Common polygenic variations for psychiatric disorders and cognition in relation to brain morphology in the general pediatric population

Short title: Polygenic scores and brain morphology

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Abstract word count: 231

Manuscript word count: 3803

Number of tables/figures: 0/2

Total number of tables and figures in supplemental material: 5

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Social Media

New study @JAACAP finds relationships between #polygenic susceptibility for #ADHD and cognition and brain morphological differences at caudate and total brain volumes in schoolchildren from @GenerationR_010

Lay Summary

Our results based on data from schoolchildren participating in the Generation R Study (The Netherlands) suggest that genetic susceptibility for attention-deficit hyperactivity disorder (ADHD) and cognition manifest early in life by influencing brain structure. Interestingly, genetic risk for ADHD was related to smaller caudate nucleus volume, a region previously associated with this disorder.

ABSTRACT

Objective: To examine the relationship between polygenic scores (PGS) for five major psychiatric disorders and two cognitive traits with brain MRI morphological measurements in a large population-based sample of children. Additionally, we tested whether differences in brain morphology mediated associations between PGS for psychiatric disorders and related behavioral phenotypes.

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

Results: Higher genetic susceptibility for ADHD was associated with smaller caudate volume (strongest prior=0.01: β =-0.07, P= 0.006). Within boys, mediation analyses estimates suggested found that 11% of the association between the polygenic score for ADHD and attention problems was mediated by differences in caudate volume (n=535), while mediation was not significant in girls or the entire sample. PGS for EA and intelligence showed positive associations with total brain volume (TBV) (strongest prior=0.5: β =0.14, P=7.12×10^{-8}; and β =0.12, P=6.87×10^{-7}, respectively).

Conclusions: Our findings indicate that the neurobiological manifestation of polygenic susceptibility for ADHD, EA, and intelligence involve early morphological differences in caudate and total brain volumes in childhood. Furthermore, the genetic risk for ADHD may influence attention problems via the caudate nucleus in boys.

INTRODUCTION

Findings from genome-wide association studies (GWAS) 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 (PGS) 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 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 (years of schooling) was inversely related to child behavioral problems.[4] In a large prospective study, polygenic risk for major depressive disorder was shown to be associated with emotional problems in adulthood, but not earlier in life.[6] Similarly, genetic risk for bipolar disorder has been studied in adult samples. suggesting an association with increased risk for different psychiatric disorders.[7] Regarding child onset psychiatric disorders, PGS 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]

Since genetic susceptibility to psychopathology and cognitive function has been linked to behavior,[4] it 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 highly influenced by genetic factors.[10] Furthermore, widespread morphological brain abnormalities have been associated with the pathophysiology of major

psychiatric disorders.[11–15] Although both 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 report relationships between PGS for psychiatric disorders and structural brain MRI measurements in adults using medium to large sample sizes within the context of the field of imaging genetics.[16–19] Higher genetic risk for schizophrenia was related to total brain volume in both patients with schizophrenia (N=152) and controls (N=142),[16] although this finding was not replicated using two large general population-based samples (N=763 and N=707).[17] Other studies in healthy populations have related polygenic risk for both schizophrenia and bipolar disorder with 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 schizophrenia, bipolar disorder or major depression 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. Since ASD and ADHD are child-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.

Within this backdrop, it was the goal of our study to examine the association between polygenic susceptibility for five psychiatric disorders and two cognitive outcomes with global and subcortical brain volumes in a large population-based sample of school-age children. As a secondary aim, we investigated the potential mediating role of brain morphological variation on

associations between polygenic scores for psychiatric disorders and related behavioral phenotypes.

We hypothesized that polygenic susceptibility for schizophrenia, bipolar disorder, major depression disorder, autism spectrum disorders and ADHD are associated with brain morphological characteristics that overlap with brain abnormalities consistently reported in patients affected by these disorders. Regarding EA and intelligence, we hypothesized that PGS for these traits positively associated with global brain morphology measures.

METHOD

Study population

Participants were drawn from the Generation R Study, an ongoing population-based cohort aimed to study many domains of child development.[20] As part of the cohort's magnetic resonance imaging (MRI) study, 3,992 children were scanned between March 2013 and November 2015 corresponding to the 9-to-11 years-of-age Generation R visit.[21] Of these children, 3,937 had images that were reconstructed using FreeSurfer (version 6.0 [http://surfer.nmr.mgh.harvard.edu/]). One-hundred thirty-one children were excluded due to either the use of a different sequence (n=22), dental braces (n=87), and the presence of incidental findings (n=22).[22] From 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 was available for 1,189 children with European ancestry. Finally, relatedness and genotype quality resulted in an additional exclusion of 50 children. Thus, the final sample included 1,139 participants (see flowchart in Figure S1, available online).

The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Centre. Written informed consent was obtained from the legal representatives of all participants.

MRI

To familiarize participants with the MRI scanning environment, all children underwent a mock scanning session. Structural MRI scans were obtained on a 3-Tesla scanner (Discovery MR750W, GE Worldwide, Milwaukee, USA). Whole-brain high-resolution T1-weighted inversion recovery fast spoiled gradient recalled (IR-FSPGR) sequences were obtained using an 8-channel head coil. The scan parameters were: TR = 8.77 ms, TE = 3.4 ms, TI=600ms, flip angle = 10º, field of view= 220mm x 220mm, acquisition matrix= 220 x 220, asset acceleration factor = 2, b = 900 s/mm^2, 230 contiguous slices with a thickness of 1.0 mm, and in-plane resolution = 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 the FreeSurfer image analysis suite version 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 method.[24] Based on previous research investigating brain abnormalities in psychiatric disorders,[11–15] ten volumetric brain measures were studied as outcomes; including total brain volume (TBV), cortical gray matter (GM), total white matter (WM), 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 the 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 SNP arrays depending on collection time (Illumina, San Diego, CA, USA). Further details on genotype calling procedures in Generation R Study can be found elsewhere.[25] Information on quality control procedures of the genotype data and principal component analysis can be in in Supplementary Material (see Supplement 1, available online).

Polygenic scoring

Only participants with European ancestry were selected for the polygenic scoring. Genotype data that passed quality control was used to compute polygenic scores based on GWAS results for five psychiatric traits, including schizophrenia (SCZ), bipolar disorder (BD), major depression (MDD), attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) from the Psychiatric Genomics Consortium. In addition, we calculated polygenic scores for educational attainment (EA) and intelligence. Supplementary Table S1 (available online) provides an overview of the GWAS studies used for PGS calculation. For intelligence, we repeated the GWAS meta-analysis after exclusion of Generation R to ensure independence of discovery and target sample.

Polygenic scores were computed using LDpred.[26] This polygenic scoring method infers the posterior mean effect size of each marker by using a prior on effect size distribution and LD information from a reference genotype panel. The LDpred algorithm has improved prediction accuracy compared to traditional methods. Six PGS were computed for each trait corresponding to six priors that determined the proportion of SNPs with a causal effect (0.01, 0.05, 0.1, 0.5, 1

and infinitesimal). All polygenic scores were standardized to a mean of 0 and a standard deviation of 1. Correlations between the PGS are shown in Figure S3, available online.

Statistical Analysis

Multiple linear regression analyses were conducted using R statistical software package, version 3.3.1 (http: 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 the dependent variables with PGS for SCZ, BD, ADHD, ASD, EA or intelligence generated at six LDpred priors as independent variables. Models with TBV as outcome were adjusted by sex, age and four genetic principal components. Models for the rest of brain measurements were additionally adjusted by total intracranial volume.

We corrected for multiple testing across all PGS, generated at six different priors, tested for association with ten brain measurements using the false discovery rate (FDR) method.[27] Results at P_{FDR}<0.05 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 PGS trait. Multiple linear regressions analyses were conducted to examine associations between PGS, brain measurements and behavioral phenotypes adjusting for the same covariates included in the primary analyses and age at behavioral assessment. The direct effect (DE), indirect effect (IE), and total effect (TE) were estimated using the "mediation" package in R. As long as the assumptions of the mediation analysis are met, the DE represents the effect of genetic susceptibility on behavioral phenotypes after controlling for variation in brain morphology, and the IE represents the

11

estimated effect of polygenic susceptibility operating through brain morphology.[28] The proportion of mediation by brain morphology can be calculated as the ratio of IE to TE. Given the data available in Generation R, mediation analyses were only feasible for associations with PGS for psychiatric disorders for which behavioral data was assessed when children were between 8-11 years of age (Mean=9.7, SD=0.23, range=8.85-11.54) using the (CBCL/6-18).[29] Genetic, neuroimaging and behavioral data were available for 1053 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 variation in the brain measurement, we performed sensitivity analyses for the analyses between the PGS for EA and intelligence with TBV, mutually adjusting using the PGS for intelligence and EA, respectively.

RESULTS

Sample characteristics

A total of 1,139 children were included in the present study of whom 49.30% (n=561) were females, and the mean age was 10.16 years (SD=0.60, range= 8.72-11.99).

Effects of PGS on brain morphology

Figure 1 summarizes associations between the PGS for psychiatric disorders and cognition calculated at six priors and brain volumes. Full results for these associations are detailed in Table S2, available online.

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

Higher genetic susceptibility for MDD was consistently related to smaller TBV showing the strongest association for the infinitesimal prior (β =-0.07, SE=0.03; $P_{uncorrected}$ = 0.009). PGS for MDD also showed negative associations with total WM (prior=0.01: β =-0.03, SE=0.01, $P_{uncorrected}$=0.043), cerebellum volume (prior=0.5: β =-0.05, SE=0.02, $P_{uncorrected}$ =0.042; prior=1: β =-0.05, SE=0.02, $P_{uncorrected}$ =0.040), and thalamus volume (prior=0.01: β =-0.05, SE=0.02, $P_{uncorrected}$ =0.009). However, following FDR-correction none of these associations remained significant.

PGS 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 (β =-0.07, SE=0.03; $P_{uncorrected}$ = 0.006) while the strongest association with caudate volume was observed at prior 0.01 (β =-0.08, SE=0.03; $P_{uncorrected}$ = 7.49×10^{-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 (β =0.07, SE=0.03; $P_{uncorrected}$=7.75×10^{-3}). These associations did not surpass FDR-correction.

The EA PGS were consistently associated with larger TBV (strongest prior 0.5: β=0.14, SE=0.03, $P_{uncorrected}$=7.12×10^{-8}) and remained significant after FDR-correction. Associations at prior 0.05 did not reach significance but showed the same direction of effect. Higher genetic susceptibility for EA was also associated with larger volumes of subcortical GM (prior=0.05: β=0.04, SE=0.02, $P_{uncorrected}$=0.046), cerebellum (prior=0.1: β=0.05, SE=0.02, $P_{uncorrected}$=0.047),

putamen (prior=0.05: β=0.06, SE=0.03, $P_{uncorrected}$=0.016) and thalamus at multiples priors (strongest prior=1: β=0.05, SE=0.02, $P_{uncorrected}$=0.012).

Higher genetic susceptibility for intelligence was significantly related to larger TBV for most of the priors, used even after FDR-correction (strongest prior 0.5: β=0.12, SE=0.03; $P_{uncorrected}$ = 6.87×10^{-7}). Other associations not surviving FDR-correction included a positive association with subcortical GM (Infinitesimal prior: β =0.04, SE=0.02, $P_{uncorrected}$=0.024) and positive associations with cerebellum volume (priors 0.01 and 0.05: β=0.07, SE=0.02, $P_{uncorrected}$ =0.003).

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, since it showed a negative significant association with attention problems (β=-0.06, SE=0.00, P=0.029). Similarly, polygenic risk for ADHD was significantly associated with attention problems (β=0.12, SE=0.00, P=5.36x10-5). 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 may 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 PGS for both traits were independently associated with TBV (PGS for EA: β=0.10, SE=0.03; P=2.6×10^{-4}; PGS for intelligence= β=0.08, SE=0.03; P=0.003).

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 with at prior of 0.01 surviving multiple testing correction. Polygenic susceptibility for intelligence and EA showed a positive relationship with TBV that was consistent across all priors used, although generally not significant for the more stringent priors (i.e. 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 PGS 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 morphological differences in caudate and total brain volume 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 would also 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 may be, at least partially, underlying TBV and caudate reductions in childhood. These findings are particularly relevant in the case of the caudate volume reduction, one of the most replicated findings in ADHD.[31] Interestingly, our results suggest that reduced caudate volume may 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] Gender differences in brain morphology have been used to investigate whether ADHD-related brain

abnormalities are more pronounced in males compared to females. Although caudate volume did not show sex effects in the mega-analysis conducted by Hoogman et al,[14] another study examining volume and shape of the basal ganglia observed smaller caudate volumes in boys with ADHD compared to male controls and no differences among girls.[33] Similarly, smaller caudate volumes have been found in adult male ADHD patients compared to male controls, while no differences were observed among females.[34] Our findings are in line with these studies supporting that different genetically-influenced neurobiological mechanisms may be operating in males and females in the context of ADHD.

The EA polygenic scores were associated with larger TBV. Intracranial volume has been previously related to EA genetic variants by applying LD Score regression methodology.[35] Genetic variants for EA or other traits, may affect TBV directly, through direct gene expression, via gene-environment interaction or correlation mechanisms, or through intermediate phenotypes. Remarkably, an important number of SNPs 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 impacts brain development.[37] Finally, it is also important to note that genetic associations with EA may 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 relationship between polygenic susceptibility for cognitive functions relevant for education attainment with increased volume of the thalamus is neurobiologically plausible.

Not surprisingly, our findings on polygenic susceptibility for intelligence and EA largely overlap in terms of strength of the association and variance explained of TBV. Similarly to EA, genetic variants related to intelligence were identified in genes predominantly expressed in brain tissue.[40] Interestingly, polygenic susceptibility for both EA and intelligence influenced TBV independently of each other. Since the correlation between the PRS for EA and intelligence were not extremely strong (Figure S3, available online), we speculate that genetic variants related to these traits may act through different pathways. Studies have shown that TBV is positively correlated with intelligence, accounting for about 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 morphological variation between the ages of 9-to-11 years. This is in line with previous research in adults.[17,19] However, this null finding was surprising, as we found an association between the PGS for SCZ and internalizing symptoms, and especially thought problems.[4] Behavioral effects of polygenic risk for SCZ must have neural correlates that we were unable to detect for several potential reasons. First, it is possible that the neural correlates of SCZ PGS are 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 association with polygenic risk for SCZ in this sample, revealing negative results.[43] Also, polygenic risk for SCZ has been associated with functional brain parameters, such as brain activation patterns detectable with fMRI during cognitive tasks in adolescents.[44,45] Second, brain structural abnormalities related to genetic risk for schizophrenia may only be detectable in young individuals beginning in the prodromal phase, when the illness has begun to show clinical manifestations. These finding become 'unmasked' as the illness progresses, making it very difficult to observe in general population samples, especially early in life. Finally, genetic risk for SCZ has been related to nonparticipation in a large longitudinal population-based cohort studies,[46] implying that individuals at high genetic risk may be underrepresented. This would lead to underestimating effects of these genetic variants on neurodevelopmental outcomes. However, PGS for SCZ were very similar within the Generation R participants with EU ancestry comparing those included versus excluded in the current study (Table S3, available online).

Other interesting findings, albeit not surpassing multiple testing correction, include positive relationships 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 may be accounted by common genetic variants increasing the risk for ASD. Although it may seem counterintuitive that polygenic risk for ASD shows the same direction of effects on TBV as PGS for EA and intelligence, it has been shown that polygenic risk for these traits is highly correlated and that genetic risk for ASD may act through different etiological pathways.[48] Regarding MDD PGS, widespread GM and subcortical volume reductions have been reported in individuals affected by

MDD.[49] Comparatively, 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 current study include the large sample size and homogeneity with respect to recruitment, exclusion criteria, scanner, image acquisition and pre-processing methods, which is especially valuable in the imaging genetics field. That said, the current sample is adequate for detecting significant effect sizes above 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 morphological measurements at multiple time points are needed to examine whether polygenic risk for psychiatric disorders and cognition contribute to changes in developmental trajectories. Another limitation is that the polygenic scores typically explain only a small proportion of the total phenotypic variance of complex traits.[1,2] It is also important to notice that predictive accuracy of PGS is related to sample size in the discovery sample, which substantially varies among the different traits for PGS examined in the current 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 GWAS conducted on psychiatric disorders to date, which represents an advantage over previous studies using PGS based on GWAS conducted on smaller samples.

To conclude, we found a relationship between polygenic susceptibility for intelligence and EA and TVB in school-age children. We also found effects of ADHD polygenic risk for caudate volume. Interestingly, we found evidence for mediation only in boys, where differences in the 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 relationship between polygenic susceptibility for cognition and ADHD with early differences in brain morphology.

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Figure Legends

Figure 1. Associations between polygenic scores for schizophrenia (SCZ), bipolar disorder (BD), major depression disorder (MDD), attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), educational attainment (EA) and intelligence computed at six priors (0.01, 0.05, 0.1, 0.5, 1 and infinitesimal) and brain volumes adjusted for sex, age, total intracranial volume (except associations with TBV) and the first four genetic components (n=1139). *P*-uncorrected values <0.05 are indicated with asterisk (*), *P*-FDR<0.05 are indicated with a cross (X).

Figure 2. Mediation analysis of the estimated effect (95% CIs) of polygenic risk for ADHD (prior=0.01) on attention problems (CBCL syndrome scale reported by mothers) through caudate volume in the entire sample (n=1053) and stratified by sex (boys, n=535; girls, n=518). The figure shows caudate volume as a potential mediator, the estimates of indirect and direct effect, and the proportion of mediation. All models were adjusted for age at MRI scan, age at CBCL administration, total intracranial volume and the first four genetic components.

Figure 1. Associations between polygenic scores for schizophrenia (SCZ), bipolar disorder (BD), major depression disorder (MDD), attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), educational attainment (EA) and intelligence computed at six priors (0.01, 0.05, 0.1, 0.5, 1 and infinitesimal) and brain volumes adjusted for sex, age, total intracranial volume (except associations with TBV) and the first four genetic components (n=1139). *P*-uncorrected values <0.05 are indicated with asterisk (*), *P*-FDR<0.05 are indicated with a cross (X).

Direct Effects:
Entire sample= 0.37 (0.18, 0.56)
Girls= 0.32 (0.04, 0.58)
Boys= 0.39 (0.11, 0.65)

Polygenic risk for ADHD (prior=0.01)

Attention Problems

Indirect Effects:
Entire sample= 0.02 (-0.00, 0.05)
Girls= 0.00 (-0.02, 0.03)
Boys= 0.05 (0.01, 0.11)

Proportion of mediation:
Entire sample= 4.6% (-0.9, 13.6)
Girls= 0.90% (-7.8, 15.9)
Boys= 11% (1.0, 39.3)

Caudate volume

Figure 2. Mediation analysis of the estimated effect (95% CIs) of polygenic risk for ADHD (prior=0.01) on attention problems (CBCL syndrome scale reported by mothers) through caudate volume in the entire sample (n=1053) and stratified by sex (boys, n=535; girls, n=518). The figure shows caudate volume as a potential mediator, the estimates of indirect and direct effect, and the proportion of mediation. All models were adjusted for age at MRI scan, age at CBCL administration, total intracranial volume and the first four genetic components.

SUPPLEMENTARY MATERIAL

Title: Common polygenic variation for psychiatric disorders and cognitive traits and structural brain imaging in the general pediatric population

Short title: Polygenic scores and brain structure in children

Authors: Silvia Alemany. Philip R. Jansen. Ryan L. Muetzel. Natalia Marqués. Hanan El Marroun. Vincent W.V. Jaddoe. Tinca J.C. Polderman. Henning Tiemeier. Danielle Posthuma. Tonya White.

References

Supplement 1. 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 SNP arrays depending on collection time (Illumina, San Diego, CA, USA). Further details on genotype calling procedures in Generation R Study can be found elsewhere (Medina-Gomez et al. 2015). Quality control at the genotype and individual data level was conducted using PLINK (v1.9) (Purcell et al. 2007). Genotype data quality control included filtering variants for minor allele frequency (MAF< 1%), Hardy-Weinberg disequilibrium (HWE, $P<1\times10^{-5}$) and missing rate (>5%). Individuals were filtered on relatedness (pairwise identity-by-descent (IBD) >0.185), genetic and phenotypic sex mismatch, and genotype quality (<5% missing). Polygenic scoring was performed on genotyped SNPs only.
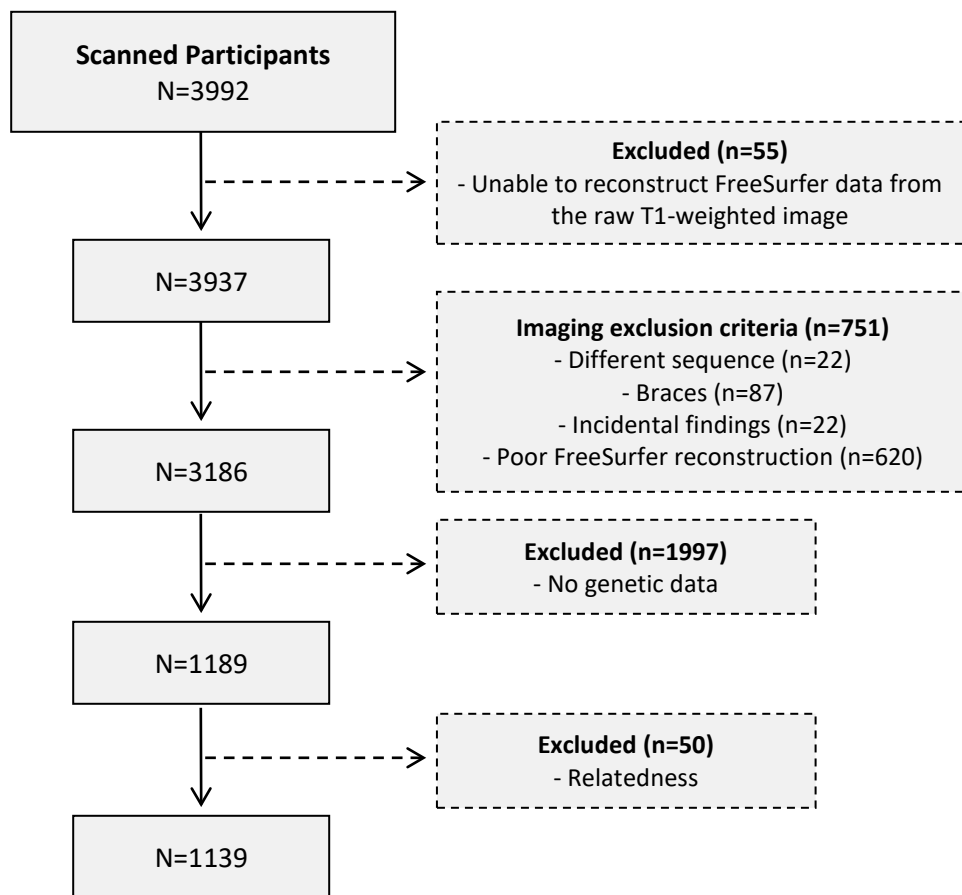
Figure S1. Flow chart of the study population.
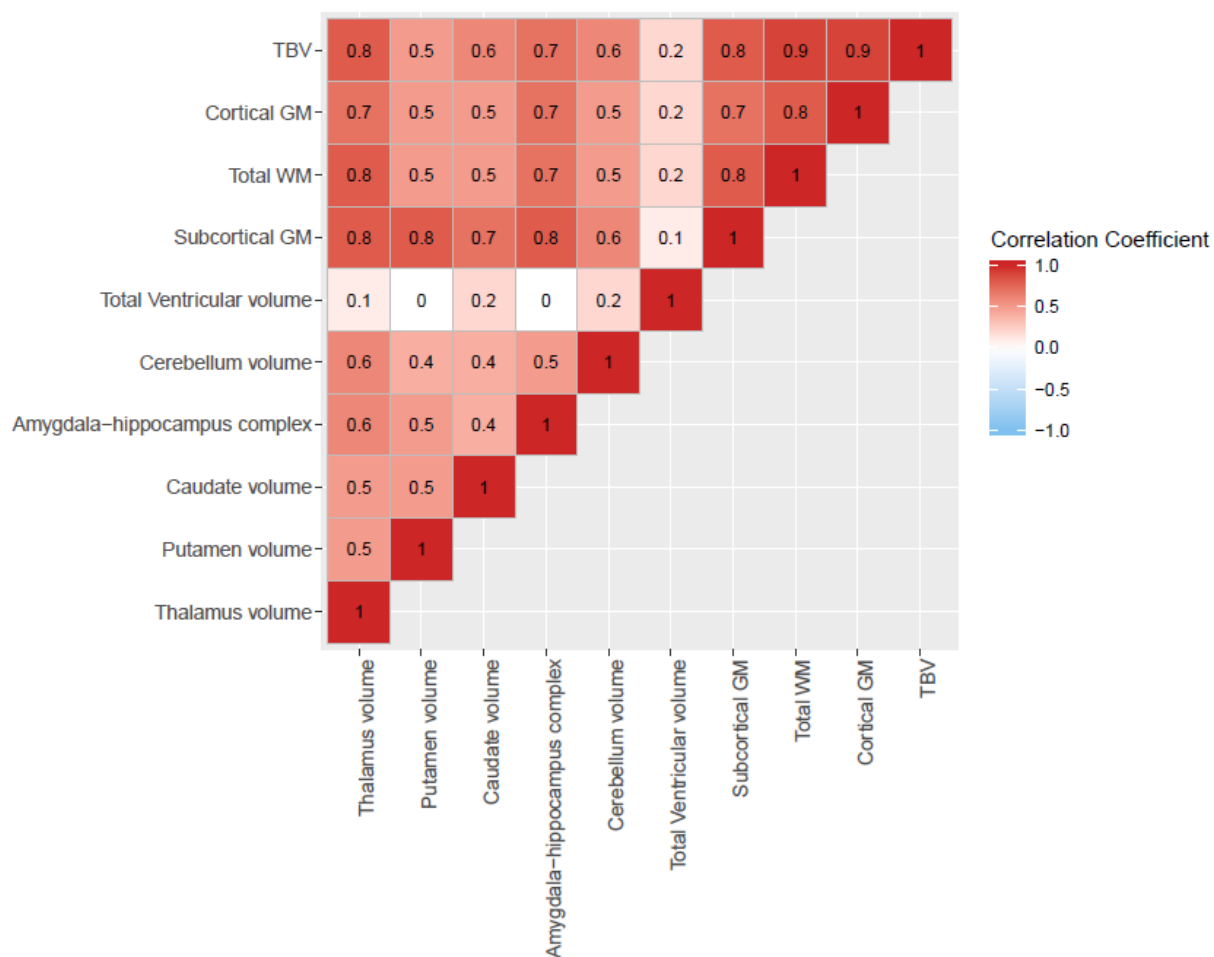
Figure S2. Pearson correlations between brain MRI measurements (N=1139). Intensity of the color of shaded boxes indicates the magnitude of the correlation. Colored boxes indicate significant correlations at P<0.05.
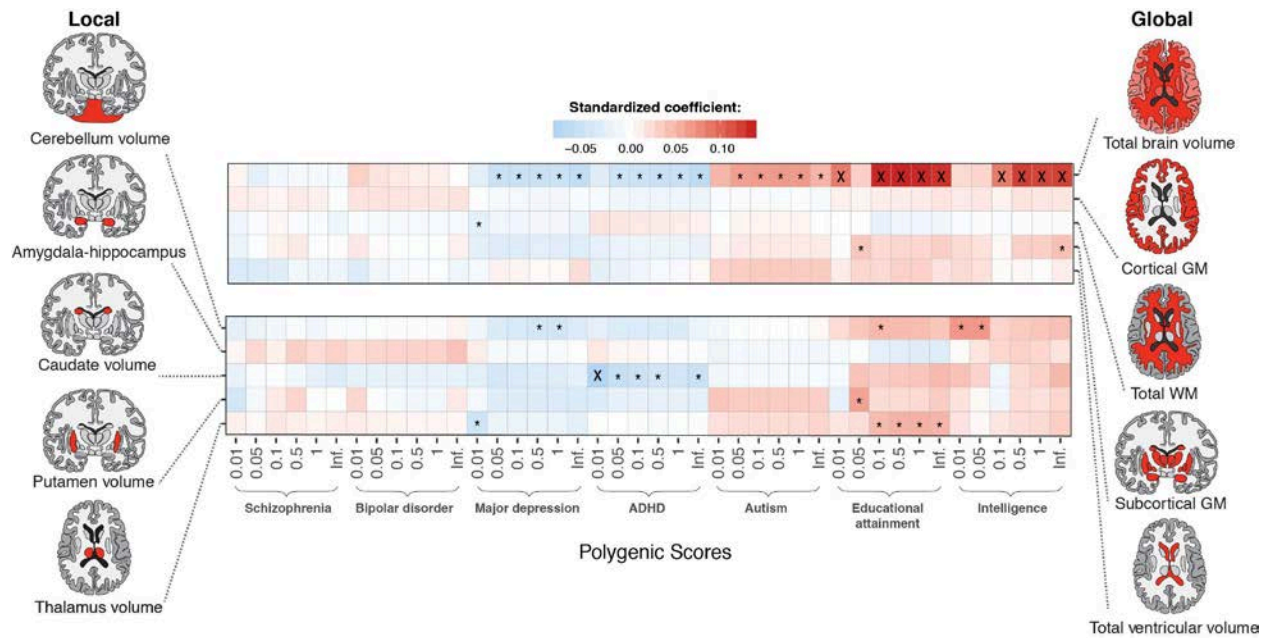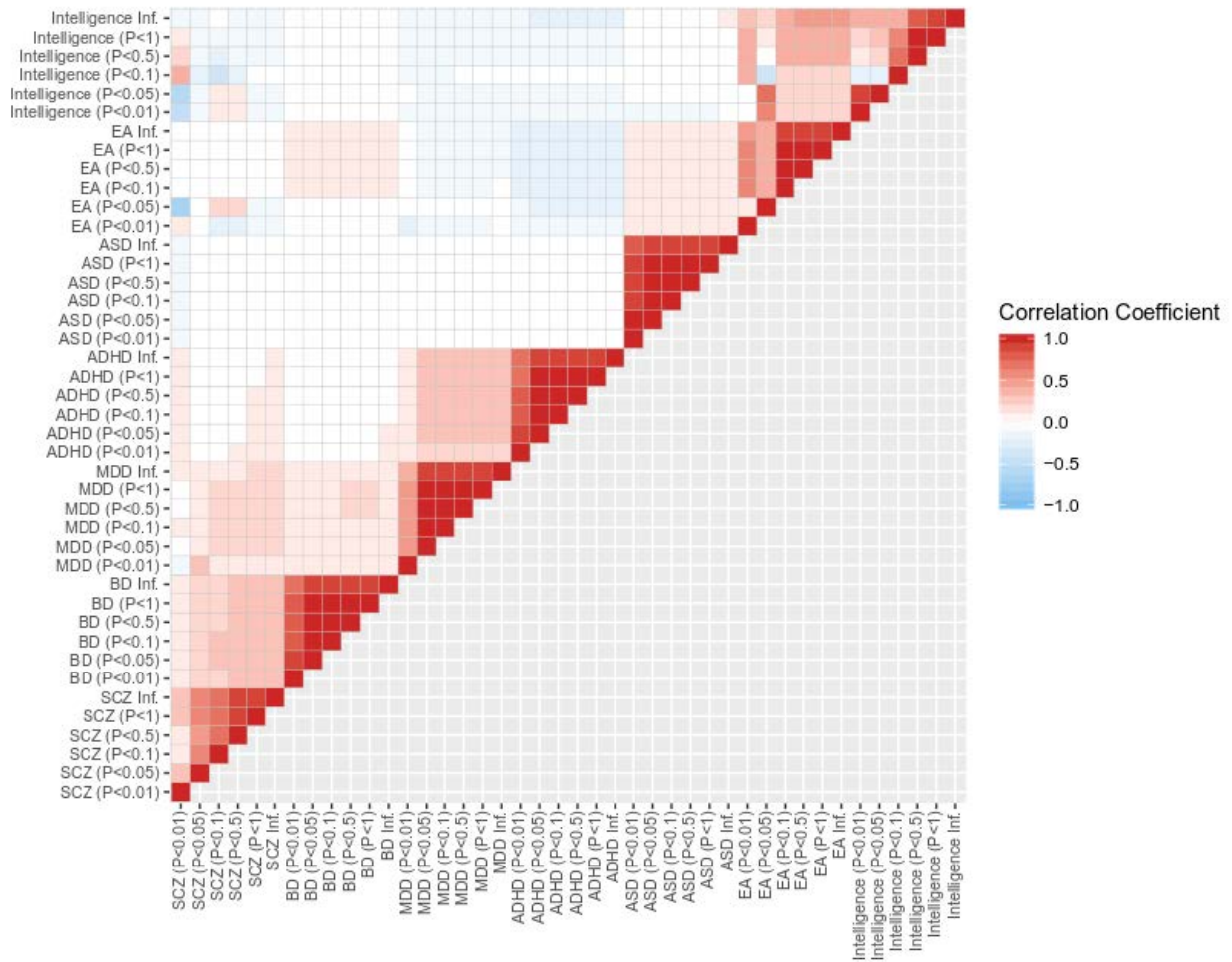
Figure S2. Pearson correlations between the polygenic scores for schizophrenia (SCZ), bipolar disorder (BD), major depression disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD), educational attainment (EA) and intelligence computed at six priors (0.01, 0.05, 0.1, 0.5, 1 and infinitesimal) (N=1139). Intensity of the color of shaded boxes indicates the magnitude of the correlation. Colored boxes indicate significant correlations at P<0.05.

Table S1. Summary statistics used to calculate polygenic scores were obtained from the following GWAS. Number of SNPs (N SNPs) included in the PGRS for each trait is indicated.

Consortium/Cohorts	Trait	N	N SNPs	Reference
PGC	Schizophrenia	77.096	481,162	(Ripke et al. 2014)
PGC	Bipolar Disorder	16.731	473,445	(PGC Bipolar Disorder Working Group 2011)
PGC	MDD	307.354	480,813	(Wray et al. 2018)
PGC	ADHD	55.374	450,347	(Demontis et al. 2017)
PGC	ASD	15.954	480,374	(PGC Autism Spectrum Disorders Working Group 2017)
SSGAC	Educational Attainment	293,723	479,695	(Okbay et al. 2016)
CTG	Intelligence	269.867	458,676	(Savage et al. 2018)

Note: PGC, Psychiatric Genomics Consortium; SSGAC, Social Science Genetic Association Consortium; CTG, Complex Trait Genetics.

Table S2. Association results between polygenic scores for schizophrenia (SCZ), bipolar disorder (BD), major depression disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD), educational attainment (EA) and intelligence computed at six priors (0.01, 0.05, 0.1, 0.5, 1 and infinitesimal) and brain measurements including: total brain volume (TBV), cortical gray matter (GM), total white matter (WM), subcortical GM, total ventricular volume, cerebellum volume, amygdala-hippocampus complex, caudate volume, putamen volume and thalamus volume. Models with TBV as outcome were adjusted by sex, age and four genetic principal components. Models for the rest of brain measurements were additionally adjusted by total intracranial volume. Significant results are indicated with an asterisk.

PGS	Brain measurement	β	SE	P-uncorr.	P-FDR	ΔR²
SCZ (prior= 0.01)	TBV	0.006	0.025	7.96E-01	9.47E-01	-0.001
	Cortical GM	0.011	0.015	4.47E-01	7.78E-01	0.000
	Total WM	-0.015	0.014	2.91E-01	6.73E-01	0.000
	Subcortical GM	-0.019	0.018	2.97E-01	6.73E-01	0.000
	Total Ventricular volume	-0.040	0.027	1.45E-01	6.73E-01	0.001
	Cerebellum volume	-0.028	0.023	2.16E-01	6.73E-01	0.000
	Amygdala-hippocampus complex	0.005	0.020	8.11E-01	9.56E-01	0.000
	Caudate volume	-0.023	0.025	3.54E-01	6.95E-01	0.000
	Putamen volume	-0.046	0.025	7.11E-02	5.57E-01	0.001
	Thalamus volume	0.009	0.022	6.38E-01	8.99E-01	0.000
SCZ (prior= 0.05)	TBV	-0.028	0.025	2.66E-01	6.73E-01	0.000
	Cortical GM	0.009	0.015	5.33E-01	8.46E-01	0.000
	Total WM	-0.006	0.014	6.72E-01	9.12E-01	0.000
	Subcortical GM	-0.002	0.018	9.17E-01	9.98E-01	0.000
	Total Ventricular volume	-0.039	0.027	1.54E-01	6.73E-01	0.001
	Cerebellum volume	-0.021	0.023	3.67E-01	7.14E-01	0.000
	Amygdala-hippocampus complex	0.024	0.020	2.88E-01	6.73E-01	0.000
	Caudate volume	-0.005	0.025	8.39E-01	9.66E-01	-0.001
	Putamen volume	-0.008	0.025	7.61E-01	9.30E-01	-0.001
	Thalamus volume	0.003	0.022	8.97E-01	9.98E-01	0.000
SCZ (prior= 0.1)	TBV	-0.011	0.025	6.50E-01	9.00E-01	-0.001
	Cortical GM	0.006	0.015	7.07E-01	9.23E-01	0.000
	Total WM	0.004	0.014	7.63E-01	9.30E-01	0.000
	Subcortical GM	0.008	0.018	6.47E-01	9.00E-01	0.000
	Total Ventricular volume	-0.034	0.027	2.07E-01	6.73E-01	0.000
	Cerebellum volume	-0.013	0.023	5.72E-01	8.68E-01	0.000
	Amygdala-hippocampus complex	0.010	0.020	6.60E-01	9.02E-01	0.000
	Caudate volume	0.001	0.025	9.75E-01	9.98E-01	-0.001
	Putamen volume	0.013	0.025	6.23E-01	8.90E-01	0.000
	Thalamus volume	0.015	0.022	4.70E-01	7.84E-01	0.000
SCZ (prior= 0.5)	TBV	-0.008	0.025	7.44E-01	9.29E-01	-0.001
	Cortical GM	0.012	0.015	4.02E-01	7.46E-01	0.000
	Total WM	-0.005	0.014	7.12E-01	9.23E-01	0.000
	Subcortical GM	0.013	0.018	4.65E-01	7.84E-01	0.000
	Total Ventricular volume	-0.013	0.027	6.31E-01	8.95E-01	-0.001
	Cerebellum volume	-0.005	0.023	8.22E-01	9.62E-01	-0.001

	Amygdala-hippocampus complex	0.031	0.020	1.65E-01	6.73E-01	0.000
	Caudate volume	-0.013	0.025	5.85E-01	8.75E-01	0.000
	Putamen volume	0.028	0.025	2.72E-01	6.73E-01	0.000
	Thalamus volume	0.010	0.022	6.08E-01	8.90E-01	0.000
	TBV	-0.008	0.025	7.60E-01	9.30E-01	-0.001
	Cortical GM	0.009	0.015	5.59E-01	8.68E-01	0.000
	Total WM	-0.006	0.014	6.83E-01	9.16E-01	0.000
	Subcortical GM	-0.002	0.018	8.95E-01	9.98E-01	0.000
SCZ (prior= 1)	Total Ventricular volume	-0.017	0.027	5.29E-01	8.45E-01	0.000
	Cerebellum volume	-0.015	0.023	5.02E-01	8.14E-01	0.000
	Amygdala-hippocampus complex	0.022	0.020	3.12E-01	6.73E-01	0.000
	Caudate volume	-0.028	0.025	2.56E-01	6.73E-01	0.000
	Putamen volume	-0.001	0.025	9.65E-01	9.98E-01	-0.001
	Thalamus volume	0.007	0.022	7.42E-01	9.29E-01	0.000
	TBV	-0.009	0.025	7.23E-01	9.24E-01	-0.001
	Cortical GM	-0.001	0.015	9.58E-01	9.98E-01	0.000
	Total WM	-0.016	0.014	2.62E-01	6.73E-01	0.000
	Subcortical GM	-0.001	0.018	9.38E-01	9.98E-01	0.000
SCZ (Infinitesimal prior)	Total Ventricular volume	-0.019	0.027	4.93E-01	8.06E-01	0.000
	Cerebellum volume	-0.005	0.023	8.27E-01	9.64E-01	-0.001
	Amygdala-hippocampus complex	0.029	0.020	1.82E-01	6.73E-01	0.000
	Caudate volume	-0.035	0.025	1.55E-01	6.73E-01	0.001
	Putamen volume	0.000	0.025	9.98E-01	9.98E-01	-0.001
	Thalamus volume	0.012	0.022	5.68E-01	8.68E-01	0.000
	TBV	0.029	0.025	2.42E-01	6.73E-01	0.000
	Cortical GM	0.017	0.015	2.57E-01	6.73E-01	0.000
	Total WM	-0.003	0.014	8.02E-01	9.49E-01	0.000
	Subcortical GM	0.014	0.018	4.46E-01	7.78E-01	0.000
BD (prior= 0.01)	Total Ventricular volume	-0.036	0.027	1.91E-01	6.73E-01	0.001
	Cerebellum volume	-0.004	0.023	8.45E-01	9.70E-01	-0.001
	Amygdala-hippocampus complex	0.022	0.020	3.18E-01	6.73E-01	0.000
	Caudate volume	-0.025	0.025	3.10E-01	6.73E-01	0.000
	Putamen volume	0.026	0.025	3.07E-01	6.73E-01	0.000
	Thalamus volume	0.012	0.022	5.62E-01	8.68E-01	0.000
	TBV	0.018	0.025	4.64E-01	7.84E-01	0.000
	Cortical GM	0.018	0.015	2.10E-01	6.73E-01	0.000
	Total WM	-0.008	0.014	5.83E-01	8.74E-01	0.000
BD (prior= 0.05)	Subcortical GM	0.002	0.018	9.00E-01	9.98E-01	0.000
	Total Ventricular volume	-0.014	0.027	6.10E-01	8.90E-01	-0.001
	Cerebellum volume	-0.001	0.023	9.80E-01	9.98E-01	-0.001

	Amygdala-hippocampus complex	0.027	0.020	2.23E-01	6.73E-01	0.000
	Caudate volume	-0.026	0.025	2.88E-01	6.73E-01	0.000
	Putamen volume	-0.001	0.025	9.67E-01	9.98E-01	-0.001
	Thalamus volume	0.008	0.022	6.96E-01	9.23E-01	0.000
	TBV	0.014	0.025	5.77E-01	8.68E-01	0.000
	Cortical GM	0.017	0.015	2.50E-01	6.73E-01	0.000
	Total WM	-0.009	0.014	5.35E-01	8.46E-01	0.000
	Subcortical GM	-0.001	0.018	9.56E-01	9.98E-01	0.000
BD (prior= 0.1)	Total Ventricular volume	-0.009	0.027	7.42E-01	9.29E-01	-0.001
	Cerebellum volume	-0.002	0.023	9.44E-01	9.98E-01	-0.001
	Amygdala-hippocampus complex	0.028	0.020	2.11E-01	6.73E-01	0.000
	Caudate volume	-0.026	0.025	2.97E-01	6.73E-01	0.000
	Putamen volume	-0.009	0.025	7.37E-01	9.29E-01	-0.001
	Thalamus volume	0.006	0.022	7.58E-01	9.30E-01	0.000
	TBV	0.010	0.025	6.94E-01	9.23E-01	-0.001
	Cortical GM	0.015	0.015	2.96E-01	6.73E-01	0.000
	Total WM	-0.009	0.014	4.97E-01	8.10E-01	0.000
	Subcortical GM	-0.002	0.018	9.01E-01	9.98E-01	0.000
BD (prior= 0.5)	Total Ventricular volume	-0.004	0.027	8.95E-01	9.98E-01	-0.001
	Cerebellum volume	-0.001	0.023	9.58E-01	9.98E-01	-0.001
	Amygdala-hippocampus complex	0.029	0.020	1.95E-01	6.73E-01	0.000
	Caudate volume	-0.024	0.025	3.36E-01	6.91E-01	0.000
	Putamen volume	-0.013	0.025	6.23E-01	8.90E-01	0.000
	Thalamus volume	0.006	0.022	7.83E-01	9.44E-01	0.000
	TBV	0.009	0.025	7.07E-01	9.23E-01	-0.001
	Cortical GM	0.015	0.015	3.04E-01	6.73E-01	0.000
	Total WM	-0.010	0.014	4.92E-01	8.06E-01	0.000
	Subcortical GM	-0.003	0.018	8.89E-01	9.98E-01	0.000
BD (prior= 1)	Total Ventricular volume	-0.003	0.027	9.17E-01	9.98E-01	-0.001
	Cerebellum volume	-0.002	0.023	9.47E-01	9.98E-01	-0.001
	Amygdala-hippocampus complex	0.029	0.020	1.94E-01	6.73E-01	0.000
	Caudate volume	-0.023	0.025	3.44E-01	6.91E-01	0.000
	Putamen volume	-0.013	0.025	6.06E-01	8.90E-01	0.000
	Thalamus volume	0.005	0.022	7.93E-01	9.46E-01	0.000
	TBV	0.000	0.025	9.90E-01	9.98E-01	-0.001
BD (Infinitesimal prior)	Cortical GM	0.018	0.015	2.23E-01	6.73E-01	0.000
	Total WM	-0.011	0.014	4.43E-01	7.78E-01	0.000

Group	Region					
	Subcortical GM	0.009	0.018	6.38E-01	8.99E-01	0.000
	Total Ventricular volume	-0.016	0.027	5.66E-01	8.68E-01	-0.001
	Cerebellum volume	0.006	0.023	7.87E-01	9.44E-01	0.000
	Amygdala-hippocampus complex	0.040	0.020	7.29E-02	5.57E-01	0.001
	Caudate volume	-0.024	0.025	3.37E-01	6.91E-01	0.000
	Putamen volume	0.013	0.025	6.23E-01	8.90E-01	0.000
	Thalamus volume	0.004	0.022	8.38E-01	9.66E-01	0.000
	TBV	-0.030	0.025	2.31E-01	6.73E-01	0.000
	Cortical GM	0.000	0.015	9.81E-01	9.98E-01	0.000
	Total WM	-0.028	0.014	4.31E-02*	4.64E-01	0.001
	Subcortical GM	-0.030	0.018	1.00E-01	6.23E-01	0.001
MDD (prior= 0.01)	Total Ventricular volume	-0.010	0.027	7.24E-01	9.24E-01	-0.001
	Cerebellum volume	-0.015	0.023	5.26E-01	8.42E-01	0.000
	Amygdala-hippocampus complex	0.011	0.020	6.27E-01	8.93E-01	0.000
	Caudate volume	-0.030	0.026	2.18E-01	6.73E-01	0.000
	Putamen volume	-0.010	0.025	6.85E-01	9.16E-01	-0.001
	Thalamus volume	-0.052	0.022	9.41E-03*	2.21E-01	0.002
	TBV	-0.059	0.025	1.87E-02*	2.92E-01	0.003
	Cortical GM	-0.008	0.015	5.90E-01	8.78E-01	0.000
	Total WM	-0.016	0.014	2.45E-01	6.73E-01	0.000
	Subcortical GM	-0.035	0.018	5.69E-02	5.04E-01	0.001
MDD (prior= 0.05)	Total Ventricular volume	0.007	0.028	7.86E-01	9.44E-01	-0.001
	Cerebellum volume	-0.038	0.023	1.03E-01	6.28E-01	0.001
	Amygdala-hippocampus complex	-0.008	0.020	7.08E-01	9.23E-01	0.000
	Caudate volume	-0.044	0.026	7.58E-02	5.61E-01	0.001
	Putamen volume	-0.034	0.025	1.82E-01	6.73E-01	0.001
	Thalamus volume	-0.022	0.022	2.87E-01	6.73E-01	0.000
	TBV	-0.060	0.025	1.78E-02*	2.92E-01	0.003
	Cortical GM	-0.010	0.015	4.90E-01	8.06E-01	0.000
	Total WM	-0.015	0.014	2.74E-01	6.73E-01	0.000
	Subcortical GM	-0.035	0.018	5.52E-02	5.04E-01	0.001
MDD (prior= 0.1)	Total Ventricular volume	0.007	0.028	8.13E-01	9.57E-01	-0.001
	Cerebellum volume	-0.042	0.023	7.27E-02	5.57E-01	0.001
	Amygdala-hippocampus complex	-0.009	0.020	7.01E-01	9.23E-01	0.000
	Caudate volume	-0.041	0.026	1.01E-01	6.23E-01	0.001
	Putamen volume	-0.036	0.025	1.61E-01	6.73E-01	0.001
	Thalamus volume	-0.022	0.022	2.82E-01	6.73E-01	0.000
MDD (prior= 0.5)	TBV	-0.056	0.025	2.57E-02*	3.39E-01	0.003

	Cortical GM	-0.012	0.015	4.28E-01	7.68E-01	0.000
	Total WM	-0.012	0.014	3.90E-01	7.42E-01	0.000
	Subcortical GM	-0.032	0.018	7.86E-02	5.61E-01	0.001
	Total Ventricular volume	0.003	0.027	9.13E-01	9.98E-01	-0.001
	Cerebellum volume	-0.047	0.023	4.17E-02*	4.61E-01	0.002
	Amygdala-hippocampus complex	-0.007	0.020	7.60E-01	9.30E-01	0.000
	Caudate volume	-0.035	0.026	1.60E-01	6.73E-01	0.001
	Putamen volume	-0.037	0.025	1.50E-01	6.73E-01	0.001
	Thalamus volume	-0.020	0.022	3.32E-01	6.91E-01	0.000
	TBV	-0.056	0.025	2.73E-02*	3.48E-01	0.002
	Cortical GM	-0.012	0.015	4.20E-01	7.59E-01	0.000
	Total WM	-0.012	0.014	4.05E-01	7.46E-01	0.000
	Subcortical GM	-0.032	0.018	7.89E-02	5.61E-01	0.001
MDD (prior= 1)	Total Ventricular volume	0.003	0.027	9.15E-01	9.98E-01	-0.001
	Cerebellum volume	-0.048	0.023	3.98E-02*	4.52E-01	0.002
	Amygdala-hippocampus complex	-0.007	0.020	7.64E-01	9.30E-01	0.000
	Caudate volume	-0.034	0.026	1.65E-01	6.73E-01	0.001
	Putamen volume	-0.037	0.025	1.43E-01	6.73E-01	0.001
	Thalamus volume	-0.020	0.022	3.36E-01	6.91E-01	0.000
	TBV	-0.066	0.025	8.78E-03*	2.21E-01	0.004
	Cortical GM	-0.006	0.015	6.73E-01	9.12E-01	0.000
	Total WM	-0.019	0.014	1.85E-01	6.73E-01	0.000
	Subcortical GM	-0.034	0.018	6.22E-02	5.21E-01	0.001
MDD (Infinitesimal prior)	Total Ventricular volume	0.022	0.027	4.33E-01	7.71E-01	0.000
	Cerebellum volume	-0.037	0.023	1.09E-01	6.30E-01	0.001
	Amygdala-hippocampus complex	0.000	0.020	9.93E-01	9.98E-01	0.000
	Caudate volume	-0.028	0.026	2.56E-01	6.73E-01	0.000
	Putamen volume	-0.040	0.025	1.22E-01	6.66E-01	0.001
	Thalamus volume	-0.029	0.022	1.49E-01	6.73E-01	0.000
	TBV	-0.033	0.025	1.94E-01	6.73E-01	0.000
	Cortical GM	-0.007	0.015	6.49E-01	9.00E-01	0.000
	Total WM	0.018	0.014	1.93E-01	6.73E-01	0.000
	Subcortical GM	-0.027	0.018	1.34E-01	6.73E-01	0.000
ADHD (prior= 0.01)	Total Ventricular volume	-0.030	0.027	2.81E-01	6.73E-01	0.000
	Cerebellum volume	-0.029	0.023	2.10E-01	6.73E-01	0.000
	Amygdala-hippocampus complex	0.014	0.020	5.16E-01	8.30E-01	0.000
	Caudate volume	-0.083	0.026	7.49E-04*	3.15E-02*	0.006
	Putamen volume	-0.037	0.025	1.53E-01	6.73E-01	0.001

Group	Region					
	Thalamus volume	-0.001	0.022	9.53E-01	9.98E-01	0.000
ADHD (prior= 0.05)	TBV	-0.053	0.025	3.54E-02*	4.13E-01	0.002
	Cortical GM	-0.014	0.015	3.50E-01	6.95E-01	0.000
	Total WM	0.015	0.014	2.92E-01	6.73E-01	0.000
	Subcortical GM	-0.021	0.018	2.50E-01	6.73E-01	0.000
	Total Ventricular volume	-0.023	0.027	4.09E-01	7.50E-01	0.000
	Cerebellum volume	-0.036	0.023	1.19E-01	6.59E-01	0.001
	Amygdala-hippocampus complex	0.005	0.020	8.17E-01	9.58E-01	0.000
	Caudate volume	-0.061	0.026	1.30E-02*	2.52E-01	0.003
	Putamen volume	-0.025	0.025	3.24E-01	6.79E-01	0.000
	Thalamus volume	0.000	0.022	9.93E-01	9.98E-01	0.000
ADHD (prior= 0.1)	TBV	-0.055	0.025	3.00E-02*	3.60E-01	0.002
	Cortical GM	-0.016	0.015	2.84E-01	6.73E-01	0.000
	Total WM	0.014	0.014	3.19E-01	6.73E-01	0.000
	Subcortical GM	-0.019	0.018	2.86E-01	6.73E-01	0.000
	Total Ventricular volume	-0.016	0.027	5.56E-01	8.68E-01	0.000
	Cerebellum volume	-0.037	0.023	1.06E-01	6.30E-01	0.001
	Amygdala-hippocampus complex	0.005	0.020	8.29E-01	9.64E-01	0.000
	Caudate volume	-0.055	0.026	2.58E-02*	3.39E-01	0.002
	Putamen volume	-0.024	0.025	3.41E-01	6.91E-01	0.000
	Thalamus volume	-0.001	0.022	9.67E-01	9.98E-01	0.000
ADHD (prior= 0.5)	TBV	-0.058	0.025	2.02E-02*	2.92E-01	0.003
	Cortical GM	-0.016	0.015	2.85E-01	6.73E-01	0.000
	Total WM	0.012	0.014	3.98E-01	7.46E-01	0.000
	Subcortical GM	-0.020	0.018	2.64E-01	6.73E-01	0.000
	Total Ventricular volume	-0.008	0.027	7.71E-01	9.36E-01	-0.001
	Cerebellum volume	-0.038	0.023	1.01E-01	6.23E-01	0.001
	Amygdala-hippocampus complex	0.001	0.020	9.60E-01	9.98E-01	0.000
	Caudate volume	-0.049	0.026	4.72E-02*	4.72E-01	0.002
	Putamen volume	-0.026	0.025	3.11E-01	6.73E-01	0.000
	Thalamus volume	-0.003	0.022	8.71E-01	9.93E-01	0.000
ADHD (prior= 1)	TBV	-0.059	0.025	2.01E-02*	2.92E-01	0.003
	Cortical GM	-0.016	0.015	2.88E-01	6.73E-01	0.000
	Total WM	0.012	0.014	4.01E-01	7.46E-01	0.000
	Subcortical GM	-0.020	0.018	2.70E-01	6.73E-01	0.000
	Total Ventricular volume	-0.007	0.027	7.88E-01	9.44E-01	-0.001
	Cerebellum volume	-0.038	0.023	9.69E-02	6.23E-01	0.001

	Amygdala-hippocampus complex	0.001	0.020	9.70E-01	9.98E-01	0.000
	Caudate volume	-0.048	0.025	5.26E-02	5.02E-01	0.002
	Putamen volume	-0.026	0.025	3.12E-01	6.73E-01	0.000
	Thalamus volume	-0.003	0.022	8.77E-01	9.93E-01	0.000
ADHD (Infinitesimal prior)	TBV	-0.069	0.025	5.98E-03*	1.93E-01	0.004
	Cortical GM	-0.018	0.015	2.11E-01	6.73E-01	0.000
	Total WM	0.008	0.014	5.43E-01	8.51E-01	0.000
	Subcortical GM	-0.023	0.018	2.04E-01	6.73E-01	0.000
	Total Ventricular volume	0.004	0.027	8.82E-01	9.96E-01	-0.001
	Cerebellum volume	-0.019	0.023	4.11E-01	7.50E-01	0.000
	Amygdala-hippocampus complex	-0.002	0.020	9.26E-01	9.98E-01	0.000
	Caudate volume	-0.058	0.026	1.91E-02*	2.92E-01	0.003
	Putamen volume	-0.029	0.025	2.61E-01	6.73E-01	0.000
	Thalamus volume	-0.002	0.022	9.17E-01	9.98E-01	0.000
ASD (prior= 0.01)	TBV	0.048	0.025	5.62E-02	5.04E-01	0.002
	Cortical GM	-0.005	0.015	7.48E-01	9.29E-01	0.000
	Total WM	0.000	0.014	9.96E-01	9.98E-01	0.000
	Subcortical GM	0.007	0.018	6.81E-01	9.16E-01	0.000
	Total Ventricular volume	0.028	0.027	3.15E-01	6.73E-01	0.000
	Cerebellum volume	-0.013	0.023	5.75E-01	8.68E-01	0.000
	Amygdala-hippocampus complex	-0.019	0.020	3.94E-01	7.42E-01	0.000
	Caudate volume	-0.014	0.025	5.62E-01	8.68E-01	0.000
	Putamen volume	0.037	0.025	1.43E-01	6.73E-01	0.001
	Thalamus volume	0.019	0.022	3.37E-01	6.91E-01	0.000
ASD (prior= 0.05)	TBV	0.063	0.025	1.25E-02*	2.52E-01	0.003
	Cortical GM	-0.005	0.015	7.28E-01	9.24E-01	0.000
	Total WM	0.006	0.014	6.70E-01	9.12E-01	0.000
	Subcortical GM	0.013	0.018	4.88E-01	8.06E-01	0.000
	Total Ventricular volume	0.033	0.027	2.35E-01	6.73E-01	0.000
	Cerebellum volume	-0.003	0.023	8.93E-01	9.98E-01	-0.001
	Amygdala-hippocampus complex	-0.011	0.020	6.05E-01	8.90E-01	0.000
	Caudate volume	-0.009	0.026	7.02E-01	9.23E-01	-0.001
	Putamen volume	0.035	0.025	1.76E-01	6.73E-01	0.001
	Thalamus volume	0.022	0.022	2.71E-01	6.73E-01	0.000
ASD (prior= 0.1)	TBV	0.065	0.025	9.46E-03*	2.21E-01	0.004
	Cortical GM	-0.005	0.015	7.18E-01	9.24E-01	0.000
	Total WM	0.006	0.014	6.49E-01	9.00E-01	0.000
	Subcortical GM	0.013	0.018	4.75E-01	7.89E-01	0.000

	Total Ventricular volume	0.034	0.027	2.16E-01	6.73E-01	0.000
	Cerebellum volume	-0.001	0.023	9.58E-01	9.98E-01	-0.001
	Amygdala-hippocampus complex	-0.011	0.020	6.17E-01	8.90E-01	0.000
	Caudate volume	-0.008	0.026	7.32E-01	9.25E-01	-0.001
	Putamen volume	0.034	0.025	1.86E-01	6.73E-01	0.000
	Thalamus volume	0.022	0.022	2.74E-01	6.73E-01	0.000
	TBV	0.067	0.025	7.89E-03*	2.21E-01	0.004
	Cortical GM	-0.005	0.015	7.26E-01	9.24E-01	0.000
	Total WM	0.007	0.014	6.22E-01	8.90E-01	0.000
	Subcortical GM	0.013	0.018	4.59E-01	7.84E-01	0.000
ASD (prior= 0.5)	Total Ventricular volume	0.034	0.027	2.14E-01	6.73E-01	0.000
	Cerebellum volume	0.000	0.023	9.97E-01	9.98E-01	-0.001
	Amygdala-hippocampus complex	-0.010	0.020	6.50E-01	9.00E-01	0.000
	Caudate volume	-0.008	0.026	7.50E-01	9.29E-01	-0.001
	Putamen volume	0.033	0.025	1.96E-01	6.73E-01	0.000
	Thalamus volume	0.022	0.022	2.72E-01	6.73E-01	0.000
	TBV	0.067	0.025	7.75E-03*	2.21E-01	0.004
	Cortical GM	-0.005	0.015	7.27E-01	9.24E-01	0.000
	Total WM	0.007	0.014	6.19E-01	8.90E-01	0.000
	Subcortical GM	0.014	0.018	4.58E-01	7.84E-01	0.000
ASD (prior= 1)	Total Ventricular volume	0.034	0.027	2.12E-01	6.73E-01	0.000
	Cerebellum volume	0.000	0.023	9.98E-01	9.98E-01	-0.001
	Amygdala-hippocampus complex	-0.010	0.020	6.54E-01	9.00E-01	0.000
	Caudate volume	-0.008	0.026	7.50E-01	9.29E-01	-0.001
	Putamen volume	0.033	0.025	1.96E-01	6.73E-01	0.000
	Thalamus volume	0.022	0.022	2.73E-01	6.73E-01	0.000
	TBV	0.050	0.025	4.89E-02*	4.78E-01	0.002
	Cortical GM	-0.008	0.015	5.94E-01	8.82E-01	0.000
	Total WM	-0.001	0.014	9.32E-01	9.98E-01	0.000
	Subcortical GM	0.013	0.018	4.59E-01	7.84E-01	0.000
ASD (Infinitesimal prior)	Total Ventricular volume	0.034	0.027	2.19E-01	6.73E-01	0.000
	Cerebellum volume	0.004	0.023	8.75E-01	9.93E-01	-0.001
	Amygdala-hippocampus complex	-0.012	0.020	5.74E-01	8.68E-01	0.000
	Caudate volume	-0.007	0.025	7.89E-01	9.44E-01	-0.001
	Putamen volume	0.031	0.025	2.24E-01	6.73E-01	0.000
	Thalamus volume	0.027	0.022	1.79E-01	6.73E-01	0.000
EA (prior= 0.01)	TBV	0.087	0.025	4.98E-04*	2.44E-02*	0.007
	Cortical GM	0.009	0.015	5.43E-01	8.51E-01	0.000

	Total WM	0.000	0.014	9.78E-01	9.98E-01	0.000
	Subcortical GM	0.001	0.018	9.54E-01	9.98E-01	0.000
	Total Ventricular volume	0.012	0.027	6.56E-01	9.00E-01	-0.001
	Cerebellum volume	0.022	0.023	3.43E-01	6.91E-01	0.000
	Amygdala-hippocampus complex	-0.008	0.020	7.11E-01	9.23E-01	0.000
	Caudate volume	-0.009	0.026	7.05E-01	9.23E-01	-0.001
	Putamen volume	-0.026	0.025	3.17E-01	6.73E-01	0.000
	Thalamus volume	0.015	0.022	4.52E-01	7.84E-01	0.000
	TBV	0.031	0.025	2.20E-01	6.73E-01	0.000
	Cortical GM	0.007	0.015	6.55E-01	9.00E-01	0.000
	Total WM	0.001	0.014	9.59E-01	9.98E-01	0.000
	Subcortical GM	0.036	0.018	4.62E-02*	4.72E-01	0.001
EA (prior= 0.05)	Total Ventricular volume	0.026	0.027	3.43E-01	6.91E-01	0.000
	Cerebellum volume	0.037	0.023	1.13E-01	6.30E-01	0.001
	Amygdala-hippocampus complex	-0.002	0.020	9.12E-01	9.98E-01	0.000
	Caudate volume	0.039	0.025	1.10E-01	6.30E-01	0.001
	Putamen volume	0.062	0.025	1.55E-02*	2.84E-01	0.003
	Thalamus volume	0.022	0.022	2.80E-01	6.73E-01	0.000
	TBV	0.134	0.025	9.36E-08*	1.35E-05*	0.017
	Cortical GM	0.011	0.015	4.67E-01	7.84E-01	0.000
	Total WM	-0.023	0.014	1.11E-01	6.30E-01	0.000
	Subcortical GM	0.025	0.018	1.84E-01	6.73E-01	0.000
	Total Ventricular volume	0.025	0.028	3.76E-01	7.27E-01	0.000
EA (prior= 0.1)	Cerebellum volume	0.047	0.023	4.66E-02*	4.72E-01	0.002
	Amygdala-hippocampus complex	-0.028	0.020	2.21E-01	6.73E-01	0.000
	Caudate volume	0.032	0.026	1.98E-01	6.73E-01	0.000
	Putamen volume	0.023	0.025	3.81E-01	7.31E-01	0.000
	Thalamus volume	0.045	0.023	2.88E-02*	3.55E-01	0.002
	TBV	0.135	0.025	7.12E-08*	1.35E-05*	0.018
	Cortical GM	0.012	0.015	4.42E-01	7.78E-01	0.000
	Total WM	-0.016	0.014	2.45E-01	6.73E-01	0.000
	Subcortical GM	0.026	0.018	1.61E-01	6.73E-01	0.000
	Total Ventricular volume	0.030	0.028	2.80E-01	6.73E-01	0.000
EA (prior= 0.5)	Cerebellum volume	0.045	0.023	5.76E-02	5.04E-01	0.001
	Amygdala-hippocampus complex	-0.032	0.020	1.58E-01	6.73E-01	0.000
	Caudate volume	0.036	0.026	1.50E-01	6.73E-01	0.001
	Putamen volume	0.023	0.025	3.77E-01	7.27E-01	0.000
	Thalamus volume	0.051	0.023	1.32E-02*	2.52E-01	0.002

EA (prior= 1)	TBV	0.134	0.025	9.65E-08*	1.35E-05*	0.017
	Cortical GM	0.012	0.015	4.21E-01	7.59E-01	0.000
	Total WM	-0.015	0.014	2.92E-01	6.73E-01	0.000
	Subcortical GM	0.026	0.018	1.51E-01	6.73E-01	0.000
	Total Ventricular volume	0.031	0.028	2.72E-01	6.73E-01	0.000
	Cerebellum volume	0.044	0.023	6.02E-02	5.16E-01	0.001
	Amygdala-hippocampus complex	-0.033	0.020	1.46E-01	6.73E-01	0.001
	Caudate volume	0.037	0.026	1.37E-01	6.73E-01	0.001
	Putamen volume	0.024	0.025	3.59E-01	7.02E-01	0.000
	Thalamus volume	0.052	0.023	1.12E-02*	2.48E-01	0.002
EA (Infinitesimal prior)	TBV	0.129	0.025	2.66E-07*	2.79E-05*	0.016
	Cortical GM	0.017	0.015	2.60E-01	6.73E-01	0.000
	Total WM	-0.017	0.014	2.21E-01	6.73E-01	0.000
	Subcortical GM	0.031	0.018	9.51E-02	6.23E-01	0.001
	Total Ventricular volume	0.017	0.028	5.36E-01	8.46E-01	0.000
	Cerebellum volume	0.037	0.023	1.10E-01	6.30E-01	0.001
	Amygdala-hippocampus complex	-0.034	0.020	1.32E-01	6.73E-01	0.001
	Caudate volume	0.046	0.026	6.85E-02	5.53E-01	0.001
	Putamen volume	0.033	0.025	1.98E-01	6.73E-01	0.000
	Thalamus volume	0.049	0.023	1.70E-02*	2.92E-01	0.002
Intelligence (prior= 0.01)	TBV	0.023	0.025	3.54E-01	6.95E-01	0.000
	Cortical GM	0.014	0.015	3.52E-01	6.95E-01	0.000
	Total WM	-0.005	0.014	7.18E-01	9.24E-01	0.000
	Subcortical GM	0.023	0.018	2.04E-01	6.73E-01	0.000
	Total Ventricular volume	0.023	0.027	4.05E-01	7.46E-01	0.000
	Cerebellum volume	0.068	0.023	3.19E-03*	1.11E-01	0.004
	Amygdala-hippocampus complex	0.002	0.020	9.23E-01	9.98E-01	0.000
	Caudate volume	0.041	0.026	1.01E-01	6.23E-01	0.001
	Putamen volume	0.019	0.025	4.66E-01	7.84E-01	0.000
	Thalamus volume	0.017	0.022	3.92E-01	7.42E-01	0.000
Intelligence (prior= 0.05)	TBV	0.027	0.025	2.90E-01	6.73E-01	0.000
	Cortical GM	0.015	0.015	3.14E-01	6.73E-01	0.000
	Total WM	0.001	0.014	9.42E-01	9.98E-01	0.000
	Subcortical GM	0.019	0.018	3.04E-01	6.73E-01	0.000
	Total Ventricular volume	0.020	0.027	4.71E-01	7.84E-01	0.000
	Cerebellum volume	0.068	0.023	3.04E-03*	1.11E-01	0.004
	Amygdala-hippocampus complex	0.016	0.020	4.60E-01	7.84E-01	0.000
	Caudate volume	0.028	0.025	2.51E-01	6.73E-01	0.000

	Putamen volume	0.004	0.025	8.73E-01	9.93E-01	-0.001
	Thalamus volume	0.004	0.022	8.39E-01	9.66E-01	0.000
Intelligence (prior= 0.1)	TBV	0.087	0.025	5.22E-04*	2.44E-02*	0.007
	Cortical GM	0.007	0.015	6.16E-01	8.90E-01	0.000
	Total WM	-0.004	0.014	7.98E-01	9.47E-01	0.000
	Subcortical GM	0.004	0.018	8.31E-01	9.64E-01	0.000
	Total Ventricular volume	0.002	0.027	9.33E-01	9.98E-01	-0.001
	Cerebellum volume	0.027	0.023	2.36E-01	6.73E-01	0.000
	Amygdala-hippocampus complex	0.026	0.020	2.39E-01	6.73E-01	0.000
	Caudate volume	-0.016	0.026	5.15E-01	8.30E-01	0.000
	Putamen volume	-0.014	0.025	5.72E-01	8.68E-01	0.000
	Thalamus volume	0.016	0.022	4.30E-01	7.68E-01	0.000
Intelligence (prior= 0.5)	TBV	0.124	0.025	6.87E-07*	5.77E-05*	0.015
	Cortical GM	0.018	0.015	2.33E-01	6.73E-01	0.000
	Total WM	0.001	0.014	9.41E-01	9.98E-01	0.000
	Subcortical GM	0.031	0.018	9.38E-02	6.23E-01	0.001
	Total Ventricular volume	0.004	0.028	8.75E-01	9.93E-01	-0.001
	Cerebellum volume	0.034	0.023	1.45E-01	6.73E-01	0.001
	Amygdala-hippocampus complex	0.030	0.020	1.77E-01	6.73E-01	0.000
	Caudate volume	0.023	0.026	3.51E-01	6.95E-01	0.000
	Putamen volume	0.022	0.025	3.88E-01	7.41E-01	0.000
	Thalamus volume	0.021	0.022	2.95E-01	6.73E-01	0.000
Intelligence (prior= 1)	TBV	0.121	0.025	1.32E-06*	7.90E-05*	0.014
	Cortical GM	0.015	0.015	3.13E-01	6.73E-01	0.000
	Total WM	-0.001	0.014	9.30E-01	9.98E-01	0.000
	Subcortical GM	0.031	0.018	8.73E-02	6.11E-01	0.001
	Total Ventricular volume	0.001	0.028	9.83E-01	9.98E-01	-0.001
	Cerebellum volume	0.038	0.023	1.01E-01	6.23E-01	0.001
	Amygdala-hippocampus complex	0.026	0.020	2.41E-01	6.73E-01	0.000
	Caudate volume	0.030	0.026	2.27E-01	6.73E-01	0.000
	Putamen volume	0.020	0.025	4.46E-01	7.78E-01	0.000
	Thalamus volume	0.023	0.022	2.49E-01	6.73E-01	0.000
Intelligence (Infinitesimal prior)	TBV	0.122	0.025	1.18E-06*	7.90E-05*	0.014
	Cortical GM	0.016	0.015	2.89E-01	6.73E-01	0.000
	Total WM	0.002	0.014	9.05E-01	9.98E-01	0.000
	Subcortical GM	0.041	0.018	2.35E-02*	3.28E-01	0.001
	Total Ventricular volume	0.012	0.028	6.76E-01	9.13E-01	-0.001

	β	SE	P-uncorr.	P-FDR	ΔAdj-R²
Cerebellum volume	0.041	0.023	7.61E-02	5.61E-01	0.001
Amygdala-hippocampus complex	0.018	0.020	4.14E-01	7.54E-01	0.000
Caudate volume	0.046	0.026	6.32E-02	5.21E-01	0.001
Putamen volume	0.026	0.025	3.09E-01	6.73E-01	0.000
Thalamus volume	0.031	0.022	1.24E-01	6.66E-01	0.001

Note: β, standardized coefficient; SE, standardized error; P-uncorr., uncorrected p-value; P-FDR, false discovery rate adjusted p-value; ΔAdj-R², difference between the adjusted R^2 of the full model (PGS + covariates) compared to the adjusted R^2 of the baseline model (only covariates).

Table S3. Mean and SD for polygenic scores for schizophrenia in the entire sample of participants with EU ancestry, included (n=1139) and excluded (n=1691) in the current study. *P*-value derived from t-test.

	All EU children	**Included**	**Excluded**	*P*-value
Prior=0.01	0.65 (2.57)	0.74 (2.56)	0.59 (2.58)	0.127
Prior=0.05	-15.55 (0.90)	-15.55 (0.87)	-15.55 (0.92)	0.973
Prior=0.1	-16.91 (0.69)	-16.90 (0.68)	-16.92 (0.70)	0.411
Prior=0.5	-16.16 (0.46)	-16.16 (0.45)	-16.16 (0.47)	0.832
Prior=1	-15.99 (0.44)	-'15.99 (0.43)	-15.99 (0.44)	0.911
Infinitesimal prior	-6.97 (0.22)	-6.97 (0.22)	-6.97 (0.22)	0.885

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