

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 population¹. 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 use⁵. 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 schizophrenia³

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}.

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Received 10 August 2015; accepted 22 December 2015; published online 1 February 2016; doi:10.1038/nn.4228

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

^aAmygdala heritability was too low to allow a valid analysis.

Genetic predisposition scores. In the genetic risk score approach¹⁵, 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 disorders¹⁶.

Rank-rank hypergeometric overlap test¹⁷. 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 structure¹⁸ 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 coefficients³ 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 SNPs³ for association with brain volumes⁹. 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 controls⁶ (Supplementary Table 2). Starting with the eight SNPs previously found to be associated with the brain volumes⁹, 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 test¹⁹. 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,

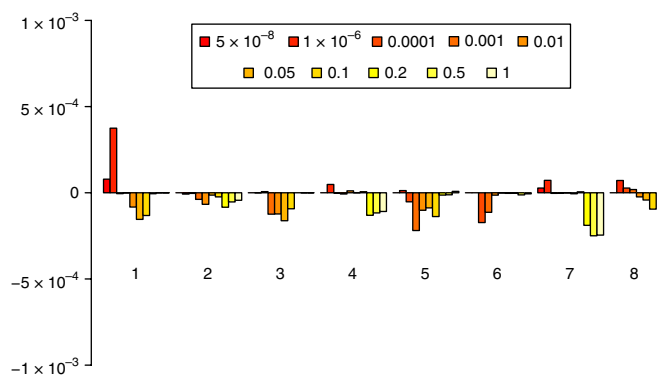


Figure 1 Genetic predisposition score analyses examining the predictive capacity of ENIGMA brain volumetric results on schizophrenia case-control status using different P -value thresholds. x axis: (1) hippocampus, (2) ICV, (3) nucleus accumbens, (4) amygdala, (5) caudate nucleus, (6) pallidum, (7) putamen, (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.

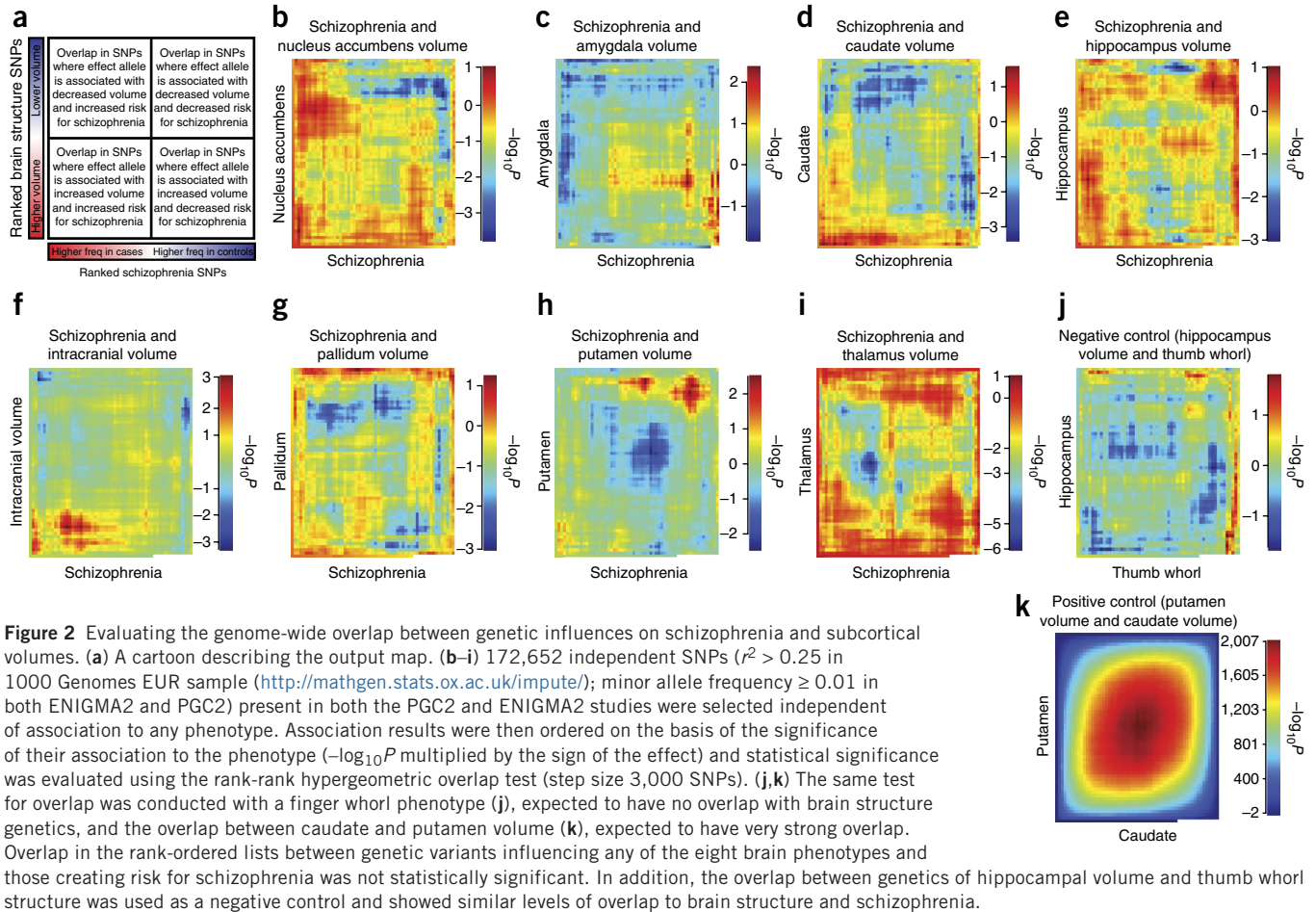


Figure 2 Evaluating the genome-wide overlap between genetic influences on schizophrenia and subcortical volumes. **(a)** A cartoon describing the output map. **(b–i)** 172,652 independent SNPs ($r^2 > 0.25$ in 1000 Genomes EUR sample (<http://mathgen.stats.ox.ac.uk/impute/>); minor allele frequency ≥ 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 height²⁴.

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 causation²⁵. 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 disorder²⁸, 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 variation², 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 arc²⁹.

Heritability estimates from genome-wide data obtained using LDSR¹⁴ were lower than observed in previous studies³⁰. 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.

ACKNOWLEDGMENTS

PGC. The authors are grateful to the many family members who participated in the studies that recruited these samples, to the many clinicians who assisted in their recruitment, and to our team members, without whom this study would have been impossible. Core funding for the PGC is from the US National Institute of Mental Health (NIMH; U01 MH094421). Statistical analyses were carried out on the Genetic Cluster Computer (<http://www.geneticcluster.org/>) hosted by SURFara and financially supported by the Netherlands Scientific Organization (NWO 480-05-003), along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam. The GRAS data collection was supported by the Max Planck Society, the Max-Planck-Förderstiftung and the DFG Center for Nanoscale Microscopy & Molecular Physiology of the Brain (CNMPB), Göttingen, Germany. The Boston CIDAR project was supported by the NIMH (P50 MH080272, R.W.M.; U01 MH081928, L.J.S.; R01 MH092380, T.L.P.) and the Massachusetts General Hospital Executive Committee on Research (T.L.P.). P.H.L. is supported by NIMH K99 MH101367. ISC Portugal: C.N.P. and M.T.P. have been supported by NIMH grants MH085548, MH085542, MH071681, MH061884, MH58693 and MH52618 and NCRR grant RR026075. C.N.P., M.T.P. and A.H.F. have been supported by grants from the Department of Veterans Affairs Merit Review Program. The Danish Aarhus study was supported by grants from Lundbeck Foundation, Danish Strategic Research Council, Aarhus University, and Stanley Research Foundation. Work in Cardiff was supported by UK Medical Research Council (MRC) Centre (G0800509) and MRC Programme (G0801418) grants, the European Community's Seventh Framework Programme (HEALTH-F2-2010-241909, Project EU-GEI) the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement 279227, a fellowship to J.W. from the MRC/Welsh Assembly Government and the Margaret Temple Award from the British Medical Association. We thank Novartis for their input in obtaining CLOZUK samples, staff at The Doctor's Laboratory (L. Levett and A. Levett) for help with sample acquisition and data linkage, and staff in Cardiff (K. Mantripragada and L. Hopkins) for sample management. CLOZUK and some other samples were genotyped at the Broad Institute or by the Wellcome Trust Case Control Consortium (WTCCC) and Wellcome Trust Case Control Consortium 2 (WTCCC2) (WT 083948/Z/07/Z). We acknowledge use of the British 1958 Birth Cohort DNA (MRC: G0000934) and the Wellcome Trust (068545/Z/0 and 076113/C/04/Z), the UK Blood Services Common Controls (UKBS-CC collection), funded by the Wellcome Trust (076113/C/04/Z) and by a National Institute for Health Research programme grant to National Health Service Blood and Transplant (RP-PG-0310-1002). Virginia Commonwealth University investigators were supported by NIMH grants R01 MH083094, R01 MH041953, and R01 MH068881 and WTCCC2 grant WTCCC-084710. Recruitment of families in Bulgaria was funded by the Janssen Research Foundation, Beerse, Belgium. We thank the staff in the Neuroscience Biomarkers Genomic Lab led by R. Favis at Janssen for sample processing and the staff at Illumina for genotyping Janssen DNA samples. We also thank A. Santos, N. Bottrel, M.-A. Franc and W. Cafferty of Janssen Research & Development) for operational support. Dutch samples were funded by the Netherlands Organization for Health Research and Development (ZonMw) in the Mental Health program and by NIMH R01 MH078075. Danish samples were funded by the Danish Council for Strategic Research (Journ.nr. 09-067048), the Danish National Advanced Technology Foundation (Journ.nr. 001-2009-2), the Lundbeck Foundation (Journ.nr. R24-A3243), and the EU 7th Framework Programme. The Wellcome Trust supported this study as part of the WTCCC2 project. E. Bramon holds a MRC New Investigator Award and a MRC Centenary Award. The TOP Study was supported by the Research Council of Norway (213837, 217776, 223273), South-East Norway Health Authority (2013-123) and K.G. Jepsen Foundation. This work was supported by the Donald and Barbara Zucker Foundation, the North Shore – Long Island Jewish Health System Foundation and grants from the Stanley Foundation (A.K.M.), NARSAD (A.K.M.), NIMH (MH065580 to T. Lencz; MH001760 to

A.K.M.), and NIMH RC2 MH089964 and R01 MH084098. Finnish samples were funded by SynSys (EU FP7-242167), Sigrid Juselius Foundation, the Academy of Finland (grant 251704), and the Sohlberg Foundation. The Swedish Research Council (grants 2006-4472, 2009-5269, 2009-3413) and the County Councils of Västerbotten and Norrbotten, Sweden, supported the collection of the Umeå samples. The Betula Study, from which the Umeå controls were recruited, is supported by grants from the Swedish Research Council (grants 345-2003-3883, 315-2004-6977) and the Bank of Sweden Tercentenary Foundation, the Swedish Council for Planning and Coordination of Research, the Swedish Council for Research in the Humanities and Social Sciences and the Swedish Council for Social Research. We acknowledge support from NIMH K01 MH085812 (M.C.K.) and NIMH R01 MH100141 (M.C.K.). Estonian Genome Center at the University of Tartu (EGCUT) work was supported by Targeted Financing from the Estonian Ministry of Science and Education (SF0180142s08), US National Institutes of Health (NIH) grant R01 DK075787, the Development Fund of the University of Tartu (grant SP1GVARENG), the European Regional Development Fund to the Centre of Excellence in Genomics (EXCEGEN; grant 3.2.0304.11-0312) and FP7 grant 313010. M. Macek was supported by CZ.2.16/3.1.00/24022OPPK, NT/13770-4 and 00064203 FN Motol. Funding from the Singapore National Medical Research Council (NMRC/TCR/003/2008) and the Singapore Biomedical Research Council. We acknowledge the support of the Singapore Agency for Science, Technology and Research (A*STAR). Genotyping of the Swedish Hubin sample was performed by the SNP&SEQ Technology Platform in Uppsala, which is supported by Uppsala University, Uppsala University Hospital, Science for Life Laboratory and the Swedish Research Council (contracts 80576801 and 70374401). The Swedish Hubin sample was supported by Swedish Research Council (I.A., E.G.J.) and Stockholm County Council and the Karolinska Institutet (E.G.J.). B.J.M., V.J.C., R.J.S., S.V.C., F.A.H., A.V.J., C.M.L., P.T.M., C.P. and U.S. were supported by the Australian Schizophrenia Research Bank, which is supported by an enabling grant from the National Health and Medical Research Council (386500), the Pratt Foundation, Ramsay Health Care, the Viertel Charitable Foundation, the Schizophrenia Research Institute and the NSW Department of Health. C.P. is supported by a Senior Principal Research Fellowship from the National Health and Medical Research Council (Australia). The Perth sample collection was funded by Australian National Health and Medical Research Council project grants and the Australian Schizophrenia Research Bank. The Bonn/Mannheim sample was genotyped in a study that was supported by the German Federal Ministry of Education and Research (BMBF) through the Integrated Genome Research Network MooDS (Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia; grant 01GS08144 to M.M.N. and S.C., grant 01GS08147 to M.R.), under the National Genome Research Network plus (NGFNplus), and the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under e:Med Programme (GlaxoSmithKline control sample; B.M.-M.) This work has been funded by the Bavarian Ministry of Commerce and by the BMBF in the framework of the National Genome Research Network, Förderkennzeichen 01GS0481 and the Bavarian Ministry of Commerce. M.M.N. is a member of the German Research Foundation (DFG)-funded Excellence Cluster ImmunoSensation. M.M.N. also received support from the Alfried Krupp von Bohlen und Halbach-Stiftung. M.R. was supported by the 7th Framework Programme of the European Union (ADAMS project, HEALTH-F4-2009-242257; CRESTAR project, HEALTH-2011-1.1-2) grant 279227. J. Knight holds the Joanne Murphy Professorship in Behavioural Science. The Stanley Center for Psychiatric Research at the Broad Institute acknowledges funding from the Stanley Medical Research Institute. Support for the Sweden Schizophrenia Study (principal investigators P.F.S., C.M.H. and P. Sklar) was provided by the NIMH (R01 MH077139 and R01 MH095034), the Stanley Center for Psychiatric Research, the Sylvan Herman Foundation, the Friedman Brain Institute at the Mount Sinai School of Medicine, the Karolinska Institutet, Karolinska University Hospital, the Swedish Research Council, the Swedish County Council and the Söderström Königskå Foundation. We acknowledge use of DNA from the UK Blood Services Collection of Common Controls (UKBS collection), funded by the Wellcome Trust grant 076113/C104/Z, by Juvenile Diabetes Research Foundation grant WT0618S8, and by the National Institute of Health Research of England. The Multicenter Genetics Studies of Schizophrenia and Molecular Genetics of Schizophrenia studies were supported by NIMH grant R01 MH062276 (to D.F.L., C.L., M.J.O. and D.B.W.), grant R01 MH068922 (to P.V.G.), grant R01 MH068921 (to A.E.P.) and grant R01 MH068881 (to B.P.R.). D.F.L. was supported by the Walter E. Nichols, M.D., Professorship in the School of Medicine, the Eleanor Nichols Endowment, the Walter F. & Rachael L. Nichols Endowment and the William and Mary McIvor Endowment, Stanford University. This study was supported by NIH R01 grants (MH67257 to N.G.B., MH59588 to B.J.M., MH59571 to P.V.G., MH59565 to R.F., MH59587 to F.A., MH60870 to W.F.B., MH59566 to D.W.B., MH59586 to J.M.S., MH61675 to D.F.L., MH60879 to C.R.C. and

MH81800 to P.V.G.), NIH U01 grants (MH46276 to C.R.C., MH46289 to C. Kaufmann, MH46318 to M.T. Tsuang, MH79469 to P.V.G. and MH79470 to D.F.L.), the Genetic Association Information Network (GAIN) and The Paul Michael Donovan Charitable Foundation. Genotyping was carried out by the Center for Genotyping and Analysis at the Broad Institute of Harvard and MIT (S. Gabriel and D.B. Mirel), supported by grant U54 RR020278 from the National Center for Research Resources. D.R.W. and R.E.S. thank the staff of the Lieber Institute and the Clinical Brain Disorders Branch of the Intramural Research Program of the NIMH for their assistance in data collection and management. We acknowledge the Irish contribution to the International Schizophrenia Consortium (ISC) study, the WTCCC2 schizophrenia study and WTCCC2 controls from the 1958BC and UKNBS, the Science Foundation Ireland (08/IN.1/B1916). We acknowledge use of the Trinity Biobank sample from the Irish Blood Transfusion Service and the Trinity Centre for High Performance Computing. Funding for this study was provided by the WTCCC2 project (085475/B/08/Z and 085475/Z/08/Z), the Wellcome Trust (072894/Z/03/Z, 090532/Z/09/Z and 075491/Z/04/B), NIMH grants (MH 41953 and MH083094) and British 1958 Birth Cohort DNA collection funded by the MRC (grant G0000934) and the Wellcome Trust (grant 068545/Z/02). Collection of the UK National Blood Service controls was funded by the Wellcome Trust. We acknowledge Hong Kong Research Grants Council project grants GRF 774707M, 777511M, 776412M and 776513M. ENIGMA. ENIGMA was supported in part by a consortium grant (U54 EB020403 to P.M.T.) from the NIH institutes contributing to the Big Data to Knowledge (BD2K) initiative, including the NIBIB and NCI. ADNI and ADNI2GO: Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (NIH grant U01 AG024904) and US Department of Defense (award W81XWH-12-2-0012). ADNI is funded by the US National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health. The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory of Neuro Imaging at the University of Southern California. Betula: this sample collection was supported by a Wallenberg Scholar grant from the Knut and Alice Wallenberg Foundation and a grant from Torsten and Ragnar Söderbergs Foundation to L.N., and a grant from HelseVest RHF (grant 911554) to S.L.H. Bipolar Family Study: The Bipolar Family Study wishes to thank the Scottish Mental Health Research Network for research assistant support; the Brain Research Imaging Centre Edinburgh, a center in the Scottish Funding Council Scottish Imaging Network—A Platform for Scientific Excellence (SINAPSE) Collaboration, for image acquisition; and the Wellcome Trust Clinical Research Facility for genotyping. Genotyping was supported by a National Alliance for Research on Schizophrenia and Depression (NARSAD) Independent Investigator Award (to A.M.M.), and data collection was supported by the Health Foundation Clinician Scientist Fellowship. BIG: This work makes use of the BIG (Brain Imaging Genetics) database, first established in Nijmegen, the Netherlands, in 2007. This resource is now part of the Cognomics Initiative (<http://www.cognomics.nl/>), a joint initiative by researchers of the Donders Centre for Cognitive Neuroimaging, the Human Genetics and Cognitive Neuroscience departments of the Radboud University Medical Centre and the Max Planck Institute for Psycholinguistics in Nijmegen. The Cognomics Initiative is supported by the participating departments and centers and by external grants from the Biobanking and Biomolecular Resources Research Infrastructure (Netherlands) (BBMRI-NL), the Hersenstichting Nederland and the Netherlands Organization for Scientific Research (NWO). We wish to thank all persons who kindly participated in the BIG research. The research leading to these results also receives funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreements 602450 (IMAGEMEND) and 602805 (Aggressotype) and from ERC-2010-AdG 268800-NEUROSCHEMA. B.F. is supported by a Vici grant from the NWO (grant 016.130.669). Brain Genomics Superstruct Project (GSP): Data were provided [in part] by the Brain GSP of Harvard University and the Massachusetts General Hospital, with support from the Center for Brain

Science Neuroinformatics Research Group, the Athinoula A. Martinos Center for Biomedical Imaging and the Center for Human Genetic Research. Twenty individual investigators at Harvard and Massachusetts General Hospital generously contributed data to GSP. GIG: The GIG (Genomic Imaging Göttingen) sample was established at the Center for Translational Research in Systems Neuroscience and Psychiatry at Göttingen University. We thank M. Keil, E. Diekhof, T. Melcher and I. Henseler for assistance in MRI data acquisition, and E. Binder and H. Mohr for help with genotyping. We are grateful to all persons who kindly participated in the GIG study. IMAGEN: IMAGEN was supported by the European Union-funded FP6 Integrated Project IMAGEN (Reinforcement-Related Behaviour in Normal Brain Function and Psychopathology) (LSHM-CT- 2007-037286), the FP7 projects IMAGEMEND (602450) and MATRICS (603016), and the Innovative Medicine Initiative Project EU-AIMS (115300-2), the Medical Research Council programme grant “Developmental pathways into adolescent substance abuse” (93558), as well as the NIHR Biomedical Research Center “Mental Health”. Further support was provided by the Swedish Research Council (FORMAS) and the BMBF (eMED SysAlc 01ZX1311A; Forschungsnetz AERIAL; 1EV0711). MoodS: The establishment of the MoodS sample was funded by the BMBF through the Integrated Genome Research Network MoodS (grant 01GS08144 to M.M.N. and S.C., grant 01GS08147 to M.R. and A.M.-L. and grant 01GS08148 to A. Heinz), under the auspices of the National Genome Research Network plus (NGFNplus), and through the Integrated Network IntegraMent, under the auspices of the e:Med Programme (grant 01ZX1314A to M.M.N., grant 01ZX1314C to H. Walter, grant 01ZX1314G to M.R.). MPiP: The MPiP Munich Morphometry Sample comprises images acquired as part of the Munich Antidepressant Response Signature Study and the Recurrent Unipolar Depression (RUD) Case-Control study performed at the MPiP, and control subject data acquired at the Ludwig Maximilians University, Munich, Department of Psychiatry. We wish to acknowledge A. Olynyk and radiographers R. Schirmer, E. Schreier, R. Borschke and I. Eidner for image acquisition and data preparation. We thank D.P. Auer for local study management in the initial phase of the RUD study. We are grateful to GlaxoSmithKline for providing the genotypes of the RUD case-control sample. We thank the staff of the Center of Applied Genotyping for generating the genotypes of the MARS cohort. The study is supported by a grant of the Exzellenz-Stiftung of the Max Planck Society. This work has also been funded by the BMBF in the framework of the National Genome Research Network (NGFN), FKZ 01GS0481. NCNG: Sample collection was supported by grants from the Bergen Research Foundation and the University of Bergen, the Dr Einar Martens Fund, the K.G. Jebsen Foundation and the Research Council of Norway, to S.L.H., V.M.S. and T.E. NESDA: Funding was obtained from the Netherlands Organization for Scientific Research (Geestkracht program grant 10-000-1002), the Center for Medical Systems Biology (CSMB, NWO Genomics), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL), VU University's Institutes for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam, University Medical Center Groningen, Leiden University Medical Center and NIH (R01D0042157-01A, MH081802, Grand Opportunity grants 1RC2 MH089951 and 1RC2 MH089995). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health. Computing was supported by BiG Grid, the Dutch e-Science Grid, which is financially supported by NWO. NeuroIMAGE: NeuroIMAGE was supported by NIH grant R01MH62873 (to S.V. Faraone), NWO large investment grant 1750102007010 (to J. Buitelaar) and grants from Radboud University Nijmegen Medical Center, University Medical Center Groningen and Accare, and VU University Amsterdam. The research leading to these results also receives funding from the European Community's Seventh Framework Programme (FP7/2007– 2013) under grant agreements 602450 (IMAGEMEND), 278948 (TACTICS) and 602805 (Aggrestotype). NTR-Adults and Brainscale: We would like to thank all twin participants from the Netherlands Twin Register. The NTR-Adult and Brainscale studies were supported by the NWO (MW904-61-193 (E.J.C.d.G. and D.I.B.), MaGW-nr 400-07-080 (D.v.t.E.), MagW 480-04-004 (D.B.), (51.02.060 (H.H.), 668.772 (D.B. and H.H.); NWO/SPI 56-464-14192 (D.B.), the European Research Council (ERC-230374) (D.B.), High Potential Grant Utrecht University (H.H.), NWO Brain and Cognition 433-09-220 (H.H.) and the Neuroscience Campus Amsterdam. Older Australian Twins Study (OATS): We would like to acknowledge and thank the OATS participants, their supporters and respective research teams. OATS is supported by Australian National Health and Medical Research Council (NHMRC)/Australian Research Council Strategic Award 401162 and NHMRC project grant 1045325 to P.S.S. and colleagues. OATS was facilitated through access to the Australian Twin Registry, a national research resource supported by NHMRC enabling grant 310667, administered by the University of Melbourne. DNA was extracted by Genetic Repositories Australia, an Enabling Facility supported by NHMRC grant 401184. OATS genotyping was partly funded by a Commonwealth Scientific and Industrial Research Organisation Flagship Collaboration Fund grant. H.B. is supported by the Australian

Government funded Dementia Collaborative Research Centre, UNSW. N.J.A. was supported by NHMRC project grant 525453 and K.A.M. is supported by an Alzheimer's Australia Dementia Research Foundation postdoctoral fellowship and NHMRC capacity building grant 568940. QTIM: D.P.H., N.J., C.R.K.C. and P.M.T. are supported, in part, by NIH grants R01 NS080655, R01AG040060, R01 EB008432, R01 MH097268, U01 AG024904, R01 MH085667, R01 MH089722, P41 EB015922 and R01 MH094343. R.K.W. is supported by National Science Foundation (BCS-1229450). J.L.S. was supported by the NIMH (K99MH102357) and Autism Speaks. S.E.M. and G.I.d.Z. are supported by Future Fellowships (FT110100548, FT0991634) from the Australian Research Council, and G.W.M. is supported by an NHMRC fellowship (619667). The QTIM study is supported by grants from the NIH (R01 HD050735) and the NHMRC (389875, 486682, 1009064). We thank the twins and siblings for their participation, M. Grace and A. Eldridge for twin recruitment, A. Al Najjar and other radiographers for scanning, K. McAloney and D. Park for research support, and A. Henders and staff for DNA sample processing and preparation. SHIP: The Study of Health in Pomerania (SHIP) is supported by the BMBF (grants 01ZZ9603, 01ZZ0103 and 01ZZ0403) and the DFG (GR 1912/5-1). Genome-wide data and MRI scans were supported by a joint grant from Siemens Healthcare, Erlangen, Germany, and the Federal State of Mecklenburg–West Pomerania. SHIP-TREND-0: This cohort is part of the Community Medicine Research (CMR) net of the University of Greifswald, which is funded by the BMBF and the German Ministry of Cultural Affairs, as well as by the Social Ministry of the Federal State of Mecklenburg–West Pomerania. CMR encompasses several research projects that share data from SHIP. MRI scans were supported by a joint grant from Siemens Healthcare, Erlangen, Germany, and the Federal State of Mecklenburg–West Pomerania. The SHIP authors are grateful to M. Stanke for the opportunity to use his server cluster for SNP imputation as well as to H. Prokisch and T. Meitinger (Helmholtz Zentrum München) for genotyping the SHIP-TREND cohort, which was supported by the BMBF (grant 03ZIK012). We thank all staff members and participants of the SHIP studies, as well as all of the genotyping staff for generating the SHIP SNP data set. D.J. is supported by a scholarship from the Gerhard-Domagk Programme of the University Medicine Greifswald. Sydney Memory and Ageing Study (Sydney MAS): We would like to thank the Sydney MAS participants, their supporters and respective research teams. Sydney MAS was supported by NHMRC program grants 350833 and 568969 to P.S.S., H.B. and G. Andrews. DNA was extracted by Genetic Repositories Australia, an Enabling Facility supported by NHMRC grant 401184. H.B. is supported by the Australian Government funded Dementia Collaborative Research Centre, UNSW. N.J.A. was supported by NHMRC project grant 525453 and K.A.M. is supported by an Alzheimer's Australia Dementia Research Foundation postdoctoral fellowship. Both S. Reppermund and K.A.M. are supported by NHMRC capacity building grant 568940. Data used in preparing this article were obtained from the ADNI database (<http://adni.loni.usc.edu/>). Many investigators in ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the [online version of the paper](#).

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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 imputation³⁴. 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, age², 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 METAL³⁵.

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 of 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 described¹⁵ 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). RRHO¹⁷ 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 $MAF \geq 0.01$ 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 Research¹⁸, 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/daledN/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 analysis¹⁹. 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 $P_{\text{conj}} = \max(P_{\text{brain}}, P_{\text{case-control}})$, where P_{brain} is the significance of the SNP associated to brain structure and $P_{\text{case-control}}$ is the significance of the SNP association to schizophrenia. As conjunction tests can be very conservative, an adjustment to this test³⁶ 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 $\text{MAF} \geq 0.01$ 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 Storey³⁷,

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 METAL³⁵, 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 $\text{MAF} < 1\%$ (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 traits²³. For brain structures, height and EduYears, percent variance explained was calculated as $R^2_{\text{glc}}/(1 - R^2_c) = (t^2/[(n - k - 1) + t^2]) \times 100$, 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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