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Author manuscript

*Nat Neurosci.* Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

*Nat Neurosci.* 2016 March ; 19(3): 420–431. doi:10.1038/nn.4228.**Genetic influences on schizophrenia and subcortical brain volumes: large-scale proof-of-concept and roadmap for future studies**

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Psychiatric Genomics Consortium (<http://pgc.unc.edu>); ENIGMA (<http://enigma.ini.usc.edu>); 1000 Genomes Project imputation panel (<http://mathgen.stats.ox.ac.uk/impute>); matSpD interface (<http://genepi.qimr.edu.au/general/daleN/matSpD>).

Conflicts of Interest

Several of the authors/contributors are employees of companies: Johnson and Johnson, Pfizer (C.R.S., J.R.W., H.S.X), F. Hoffman-La Roche (E.D., L.E), Eli Lilly (D.C., Y.M., L.N), Janssen (S.G., D.W., Q.S.L.), and deCODE genetics (S.G, K.S., H.S.). P.F.S is a scientific advisor to Pfizer. None of these companies influenced the design of the study, the interpretation of the data, the amount of data reported, or financially profit by publication of these pre-competitive results. The other authors do not report conflicts of interest.

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## Abstract

Schizophrenia is a devastating psychiatric illness with high heritability. Brain structure and function differ, on average, between schizophrenia cases 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. The current study provides proof-of-concept (albeit based on a limited set of structural brain measures), and defines a roadmap for future studies investigating the genetic covariance between structural/functional brain phenotypes and risk for psychiatric disorders.

## Keywords

schizophrenia; MRI; brain imaging; genetics; GWAS; meta-analysis; endophenotype

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## Introduction

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

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

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

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 mega-analyses by the PGC (Psychiatric Genomics Consortium) for schizophrenia<sup>3</sup> and meta-analyses from the ENIGMA consortium (Enhancing NeuroImaging Genetics through Meta-Analysis) for eight MRI volumetric measures (amygdala, caudate nucleus, hippocampus, nucleus accumbens, pallidum, putamen, thalamus, and intracranial volume (ICV)).<sup>9</sup> 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 comparisons of common variant genetic sharing between schizophrenia and brain volumetric measures.

### Comparisons of common variant genetic architectures

**Linkage disequilibrium score regression (LDSR)**—Using GWA summary statistics (excluding the extended MHC region), we used LDSR<sup>12</sup> to estimate the heritability of schizophrenia due to common SNPs at 25.5% (SE=1.1%) along with eight brain volumetric measures (*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 non-significant in this sample. The genetic correlations of MRI volumetric measures with schizophrenia were all non-significant (*Table 1*). These negative findings stand in contrast to the relatively high common-variant correlations of schizophrenia with bipolar disorder and major depressive disorder.<sup>13,14</sup>

**Genetic predisposition scores**—In the genetic “risk” score approach,<sup>15</sup> 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 (*Figure 1* and *Table 2*). The strongest effect (for hippocampal volume) was almost entirely driven by one SNP (rs2268894),<sup>9</sup> but only three SNPs met the p-value threshold of  $1 \times 10^{-6}$  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.<sup>16</sup>

**Rank-rank hypergeometric overlap test (RRHO)**<sup>17</sup>—We quantified overlap between pairs of GWA results ranked by their association statistics using RRHO based on 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 (*Figure 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 whorl structure<sup>18</sup> 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<sup>3</sup> 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 evaluated the 128 genome-wide significant schizophrenia index SNPs<sup>3</sup> for association with brain volumes.<sup>9</sup> 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= $-23\text{ mm}^3$  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 (*Supplementary Table 2*).<sup>6</sup> Starting with the eight SNPs previously found associated with the brain volumes,<sup>9</sup> 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.<sup>19</sup> No SNP showed genome-wide significant association with both schizophrenia and brain structure, although several loci were detected at sub-threshold levels (*Supplementary Figure 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 (e.g., schizophrenia).<sup>20,22</sup> To test this hypothesis, we compared the maximum effect sizes from replicated genetic associations for each trait. For comparability across quantitative or binary traits, effect sizes were assessed as percent of variance explained (for MRI volumes) or percent of variance explained on the liability scale (for schizophrenia).<sup>23</sup> As shown in *Supplementary Figure 10*, individual common variants had only a small influence on either brain structure or schizophrenia. Effect sizes for individual SNPs were similar for both brain structure and schizophrenia, and of the same order as those observed for anthropometric traits such as height.<sup>24</sup>

### 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 (i.e., 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 cases may be epiphenomena unrelated to its primary genetic causes, a result of prenatal environment, or result from reverse causation.<sup>25</sup> 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 (e.g., caudate and putamen volumes are uncorrelated with schizophrenia,<sup>5,6</sup> and amygdala volume did not have SNP-heritability different from zero in our study). Second, other neuroimaging phenotypes could be more informative for schizophrenia (e.g., cortical thickness, ventricular volume, diffusion tensor imaging, or functional activity).<sup>26,27</sup> 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 this performs well, 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,<sup>28</sup> 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 datasets in a meta-analytic framework (e.g., 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,<sup>2</sup> 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.<sup>29</sup>

Brain volume heritability estimates from genome-wide data obtained using LDSR<sup>14</sup> were lower than observed in previous studies.<sup>30</sup> This was expected for the subcortical regions, as

those were corrected for ICV. For ICV, 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.<sup>31,33</sup> An endophenotype that lies on a causal pathway to a clinical disorder could increase power for genetic studies. Prior 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. Importantly, the endophenotype concept is unlikely to be sufficiently addressed in these analyses given the reasons noted above.

In conclusion, this paper presents a roadmap for comprehensive evaluation of genetic covariation between neuropsychiatric disease liability and brain imaging measures. The current 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.

## Online Methods

A supplementary methods checklist is available. 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 mega-analyzed individual genotype data from 46 European-ancestry schizophrenia GWAS datasets (full details in reference<sup>3</sup>). Briefly, quality control and imputation were performed by the PGC Statistical Analysis Group for each dataset 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 dataset (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 datasets 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 reference<sup>9</sup>). 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.<sup>34</sup> 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<sup>2</sup>, sex, 4 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.<sup>35</sup>

### Removal of duplicated individuals

Subject overlap between all PGC and ENIGMA cohorts was evaluated using a checksum algorithm in order 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 dataset 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 datasets. The schizophrenia analysis included only results from European studies were used (LDSR requires LD data from a comparable sample). For the ENIGMA amygdala results, the mean  $X^2$  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.<sup>12,14</sup> 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 (note that 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 described<sup>15</sup> for several  $P$ -value thresholds ( $5 \times 10^{-8}$ ,  $1 \times 10^{-6}$ ,  $1 \times 10^{-4}$ , 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 due 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<sup>17</sup> 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 based on the 1000 Genomes European dataset 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  $-\log_{10}(\text{p-value})$  of association multiplied by the effect size. A two-sided RRHO test that allowed testing for either over- or under-enrichment was used with a step-size of 3000 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,<sup>18</sup> 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 a look-up of results in the PGC data.

Multiple comparison correction was performed by estimating the effective number of independent tests ( $M_{\text{eff}}$ ). This method considers the correlation structure (**Supplementary Table 4**) between brain measures and calculates the  $M_{\text{eff}}$  based on the observed eigenvalue variance of the different brain volume measures using matSpD (see URLs). The p-value for significance was 0.05 divided by the sum of (a)  $M_{\text{eff}}$  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 dataset (94 LD-independent genome-wide significant SNPs, 231 with  $P < 1 \times 10^{-6}$ ) in the different brain structure datasets 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, a conjunction analysis was used.<sup>19</sup> 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  $P_{\text{brain}}$  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 test<sup>36</sup> based on the estimated fraction of false nulls was used here with modifications ( $P'_{\text{conj}}$ ). Over 7.5 million SNPs found in both the ENIGMA and PGC datasets 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.<sup>36</sup> 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<sup>37</sup>, who posed it as an estimate of the proportion of *true* null hypotheses. Deng et al.<sup>36</sup> 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  $\lambda$  parameter 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,<sup>35</sup> we conducted a sample size-weighted meta-analysis for schizophrenia (effective sample size 71,715) and ENIGMA (variable sample sizes per SNP ranging from 8,000-11,000). SNPs were excluded if they were not present in both datasets 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),<sup>9</sup> schizophrenia (PGC),<sup>3</sup> height (GIANT),<sup>24</sup> and educational attainment (EduYears).<sup>38</sup> 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.<sup>23</sup> For brain structures, height, and EduYears, percent variance explained was calculated as  $R_{gl}^2 / (1 - R_c^2) = (t^2 / ((n - k - 1) + t^2)) * 100$ , where the *t*-statistic is calculated as the  $\beta$ -coefficient for a given SNP from the regression model (controlling for covariates) divided by the standard error of the  $\beta$ -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.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

Psychiatric Genomics Consortium (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 (U01 MH094421). Statistical analyses were carried out on the Genetic Cluster Computer (<http://www.geneticcluster.org>) hosted by SURFsara 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, RWM; U01 MH081928, LJS; R01 MH092380, TLP) and the Massachusetts General Hospital Executive Committee on Research (TLP). P.H.L. is supported by NIMH K99 MH101367. ISC Portugal: CNP and MTP have been supported by NIMH grants MH085548, MH085542, MH071681, MH061884, MH58693, and MH52618, and the NCRR RR026075. CNP, MTP, and AHF 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 MRC Centre (G0800509) and MRC Programme (G0801418) Grants, the European Community's Seventh Framework Programme (HEALTH-F2-2010-241909, Project EU-GEL) the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n°279227, a fellowship to JW 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, and staff at The Doctor's Laboratory (Lisa Levett/Andrew Levett) for help with sample acquisition and data linkage, and in Cardiff (Kiran Mantripragada/Lucinda Hopkins) for sample management. CLOZUK and some other samples were genotyped at the Broad Institute or by the WTCCC and 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 WT (076113/C/04/Z) and by NIHR programme grant to NHSBT (RP-PG-0310-1002). VCU 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 Reyna Favis at Janssen for sample processing and the staff at Illumina for genotyping Janssen DNA samples. We also thank Anthony Santos, Nicole Bottrel, Monique-Andree Franc, William Cafferty of Janssen Research & Development) for operational support. Funding from the Netherlands Organization for Health Research and Development (ZonMw), within the Mental Health program (GROUP consortium), and NIMH R01 MH078075. 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); EU 7th Framework Programme (PsychGene; Grant agreement nr. 218251); EU 7th Framework Programme (PsychDPC; Grant agreement nr. 286213). 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. Jebsen Foundation. This work was supported by the Donald and Barbara Zucker Foundation, the North Shore – Long Island Jewish Health System Foundation, and grants from Stanley Foundation (AKM), NARSAD (AKM), NIMH (MH065580 to TL; MH001760 to AKM), and NIMH RC2 MH089964 and R01 MH084098. SynSys, EU FP7-242167, Sigrid Juselius Foundation, The Academy of Finland (grant number: 251704), 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 (PI Keller) and NIMH R01 MH100141 (PI Keller). EGCUT work was supported by the Targeted Financing from the Estonian Ministry of Science and Education (SF0180142s08); NIH R01 DK075787; the Development Fund of the University of Tartu (grant SPIGVARENG); the European Regional Development Fund to the Centre of Excellence in Genomics (EXCEGEN; grant 3.2.0304.11-0312); and FP7 grant 313010. MM was supported by CZ.2.16/3.1.00/24022OPPK, NT/13770-4and 00064203 FN Motol. Funding from the National Medical Research Council (NMRC/TCR/003/2008) and the Biomedical Research Council (A\*STAR) is acknowledged. 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 (IA, EGJ) and Stockholm County Council and the Karolinska Institutet (EGJ). 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 (No. 386500), the Pratt Foundation, Ramsay Health Care, the Viertel Charitable Foundation and 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 within a study that was

supported by the German Federal Ministry of Education and Research (BMBF) through the Integrated Genome Research Network (IG) MoodDS (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 (GSK control sample; Müller-Myhsok). This work has been funded by the Bavarian Ministry of Commerce and by the Federal Ministry of Education and Research 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 DFG-funded Excellence-Cluster ImmunoSensation. M.M.N. also received support from the Alfred 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.K. holds the Joanne Murphy Professor 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 (PIs Sullivan, Hultman, and 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, the Söderström Königska Foundation. We acknowledge use of DNA from The UK Blood Services collection of Common Controls (UKBS collection), funded by the Wellcome Trust grant 076113/CI04/Z, by the 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 study were supported by NIMH grant R01 MH062276 (to DF Levinson, C Laurent, M Owen and D Wildenauer), grant R01 MH068922 (to PV Gejman), grant R01 MH068921 (to AE Pulver) and grant R01 MH068881 (to B Riley). 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 by 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. We thank S. We (DRW, RS) thank the staff of the Lieber Institute and the Clinical Brain Disorders Branch of the IRP, NIMH for their assistance in data collection and management. We acknowledge the Irish contribution to the International Schizophrenia Consortium (ISC) study, the WTCCC2 SCZ study & 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 & the Trinity Centre for High Performance Computing. Funding for this study was provided by the Wellcome Trust Case Control Consortium 2 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 Medical Research Council (grant G0000934) and the Wellcome Trust (grant 068545/Z/02) and of the UK National Blood Service controls 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 PMT) 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) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the 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 ([www.fnih.org](http://www.fnih.org)). 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 (KAW) foundation and a grant from Torsten and Ragnar Söderbergs Foundation to LN, a grant from Helse Vest RHF (Grant 911554) to SLH. **Bipolar Family Study (BFS):** 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 the 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 Cognomics ([www.cognomics.nl](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 centres and by external grants, i.e. the Biobanking and Biomolecular Resources Research Infrastructure (Netherlands) (BBMRI-NL), the Hersenstichting Nederland, and the Netherlands Organisation 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. Franke is supported by a Vici grant from the Netherlands Organisation for Scientific Research (NWO; grant # 016.130.669). **Brain Genomics Superstruct Project (GSP):** Data were provided [in part] by the Brain Genomics Superstruct Project 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. 20 individual investigators at Harvard and MGH 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 Maria Keil, Esther Diekhof, Tobias Melcher and Ilona Henseler for assistance in MRI data acquisition, and Elisabeth Binder and Holger Mohr for their valuable 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 German Federal Ministry for Education and Research BMBF (eMED SysAlc 01ZX1311A; Forschungsnetz AERIAL; 1EV0711). **MooDS:** The establishment of the MooDS sample was funded by the German Federal Ministry of Education and Research (BMBF) through the Integrated Genome Research Network (IG) MooDS (Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia; grant 01GS08144 to Markus M. Nöthen and Sven Cichon, grant 01GS08147 to Marcella Rietschel and Andreas Meyer-Lindenberg and grant 01GS08148 to Andreas Heinz), under the auspices of the National Genome Research Network plus (NGFNplus), and through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med Programme (grant 01ZX1314A to Markus M. Nöthen, grant 01ZX1314C to Hendrik Walter, grant 01ZX1314G to Marcella Rietschel). **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 subjects acquired at the Ludwig-Maximilians-University, Munich, Department of Psychiatry. We wish to acknowledge Anna Olynyk and radiographers Rosa Schirmer, Elke Schreiter, Reinhold Borschke and Ines Eidner for image acquisition and data preparation. We thank Dorothee 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 Recurrent Unipolar Depression Case-Control Sample. We thank the staff of the Center of Applied Genotyping (CAGT) 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 Federal Ministry of Education and Research (BMBF) in the framework of the National Genome Research Network (NGFN), FKZ 01GS0481. **NCNG:** this sample collection was supported by grants from the Bergen Research Foundation and the University of Bergen, the Dr Einar Martens Fund, the K.G. Jepsen Foundation, the Research Council of Norway, to SLH, VMS and TE. **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, National Institutes of Health (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:** The NeuroIMAGE was supported by NIH Grant R01MH62873 (to Stephen V. Faraone), NWO Large Investment Grant 1750102007010 (to Jan 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 n° 602450 (IMAGEMEND), n° 278948 (TACTICS) and n° 602805 (Aggressotype). **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 Netherlands Organization for Scientific Research NWO [MW904-61-193 (E.d.G & D.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. & 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 (NCA). **Older Australian Twins**

**Study (OATS):** We would like to acknowledge and thank the OATS participants, their supporters and respective Research Teams. This work was supported by a number of sources. OATS is supported by the NHMRC/Australian Research Council Strategic Award 401162 and NHMRC Project Grant 1045325 to P. Sachdev and colleagues. OATS was facilitated through access to the Australian Twin Registry, a national research resource supported by the NHMRC Enabling Grant 310667, administered by the University of Melbourne. DNA was extracted by Genetic Repositories Australia, an Enabling Facility supported by the NHMRC Grant 401184. OATS genotyping was partly funded by a Commonwealth Scientific and Industrial Research Organisation Flagship Collaboration Fund Grant. Henry Brodaty is supported by the Australian Government funded Dementia Collaborative Research Centre (DCRC), UNSW. Nicola Armstrong was supported by the NHMRC Project Grant 525453 and Karen Mather is supported by an Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship and the NHMRC Capacity Building Grant 568940. **QTIM:** DPH, NJ, CRKC, and PMT 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. RKW is supported by National Science Foundation (BCS-1229450). JLS was supported by the NIMH (K99MH102357) and Autism Speaks. SEM and GZ are supported by Future Fellowships (FT110100548, FT0991634) from the Australian Research Council, and GWM is supported by a National Health and Medical Research Council (NHMRC), Australia, Fellowship (619667). The QTIM study is supported by grants from NIH (R01 HD050735) and the NHMRC (389875, 486682, 1009064). We thank the twins and siblings for their participation, Marlene Grace and Ann Eldridge for twin recruitment, Aiman Al Najjar and other radiographers for scanning, Kerrie McAloney and Daniel Park for research support, and Anjali Henders and staff for DNA sample processing and preparation. **SHIP:** The Study of Health in Pomerania (SHIP) is supported by the German Federal Ministry of Education and Research (grants 01ZZ9603, 01ZZ0103 and 01ZZ0403) and the German Research Foundation (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 net (CMR) of the University of Greifswald, which is funded by the German Federal Ministry of Education and Research 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 the population-based Study of Health in Pomerania (SHIP; see URLs). 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 Mario Stanke for the opportunity to use his server cluster for SNP imputation as well as to Holger Prokisch and Thomas Meitinger (Helmholtz Zentrum München) for genotyping the SHIP-TREND cohort which was supported by the Federal Ministry of Education and Research (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 the Australian National Health and Medical Research Council (NHMRC) Program Grants 350833 and 568969 to P. Sachdev, H. Brodaty and G. Andrews. DNA was extracted by Genetic Repositories Australia, an Enabling Facility supported by the NHMRC Grant 401184. Henry Brodaty is supported by the Australian Government funded Dementia Collaborative Research Centre (DCRC), UNSW. Nicola Armstrong was supported by the NHMRC Project Grant 525453 and Karen Mather is supported by an Alzheimer's Australia Dementia Research Foundation Postdoctoral Fellowship. Both Simone Reppermund and Karen Mather are supported by the NHMRC Capacity Building Grant 568940.

Data used in preparing this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). Many investigators within 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](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf).

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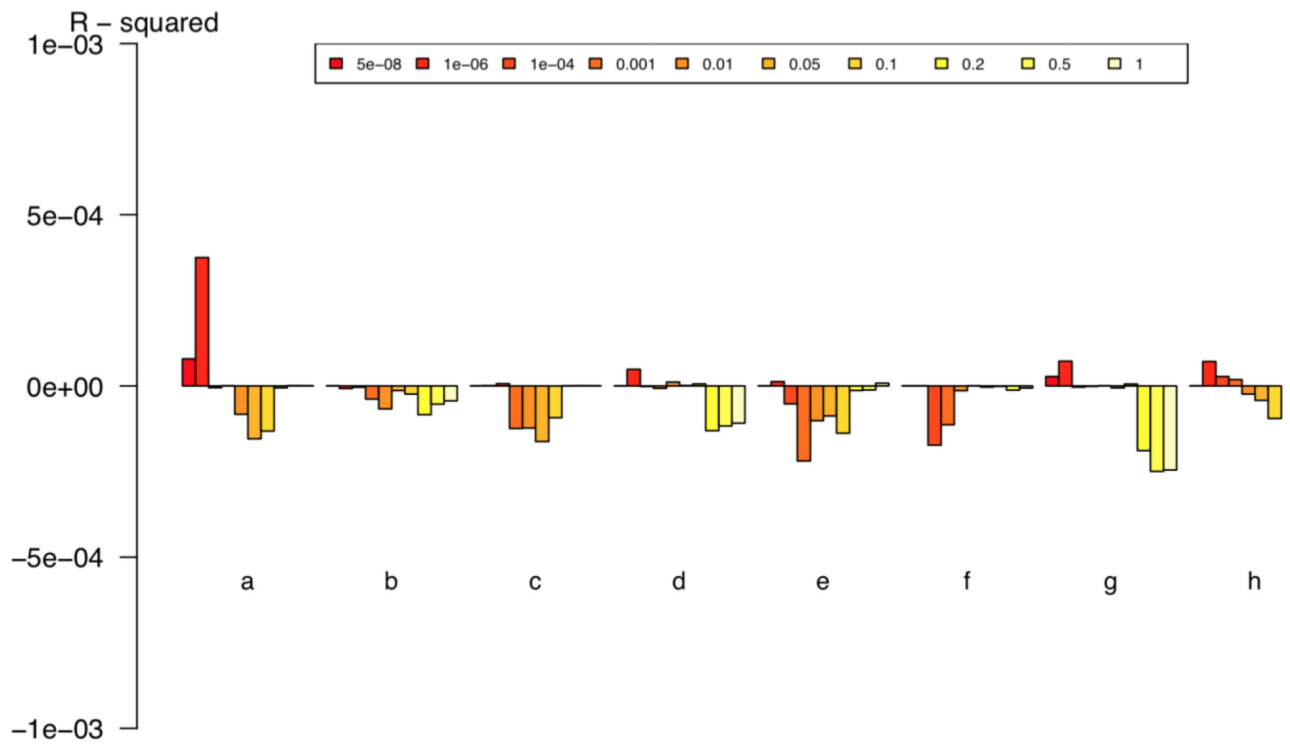
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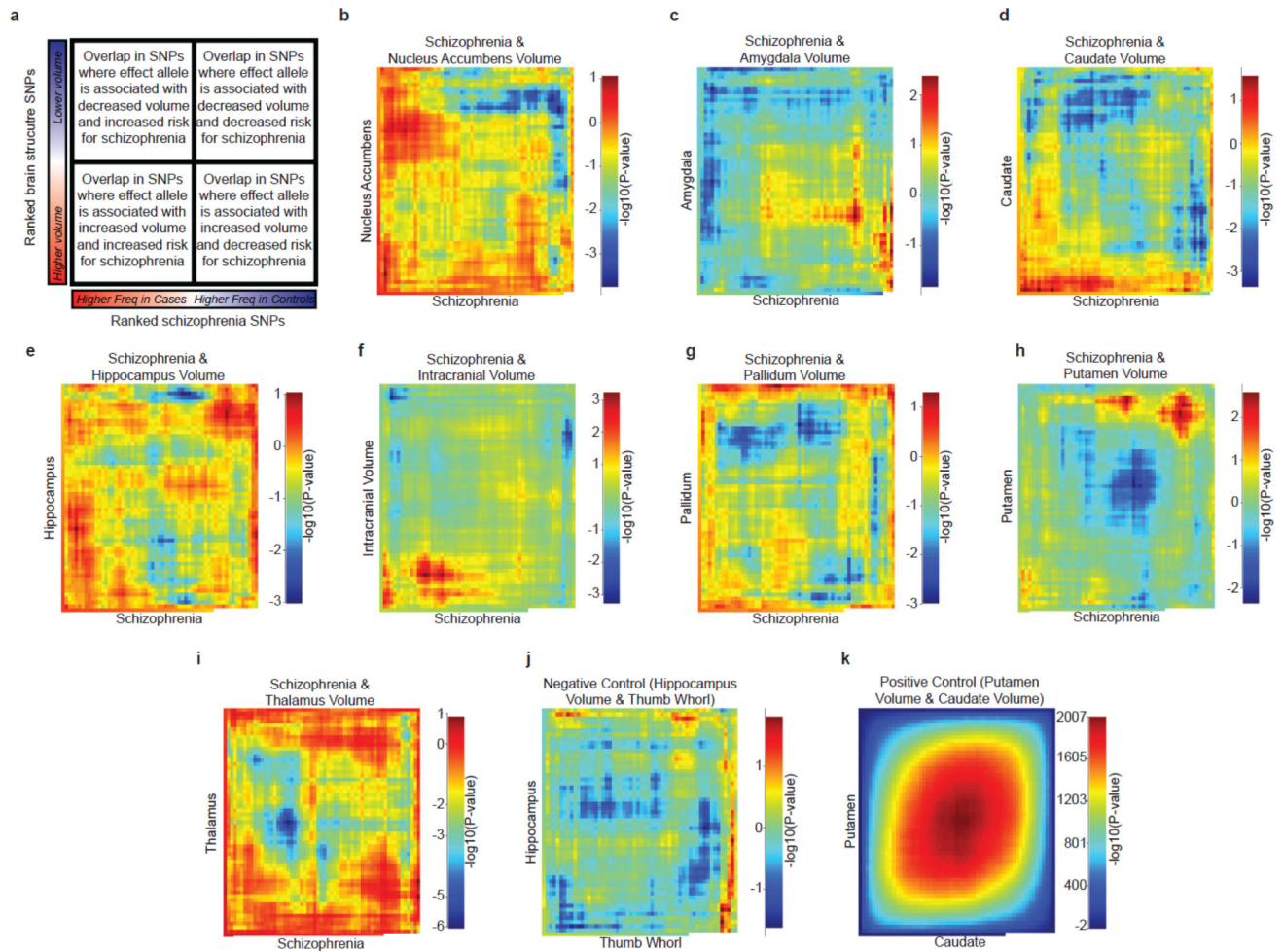
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### Summary

The authors defined a roadmap for the investigation of the genetic covariance between structural/functional brain phenotypes and risk for psychiatric disorders. Their proof-of-concept study using the largest available common variant datasets for schizophrenia and volumes of several (mainly subcortical) brain structures did not find evidence of genetic overlap.



**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: (a) hippocampus, (b) ICV, (c) nucleus accumbens, (d) amygdala, (e) caudate nucleus, (f) pallidum, (g) putamen, (h) 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 in and increased risk for schizophrenia. Significance values are given in **Table 2**.



**Figure 2.** Evaluating the genome-wide overlap between genetic influences on schizophrenia and subcortical volumes. (a) A cartoon describing the output map. (b-i) independent SNPs present in both ENIGMA and PGC schizophrenia results were selected independent of association to any phenotype (see on-line methods). Association results were ordered based on the significance of their association to the phenotype ( $-\log_{10}(\text{P-value})$ ) multiplied by the sign of the effect), and statistical significance was evaluated using RRHO test. The same test for overlap was conducted with a (j) finger whorl phenotype, expected to have no overlap with brain structure genetics, and (k) the overlap between caudate and putamen volume, 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. The overlap between hippocampal volume and presence of a whorl on the left thumb was used as a negative control and showed similar levels of overlap to brain structure and schizophrenia.



**Table 1**

SNP-heritability analyses for MRI brain volume and genetic correlations with schizophrenia<sup>\*</sup>.

<b>Brain region<sup>*</sup></b>	<b>N</b>	<b>Heritability</b>	<b>SE</b>	<b>Genetic correlation with SCZ</b>	<b>SE</b>	<b>Z</b>	<b>P</b>	
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

<sup>\*</sup> amygdala heritability was too low to allow a valid analysis

**Table 2**

Two outcome variables derived from genetic predisposition analysis.

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

P=significance uncorrected for multiple testing. R<sup>2</sup>=correlation (Nagelkerke) on the observed scale corrected for principal components. AUC=area under receiver operating characteristic curve. OR=odds ratio. CI=confidence interval

**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	<i>P</i> threshold	N same direction	Proportion	<i>P</i>
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 is 0.5.