ARTICLES

Genetic influences on schizophrenia and subcortical brain volumes: large-scale proof of concept

Schizophrenia is a devastating psychiatric illness with high heritability. Brain structure and function differ, on average, between people with schizophrenia and healthy individuals. As common genetic associations are emerging for both schizophrenia and brain imaging phenotypes, we can now use genome-wide data to investigate genetic overlap. Here we integrated results from common variant studies of schizophrenia (33,636 cases, 43,008 controls) and volumes of several (mainly subcortical) brain structures (11,840 subjects). We did not find evidence of genetic overlap between schizophrenia risk and subcortical volume measures either at the level of common variant genetic architecture or for single genetic markers. These results provide a proof of concept (albeit based on a limited set of structural brain measures) and define a roadmap for future studies investigating the genetic covariance between structural or functional brain phenotypes and risk for psychiatric disorders.

Schizophrenia is a devastating, highly heritable psychiatric disorder that affects approximately 1% of the population[1]. Despite marked recent successes in identifying genetic risk factors and pathways involved in schizophrenia[1–4], the neurobiology of schizophrenia remains poorly understood.

Many differences in brain function and structure have been reported in cases of schizophrenia as compared with controls, although there is considerable inter-individual heterogeneity. Of specific relevance to this study, recent meta-analyses found that people with schizophrenia have smaller hippocampus, amygdala, thalamus, nucleus accumbens and intracranial volumes, along with larger pallidum and lateral ventricle volumes[5,6]. Hippocampal and lateral ventricle volumes are influenced by antipsychotic medication use[5]. In addition, mean hippocampal volume is smaller in high-risk individuals and in unaffected first-degree relatives of those with schizophrenia[7,8].

Structural brain measurements, such as those from magnetic resonance imaging (MRI), typically have high reproducibility and low measurement error and can be highly heritable[9,10]. Increasingly large studies of brain morphometry are being performed and are being used to evaluate the contributions of common and rare genetic variants to brain structure[9,11].

With genome-wide association results available from large samples for schizophrenia and for MRI-based brain phenotypes, we can now use genomic approaches to evaluate the genetic link between disease risk and such brain measures. Findings of covariation would help us develop new hypotheses about the structures involved in the primary disease process of schizophrenia. In this proof-of-concept study, we created a roadmap for the analysis of genetic covariation using a battery of complementary methods. We evaluated the overlap of common genetic variation at the high level of genetic architecture as well as of individual genetic variants. We also evaluated common genetic variant effect sizes on neuroimaging phenotypes and schizophrenia. The data we analyzed are from large meta-analyses by the Psychiatric Genomics Consortium (PGC; http://pgc.unc.edu/) for schizophrenia[3]

and meta-analyses from the ENIGMA Consortium (Enhancing NeuroImaging Genetics through Meta-Analysis; http://enigma.ini.usc.edu/) for eight MRI volumetric measures (amygdala, caudate nucleus, hippocampus, nucleus accumbens, pallidum, putamen, thalamus, and intracranial volume (ICV))[9]. Our results suggest that common genetic variation predisposing to schizophrenia does not show evidence of overlap with common genetic variation influencing these eight brain structure volumes. Genetic effect sizes did not differ significantly for neuroimaging and schizophrenia phenotypes.

RESULTS
We analyzed genome-wide association data for schizophrenia (33,636 cases and 43,008 controls) and eight structural MRI brain measures (11,840 individuals). Sample characteristics are presented in **Supplementary Table 1**. These data were used for a comprehensive set of analyses of common variant genetic sharing between schizophrenia and brain volumetric measures.

Comparisons of common variant genetic architectures
Linkage disequilibrium score regression. We first used genome-wide results to evaluate the high-level features of these traits and their genetic interrelations. Using genome-wide association (GWA) summary statistics, excluding the extended major histocompatibility complex region, we used linkage disequilibrium score regression (LDSR)[12] to estimate the heritability of schizophrenia due to common genetic variants, along with that of eight brain volumetric measures. The single nucleotide polymorphism (SNP)-based heritability of schizophrenia was 25.5% (s.e.m. = 1.1%) (**Table 1**). The SNP-based heritability estimates for the MRI measures ranged from 11% (nucleus accumbens) to 30% (putamen). The heritability for amygdala volume was nonsignificant in this sample. The genetic correlations of MRI volumetric measures with schizophrenia were all nonsignificant (**Table 1**). These negative findings stand in contrast to the relatively high common-variant correlations of schizophrenia with bipolar disorder and major depressive disorder[13,14].

Table 1 SNP heritability analyses for MRI brain volume and genetic correlations with schizophrenia[a]

Brain region[a]	N	Heritability	s.e.m.	Genetic correlation with SCZ	s.e.m.	Z	P
Intracranial volume	9,826	0.157	0.050	−0.010	0.072	−0.137	0.891
Caudate nucleus	11,624	0.260	0.043	−0.095	0.057	−1.674	0.094
Hippocampus	11,621	0.135	0.041	−0.147	0.081	−1.826	0.068
Nucleus accumbens	11,603	0.105	0.045	−0.094	0.090	−1.051	0.293
Pallidum	11,595	0.137	0.047	−0.038	0.069	−0.546	0.585
Putamen	11,598	0.303	0.052	0.013	0.052	0.256	0.798
Thalamus	11,646	0.118	0.041	−0.113	0.087	−1.298	0.194

[a]Amygdala heritability was too low to allow a valid analysis.

Genetic predisposition scores. In the genetic risk score approach[15], we considered the ENIGMA GWA results as training sets in order to compute common variant genetic predisposition to (for instance) greater ICV for each schizophrenia case and control. We then compared the mean polygenic predisposition score in cases to that in controls. None of the correlations was significant after correction for eight comparisons (**Fig. 1** and **Table 2**). The strongest effect (for hippocampal volume) was almost entirely driven by one SNP (rs2268894)[9], but only three SNPs met the P-value threshold of 1×10^{-6} for inclusion in this analysis. These null results are in contrast to the robust evidence for common variant genetic correlations between schizophrenia and other psychiatric disorders[16].

Rank-rank hypergeometric overlap test[17]. We used this test to quantify overlap between pairs of GWA results ranked by their association statistics on the basis of 172,652 SNPs. The overlap of rank-ordered lists of genetic variants influencing any of the brain MRI volumes and those conferring risk for schizophrenia was not statistically significant (**Fig. 2**). The overlap between genetic contributions to putamen and caudate nucleus volumes was used as a positive control; the overlap between genetic contributions to hippocampal volume and the presumably unrelated trait of thumb fingerprint whorl structure[18] was used as a negative control. The latter comparison showed similar overlap to that of brain structure and schizophrenia.

Sign tests. We compared the pattern of GWA results by checking whether the signs of the regression coefficients[3] were consistently in the same direction between the top associations for schizophrenia and those for the MRI volumetric measures. None of the sign tests showed consistent directions of effect (**Table 3**).

Analysis of single genetic variants
Genome-wide significant associations. We next searched for specific genetic regions associated with these traits. We evaluated the 128 genome-wide significant schizophrenia index SNPs[3] for association with brain volumes[9]. One association survived correction for 876 comparisons: rs2909457*A (chr2:162,845,855, intergenic between *SLC4A10* and *DPP4*) was associated with decreased hippocampal volume ($P = 1.2 \times 10^{-6}$, effect size = −23 mm[3] per allele) and decreased risk for schizophrenia (odds ratio = 0.94, $P = 4.6 \times 10^{-8}$). However, this finding was in the opposite direction of expectations given previous observations of smaller hippocampal volumes in cases relative to controls[6] (**Supplementary Table 2**). Starting with the eight SNPs previously found to be associated with the brain volumes[9], no significant associations with schizophrenia were observed (**Supplementary Table 2**).

SNP meta-analyses. We also performed GWA meta-analyses of the schizophrenia and brain structure results. The Manhattan plots for these analyses are shown in **Supplementary Figures 1–8**. In **Supplementary Table 3**, the genome-wide significant findings are given. In most instances, the results were entirely driven by the association with schizophrenia.

Conjunction analysis. To identify individual SNPs that influence risk for both schizophrenia and brain structure, we implemented a conjunction test[19]. No SNP showed genome-wide significant association with both schizophrenia and brain structure, although several loci were detected at sub-threshold levels (**Supplementary Fig. 9**).

Comparison of genetic effect sizes for clinical and brain volume measures
Some investigators have suggested that common genetic variants underlying continuous brain imaging endophenotypes may have larger effect sizes than those for neuropsychiatric disorders (for example,
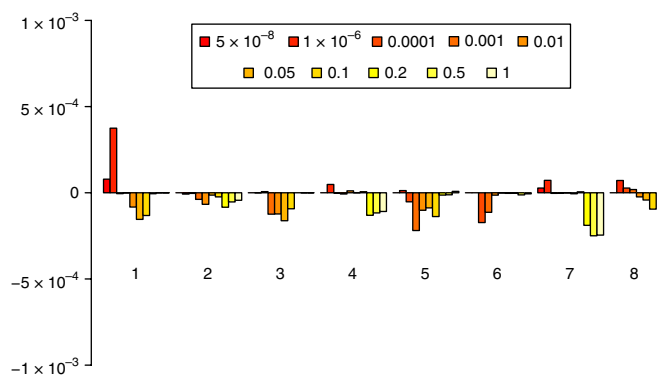

Figure 1 Genetic predisposition score analyses examining the predictive capacity of ENIGMA brain volumetric results on schizophrenia case-control status using different P-value thresholds. x axis: (1) hippocampus, (2) ICV, (3) nucleus accumbens, (4) amygdala, (5) caudate nucleus, (6) pallidum, (7) putamen, (8) thalamus. y axis shows Nagelkerke's R^2. Positive values indicate SNP effects for increasing brain structure volume and increased risk for schizophrenia. Negative values indicate SNP effects for decreasing brain structure volume and increased risk for schizophrenia. Significance values are given in **Table 2**.

Table 2 Two outcome variables derived from genetic predisposition analysis

Phenotype	P	R^2	AUC	OR (95% CI)
Intracranial volume	0.247	-2.46×10^{-5}	0.512	0.944 (0.877,1.016)
Caudate nucleus	0.033	-8.35×10^{-5}	0.502	0.928 (0.864,0.997)
Hippocampus	0.010	-1.23×10^{-4}	0.506	0.917 (0.853,0.986)
Nucleus accumbens	0.002	-1.74×10^{-4}	0.500	0.928 (0.862,0.9996)
Pallidum	0.985	6.21×10^{-9}	0.513	1.034 (0.963,1.111)
Putamen	0.607	-4.87×10^{-6}	0.515	0.971 (0.891,1.059)
Thalamus	0.221	-2.75×10^{-5}	0.510	0.959 (0.888,1.036)
Amygdala	0.806	1.11×10^{-6}	0.509	1.021 (0.951,1.096)

P is the significance, uncorrected for multiple testing. R^2 is Nagelkerke's correlation on the observed scale, corrected for principal components. AUC is area under the receiver operating characteristic curve; OR, odds ratio; CI, confidence interval.
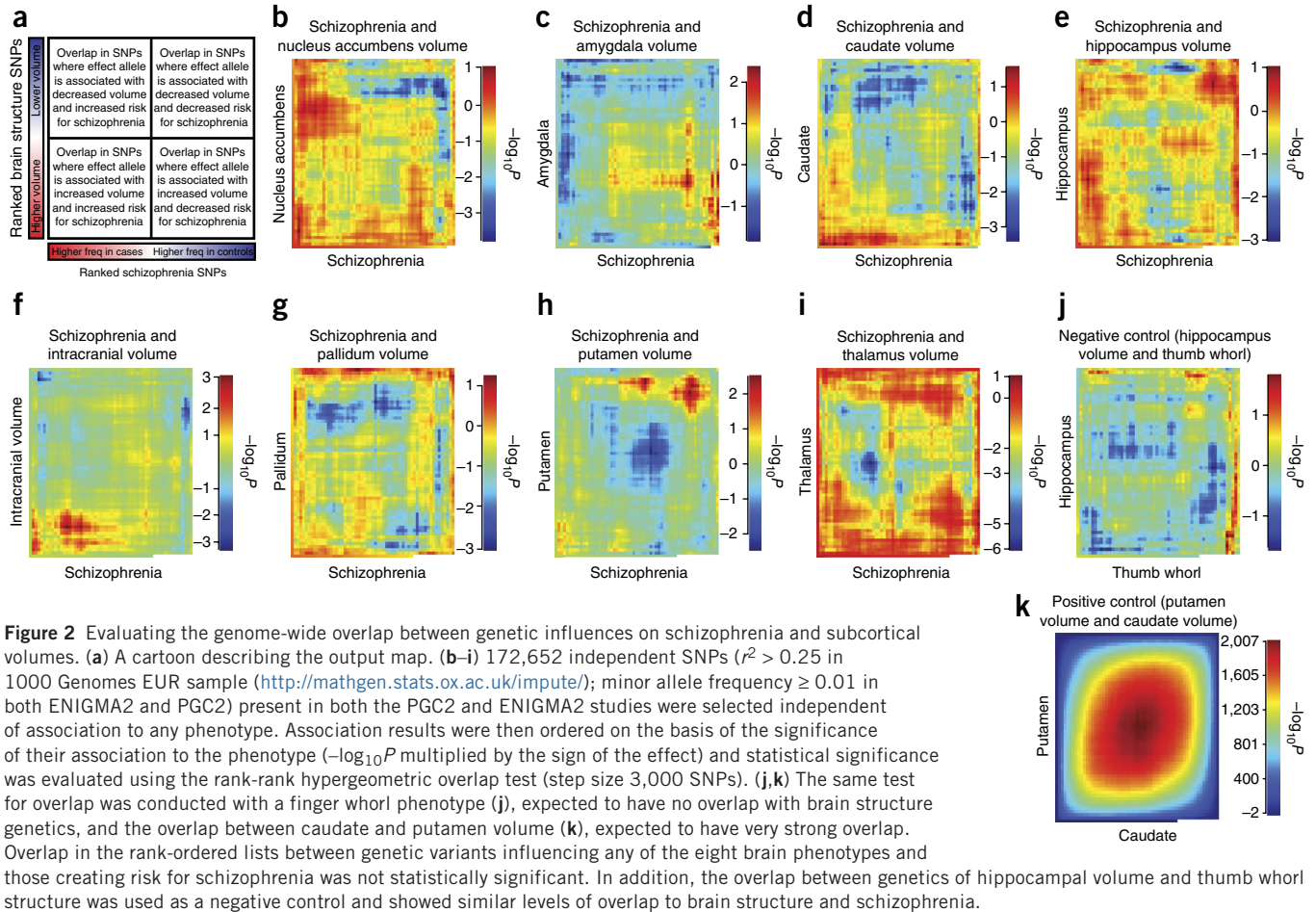
Figure 2 Evaluating the genome-wide overlap between genetic influences on schizophrenia and subcortical volumes. (**a**) A cartoon describing the output map. (**b**–**i**) 172,652 independent SNPs ($r^2 > 0.25$ in 1000 Genomes EUR sample (http://mathgen.stats.ox.ac.uk/impute/); minor allele frequency ≥ 0.01 in both ENIGMA2 and PGC2) present in both the PGC2 and ENIGMA2 studies were selected independent of association to any phenotype. Association results were then ordered on the basis of the significance of their association to the phenotype ($-\log_{10}P$ multiplied by the sign of the effect) and statistical significance was evaluated using the rank-rank hypergeometric overlap test (step size 3,000 SNPs). (**j**,**k**) The same test for overlap was conducted with a finger whorl phenotype (**j**), expected to have no overlap with brain structure genetics, and the overlap between caudate and putamen volume (**k**), expected to have very strong overlap. Overlap in the rank-ordered lists between genetic variants influencing any of the eight brain phenotypes and those creating risk for schizophrenia was not statistically significant. In addition, the overlap between genetics of hippocampal volume and thumb whorl structure was used as a negative control and showed similar levels of overlap to brain structure and schizophrenia.

schizophrenia)[20–22]. To test this hypothesis, we compared the maximum effect sizes from replicated genetic associations for each trait. For comparability across quantitative and binary traits, effect sizes were assessed as percentage of variance explained (for MRI volumes) or percentage of variance explained on the liability scale (for schizophrenia)[23]. Individual common variants had only a small influence on either brain structure or schizophrenia (**Supplementary Fig. 10**).

Table 3 Sign tests of directional effects among 94 genome-wide significant associations with schizophrenia ($P < 5 \times 10^{-8}$) and the top 231 associations ($P < 1 \times 10^{-6}$)

Brain region	P threshold	N same direction	Proportion	P
Intracranial volume	$<5 \times 10^{-8}$	49	0.52	0.379
Caudate nucleus	$<5 \times 10^{-8}$	47	0.50	0.541
Hippocampus	$<5 \times 10^{-8}$	46	0.49	0.621
Nucleus accumbens	$<5 \times 10^{-8}$	48	0.51	0.459
Pallidum	$<5 \times 10^{-8}$	51	0.54	0.235
Putamen	$<5 \times 10^{-8}$	52	0.55	0.177
Thalamus	$<5 \times 10^{-8}$	49	0.52	0.379
Amygdala	$<5 \times 10^{-8}$	49	0.52	0.379
Intracranial volume	$<1 \times 10^{-6}$	121	0.52	0.255
Caudate nucleus	$<1 \times 10^{-6}$	113	0.49	0.653
Hippocampus	$<1 \times 10^{-6}$	105	0.45	0.926
Nucleus accumbens	$<1 \times 10^{-6}$	109	0.47	0.821
Pallidum	$<1 \times 10^{-6}$	117	0.51	0.448
Putamen	$<1 \times 10^{-6}$	115	0.50	0.552
Thalamus	$<1 \times 10^{-6}$	115	0.50	0.552
Amygdala	$<1 \times 10^{-6}$	109	0.47	0.821

The expected proportion under the null hypothesis is 0.5.

Effect sizes for individual SNPs were similar for both brain structure and schizophrenia and were of the same order as those observed for anthropometric traits such as height[24].

DISCUSSION

In this proof-of-concept study, we evaluated the relationship between common genetic variants implicated in schizophrenia and those associated with subcortical brain volumes and ICV. The sample sizes were the largest yet applied to these questions. With a comprehensive set of analyses, we did not find evidence for notable genetic correlations, either at a high level (that is, common variant genetic architecture) or for single genetic markers. Our findings do not support the hypothesis that these subcortical brain volume measures and ICV are causally associated with schizophrenia risk. Similarly, we did not find evidence that common SNPs have pleiotropic effects on these MRI volumes and schizophrenia. Our results suggest alternative hypotheses that require consideration and refutation: that the volumetric differences observed in schizophrenia may be epiphenomena unrelated to its primary genetic causes, may be a result of prenatal environment or may result from reverse causation[25]. Finally, the effect sizes of SNPs implicated in schizophrenia and those associated with brain volumes were broadly similar.

We studied a limited set of brain MRI measures. Our study should be considered a proof-of-concept for evaluating genetic covariation rather than decisively addressing the full range of hypotheses pertaining to the genetic overlap of brain imaging measures with neuropsychiatric disease risk. We provide a rigorous roadmap for

more definitive and larger future studies. Full elucidation of the brain correlates of schizophrenia will require a fuller set of structural and functional imaging measures (perhaps at the voxel level) along with evaluation of common and rare genetic variation.

The null findings of this study should be interpreted in light of several qualifiers. First, several brain regions that are not expected a priori to overlap with schizophrenia were included for completeness (for example, caudate and putamen volumes are uncorrelated with schizophrenia[5,6], and amygdala volume did not have SNP heritability different from zero in our study). Second, other neuroimaging phenotypes could be more informative for schizophrenia (for example, cortical thickness, ventricular volume, diffusion tensor imaging or functional activity)[26,27]. Indeed, genetic variants associated with disease may influence distinct cell types within circumscribed neural circuits that may not be captured by MRI. Third, the ENIGMA MRI protocol served to harmonize images obtained from different scanners and protocols. While we have shown that this performs well, any genetic signal might have been lessened. Fourth, in this study of adults, we may not have observed the brain regions at the most appropriate time for identifying genetic overlap with schizophrenia, given that the volumes of most subcortical brain structures plateau in late adolescence to early adulthood. While schizophrenia is widely believed to be a neurodevelopmental disorder[28], its onset generally follows the period of greatest growth for these structures. Fifth, relatively small genetic correlations between schizophrenia and these brain volumes may have been masked by combining data sets in a meta-analytic framework; for example, heterogeneous sample characteristics such as age, sex and technical noise resulting from different MRI scanners or acquisition sequences may remain. It is conceivable that this resulted in the lower than expected SNP heritability for some of these measures. Mega-analysis could be an important way to improve control for heterogeneity. Sixth, we evaluated only common genetic variation. Although common genetic variation explains far more of the risk for schizophrenia than rare copy number variation or rare deleterious exonic variation[2], rare genetic effects on brain structure could be salient for some cases of schizophrenia. Finally, the sample sizes and statistical power of the schizophrenia and neuroimaging data sets differed. The PGC has attained a sample size sufficient to detect many common loci of small effect, whereas ENIGMA is earlier in the discovery arc[29].

Heritability estimates from genome-wide data obtained using LDSR[14] were lower than observed in previous studies[30]. This was expected for the subcortical regions, as those were corrected for ICV. For schizophrenia, a likely source of difference with previous studies is the removal of the extended MHC region from our analysis.

Although we found no evidence for genetic correlation between subcortical volumes and schizophrenia, we also investigated whether effect sizes of genetic variants are larger for brain measures than for schizophrenia. This point has been debated with respect to endophenotype studies, which attempt to identify quantifiable brain measures or other biomarkers thought to be intermediate between genotype and the liability to a disorder[31–33]. An endophenotype that lies on a causal pathway to a clinical disorder could increase power for genetic studies. Previous studies addressed this hypothesis in far smaller samples. We compared SNP effect sizes for the top findings for schizophrenia with those for subcortical volumes (hippocampus, putamen, caudate) and ICV. The results of this analysis showed similar effect sizes. The endophenotype concept is unlikely to be sufficiently addressed in these analyses given the reasons noted above.

In conclusion, this study presents a roadmap for comprehensive evaluation of genetic covariation between neuropsychiatric disease

liability and brain imaging measures. The present analysis was limited to a small number of brain volume phenotypes, and no evidence of genetic overlap was identified. More extensive brain-wide and genome-wide analyses may help in the mechanistic dissection of genetic risk for disease.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

AUTHOR CONTRIBUTIONS

Study conception and supervision: B. Franke, B.M.N., J.L.S., M.C.O'D., P.F.S., P.M.T., S.E.M. Design of ENIGMA or PGC: A.A.-V., A.M.M., B. Franke, B.M.N., D.P.H., J.A.T., J.L.S., J.W.S., K.J.E.v.H., M.C.N., M.C.O'D., O.A.A., P.F.S., P.L., P.M.T., S.E.M., S. Ripke, T.E.N., V.A., Y.Y., Y.Y.W.H. Obtained funding: B. Franke, M.C.O'D., M.J.W., N.G.M., P.F.S., P.M.T. Provided samples: PGC2 Schizophrenia Working Group and ENIGMA2 Consortium. Conducted analyses: A.A.-V., B.M.N., D.P.H., J.L.S., K.J.E.v.H., M.C.N., P.L., S.E.M., S. Ripke, T.E.N., V.A., Y.Y.W.H. Writing group: A.A.-V., B. Franke, B.M.N., D.P.H., J.L.S., K.J.E.v.H., M.C.O'D., P.F.S., P.M.T., S.E.M., S. Ripke, V.A. All authors reviewed and approved the final version of this manuscript.

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ONLINE METHODS

Data. The data used for the analyses described here are available to researchers. The ENIGMA data can be obtained from http://enigma.ini.usc.edu/enigma-vis/. The PGC data can be downloaded from http://www.med.unc.edu/pgc/downloads/.

PGC schizophrenia. We analyzed individual genotype data from 46 European-ancestry schizophrenia GWAS data sets (full details in ref. 3). Briefly, quality control and imputation were performed by the PGC Statistical Analysis Group for each data set separately. Genotype imputation was with the pre-phasing/imputation stepwise approach implemented in IMPUTE2/SHAPEIT (chunk size of 3 Mb and default parameters) using the 1000 Genomes Project data set (phase 1, August 2012, URLs). After imputation, we identified autosomal SNPs with high imputation accuracy across all samples. For robust relatedness testing and population structure analysis, we evaluated a subset of SNPs following LD-pruning ($r^2 > 0.02$) and frequency filtering (MAF > 0.05). For association testing, we evaluated the 46 data sets separately using an additive logistic regression model including ancestry principal components as covariates, and then conducted a meta-analysis of the 52 sets of results using an inverse-weighted fixed effects model. After excluding subjects who were also in ENIGMA ($N = 458$; see below), 33,636 cases and 43,008 controls were used for calculations (**Supplementary Table 1**).

ENIGMA, sample with brain volume measures and assessment of endophenotype. The data analyzed here are from the ENIGMA analysis of eight MRI volumetric measures (full details in ref. 9). MRI brain scans and genome-wide genotype data were available for 11,840 subjects from 22 cohorts (**Supplementary Table 1**). Only cohorts without schizophrenia cases and controls overlapping with the PGC schizophrenia samples were included. Participants clustered with subjects of known European ancestry as verified by multidimensional scaling (MDS) analysis. Genomic data were imputed to a reference panel (1000 Genomes, v3 phase1) comprising only European samples and with monomorphic SNPs removed. Imputation was performed at each site using MaCH for phasing and minimac for imputation[34]. Only SNPs with an imputation score of RSQ > 0.5 and minor allele counts > 10 within each site were included. Tests of association were conducted separately for eight MRI volumetric phenotypes (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, thalamus and ICV) with the following covariates in a multiple linear regression framework: age, age^2, sex, four MDS components (to account for population structure), ICV (for subcortical brain phenotypes) and diagnosis (when applicable). The GWA statistics from each of the 22 sites were combined using a fixed-effect inverse variance-weighted meta-analysis as implemented in METAL[35].

Removal of duplicated individuals. Subject overlap between all PGC and ENIGMA cohorts was evaluated using a checksum algorithm to ensure the robustness of our results, given that some analyses were sensitive to the presence of duplicate individuals. For each individual, ten checksum numbers were created based on ten batches of 50 SNP genotypes and compared between individuals from both consortia. Based on these comparisons and a general exclusion of cohorts containing schizophrenia cases, 1,517 individuals were removed from ENIGMA and 458 subjects were removed from the PGC.

Linkage disequilibrium score regression (LDSR). For LDSR, each data set underwent additional filtering. Only markers overlapping with HapMap Project Phase 3 SNPs and passing the following filters were included: INFO score > 0.9 (where available), study missingness of 0 and MAF > 1%. Indels and strand-ambiguous SNPs were removed. To remove a potential source of bias, all SNPs in the extended MHC region (chr6:25–35 Mb) were removed from all data sets. The schizophrenia analysis included only results from European studies used (LDSR requires linkage disequilibrium (LD) data from a comparable sample). For the ENIGMA amygdala results, the mean χ^2 was too low (1.0051) to reliably estimate heritability using LDSR.

The analysis was conducted using a two-step procedure with the LD-scoring analysis package[12,14]. An unconstrained regression was run to estimate the regression intercepts for each phenotype, followed by an analysis with regression intercepts constrained to those estimated in the first step and the covariance

intercept defined as zero (we took steps to exclude overlapping samples). Standard errors were estimated using a block jackknife procedure and used to calculate P-values.

Genetic predisposition analyses. To investigate the combined impact of ENIGMA association results on case-control status in the PGC schizophrenia data, we performed a series or genetic predisposition score analyses. For each ENIGMA volumetric phenotypes, we excluded SNPs with MAF <2%, indels and SNPs in the extended MHC region (chr6:25–34 Mb). We then 'clumped' the data, discarding variants within 500 kb of and in $r^2 \geq 0.1$ with another, more significant marker. We performed genetic predisposition score prediction of target subgroups as originally described[15] for several P-value thresholds (5×10^{-8}, 1×10^{-6}, 1×10^{-4}, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, 1.0), multiplying the effect size of the ENIGMA phenotype of each variant by the imputation probability for the risk allele in each individual. The resulting values were summed so that each individual had a genetic predisposition score for further analyses. Two outcome variables are reported in **Table 2**: the significance of the case-control score difference analyzed by logistic regression (including ancestry-based principal components and a study indicator as covariates) and the proportion of variance explained (Nagelkerke's R^2) computed by comparison of a full model (covariates + polygenic risk scores) score to a reduced model (covariates only). Note that these R^2 estimates are biased owing to recruitment of the case-control studies and as the numbers of cases and controls do not reflect the underlying risk of disease in the population.

Rank-rank-hypergeometric overlap test (RRHO). RRHO[17] tests the hypothesis that ordering of two lists (LD-pruned GWAS results for schizophrenia versus a brain structure phenotype) by the strength of their association is arbitrary. The number of independent SNPs in common between the two ordered lists is evaluated at specified step sizes. Two lists that show similar ordering of SNPs demonstrate a global pattern of similarity of associations. Independent SNPs were selected on the basis of the 1000 Genomes European data set for 200 SNP windows shifted at five SNP intervals using an r^2 threshold of 0.25. SNPs found in both PGC and ENIGMA data with MAF ≥ 0.01 were retained (172,652 SNPs). The SNPs were then ordered by the $-\log_{10}P$ of association multiplied by the effect size. A two-sided RRHO test that allowed testing for either over- or underenrichment was used with a step size of 3,000 SNPs.

Finger whorl data used as control in conjunction analysis. A GWAS of a dermatoglyphic trait (presence of a whorl on the left thumb), collected as part of an ongoing study at the Queensland Institute of Medical Research[18], was used to provide a negative control for the RRHO test. Briefly, rolled ink prints were collected on archival quality paper, and fingerprint patterns were manually coded. Complete data from 3,314 participants (twins and their family members) were available. Genotypes were imputed to the 1000 Genomes Project reference (phase 1 version 3). GWAS was conducted using Merlin offline to account for relatedness and zygosity.

Lookup of top GWAS SNP findings. Evidence for an effect of the reported 128 independent schizophrenia-associated SNPs on subcortical brain volumes and ICV was studied through a look-up of results. rs115329265 was not available in the ENIGMA data and was replaced by a SNP in moderate LD (chr6:28305863R; $r^2 = 0.64$); rs77149735 was not available in ENIGMA and could not be replaced by a SNP in LD. Three chrX SNPs (rs1378559, rs5937157 and rs12845396) were excluded because chrX data were not available from ENIGMA. Effects of the eight independent SNPs associated with brain volumes reported by ENIGMA on schizophrenia risk were studied through look-up of results in the PGC data.

Multiple-comparisons correction was performed by estimating the effective number of independent tests (M_{eff}). This method considers the correlation structure (**Supplementary Table 4**) between brain measures and calculates the M_{eff} based on the observed eigenvalue variance of the different brain volume measures using matSpD (http://gump.qimr.edu.au/general/daleN/matSpD/). The P value for significance was 0.05 divided by the sum of (a) M_{eff} times the number of SNPs included in the lookup from PGC to ENIGMA ($n = 124$) and (b) the number of SNPs included in the lookup from ENIGMA to PGC ($n = 8$). Eight brain volumes resulted in seven independent tests, and only SNPs with a $P < 5.7 \times 10^{-5}$ were considered significant.

SNP sign test in the top GWAS findings. To investigate a potential accumulation of same- or opposite-direction effects of SNPs between PGC schizophrenia and ENIGMA, we counted the number of same direction effects for the top findings from the schizophrenia data set (94 LD-independent genome-wide significant SNPs, 231 with $P < 1 \times 10^{-6}$) in the different brain structure data sets and tested the significance of the result in a binomial test ($n = 14$ tests for 7 effective ENIGMA phenotypes and 2 P-value thresholds).

Conjunction analysis. To determine whether a particular SNP is linked to both brain structure and risk for schizophrenia, we used a conjunction analysis[19]. This analysis makes inference on the alternative hypothesis that both null hypotheses are false. This is in distinction to a traditional meta-analysis method which infers on an alternative hypothesis that one or more null hypotheses are false. A conjunction analysis is calculated as $P_{conj} = \max(P_{brain}, P_{case\text{-}control})$, where P_{brain} is the significance of the SNP associated to brain structure and $P_{case\text{-}control}$ is the significance of the SNP association to schizophrenia. As conjunction tests can be very conservative, an adjustment to this test[36] based on the estimated fraction of false nulls was used here with modifications (P'_{conj}). Over 7.5 million SNPs found in both the ENIGMA and PGC data sets with MAF ≥ 0.01 were evaluated.

A conjunction null hypothesis is the union of the individual null hypotheses, producing a 'composite null hypothesis'. In standard testing situations a 'point null hypothesis' is used, meaning that there is exactly one configuration of the unknown parameters of interest that corresponds to the null. For example, "no gene-brain association, no case-control association" is a point null hypothesis. A composite null has multiple configurations. For example, both of these configurations fall into the conjunction null hypothesis: "true gene-brain association, no case-control association"; "no gene-brain association; true case-control association". A valid conjunction test has to control false positive risk over all possible configurations in the conjunction null. Put another way, a conjunction test has to be calibrated for the worst possible configuration of true signals, and as a result can be quite conservative when the true state of the model is not one of the extreme cases.

The method of Deng *et al.*[36] attempts to reduce the conservativeness of the conjunction procedure in the multiple testing setting. The authors propose a method that estimates prevalence of null hypotheses in each of the individual tests being combined. With this information, a 'relaxed' test can be constructed that is less conservative. However, a crucial equation in that paper is in error. The equation below provides the estimator for the proportion of false null hypothesis for each of the two tests to be combined. The expression is based on the method of Storey[37], who posed it as an estimate of the proportion of true null hypotheses. Deng *et al.*[36] apparently inverted the result incorrectly; the correct expression is

$$\hat{\pi}_i(\lambda) = 1 - \frac{\#\{p_i(j) > \lambda\}}{(1-\lambda)n}$$

In our analyses, the parameter λ in the equation above was set to 0.25.

SNP meta-analysis. We combined the association P-values of SNPs associated with schizophrenia with SNPs associated with the seven subcortical brain volumes and ICV from ENIGMA. Using METAL[35], we conducted a sample size-weighted meta-analysis for schizophrenia (effective sample size 71,715) and ENIGMA (variable sample sizes per SNP ranging from 8,000 to 11,000). SNPs were excluded if they were not present in both data sets and for MAF < 1% (per analysis). The total number of SNPs present in the eight meta-analyses ranged from 7,847,762 to 7,945,194.

SNP effect size comparisons. SNP effect sizes were extracted from studies of brain structure (ENIGMA)[9], schizophrenia (PGC)[3], height (GIANT)[24] and educational attainment (EduYears)[38]. The five highest effect size SNPs were selected for schizophrenia and height; all genome-wide significant SNPs were displayed for brain structure volumes and EduYears. Percent variance was calculated on the liability scale for schizophrenia for comparison with quantitative traits[23]. For brain structures, height and EduYears, percent variance explained was calculated as $R^2_{g|c}/(1 - R^2_c) = (t^2/[(n-k-1) + t^2]) \times 100$, where the t-statistic is calculated as the β-coefficient for a given SNP from the regression model (controlling for covariates) divided by the standard error of the β-estimate, n is the total number of subjects and k is the total number of covariates. 95% confidence intervals were calculated by transforming percent variance explained to a z-statistic using Fisher's Z transformation, finding the 95% confidence intervals of the z-statistic, and transforming this interval back into percent variance explained.

A **Supplementary Methods Checklist** is available.

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