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A Polygenic Score for Higher Educational Attainment is Associated with Larger Brains

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Abstract. People who score higher on intelligence tests tend to have larger brains. Twin studies suggest the same genetic factors influence both brain size and intelligence. This has led to the hypothesis that genetics influence intelligence partly by contributing to development of larger brains. We tested this hypothesis using 4 large imaging genetics studies (combined N=7,965) with polygenic scores derived from a genome-wide association study (GWAS) of educational attainment, a correlate of intelligence. We conducted meta-analysis to test associations among participants' genetics, total brain volume (i.e., brain size), and cognitive test performance. Consistent with previous findings, participants with higher polygenic scores achieved higher scores on cognitive tests, as did participants with larger brains. Participants with higher polygenic scores also had larger brains. We found some evidence that brain size partly mediated associations between participants' education polygenic scores and their cognitive test performance. Effect-sizes were larger in the population-based samples than in the convenience-based samples. Recruitment and retention of population-representative samples should be a priority for neuroscience research. Findings suggest promise for studies integrating GWAS discoveries with brain imaging to understand neurobiology linking genetics with cognitive performance.

Introduction

People who score higher on tests of intelligence tend to have larger brains, as measured by ex-vivo brain weight and in-vivo magnetic resonance imaging (MRI) (van Valen 1974; Haier et al. 2004; McDaniel 2005; Pietschnig et al. 2015). Twin studies indicate this relationship partly reflects genetic factors that influence both brain size (i.e., volume) and intelligence (Posthuma et al. 2003; Toga and Thompson 2005; Deary et al. 2010; Posthuma et al. 2002). These findings suggest the hypothesis that one path through which genetic differences between people influence individual differences in intelligence is by contributing to the development of larger brains. This hypothesis can now be tested using molecular genetic data.

A recent genome-wide association study (GWAS) of educational attainment identified dozens of genetic variants that showed substantial enrichment for genes expressed during brain development (Okbay et al. 2016). Follow-up studies further identified associations between an aggregate measure of GWAS-discovered influences on education, called a polygenic score, and intelligence, including in young children who had not yet entered school (Belsky et al. 2016; Selzam et al. 2017). These findings implicate brain development and intelligence in the pathway connecting people's genetics to their educational outcomes. Further, GWAS research has discovered polygenic variants associated with brain size (inferred through intracranial volume) (Adams et al. 2016) that also overlap with variants associated educational attainment (Okbay et al. 2016). Now, studies are needed to test if genetics discovered in GWAS of education are associated with in-vivo intermediate phenotypes, like brain size, that could constitute a biological pathway linking genetic variation to differences in intelligence and educational attainment.

We analyzed data from four imaging genetics studies from the United Kingdom (UK Biobank), New Zealand (Dunedin Study), and the United States (Brain Genomics Superstruct

Project (GSP) and Duke Neurogenetics Study (DNS)), including 7,965 participants, to test associations among a polygenic score for educational attainment, cognitive test performance, and brain size. We hypothesized that, consistent with previous findings, (1) participants with higher education polygenic scores would have higher cognitive test scores; and (2) that participants with larger brains as measured by total brain volume would have higher cognitive test scores. We further posed the novel hypotheses that (3) participants with higher education polygenic scores would have larger brains and that brain size would mediate the association between the education polygenic score and cognitive test performance. We combined results across our four imaging genetics datasets using random-effects meta-analysis. We also examined heterogeneity between the datasets under the hypothesis that effect-sizes might differ between the population-based UK Biobank and Dunedin Study samples and the GSP and DNS samples, for which range in cognitive performance is more restricted.

Methods

Participants. We analyzed data from European-descent participants in the United Kingdom-based UK Biobank (Sudlow et al. 2015; Miller et al. 2016) a population-based volunteer sample (N=5691), the New Zealand-based Dunedin Study, a population-representative birth cohort (N=596) (Poulton et al. 2015), and two studies in the United States consisting primarily of university students, the Brain Genomics Superstruct Project (Holmes et al. 2015) (GSP, N=1163), and the Duke Neurogenetics Study (Elliott et al. 2018) (DNS, N=515). Sample sizes reflect participants with available structural MRI, cognitive testing, and genetic data (**Table 1**). Samples are described in detail in the supplement and Table 1.

Education Polygenic Score. We computed our polygenic score based on GWAS of educational attainment rather than GWAS of cognitive performance because educational attainment is a proxy phenotype for cognitive performance (Rietveld et al. 2014) and the polygenic score for educational attainment is more predictive of cognitive performance than polygenic scores from GWAS of cognitive performance (Plomin and von Stumm 2018). Education polygenic scores were computed from genome-wide single-nucleotide polymorphism (SNP) data based on GWAS results published by the Social Science Genetics Association Consortium (Okbay et al. 2016) following methods described by Dudbridge (Dudbridge 2013) according to the procedure used in our previous work (Belsky et al. 2016). Genetic data from the Dunedin study were imputed to 1000 Genomes (Abecasis et al. 2012), data from all other studies were not imputed. Following established practice (Wray et al. 2007; Dudbridge 2013; Okbay et al. 2016), we computed polygenic scores using data from all SNPs included in the EA2 GWAS. SNPs were not clumped or pruned for LD prior to analysis (Ware et al. 2017). Briefly, for each study, we matched SNPs in the study's genetic database with published educational attainment GWAS results (Okbay et al. 2016). We then multiplied the education-associated allele of each SNP by the GWAS-estimated effect-size and computed the average of these products across all SNPs. Polygenic scores were standardized within each study to have $M=0$, $SD=1$ for analysis.

Cognitive Performance. Cognitive performance was measured in the UK Biobank using 13 reason and logic puzzles (Lyall et al. 2016). Cognitive performance was measured in the Dunedin Study, GSP, and DNS studies using intelligence tests (the Wechsler Adult Intelligence Scale (WAIS-IV) (Wechsler 1997) in the Dunedin Study, the Shipley Institute of Living Scale

(Zachary 1986) in GSP and the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 2013) in the DNS).

Total Brain Volume. Total brain volume was measured from high resolution, T1-weighted MRI images. In the UK Biobank total brain volume was estimated using SIENAX (Smith et al. 2002). In the Dunedin Study, GSP, and DNS studies, images were processed using the Freesurfer processing pipeline.

Statistical Analyses. We tested associations using linear regression models. Models were adjusted for sex. Models including the polygenic score were adjusted for the first 10 principal components estimated from the genome-wide SNP data to account for any residual population stratification within the European-descent samples analyzed (Price et al. 2006). Models of UK biobank and GSP data were adjusted for age. (The Dunedin Study is a single-year birth cohort and DNS participants vary in age by only by 1-2 years.). In addition to age, models in the GSP were also adjusted for scanner, console version and head coil (12 versus 32 channel) because the GSP was collected across multiple sites. Analyses of individual studies were conducted in R (version 3.4.0). Linear regressions were performed using the `lm` function. Mediation analyses were performed using a system of equations approach (Preacher and Hayes 2008) implemented with the *mediation* package (Tingley et al. 2014) in R, using nonparametric bootstrapping with 1000 iterations. The system of equations includes 3 regressions. The first regression tests association between the predictor (PGS) and outcome (IQ). The second regression tests association between the predictor (PGS) and the mediator (TBV). The third regression tests multivariate association between the predictor (PGS) and outcome (IQ) with covariate

adjustment for the mediator (TBV). If the regression coefficient between predictor and outcome is significantly smaller in the third model than the first, the inference of mediation is made.

Coefficients from these regressions are combined using the formula originally proposed by Sobel (Sobel 2007). Standard errors are computed using the bootstrap method described in Preacher & Hayes (Preacher and Hayes 2008). We combined estimates across studies using random effects meta-analysis (DerSimonian and Laird 1986) implemented using STATA (version 15).

Results

Participants with higher polygenic scores performed better on cognitive tests. As anticipated, participants with higher polygenic scores performed better on cognitive tests. Meta-analysis estimated the cross-study effect size as $r=.18$ ($p<.001$; 95% CI [.11, .24]) with evidence of heterogeneity in effect sizes across studies (I-squared 83%, $p=.001$; tau-squared=.004). Effect sizes were statistically significant in UK Biobank ($r=.17$, $p<.001$), Dunedin Study ($r=.28$, $p<.001$) and GSP ($r=.19$, $p<.001$) but not in the DNS ($r=.05$, $p=.220$).

Participants with larger brains had higher cognitive test scores. We next tested if participants with larger brains performed better on cognitive tests. As anticipated, participants with larger brains (i.e., those with higher total brain volume) performed better on cognitive tests. Meta-analysis estimated the cross-study effect size as $r=.20$ ($p<.001$; 95% CI [.12, .29]) with evidence of heterogeneity in effect sizes across studies (I-squared=75.8%, $p=.002$; tau-squared=.005). Effect-sizes were statistically significant in all studies (UK Biobank $r=.19$, $p<.001$; Dunedin Study $r=.35$, $p<.001$; GSP $r=.12$, $p=.002$; DNS $r=.16$, $p=.004$).

Participants with higher polygenic scores for educational attainment had larger brains in

two samples. Finally, we tested if participants with higher polygenic scores tended to have larger brains. Meta-analysis estimated the cross-study effect-size as $r=.06$ ($p=.006$; 95% CI [.02, .10]). The test for evidence of heterogeneity in effect sizes across studies was statistically significant at the $\alpha=.05$ level (I-squared=71.8%, $p=.014$; tau-squared=.001). Participants with higher polygenic scores had larger brains in the UK Biobank ($r=.09$, $p<.001$) and the Dunedin Study ($r=.07$, $p=.024$). Effect-sizes were smaller and not statistically significant in the GSP $r=.02$, $p=.380$ and DNS $r=.04$, $p=.288$.

Brain size was a weak mediator of the polygenic-score associations with cognitive test

scores in two study samples. To test the hypothesis that larger brains mediated the polygenic score association with intelligence, we used the system of equations described by Baron and Kenny (Baron and Kenny 1986) and the methods described by Preacher et al. (Preacher and Hayes 2008). Meta-analysis estimated the cross-study indirect effect to be $b=.01$, 95% CI [.00, .02], $p=.045$, with evidence of heterogeneity in effect sizes across studies (I-squared=79.5%, $p=.003$; tau-squared=.000). The mediation effect was statistically significant in the UK Biobank ($b=.02$, 95% CI [.01, .02], $p<.001$) and the Dunedin Study ($b=.02$, 95% CI [.00, .05], $p=.028$). We did not find evidence of a mediation effect in the GSP $b=.00$, 95% CI [.00, .00], $p=.36$) or DNS $b=.01$, 95% CI [-.00, .02], $p=.24$ (for details see table S2).

Sensitivity analysis: Associations among polygenic scores, brain size, and cognitive test

scores were partially attenuated by range restriction. UK Biobank and Dunedin Study participants' polygenic scores, brain size, and cognitive test performance were positively

correlated, with similar effect-sizes (Dunedin-study effect-sizes for analyses including IQ were somewhat larger, possibly reflecting greater measurement precision of the WAIS as compared to the UK Biobank reason-and-logic-puzzle test). By comparison, effect-sizes for these associations were smaller among GSP and DNS participants. To test if this difference could reflect the relatively restricted range of cognitive test performance in the GSP and DNS samples relative to the population-based UK Biobank and Dunedin samples, we conducted sensitivity analysis. Cognitive test scores were on average, 1-1.5 SDs higher in the GSP and DNS samples as compared to the general population and 30-50% less variable, indicating restricted range (Table 1). Sensitivity analysis restricted the UK Biobank sample – the largest study in our analysis – to participants with cognitive test scores 1 SD above the mean (i.e. scores of 9-13; $n=1,391$) for which the variance was approximately 45% of the full-sample variance. In this restricted sample, associations among participants' polygenic scores, brain size, and cognitive test performance were attenuated by roughly 1/3 to 1/2 relative to the full-sample estimates (Supplemental Table S3). Parallel analysis testing restriction at the other end of the cognitive test score distribution yielded similar results (Supplemental Table S4). Statistical correction of effect-sizes for range restriction using Thorndike's formula (Stauffer and Mendoza 2001) yielded similar results (Supplemental Table S7).

Discussion

We analyzed data from four imaging-genetics studies in the UK, NZ, and US to test if genetic associations with cognitive performance were mediated by differences in brain size. As anticipated, we found that participants with higher educational-attainment polygenic scores tended to score higher on tests of cognitive performance, as did those with larger brains. We also

found new information, that participants with higher education polygenic scores tended to have larger brains. In mediation analysis, brain size accounted for only a small fraction of the association between participants' educational attainment polygenic scores and their cognitive performance, and this mediation effect was statistically significant in the population-based UK Biobank and Dunedin samples, but not in the GSP and DNS samples.

Effect-size variation across the samples we analyzed followed a consistent pattern; effect-sizes were larger in the population-based UK Biobank and Dunedin Study samples than in the GSP and DNS samples (see figures and table S1). One reason for these differences may be the more restricted range of variation in cognitive performance in the GSP and DNS samples arising from, e.g. overrepresentation of university-educated individuals. Such range restriction biases association estimates (Mendoza and Mumford 1987; Bland and Altman 2011) and has previously been shown to bias brain imaging research (Falk et al. 2013; Lewinn et al. 2017). In these relatively high-IQ and restricted-range samples, average cognitive performance was 1-1.5 standard deviations above the general-population mean and the variance was reduced by 30-50%. We conducted sensitivity analysis in a UK Biobank subsample selected to have high cognitive performance similar to the GSP and DNS samples. In this sample with restricted range of cognitive test performance, effect-sizes were attenuated by roughly 30-50%. We obtained similar estimates when we performed a statistical correction for range restriction using Thorndike's formula (Stauffer and Mendoza 2001). Selective observation of high-cognitive-performance individuals in the GSP and DNS samples may have contributed to the lower effect-size estimates in these samples and to overall heterogeneity across samples in our meta-analysis.

We acknowledge limitations of our current analyses, which can be addressed in future research. First, analyses were restricted to European-descent participants. We focused on

European-descent participants to match the population studied in the GWAS of educational attainment. Application of GWAS results from European-descent samples to compute polygenic scores for samples of different ancestry has uncertain validity (Martin et al. 2017). As GWAS of education and related phenotypes in non-European samples become available, replication in additional populations will be needed. Second, polygenic scores were measured with substantial error. Genetic effect-sizes thus represent lower-bound estimates. As larger-sample GWAS become available, error in polygenic score measurement will decline and effect-sizes can be expected to increase (Cesarini and Visscher 2017). A third education polygenic score is available, but we were unable to use EA3 to compare across cohorts because the discovery sample included all of UK Biobank (supplemental table S6 reports EA3 for the other samples). Measurement error may also affect the other variables in our analysis. For example, as noted by Gignac & Bates (Gignac and Bates 2017), effect-size estimates from more-reliable cognitive tests, such as the Wechsler Adult Intelligence Scale administered in the Dunedin Study, tend to be larger compared to effect-size estimates from briefer less-reliable cognitive tests. We report effect-sizes disattenuated for estimated measurement error and reliability using the approach proposed by Tucker-Drob (Tucker-drob 2017) in Supplemental Table S8. Third, total brain volume is only one route through which the genetics linked with educational attainment could affect cognitive performance. We studied this specific phenotype because it is the best-replicated neural correlate of cognitive function (Pietschnig et al. 2015). As more refined neural phenotypes of cognitive function are developed, including measures of cortical thickness, surface area, gyrification, and brain function, it will be important to test their potential mediating role in linking genetics with cognitive performance. Importantly, the hunt for neural phenotypes mediating genetic associations with cognitive performance need not assume that education-

linked genetics directly affect brain development. For example, there is evidence that exposure to education increases cognitive performance (Ritchie and Tucker-Drob 2018). It could be that higher education-linked genetics, and higher IQs, lead to more education, which in turn enhances brain size and other neural phenotypes.

We also cannot rule out age differences as a potential explanation for the difference in findings between the population-based UK Biobank and Dunedin Study samples as compared to the GSP and DNS samples. UK Biobank and Dunedin Study participants were measured in midlife, whereas GSP and DNS samples primarily included young adults. Among midlife UK Biobank participants, restricting the range of cognitive performance to be similar to the GSP and DNS samples reduced effect-sizes for associations among polygenic scores, brain size, and cognitive test performance. Population-based samples including both young and midlife individuals with DNA, MRI, and cognitive testing are needed to evaluate whether genetic associations with brain volume and cognitive performance vary with age. A final concern is potential reverse causation between brain size and cognitive function. Higher cognitive ability and related educational and socioeconomic attainments may be protective of age-related decline in brain volume or they may promote brain development. As GWAS of these phenotypes become available, new and developing methods may help address this question (Burgess et al. 2015; Grotzinger et al. 2018). Ultimately, longitudinal studies with repeated measures of brain volume and cognition will be needed to further inform our understanding of the relationship between cognitive development and brain development.

Within the bounds of these limitations, our findings contribute to evidence that genetics discovered in GWAS of educational attainment influence brain development and cognitive function. Bioinformatic analysis of education GWAS results have identified enrichment of

variants near genes expressed in brain development, specifically neural proliferation, neural development, and dendrite formation (Okbay et al. 2016). Epidemiologic analysis of an education-GWAS-based polygenic score found that children who carried more education-associated genetic variants scored higher on cognitive tests as early as age 5 and that polygenic-score-associated differences in cognitive test scores grew larger from middle childhood through adolescence (Belsky et al. 2016, 2018). Several studies have reported that an education-GWAS-based polygenic score is predictive of cognitive test performance in adolescents and adults (Domingue et al. 2015; Selzam et al. 2017; Plomin and von Stumm 2018). Here, we show that adults with higher education-GWAS-based polygenic scores have larger brains and score higher on cognitive tests as compared to peers with lower polygenic scores. Evidence for larger brains as a statistical mediator of polygenic score associations with cognitive performance was mixed in our analysis. But findings suggest promise for future neuroscientific investigation of education-linked genetics. One design to complement formal mediation analysis is gene-environment interaction analysis to test if exposures that slow brain growth or restrict brain size, e.g., Zika virus (Calvet et al. 2016), diminish associations between genetics and cognitive performance.

Our finding that genetics associated with educational and socioeconomic attainments are also related to brain volume has implications for research on effects of poverty on the developing brain. Childhood poverty exposure is associated with smaller brain volumes (Luby et al. 2013; Hair et al. 2015). Education polygenic scores also tend to be lower in children growing up in poorer families, a gene-environment correlation that presumably reflects effects of education-linked genetics on parents' economic attainments, which children inherit along with their genotypes (Belsky et al. 2016). Studies that include controls for education genetics could

complement intervention studies (Brody et al. 2017) to help rule out potential confounding in associations between poverty and brain development.

A challenge facing research on how genetics affect the brain is the lack of population-representative samples with available brain imaging data. Human brain-imaging research has typically been conducted in samples similar to those in the GSP and DNS whose data we analyzed (Sears 1986; Peterson and Merunka 2014). Our findings illustrate how studies of samples pre-selected for high levels of cognitive functioning and related characteristics impose limitations on analysis of cognition-related neurobiology. Opportunities to understand the brain afforded by 21st Century measurement technologies must still reckon with 20th Century discoveries about selection bias (Berkson 1946; Heckman 1979). Efforts to recruit more representative samples that reflect the full range of cognitive functioning in the population are needed.

Individual differences in cognitive performance have a partial genetic etiology (Plomin and Deary 2015; Plomin and von Stumm 2018). This genetic etiology should be evident in individual differences in brain biology. As GWAS discoveries for intelligence and related traits clarify genetic etiology, follow-up in genetically-informed brain imaging studies can shed light on the neurobiological correlates of this genetic variation. Our findings encourage enthusiasm for this research, but also highlight limitations of existing data resources. Recruiting and retaining samples that are representative of the general population must be a priority in neuroscience research.

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Tables

Table 1. Samples and measures included in analysis. Polygenic scores for all samples were computed based on the most recent GWAS of educational attainment (Okbay et al. 2016) following established methods.

Sample	Cognitive Test	Total Brain Volume (cm³)
<p><i>United Kingdom Biobank (UK Biobank)</i>(Sudlow et al. 2015): An ongoing general population-based cohort of volunteers that was recruited from the UK National Health Service records beginning in 2006.</p> <p>N = 5691 54% female. Age M = 61.35, SD = 7.08</p>	<p>13 verbal-numeric reasoning puzzles completed during a 2-minute time test (Lyll et al. 2016). Scored as number of correct responses.</p> <p>M = 6.97, SD = 2.10</p>	<p>Total brain volume was derived from T1 weighted structural MRI images processed with Sienax (Smith et al. 2002)</p> <p>M = 1172.18, SD = 110.95</p>
<p><i>Dunedin Multidisciplinary Health and Development Study (DMHDS)</i> (Poulton et al. 2015): a population representative birth cohort born 1972-3 in Dunedin, New Zealand. Note: Here we report the available N, as of 2.2018, while data collection is ongoing.</p> <p>N = 596 52% female Intelligence testing age = 38, MRI testing age = 45</p>	<p>Wechsler Adult Intelligence Scale-IV (WAIS-IV) (Wechsler 1997): Scored against a population norm with mean of 100 and standard deviation of 15.</p> <p>M = 100, SD = 15</p>	<p>Total brain volume was derived from the recon-all pipeline in Freesurfer (Fischl 2012) using T1 and T2 weighted structural MRI images.</p> <p>M = 1224.48, SD = 124.19</p>
<p><i>Brain Genomics Superstruct Project (GSP)</i> (Holmes et al. 2015): a convenience sample of Boston area healthy volunteers primarily recruited from local universities and medical centers.</p> <p>N = 1163 53% Female Age M = 22.23, SD = 5.53</p>	<p>Shipley Institute of Living Scale (Zachary 1986). Scored against a population norm with mean of 100 and standard deviation of 15.</p> <p>M = 113, SD = 9</p>	<p>Total brain volume was derived from the recon-all pipeline in Freesurfer (Fischl 2012) using T1 and T2 weighted structural MRI images.</p> <p>M = 1174.58, SD = 110.64</p>
<p><i>Duke Neurogenetics Study (DNS)</i>: A convenience sample of university students primarily from Duke University.</p> <p>N = 515 53% female Age M = 20.26, SD = 1.20</p>	<p>Matrix reasoning and vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence(Wechsler 2013) (WASI) Scored against a population norm with mean of 100 and standard deviation of 15.</p> <p>M= 124, SD = 7</p>	<p>Total brain volume was derived from the recon-all pipeline in Freesurfer (Fischl 2012) using T1 weighted structural MRI images.</p> <p>M = 1162.40, SD = 110.34</p>

Figures

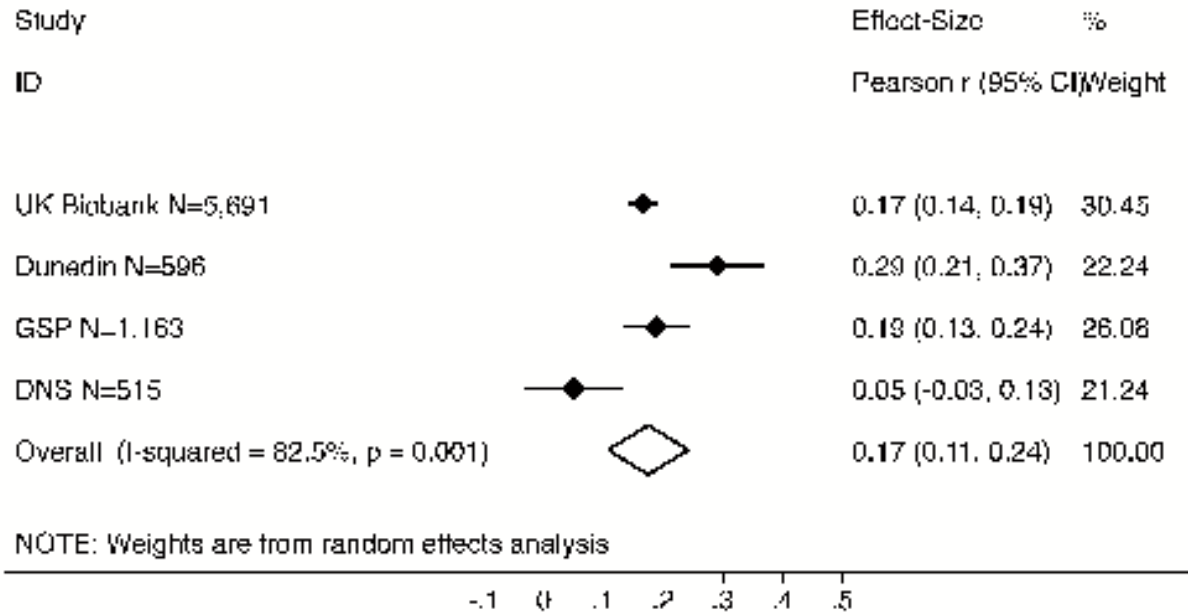


Figure 1. Educational attainment polygenic score associations with cognitive test scores. The figure shows a graph of effect-sizes for analyses of the UK Biobank, Dunedin Study (Dunedin), Brain Genomics Superstruct Project (GSP) and Duke Neurogenetics Study (DNS) samples (solid blue diamonds) and the cross-study effect-size estimated from random-effects meta-analysis (open blue diamond). Gray boxes around the solid-blue diamonds show the weighting of study-specific estimates in the meta-analysis (larger gray boxes indicate higher weights). 95% CIs for estimates are shown as error bars for the study-specific estimates and as the left- and right-extremes of the diamond for the meta-analysis effect-size. The meta-analysis estimate of between-study heterogeneity (I-squared) is listed to the left of the open blue diamond showing the meta-analysis effect-size. The table to the right of the effect-size graph reports values for effect-sizes, 95% CIs, and meta-analysis weights.

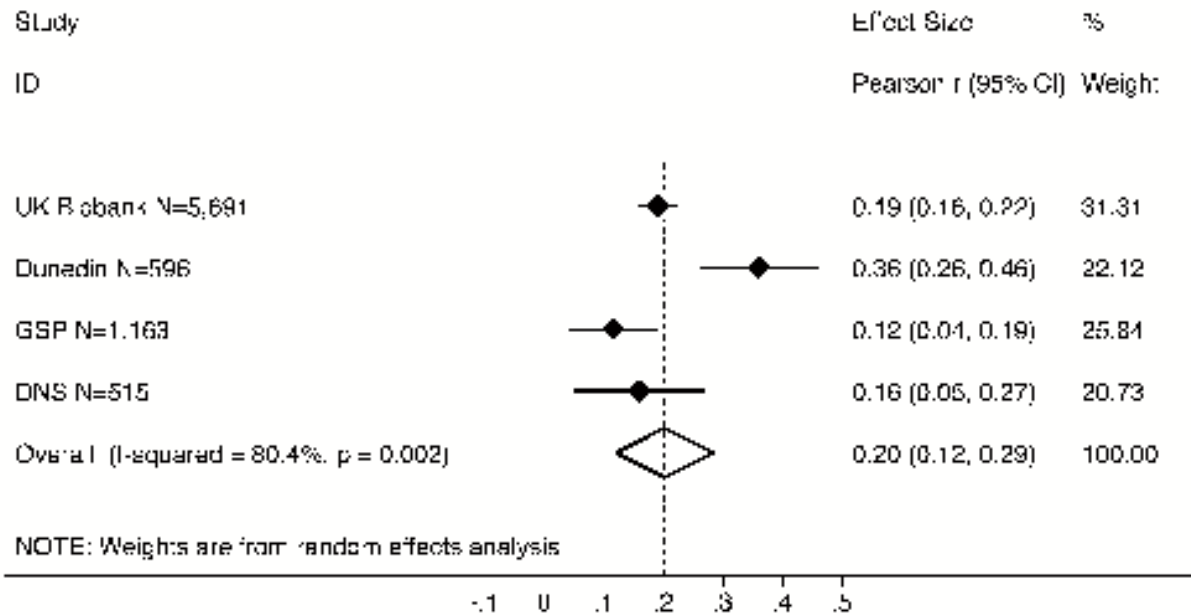


Figure 2. Associations between brain size and cognitive test scores. The figure shows a graph of effect-sizes for analyses of the UK Biobank, Dunedin Study (Dunedin), Brain Genomics Superstruct Project (GSP) and Duke Neurogenetics Study (DNS) samples (solid blue diamonds) and the cross-study effect-size estimated from random-effects meta-analysis (open blue diamond). Gray boxes around the solid-blue diamonds show the weighting of study-specific estimates in the meta-analysis (larger gray boxes indicate higher weights). 95% CIs for estimates are shown as error bars for the study-specific estimates and as the left- and right-extremes of the diamond for the meta-analysis effect-size. The meta-analysis estimate of between-study heterogeneity (I-squared) is listed to the left of the open blue diamond showing the meta-analysis effect-size. The table to the right of the effect-size graph reports values for effect-sizes, 95% CIs, and meta-analysis weights.

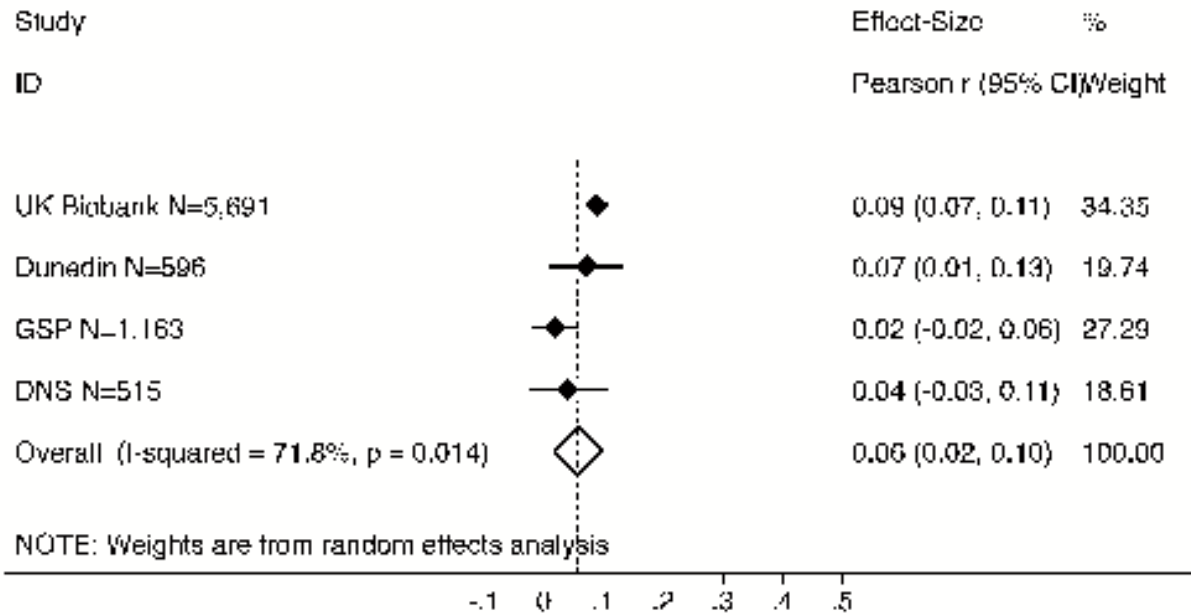


Figure 3. Educational attainment polygenic score associations with brain size. The figure shows a graph of effect-sizes for analyses of the UK Biobank, Dunedin Study (Dunedin), Brain Genomics Superstruct Project (GSP) and Duke Neurogenetics Study (DNS) samples (solid blue diamonds) and the cross-study effect-size estimated from random-effects meta-analysis (open blue diamond). Gray boxes around the solid-blue diamonds show the weighting of study-specific estimates in the meta-analysis (larger gray boxes indicate higher weights). 95% CIs for estimates are shown as error bars for the study-specific estimates and as the left- and right-extremes of the diamond for the meta-analysis effect-size. The meta-analysis estimate of between-study heterogeneity (I-squared) is listed to the left of the open blue diamond showing the meta-analysis effect-size. The table to the right of the effect-size graph reports values for effect-sizes, 95% CIs, and meta-analysis weights.

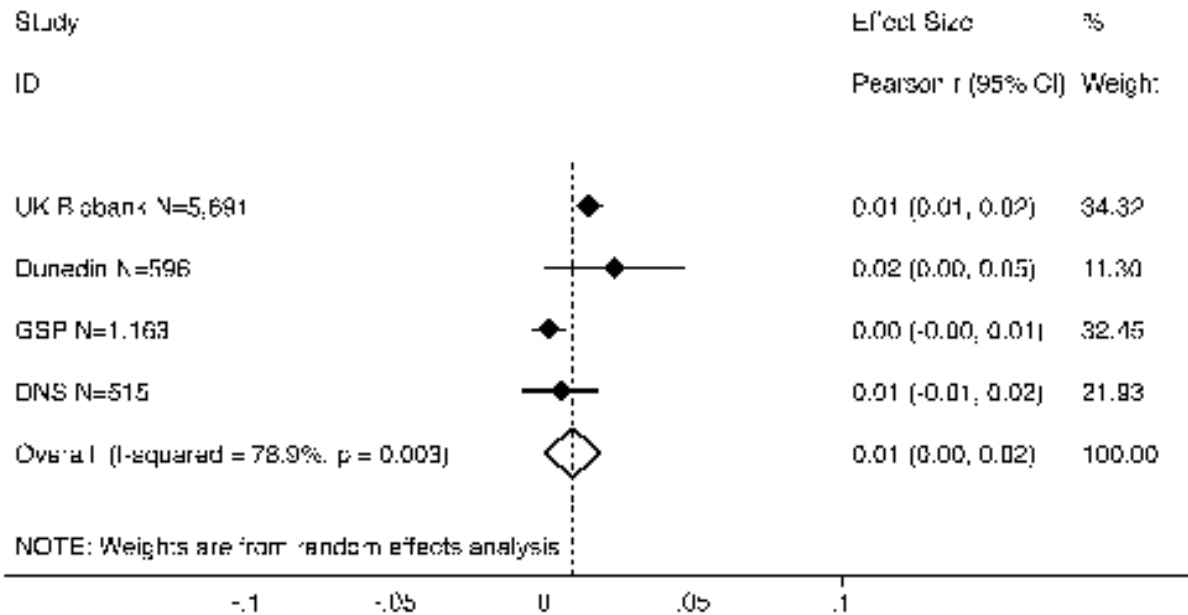


Figure 4. Mediation effect of brain size on the association between the polygenic score for educational attainment and cognitive test scores. The figure shows a graph of effect-sizes for analyses of the UK Biobank, Dunedin Study (Dunedin), Brain Genomics Superstruct Project (GSP) and Duke Neurogenetics Study (DNS) samples (solid blue diamonds) and the cross-study effect-size estimated from random-effects meta-analysis (open blue diamond). Gray boxes around the solid-blue diamonds show the weighting of study-specific estimates in the meta-analysis (larger gray boxes indicate higher weights). 95% CIs for estimates are shown as error bars for the study-specific estimates and as the left- and right-extremes of the diamond for the meta-analysis effect-size. The meta-analysis estimate of between-study heterogeneity (I-squared) is listed to the left of the open blue diamond showing the meta-analysis effect-size. The table to the right of the effect-size graph reports values for effect-sizes, 95% CIs, and meta-analysis weights.