cerebral cortical morphology. Cerebr. Cortex, 242776.
Gläscher, J., Rudrauf, D., Colom, R., Paul, L.K., Tranel, D., Damasio, H., Adolphs, R., 2010. Distributed neural system for general intelligence revealed by lesion mapping. Proc. Natl. Acad. Sci. Unit. States Am. 107 (10), 4705–4709.
Glasser, M.F., Sotiropoulos, S.N., Wilson, J.A., Coalson, T.S., Fischl, B., Andersson, J.L., et al., 2013. The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage 80, 105–124.
Grasby, K.L., Jahanshad, N., Painter, J.N., Colodro-Conde, L., Bralten, J., Hibar, D.P., et al., 2020. The genetic architecture of the human cerebral cortex. Science. In press.
Hayes, A.F., 2017. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. Guilford Publications.
Hayes, A.F., Scharkow, M., 2013. The relative trustworthiness of inferential tests of the indirect effect in statistical mediation analysis: does method really matter? Psychol. Sci. 24 (10), 1918–1927.
Hein, G., Knight, R.T., 2008. Superior temporal sulcus—it's my area: or is it? J. Cognit. Neurosci. 20 (12), 2125–2136.
Imada, T., Zhang, Y., Cheour, M., Taulu, S., Ahonen, A., Kuhl, P.K., 2006. Infant speech perception activates Broca's area: a developmental magnetoencephalography study. Neuroreport 17 (10), 957–962.
Jackson, D.N., 1998. *Multidimensional aptitude Battery II: Manual*: Sigma Assessment Systems Port Huron. MI.
Jansen, P.R., Nagel, M., Watanabe, K., Wei, Y., Savage, J.E., de Leeuw, C.A., et al., 2019. GWAS of brain volume on 54,407 individuals and cross-trait analysis with intelligence identifies shared genomic loci and genes. bioRxiv 613489.
Jha, S.C., Xia, K., Ahn, M., Girault, J.B., Li, G., Wang, L., et al., 2018. Environmental influences on infant cortical thickness and surface area. Cerebr. Cortex 29 (3), 1139–1149.
Jung, R.E., Haier, R.J., 2007. The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. Behav. Brain Sci. 30 (2), 135–154.
Kanwisher, N., Yovel, G., 2006. The fusiform face area: a cortical region specialized for the perception of faces. Phil. Trans. Biol. Sci. 361 (1476), 2109–2128.
Kaufman, A.S., 1976. Verbal-performance IQ discrepancies on the WISC-R. J. Consult. Clin. Psychol. 44 (5), 739.
Knol, M.J., Heshmatollah, A., Cremers, L.G., Ikram, M.K., Uitterlinden, A.G., van Duijn, C.M., et al., 2019. Genetic variation underlying cognition and its relation with neurological outcomes and brain imaging. Aging 11 (5), 1440.
Koenis, M.M., Brouwer, R.M., Swagerman, S.C., van Soelen, I.L., Boomsma, D.I., Hulshoff Pol, H.E., 2018. Association between structural brain network efficiency and intelligence increases during adolescence. Hum. Brain Mapp. 39 (2), 822–836.
Krapohl, E., Plomin, R., 2016. Genetic link between family socioeconomic status and children's educational achievement estimated from genome-wide SNPs. Mol. Psychiatr. 21 (3), 437.
Lee, J.J., Wedow, R., Okbay, A., Kong, E., Maghzian, O., Zacher, M., et al., 2018. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat. Genet. 50 (8), 1112.
Lemery-Chalfant, K., Kao, K., Swann, G., Goldsmith, H.H., 2013. Childhood temperament: passive gene–environment correlation, gene–environment interaction, and the hidden importance of the family environment. Dev. Psychopathol. 25 (1), 51–63.
Lenroot, R.K., Schmitt, J.E., Ordaz, S.J., Wallace, G.L., Neale, M.C., Lerch, J.P., et al., 2009. Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. Hum. Brain Mapp. 30 (1), 163–174.
Liu, H., 2019. Genetic architecture of socioeconomic outcomes: educational attainment, occupational status, and wealth. Soc. Sci. Res. 82, 137–147.
MacLullich, A., Ferguson, K., Deary, I., Seckl, J., Starr, J., Wardlaw, J., 2002. Intracranial capacity and brain volumes are associated with cognition in healthy elderly men. Neurology 59 (2), 169–174.
Matloff, W.J., Zhao, L., Ning, K., Conti, D.V., Toga, A.W., 2019. Interaction effect of alcohol consumption and Alzheimer disease polygenic risk score on the brain cortical thickness of cognitively normal subjects. Alcohol. In press.
McCandliss, B.D., Cohen, L., Dehaene, S., 2003. The visual word form area: expertise for reading in the fusiform gyrus. Trends Cognit. Sci. 7 (7), 293–299.
McDaniel, M.A., 2005. Big-brained people are smarter: a meta-analysis of the relationship between in vivo brain volume and intelligence. Intelligence 33 (4), 337–346.
McMillan, J., Beavis, A., Jones, F.L., 2009. The AUSEI06: a new socioeconomic index for Australia. J. Sociol. 45 (2), 123–149.
Mei, L., Xue, G., Lu, Z.-L., Chen, C., Wei, M., He, Q., Dong, Q., 2015. Long-term experience with Chinese language shapes the fusiform asymmetry of English reading. Neuroimage 110, 3–10.
Musso, M., Moro, A., Glauche, V., Rijntjes, M., Reichenbach, J., Büchel, C., Weiller, C., 2003. Broca's area and the language instinct. Nat. Neurosci. 6 (7), 774.
Nave, G., Jung, W.H., Karlsson Linnér, R., Kable, J.W., Koellinger, P.D., 2019. Are bigger brains smarter? Evidence from a large-scale preregistered study. Psychol. Sci. 30 (1), 43–54.
Neubauer, A.C., Fink, A., 2009. Intelligence and neural efficiency. Neurosci. Biobehav. Rev. 33 (7), 1004–1023.
Noble, K.G., Houston, S.M., Brito, N.H., Bartsch, H., Kan, E., Kuperman, J.M., et al., 2015. Family income, parental education and brain structure in children and adolescents. Nat. Neurosci. 18 (5), 773.
Nyholt, D., 2004. Matrix Spectral Decomposition (matSpD)—Estimate the Equivalent Number of Independent Variables in a Correlation (R) Matrix.
Panizzon, M.S., Fennema-Notestine, C., Eyler, L.T., Jernigan, T.L., Prom-Wormley, E., Neale, M., Franz, C.E., 2009. Distinct genetic influences on cortical surface area and cortical thickness. Cerebr. Cortex 19 (11), 2728–2735.
Pietschnig, J., Penke, L., Wicherts, J.M., Zeiler, M., Voracek, M., 2015. Meta-analysis of associations between human brain volume and intelligence differences: how strong are they and what do they mean? Neurosci. Biobehav. Rev. 57, 411–432.
Plomin, R., von Stumm, S., 2018. The new genetics of intelligence. Nat. Rev. Genet. 19 (3), 148.
Posthuma, D., De Geus, E.J., Baaré, W.F., Pol, H.E.H., Kahn, R.S., Boomsma, D.I., 2002. The association between brain volume and intelligence is of genetic origin. Nat. Neurosci. 5 (2), 83.
Price, A.L., Patterson, N.J., Plenge, R.M., Weinblatt, M.E., Shadick, N.A., Reich, D., 2006. Principal components analysis corrects for stratification in genome-wide association studies. Nat. Genet. 38 (8), 904–909.
Price, A.L., Zaitlen, N.A., Reich, D., Patterson, N., 2010. New approaches to population stratification in genome-wide association studies. Nat. Rev. Genet. 11 (7), 459–463.
Protzko, J., 2016. Does the raising IQ-raising g distinction explain the fadeout effect? Intelligence 56, 65–71.
Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., et al., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81 (3), 559–575.
Reiss, A.L., Abrams, M.T., Singer, H.S., Ross, J.L., Denckla, M.B., 1996. Brain development, gender and IQ in children: a volumetric imaging study. Brain 119 (5), 1763–1774.
Rietveld, C.A., Esko, T., Davies, G., Pers, T.H., Turley, P., Benyamin, B., et al., 2014. Common genetic variants associated with cognitive performance identified using the proxy-phenotype method. Proc. Natl. Acad. Sci. Unit. States Am. 111 (38), 13790–13794.
Rimol, L.M., Panizzon, M.S., Fennema-Notestine, C., Eyler, L.T., Fischl, B., Franz, C.E., et al., 2010. Cortical thickness is influenced by regionally specific genetic factors. Biol. Psychiatr. 67 (5), 493–499.
Ritchie, S.J., Dickie, D.A., Cox, S.R., Hernández, M.d.C.V., Sibbett, R., Pattie, A., et al., 2018. Brain structural differences between 73-and 92-year olds matched for childhood intelligence, social background, and intracranial volume. Neurobiol. Aging 62, 146–158.
Rushton, J.P., Ankney, C.D., 2009. Whole brain size and general mental ability: a review. Int. J. Neurosci. 119 (5), 692–732.
Sabb, F.W., Bilder, R.M., Chou, M., Bookheimer, S.Y., 2007. Working memory effects on semantic processing: priming differences in pars orbitalis. Neuroimage 37 (1), 311–322.
Santarnecchi, E., Galli, G., Polizzotto, N.R., Rossi, A., Rossi, S., 2014. Efficiency of weak brain connections support general cognitive functioning. Hum. Brain Mapp. 35 (9), 4566–4582.
Santarnecchi, E., Rossi, S., 2016. Advances in the neuroscience of intelligence: from brain connectivity to brain perturbation. Spanish J. Psychol. 19.
Savage, J.E., Jansen, P.R., Stringer, S., Watanabe, K., Bryois, J., De Leeuw, C.A., et al., 2018. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. Nat. Genet. 50 (7), 912.
Schmitt, J.E., Raznahan, A., Clasen, L.S., Wallace, G.L., Pritikin, J.N., Lee, N.R., et al., 2019. The Dynamic Associations between Cortical Thickness and General Intelligence Are Genetically Mediated. Cerebral Cortex (New York, NY: 1991.
Schnack, H.G., Van Haren, N.E., Brouwer, R.M., Evans, A., Durston, S., Boomsma, D.I., et al., 2014. Changes in thickness and surface area of the human cortex and their relationship with intelligence. Cerebr. Cortex 25 (6), 1608–1617.
Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., et al., 2006. Intellectual ability and cortical development in children and adolescents. Nature 440 (7084), 676.
Sobel, M.E., 1982. Asymptotic confidence intervals for indirect effects in structural equation models. Socio. Methodol. 13, 290–312.

Somerville, L.H., Bookheimer, S.Y., Buckner, R.L., Burgess, G.C., Curtiss, S.W., Dapretto, M., et al., 2018. The Lifespan Human Connectome Project in Development: a large-scale study of brain connectivity development in 5–21 year olds. Neuroimage 183, 456–468.

Strike, L.T., Hansell, N.K., Couvy-Duchesne, B., Thompson, P.M., de Zubicaray, G.I., McMahon, K.L., Wright, M.J., 2018. Genetic complexity of cortical structure: differences in genetic and environmental factors influencing cortical surface area and thickness. Cerebr. Cortex 29 (3), 952–962. https://doi.org/10.1093/cercor/bhy002.

Sugrue, L.P., Desikan, R.S., 2019. What are polygenic scores and why are they important? J. Am. Med. Assoc. 321 (18), 1820–1821.

Tan, L.H., Chen, L., Yip, V., Chan, A.H., Yang, J., Gao, J.-H., Siok, W.T., 2011. Activity levels in the left hemisphere caudate–fusiform circuit predict how well a second language will be learned. Proc. Natl. Acad. Sci. Unit. States Am. 108 (6), 2540–2544.

Thompson, P.M., Cannon, T.D., Narr, K.L., Van Erp, T., Poutanen, V.-P., Huttunen, M., et al., 2001. Genetic influences on brain structure. Nat. Neurosci. 4 (12), 1253.

Thompson, P.M., Stein, J.L., Medland, S.E., Hibar, D.P., Vasquez, A.A., Renteria, M.E., et al., 2014. The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. Brain Imag. Behav. 8 (2), 153–182.

Van Den Heuvel, M.P., Stam, C.J., Kahn, R.S., Pol, H.E.H., 2009. Efficiency of functional brain networks and intellectual performance. J. Neurosci. 29 (23), 7619–7624.

Van Essen, D.C., Smith, S.M., Barch, D.M., Behrens, T.E., Yacoub, E., Ugurbil, K., Consortium, W.-M.H., 2013. The Wu-Minn human connectome project: an overview. Neuroimage 80, 62–79.

Van Essen, D, Ugurbil, K, Auerbach, E, Barch, D, Behrens, T E J, et al., 2012. The Human Connectome Project: a data acquisition perspective. NeuroImage 62 (4), 2222–2231.

Vuoksimaa, E., Panizzon, M.S., Chen, C.-H., Fiecas, M., Eyler, L.T., Fennema-Notestine, C., et al., 2014. The genetic association between neocortical volume and general cognitive ability is driven by global surface area rather than thickness. Cerebr. Cortex 25 (8), 2127–2137.

Vuoksimaa, E., Panizzon, M.S., Chen, C.-H., Fiecas, M., Eyler, L.T., Fennema-Notestine, C., et al., 2016. Is bigger always better? The importance of cortical configuration with respect to cognitive ability. Neuroimage 129, 356–366.

Vuoksimaa, E., Panizzon, M.S., Franz, C.E., Fennema-Notestine, C., Hagler, D.J., Lyons, M.J., et al., 2018. Brain structure mediates the association between height and cognitive ability. Brain Struct. Funct. 223 (7), 3487–3494.

Walhovd, K.B., Krogsrud, S.K., Amlien, I.K., Bartsch, H., Bjørnerud, A., Due-Tønnessen, P., et al., 2016. Neurodevelopmental origins of lifespan changes in brain and cognition. In: Proceedings of the National Academy of Sciences, 113, pp. 9357–9362, 33.

Wang, L., Song, M., Jiang, T., Zhang, Y., Yu, C., 2011. Regional homogeneity of the resting-state brain activity correlates with individual intelligence. Neurosci. Lett. 488 (3), 275–278.

Watkins, K., Paus, T., 2004. Modulation of motor excitability during speech perception: the role of Broca's area. J. Cognit. Neurosci. 16 (6), 978–987.

Weintraub, S., Dikmen, S.S., Heaton, R.K., Tulsky, D.S., Zelazo, P.D., Slotkin, J., et al., 2014. The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: validation in an adult sample. J. Int. Neuropsychol. Soc. 20 (6), 567–578.

Wen, W., Thalamuthu, A., Mather, K.A., Zhu, W., Jiang, J., De Micheaux, P.L., et al., 2016. Distinct genetic influences on cortical and subcortical brain structures. Sci. Rep. 6, 32760.

Wilke, M., Sohn, J.-H., Byars, A.W., Holland, S.K., 2003. Bright spots: correlations of gray matter volume with IQ in a normal pediatric population. Neuroimage 20 (1), 202–215.

Willerman, L., Schultz, R., Rutledge, J.N., Bigler, E.D., 1991. In vivo brain size and intelligence. Intelligence 15 (2), 223–228.

Winkler, A.M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P.T., et al., 2010. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage 53 (3), 1135–1146.

Wright, M.J., Martin, N.G., 2004. Brisbane adolescent twin study: outline of study methods and research projects. Aust. J. Psychol. 56 (2), 65–78.

Yang, J., Lee, S.H., Goddard, M.E., Visscher, P.M., 2011. GCTA: a tool for genome-wide complex trait analysis. Am. J. Hum. Genet. 88 (1), 76–82.

Yang, J., Zaitlen, N.A., Goddard, M.E., Visscher, P.M., Price, A.L., 2014. Advantages and pitfalls in the application of mixed-model association methods. Nat. Genet. 46 (2), 100.