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Common Polygenic Variations for Psychiatric Disorders and Cognition in Relation to Brain Morphology in the General Pediatric Population

Silvia Alemany, PhD, Philip R. Jansen, MD, MSc, Ryan L. Muetzel, PhD, Natália Marques, BSc, Hanan El Marroun, MD, PhD, Vincent W.V. Jaddoe, MD, PhD, Tinca J.C. Polderman, PhD, Henning Tiemeier, MD, PhD, Danielle Posthuma, PhD, Tonya White, MD, PhD

Objective: This study examined the relation between polygenic scores (PGSs) for 5 major psychiatric disorders and 2 cognitive traits with brain magnetic resonance imaging morphologic measurements in a large population-based sample of children. In addition, this study tested for differences in brain morphology-mediated associations between PGSs for psychiatric disorders and PGSs for related behavioral phenotypes.

Method: Participants included 1,139 children from the Generation R Study assessed at 10 years of age with genotype and neuroimaging data available. PGSs were calculated for schizophrenia, bipolar disorder, major depression disorder, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, intelligence, and educational attainment using results from the most recent genome-wide association studies. Image processing was performed using FreeSurfer to extract cortical and subcortical brain volumes.

Results: Greater genetic susceptibility for ADHD was associated with smaller caudate volume (strongest prior = 0.01: $\beta = -0.07$, $p = .006$). In boys, mediation analysis estimates showed that 11% of the association between the PGS for ADHD and the PGS attention problems was mediated by differences in caudate volume ($n = 535$), whereas mediation was not significant in girls or the entire sample. PGSs for educational attainment and intelligence showed positive associations with total brain volume (strongest prior = 0.5: $\beta = 0.14$, $p = 7.12 \times 10^{-8}$; and $\beta = 0.12$, $p = 6.87 \times 10^{-7}$, respectively).

Conclusion: The present findings indicate that the neurobiological manifestation of polygenic susceptibility for ADHD, educational attainment, and intelligence involve early morphologic differences in caudate and total brain volumes in childhood. Furthermore, the genetic risk for ADHD might influence attention problems through the caudate nucleus in boys.

Key words: polygenic risk score, neuroimaging, ADHD, educational attainment, intelligence

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Findings from genome-wide association studies (GWASs) indicate that multiple common genetic variants of small effect contribute to the etiology of psychiatric disorders, implying a highly polygenic architecture.¹ However, it remains largely unknown how these common genetic variants ultimately contribute to the development of psychiatric symptoms.

Polygenic scores (PGSs) are increasingly being used to index individual genetic susceptibility for a given disorder or trait and explore shared genetic influences across phenotypes to improve understanding of disease etiology.² Studies in childhood have shown that the polygenic risk for schizophrenia (SCZ) is associated with lower cognitive abilities, greater social impairments, more behavioral problems, and psychopathology.^{3–5} Interestingly, previous work from our

group found that genetic susceptibility for educational attainment (EA; years of schooling) was inversely related to child behavioral problems.⁴ In a large prospective study, polygenic risk for major depressive disorder (MDD) was associated with emotional problems in adulthood, but not earlier in life.⁶ Similarly, a study of genetic risk for bipolar disorder (BD) in adult samples suggested an association with increased risk for different psychiatric disorders.⁷ For childhood-onset psychiatric disorders, PGSs for attention-deficit/hyperactivity disorder (ADHD) have been associated with inattentive and hyperactive-impulsive traits, worse educational outcomes, and lower IQ in children and adolescents from the general population.^{8,9}

Genetic susceptibility to psychopathology and cognitive function has been linked to behavior,⁴ which could imply

that heritable neurobiological mechanisms are at play in the early presentation of symptoms. Within this context, it is well established that brain morphology during development is strongly influenced by genetic factors.¹⁰ Furthermore, widespread morphologic brain abnormalities have been associated with the pathophysiology of major psychiatric disorders.¹¹⁻¹⁵ Although genetic and environmental factors can account for these brain abnormalities, we expect that genetic susceptibility for psychiatric disorders are associated with variations in brain morphology. Indeed, several studies have reported relations between PGSs for psychiatric disorders and PGSs for structural brain magnetic resonance imaging (MRI) measurements in adults using medium to large samples in the context of imaging genetics.¹⁶⁻¹⁹ Higher genetic risk for SCZ was related to total brain volume (TBV) in patients with SCZ ($n = 152$) and controls ($n = 142$),¹⁶ although this finding was not replicated using 2 large general population-based samples ($n = 763$ and $n = 707$).¹⁷ Other studies in healthy populations have related polygenic risk for SCZ and BD to reduced globus pallidus and amygdala volumes ($N = 274$).¹⁸ However, one of the largest studies to date did not find evidence for associations between polygenic risk for SCZ, BD, or MDD and subcortical brain volumes using data from the UK Biobank study ($N = 978$).¹⁹ Furthermore, to our knowledge, no study has yet been conducted in a pediatric MRI sample representative of the general population. Thus, whether associations of polygenic susceptibility for major psychiatric disorders and brain morphology are present earlier in life is largely unclear. Because autism spectrum disorders (ASD) and ADHD are childhood-onset psychiatric disorders, the study of polygenic risk for these traits in pediatric samples is particularly relevant. To date, this has been hampered by the lack of large-scale imaging studies in children that include genetic data.

Against this backdrop, the goal of this study was to examine the association of polygenic susceptibility for 5 psychiatric disorders and 2 cognitive outcomes with global and subcortical brain volumes in a large population-based sample of school-age children. As a secondary aim, this study investigated the potential mediating role of brain morphologic variation in associations between PGSs for psychiatric disorders and those for related behavioral phenotypes.

We hypothesized that polygenic susceptibility for SCZ, BD, MDD, ASDs, and ADHD would be associated with brain morphologic characteristics that overlap with brain abnormalities consistently reported in patients affected by these disorders. For EA and intelligence, we hypothesized that PGSs for these traits would be positively associated with global brain morphology measures.

METHOD

Study Population

Participants were drawn from the Generation R Study, an ongoing population-based cohort study of many domains of child development.²⁰ As part of the cohort's MRI study, 3,992 children were scanned from March 2013 through November 2015, corresponding to visits of the 9- to-11-year-old Generation R sample.²¹ Of these children, 3,937 had images that were reconstructed using FreeSurfer 6.0 (<http://surfer.nmr.mgh.harvard.edu/>). One hundred thirty-one children were excluded due to the use of a different sequence ($n = 22$), dental braces ($n = 87$), and the presence of incidental findings ($n = 22$).²² Of the remaining 3,806, 620 scans were excluded due to data rated as unusable after visual inspection of segmentation quality. This left 3,186 children with good-quality MRI data. Of these, genotype data were available for 1,189 children with European ancestry. Relatedness and genotype quality resulted in an additional exclusion of 50 children. Thus, the final sample included 1,139 participants (flowchart in Figure S1, available online).

The study protocol was approved by the medical ethics committee of the Erasmus University Medical Center (Rotterdam, the Netherlands). Written informed consent was obtained from the legal representatives of all participants.

Magnetic Resonance Imaging

To familiarize participants with the MRI scanning environment, all children underwent a mock scanning session. Structural MRI scans were obtained on a 3-T scanner (Discovery MR750W; GE Worldwide, Milwaukee, WI). Whole-brain high-resolution T1-weighted inversion recovery fast spoiled gradient recalled sequences were obtained using an 8-channel head coil. The scan parameters were repetition time of 8.77 ms, echo time of 3.4 ms, inversion time of 600 ms, flip angle of 10°, field of view of 220 × 220 mm, acquisition matrix of 220 × 220, asset acceleration factor of 2, b of 900 s/mm², 230 contiguous slices with a thickness of 1.0 mm, and in-plane resolution of 1.0 × 1.0 mm. Further details on the design and protocol of the Generation R cohort's MRI study can be found elsewhere.²¹

Cortical reconstruction and volumetric segmentation were carried out with FreeSurfer Image Analysis Suite 6.0.²³ Specifically, automatic parcellation and segmentation protocols were conducted using the recon-all stream to obtain total, cortical, and subcortical brain volumes. All images were inspected for surface reconstruction accuracy using automated and manual methods.²⁴ Based on previous research investigating brain abnormalities in psychiatric disorders,¹¹⁻¹⁵ 10 volumetric brain measures were studied as

outcomes: TBV, cortical gray matter (GM), total white matter, subcortical GM, ventricular volume, and cerebellum as global segmented brain measurements; and amygdala-hippocampus complex, caudate, putamen, and thalamus as subcortical brain volumes. Correlations between brain measurements are shown in Figure S2, available online.

Genotyping

DNA samples were collected from cord blood at birth or from venipuncture during a visit to the research center on Illumina 610K and 660K single-nucleotide polymorphism arrays depending on collection time (Illumina, San Diego, CA). Further details on genotype calling procedures in the Generation R Study can be found elsewhere.²⁵ Information on quality control procedures of the genotype data and principal component analysis can be found in Supplement 1, available online.

Polygenic Scoring

Only participants with European ancestry were selected for polygenic scoring. Genotype data that passed quality control were used to compute PGSs based on GWAS results for 5 psychiatric traits—SCZ, BD, MDD, ADHD, and ASD—from the Psychiatric Genomics Consortium. In addition, we calculated PGSs for EA and intelligence. Table S1, available online, provides an overview of the GWASs used for PGS calculation. For intelligence, we repeated the GWAS meta-analysis after exclusion of the Generation R sample to ensure independence of discovery and target sample.

The PGSs were computed using LDpred.²⁶ This polygenic scoring method infers the posterior mean effect size of each marker using a prior on effect size distribution and linkage disequilibrium information from a reference genotype panel. The LDpred algorithm has improved prediction accuracy compared with traditional methods. Six PGSs were computed for each trait corresponding to 6 priors that determined the proportion of single-nucleotide polymorphisms with a causal effect (0.01, 0.05, 0.1, 0.5, 1, and infinitesimal). All PGSs were standardized to a mean of 0 and a standard deviation (SD) of 1. Correlations between PGSs are shown in Figure S3, available online.

Statistical Analysis

Multiple linear regression analyses were conducted using R 3.3.1 (<https://www.r-project.org/>). To examine whether genetic susceptibility for major psychiatric disorders and cognition is related to brain morphology, each PGS was tested for association with each brain measure individually. In these models, brain measurements were assigned as dependent variables with PGSs for SCZ, BD, ADHD,

ASD, EA, or intelligence generated at 6 LDpred priors as independent variables. Models with TBV as the outcome were adjusted by sex, age, and 4 genetic principal components. Models for the remaining brain measurements also were adjusted by total intracranial volume.

We corrected for multiple testing across all PGSs, generated at 6 different priors, for association with 10 brain measurements using the false discovery rate (FDR) method.²⁷ Results at a *p* value less than .05 by FDR correction were considered statistically significant.

For statistically significant associations showing a consistent pattern of results, we performed mediation analyses to examine whether differences in the associated brain regions mediated associations between the PGS and the phenotypic manifestation of the polygenic trait. Multiple linear regressions analyses were conducted to examine associations among PGSs, brain measurements, and behavioral phenotypes by adjusting for the same covariates included in the primary analyses and age at behavioral assessment. Direct, indirect, and total effects were estimated using the “mediation” package in R. As long as the assumptions of the mediation analysis are met, the direct effect represents the effect of genetic susceptibility on behavioral phenotypes after controlling for variation in brain morphology, and the indirect effect represents the estimated effect of polygenic susceptibility operating through brain morphology.²⁸ The proportion of mediation by brain morphology can be calculated as the ratio of indirect effect to total effect. Given the data available in Generation R, mediation analyses were feasible only for associations with PGSs for psychiatric disorders for which behavioral data were assessed when children were 8 to 11 years of age (mean 9.7, SD 0.23, range 8.85–11.54) using the (Child Behavior Checklist [CBCL]/6-18).²⁹ Genetic, neuroimaging, and behavioral data were available for 1,053 participants. Further details on behavioral assessment can be found elsewhere.²¹ For psychiatric disorders with sex differences in prevalence, we also conducted stratified analysis by sex.

To elucidate whether each cognitive trait independently contributed to the variation in brain measurement, we performed sensitivity analyses for analyses between the PGSs for EA and intelligence and for TBV by mutually adjusting using the PGSs for intelligence and EA, respectively.

RESULTS

Sample Characteristics

A total of 1,139 children were included in the present study (561 girls [49.30%]), and the mean age was 10.16 years (SD 0.60, range 8.72–11.99).

Effects of PGS on Brain Morphology

Figure 1 presents a summary of the associations between the PGS for psychiatric disorders and the PGS for cognition calculated at 6 priors and brain volumes. Full results for these associations are presented in Table S2, available online.

No significant associations were observed between PGSs for SCZ and BD and brain measurements.

Greater genetic susceptibility for MDD was consistently related to smaller TBV, with the strongest association for the infinitesimal prior ($\beta = -0.07$, standard error [SE] 0.03; $p_{\text{uncorrected}} = .009$). PGS for MDD also showed negative associations with total white matter (prior = 0.01: $\beta = -0.03$, SE 0.01, $p_{\text{uncorrected}} = .043$), cerebellum volume (prior = 0.5: $\beta = -0.05$, SE 0.02, $p_{\text{uncorrected}} = .042$; prior = 1: $\beta = -0.05$, SE 0.02, $p_{\text{uncorrected}} = .040$), and thalamus volume (prior = 0.01: $\beta = -0.05$, SE 0.02, $p_{\text{uncorrected}} = .009$). However, after FDR correction, none of these associations remained significant.

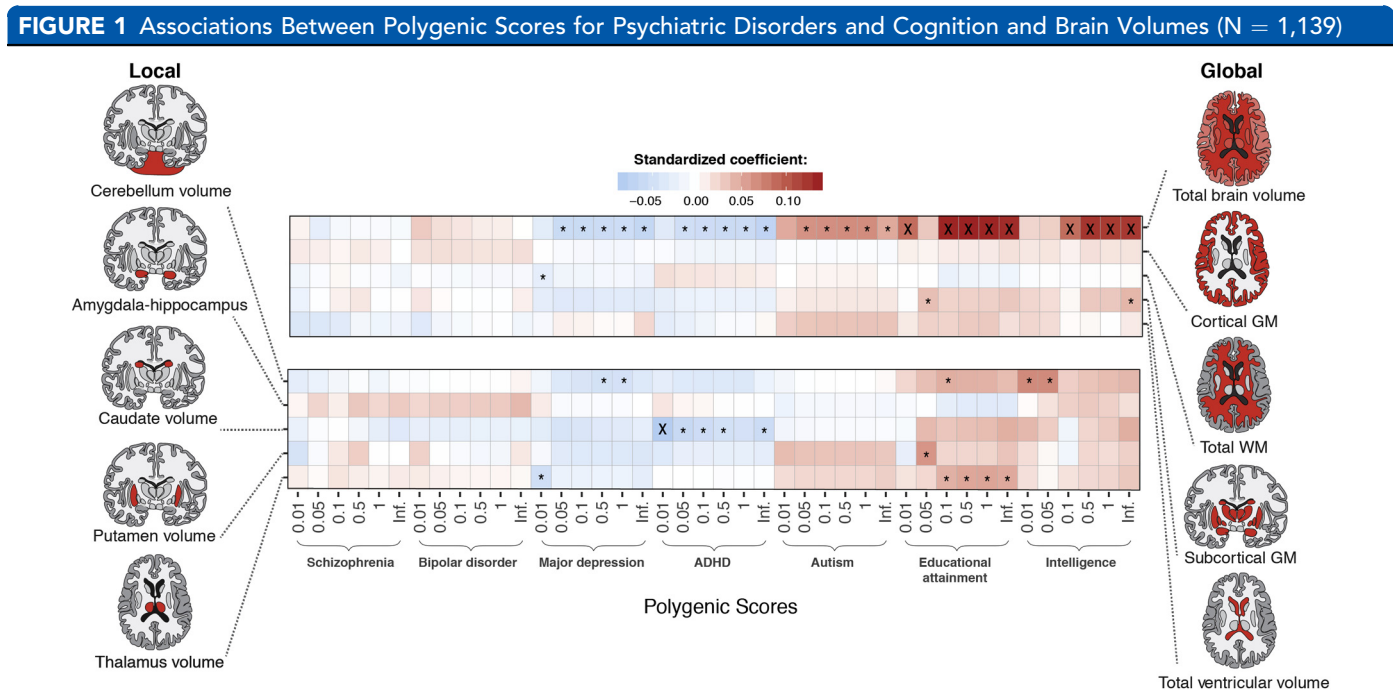
PGSs for ADHD were associated with smaller TBV and caudate volume across all priors, although associations did not reach statistical significance for prior 0.01 in the case of TBV and prior 1 in the case of caudate volume. The strongest association with TBV was observed at the infinitesimal prior ($\beta = -0.07$, SE 0.03, $p_{\text{uncorrected}} = .006$), and the strongest association with caudate volume was observed

at prior 0.01 ($\beta = -0.08$, SE 0.03, $p_{\text{uncorrected}} = 7.49 \times 10^{-4}$) and remained significant after FDR correction.

PGS for ASD showed positive associations with TBV at all priors except at prior 0.01, which did not reach significance but did show the same direction of effect. The largest magnitude of the association was observed at prior 1 ($\beta = 0.07$, SE 0.03; $p_{\text{uncorrected}} = 7.75 \times 10^{-3}$). These associations did not surpass FDR correction.

The EA PGSs were consistently associated with larger TBV (strongest prior 0.5: $\beta = 0.14$, SE 0.03, $p_{\text{uncorrected}} = 7.12 \times 10^{-8}$) and remained significant after FDR correction. Associations at prior 0.05 did not reach significance but showed the same direction of effect. Greater genetic susceptibility for EA also was associated with larger volumes of subcortical GM (prior = 0.05: $\beta = 0.04$, SE 0.02, $p_{\text{uncorrected}} = .046$), cerebellum (prior = 0.1: $\beta = 0.05$, SE 0.02, $p_{\text{uncorrected}} = .047$), putamen (prior = 0.05: $\beta = 0.06$, SE 0.03, $p_{\text{uncorrected}} = .016$), and thalamus at multiples priors (strongest prior = 1: $\beta = 0.05$, SE 0.02, $p_{\text{uncorrected}} = .012$).

Greater genetic susceptibility for intelligence was significantly related to larger TBV for most priors, even after FDR correction (strongest prior 0.5: $\beta = 0.12$, SE 0.03, $p_{\text{uncorrected}} = 6.87 \times 10^{-7}$). Other associations not surviving FDR correction included a positive association with subcortical GM (infinitesimal prior: $\beta = 0.04$, SE 0.02,



Note: All associations were adjusted for sex, age, total intracranial volume (except associations with total brain volume) and the first 4 genetic components. Uncorrected p values less than .05 (*) and p values less than .05 by false discovery rate correction (X) are presented. ADHD = attention-deficit/hyperactivity disorder; GM = gray matter; WM = white matter.

$p_{\text{uncorrected}} = .024$) and positive associations with cerebellum volume (priors 0.01 and 0.05: $\beta = 0.07$, SE 0.02, $p_{\text{uncorrected}} = .003$).

Mediation Analysis

Only the association between polygenic risk for ADHD and caudate volume survived FDR correction; therefore, we tested whether caudate volume mediated the association between polygenic risk for ADHD and the attention problems CBCL syndrome scale. The caudate nucleus met the conditions to act as a mediator, because it showed a negative significant association with attention problems ($\beta = -0.06$, SE 0.00, $p = .029$). Similarly, polygenic risk for ADHD was significantly associated with attention problems ($\beta = 0.12$, SE 0.00, $p = 5.36 \times 10^{-5}$). However, mediation was 4.6% and not significant within the entire sample (Figure 2). In analyses stratified by sex, mediation was significant only in boys, indicating that 11% of the association between polygenic risk for ADHD (prior = 0.01) and attention problems might be mediated by differences in caudate volume (Figure 2).

Sensitivity Analysis

Analyses mutually adjusting for polygenic susceptibility for EA and intelligence at prior 0.05 showed that the PGSs for these 2 traits were independently associated with TBV (PGS for EA: $\beta = 0.10$, SE 0.03, $p = 2.6 \times 10^{-4}$; PGS for intelligence: $\beta = 0.08$, SE 0.03, $p = .003$).

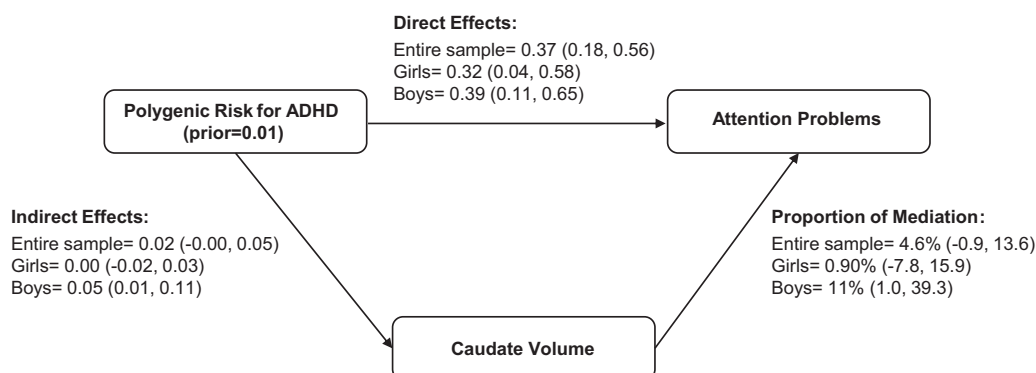
DISCUSSION

We examined whether polygenic susceptibility for psychiatric disorders and cognition was associated with brain morphology in children. We found a consistent pattern of

results across priors, indicating that the polygenic risk for ADHD was negatively associated with caudate volume, with the finding of a prior of 0.01 surviving multiple testing correction. Polygenic susceptibility for intelligence and EA showed a positive relation with TBV that was consistent across all priors used, although generally not significant for the more stringent priors (ie, 0.05 and 0.01). Polygenic risk for SCZ and BD did not show significant associations with brain morphology; however, several brain measurements were related to PGSs for MDD and ASD, although none of these associations survived multiple testing correction. These findings indicate the neurobiological manifestation of polygenic susceptibility for ADHD, intelligence, and EA involves early morphologic differences in caudate volume and TBV during development.

Whole-brain and caudate volume reductions have been related to ADHD in a recent mega-analysis.¹⁴ Given the high heritability of ADHD,³⁰ we expected that regions previously associated with the disorder also would be associated with polygenic risk for ADHD. To the best of our knowledge, this is the first study providing evidence indicating that polygenic risk for ADHD might be, at least in part, underlying TBV and caudate reductions in childhood. These findings are particularly relevant for caudate volume reduction, one of the most replicated findings in ADHD.³¹ Interestingly, our results suggest that reduced caudate volume might be mediating the association between polygenic risk for ADHD and attention problems in boys. ADHD is 2 to 9 times more prevalent in boys during childhood and adolescence.³² Sex differences in brain morphology have been used to investigate whether ADHD-related brain abnormalities are more pronounced in male versus female individuals. Although caudate volume did not show sex

FIGURE 2 Mediation Analysis of Estimated Effect (95% CI) of Polygenic Risk for Attention-Deficit/Hyperactivity Disorder (ADHD; Prior = 0.01) on Attention Problems (Child Behavior Checklist Syndrome Scale) Through Caudate Volume



Note: The figure shows caudate volume as a potential mediator, estimates of indirect and direct effects, and the proportion of mediation. All models were adjusted for age at magnetic resonance imaging, age at Child Behavior Checklist administration, total intracranial volume, and the first 4 genetic components. The entire sample ($N = 1,053$) was stratified by sex ($n = 535$ Boys; $n = 518$ Girls).

effects in the mega-analysis conducted by Hoogman *et al.*,¹⁴ another study examining the volume and shape of basal ganglia observed smaller caudate volumes in boys with ADHD compared with male controls and no differences among girls.³³ Similarly, smaller caudate volumes have been found in adult male patients with ADHD compared with male controls, whereas no differences were observed in women.³⁴ Our findings are in line with these studies supporting that different genetically influenced neurobiological mechanisms might be operating in male and female individuals in the context of ADHD.

The EA PGSs were associated with larger TBV. Intracranial volume has been previously related to EA genetic variants by applying linkage disequilibrium score regression methodology.³⁵ Genetic variants for EA or other traits can affect TBV directly, through direct gene expression, through gene-environment interaction or correlation mechanisms, or through intermediate phenotypes. Remarkably, an important number of single-nucleotide polymorphisms related to EA are located within genomic regions regulating gene expression in the fetal brain and genes mainly expressed in neural tissue.³⁵ These genes are especially active during the prenatal period and enriched for biological pathways involved in neural development.³⁵ Thus, it is likely that polygenic susceptibility for EA includes variants that directly promote optimal brain development. Another possibility would be that EA genetic variants could influence brain morphology through environmental exposures that positively affect brain development, which would imply gene-environment correlation effects. In fact, children with higher genetic loading for EA tend to be raised in socioeconomically advantaged environments,³⁶ which positively affects brain development.³⁷ It also is important to note that genetic associations with EA can be mediated by other phenotypes such as intelligence or personality traits, which are considered intermediate phenotypes for EA.³⁸ In addition, higher genetic loading for EA was nominally associated with larger thalamus volumes at multiple priors. The thalamus is a major hub in the brain, relaying multimodal information covering a wide range of cognitive functions, including learning, memory, inhibitory control, decision making, control of visual orienting responses, and attention.³⁹ Thus, a relation between polygenic susceptibility for cognitive functions relevant for EA with increased volume of the thalamus is neurobiologically plausible.

Not surprisingly, our findings on polygenic susceptibility for intelligence and EA largely overlap in the strength of the association and variance explained by TBV. Similarly to EA, genetic variants related to intelligence were identified in genes predominantly expressed in brain tissue.⁴⁰ Interestingly, polygenic susceptibility for EA and for intelligence

influenced TBV independently of each other. Because the correlation between the PGSs for EA and intelligence was not extremely strong (Figure S3, available online), we speculate that genetic variants related to these traits might act through different pathways. Studies have shown that TBV is positively correlated with intelligence, accounting for approximately 16% of the variance in IQ.⁴¹ Furthermore, our results indicate a shared genetic overlap between IQ and brain size, which is in line with twin studies suggesting that the association between these phenotypes is mainly of genetic origin.⁴²

Contrary to our hypothesis, polygenic risk for SCZ was not associated with brain morphologic variation at 9 to 11 years of age. This is in line with previous research in adults.^{17,19} However, this null finding was surprising, because we found an association between the PGSs for SCZ and internalizing symptoms, and especially thought problems.⁴ Behavioral effects of polygenic risk for SCZ must have neural correlates that we could not detect for several potential reasons. First, the neural correlates of SCZ PGS might be related to other neurobiological phenotypes not quantified in our study. This would not be the case for white matter measurements, including global and tract-specific fractional anisotropy and mean diffusivity, that were tested for an association with polygenic risk for SCZ in this sample and showed negative results.⁴³ Also, polygenic risk for SCZ has been associated with functional brain parameters, such as brain activation patterns detectable with functional MRI during cognitive tasks in adolescents.^{44,45} Second, brain structural abnormalities related to genetic risk for SCZ might be detectable only in young individuals beginning in the prodromal phase, when the illness has begun to show clinical manifestations. These finding is “unmasked” as the illness progresses, making it very difficult to observe in general population samples, especially early in life. Third, genetic risk for SCZ has been related to nonparticipation in a large longitudinal population-based cohort study,⁴⁶ implying that individuals at high genetic risk might be underrepresented. This would lead to underestimating effects of these genetic variants on neurodevelopmental outcomes. However, PGSs for SCZ were very similar among Generation R participants with European ancestry when comparing those included with those excluded in the present study (Table S3, available online).

Other interesting findings, albeit not surpassing multiple testing correction, include positive relations between PGS for ASD and TBV and negative associations between MDD PGS and TBV. Converging evidence points to an increased brain size as a characteristic brain abnormality of young children with ASD.⁴⁷ Our results suggest that this association could be accounted for by common genetic

variants increasing the risk for ASD. Although it might seem counterintuitive that polygenic risk for ASD shows the same direction of effects on TBV as PGSs for EA and intelligence, it has been shown that polygenic risk for these traits is highly correlated and that genetic risk for ASD might act through different etiologic pathways.⁴⁸ For MDD PGS, widespread GM and subcortical volume reductions have been reported in individuals affected by MDD.⁴⁹ In contrast, less research has been conducted on global structural brain measures such as TVB. Overall, further research is needed to confirm these potential associations.

Our results should be interpreted in the context of several strengths and limitations. The strengths of the present study include the large sample and homogeneity with respect to recruitment, exclusion criteria, scanner, image acquisition, and preprocessing methods, which are especially valuable in imaging genetics. That said, the present sample is adequate for detecting significant effect sizes larger than 0.08 at 80% power; thus, reported smaller effect sizes, which correspond to negative findings, should be interpreted with caution. The main limitation of the study is the cross-sectional design. Studies including brain morphologic measurements at multiple time points are needed to examine whether polygenic risk for psychiatric disorders and cognition contributes to changes in developmental trajectories. Another limitation is that the PGSs typically explain only a small proportion of the total phenotypic variance of complex traits.^{1,2} Moreover, it is important to note that the predictive accuracy of the PGS is related to sample size in the discovery sample, which substantially varies among different traits for the PGSs examined in the present study.⁵⁰ This should be considered when comparing results for the different traits examined. Nevertheless, we used summary statistics from the most recent, and thus more powerful, GWASs conducted on psychiatric disorders to date, which represents an advantage over previous studies using PGSs based on GWASs conducted on smaller samples.

To conclude, we found a relation between polygenic susceptibility for intelligence and EA and TBV in school-age children. We also found effects of ADHD polygenic risk for caudate volume. Interestingly, we found evidence for mediation only in boys, in whom differences in caudate volume accounted for 11% of the association between polygenic risk for ADHD and attention

problems at 9 years of age. Overall, our findings provide molecular genetic evidence for the relation between polygenic susceptibility for cognition and ADHD with early differences in brain morphology.

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Dr. Alemany is with the Barcelona Institute for Global Health and the Universitat Pompeu Fabra (UPF), Barcelona, Spain and with the CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain. Drs. Jansen, Muetzel, El Marroun, Jaddoe, Tiemeier, and White are with the Erasmus University Medical Center, Rotterdam, the Netherlands. Drs. Jansen, Marroun, and Jaddoe also are with the Generation R Study Group, Erasmus University Medical Center. Dr. Tiemeier also is with the Harvard TH Chan School of Public Health, Boston, MA. Dr. Jansen, Polderman, and Posthuma are with Amsterdam Neuroscience, VU University, Amsterdam, the Netherlands. Ms. Marques is with the Instituto de Biofísica e Engenharia Biomédica, Faculdade de Ciências, Universidade de Lisboa, Portugal. Drs. Jansen, Polderman and Posthuma also are with the Center for Neurogenomics and Cognitive Research (CNCR), Amsterdam Neuroscience, VU University Amsterdam, the Netherlands. Dr. Posthuma also is with the VU University Medical Center (VUMC), Amsterdam.

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Correspondence to Silvia Alemany, PhD, Barcelona Institute for Global Health (ISGlobal), C. Doctor Aiguader 88, 08003 Barcelona, Spain; e-mail: silvia.alemany@isglobal.org

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