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Genetic influences on schizophrenia and subcortical brain volumes: large-scale proof-of-concept and roadmap for future studies

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URLs

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

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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

Introduction

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

Many differences in brain function and structure have been reported in cases 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.[5,6] Hippocampal and lateral ventricle volumes were influenced by antipsychotic medication use.[5] In addition, mean hippocampal volume is smaller in high-risk individuals and in unaffected first-degree relatives of schizophrenia cases. [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 effects of common and rare genetic contributions on 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 mega-analyses by the PGC (Psychiatric Genomics Consortium) for schizophrenia [3] 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)). [9] Our results suggest that common genetic variation predisposing to schizophrenia does not show evidence of overlap

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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 [12] 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. [13,14]

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

Rank-rank hypergeometric overlap test (RRHO) [17]—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 [18] was used as a negative control. The latter comparison showed similar overlap to that of brain structure and schizophrenia.

Sign tests

We compared the pattern of GWA results by checking whether the signs of the regression coefficients [3] were consistently in the same direction between the top associations for

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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 [3] for association with brain volumes. [9] One association survived correction for 876 comparisons: rs2909457*A (chr2:162,845,855, intergenic between *SLC4A10* and *DPP4*) was associated with decreased hippocampal volume (P=1.2×10^{-6}, effect size=−23 mm^3 per allele) and decreased risk for schizophrenia (odds ratio=0.94, P=4.6×10^{-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***). [6] Starting with the eight SNPs previously found associated with the brain volumes, [9] no significant associations with schizophrenia were observed (***Supplementary Table 2***).

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

Conjunction analysis—To identify individual SNPs that influence risk for both schizophrenia and brain structure, we implemented a conjunction test. [19] No SNP showed genome-wide significant association with both schizophrenia and brain structure, although several loci were detected at sub-threshold levels (***Supplementary 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). [20–22] 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). [23] 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. [24]

Discussion

In this proof-of-concept study, we evaluated the relationship between common genetic variants implicated in schizophrenia and those associated with subcortical brain volumes and ICV. The sample sizes were the largest yet applied to these questions. With a comprehensive set of analyses, we did not find evidence for notable genetic correlations, either at a high level (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

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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. [25] Finally, the effect sizes of SNPs implicated in schizophrenia and those associated with brain volumes were broadly similar.

We studied a limited set of brain MRI measures. Our study should be considered a proof-of-concept for evaluating genetic covariation rather than decisively addressing the full range of hypotheses pertaining to the genetic overlap of brain imaging measures with neuropsychiatric disease risk. We provide a rigorous roadmap for more definitive and larger future studies. Full elucidation of the brain correlates of schizophrenia will require a fuller set of structural and functional imaging measures (perhaps at the voxel level) along with evaluation of common and rare genetic variation.

The null findings of this study should be interpreted in light of several qualifiers. First, several brain regions that are not expected *a priori* to overlap with schizophrenia were included for completeness (e.g., 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 (e.g., 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 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, [28] its onset generally follows the period of greatest growth for these structures. Fifth, relatively small genetic correlations between schizophrenia and these brain volumes may have been masked by combining 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, [2] rare genetic effects on brain structure could be salient for some cases of schizophrenia. Finally, the sample sizes and statistical power of the schizophrenia and neuroimaging data sets differed. The PGC has attained a sample size sufficient to detect many common loci of small effect, whereas ENIGMA is earlier in the discovery arc. [29]

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

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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.[31–33] 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 [3]). 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***).

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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 [9]). MRI brain scans and genome-wide genotype data were available for 11,840 subjects from 22 cohorts (***Supplementary Table 1***). Only cohorts without schizophrenia cases and controls overlapping with the PGC schizophrenia samples were included. Participants clustered with subjects of known European ancestry as verified by multidimensional scaling (MDS) analysis. Genomic data were imputed to a reference panel (1000 Genomes, v3 phase1) comprising only European samples and with monomorphic SNPs removed. Imputation was performed at each site using MaCH for phasing and minimac for imputation. [34] Only SNPs with an imputation score of RSQ > 0.5 and minor allele counts > 10 within each site were included. Tests of association were conducted separately for eight MRI volumetric phenotypes (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, thalamus, and ICV) with the following covariates in a multiple linear regression framework: age, age^2, sex, 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. [35]

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. [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 (note that we took steps to exclude overlapping samples). Standard errors were estimated using a block jackknife procedure and used to calculate *P*-values.

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Genetic predisposition analyses

To investigate the combined impact of ENIGMA association results on case-control status in the PGC schizophrenia data, we performed a series or genetic predisposition score analyses. For each ENIGMA volumetric phenotypes, we excluded SNPs with MAF <2%, indels, and SNPs in the extended MHC region (chr6:25-34 Mb). We then "clumped" the data, discarding variants within 500 kb of and in $r^2 \geq 0.1$ with another more significant marker. We performed genetic predisposition score prediction of target subgroups as originally described [15] for several *P*-value thresholds (5×10^{-8}, 1×10^{-6}, 1×10^{-4}, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, 1.0), multiplying the effect size of the ENIGMA phenotype of each variant by the imputation probability for the risk allele in each individual. The resulting values were summed so that each individual had a genetic predisposition score for further analyses. Two outcome variables are reported in **Table 2**: the significance of the case-control score difference analyzed by logistic regression (including ancestry-based principal components and a study indicator as covariates) and the proportion of variance explained (Nagelkerke's R^2) computed by comparison of a full model (covariates + polygenic risk scores) score to a reduced model (covariates only). Note that these R^2 estimates are biased 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 [17] tests the hypothesis that ordering of two lists (LD-pruned GWAS results for schizophrenia versus a brain structure phenotype) by the strength of their association is arbitrary. The number of independent SNPs in common between the two ordered lists is evaluated at specified step sizes. Two lists that show similar ordering of SNPs demonstrate a global pattern of similarity of associations. Independent SNPs were selected 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 ≥ 0.01 were retained (172,652 SNPs). The SNPs were then ordered by the –log10(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, [18] was used to provide a negative control for the RRHO test. Briefly, rolled ink prints were collected on archival quality paper, and fingerprint patterns were manually coded. Complete data from 3,314 participants (twins and their family members) were available. Genotypes were imputed to the 1000 Genomes Project reference (phase 1 version 3). GWAS was conducted using Merlin-offline to account for relatedness and zygosity.

Lookup of top GWAS SNP findings

Evidence for an effect of the reported 128 independent schizophrenia-associated SNPs on subcortical brain volumes and ICV was studied through a look-up of results. rs115329265 was not available in the ENIGMA data and was replaced by a SNP in moderate LD

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(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_{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 (see URLs). 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 $P < 5.7\times10^{-5}$ 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 $P < 1\times10^{-6}$) 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. [19] This analysis makes inference on the alternative hypothesis that both null hypotheses are false. This is in distinction to a traditional meta-analysis method which infers on an alternative hypothesis that one or more null hypotheses are false. A conjunction analysis is calculated as: $P_{conj} = \max(P_{brain}, P_{case\text{-}control})$, where P_{brain} is the significance of the SNP associated to brain structure and $P_{case\text{-}control}$ is the significance of the SNP association to schizophrenia. As conjunction tests can be very conservative, an adjustment to this test [36] based on the estimated fraction of false nulls was used here with modifications (P'_{conj}). Over 7.5 million SNPs found in both the ENIGMA and PGC 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

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calibrated for the worst possible configuration of true signals, and as a result can be quite conservative when the true state of the model is not one of the extreme cases.

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

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

In our analyses, the λ 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, [35] we conducted a sample size-weighted meta-analysis for schizophrenia (effective sample size 71,715) and ENIGMA (variable sample sizes per SNP ranging from 8,000-11,000). 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), [9] schizophrenia (PGC), [3] height (GIANT), [24] and educational attainment (EduYears). [38] The five highest effect size SNPs were selected for schizophrenia and height, all genome-wide significant SNPs were displayed for brain structure volumes and EduYears. Percent variance was calculated on the liability scale for schizophrenia for comparison with quantitative traits. [23] For brain structures, height, and EduYears, percent variance explained was calculated as $R^2_{g|c}/(1-R^2_c) = (t^2/((n-k-1)+t^2))*100$, where the t-statistic is calculated as the ß-coefficient for a given SNP from the regression model (controlling for covariates) divided by the standard error of the ß-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

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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.

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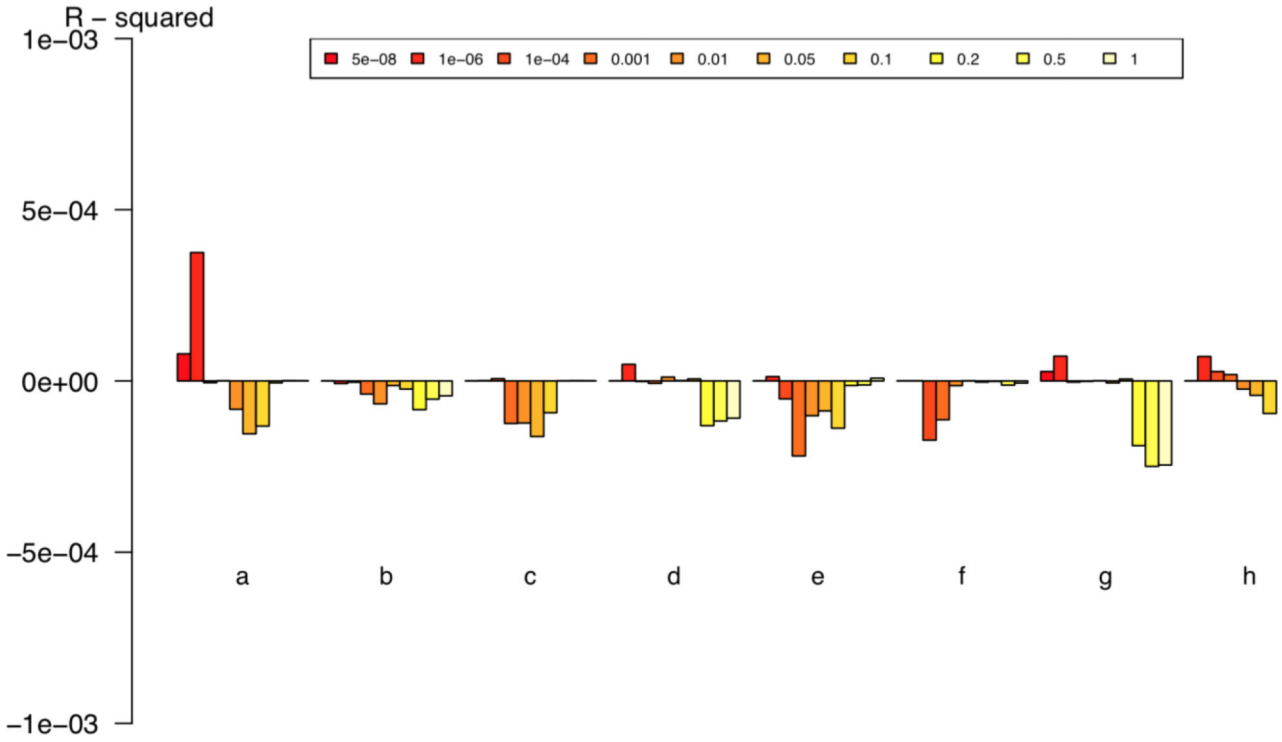

Figure 1.

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**.

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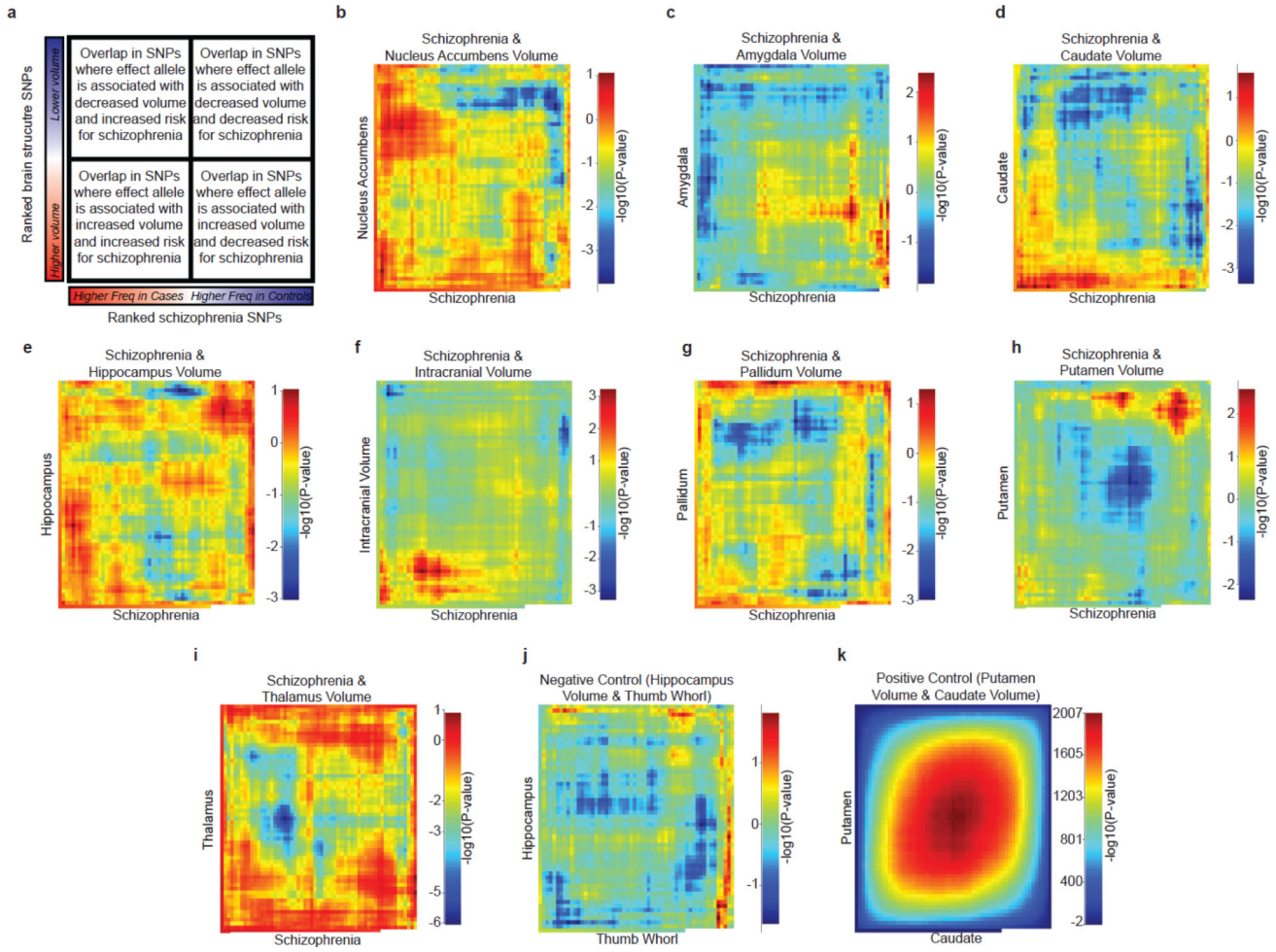

Figure 2.

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 ($-\log_{10}$(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.

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Table 1

SNP-heritability analyses for MRI brain volume and genetic correlations with schizophrenia [*].

Brain region [*]	N	Heritability	SE	Genetic correlation with SCZ	SE	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

[*] amygdala heritability was too low to allow a valid analysis

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

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Table 3

Sign tests of directional effects among 94 genome-wide significant associations with schizophrenia ($P<5\times10^{-8}$) and the top 231 associations ($P<1\times10^{-6}$).

Brain region	*P* threshold	N same direction	Proportion	*P*
Intracranial volume	$<5\times10^{-8}$	49	0.52	0.379
Caudate nucleus	$<5\times10^{-8}$	47	0.50	0.541
Hippocampus	$<5\times10^{-8}$	46	0.49	0.621
Nucleus accumbens	$<5\times10^{-8}$	48	0.51	0.459
Pallidum	$<5\times10^{-8}$	51	0.54	0.235
Putamen	$<5\times10^{-8}$	52	0.55	0.177
Thalamus	$<5\times10^{-8}$	49	0.52	0.379
Amygdala	$<5\times10^{-8}$	49	0.52	0.379
Intracranial volume	$<1\times10^{-6}$	121	0.52	0.255
Caudate nucleus	$<1\times10^{-6}$	113	0.49	0.653
Hippocampus	$<1\times10^{-6}$	105	0.45	0.926
Nucleus accumbens	$<1\times10^{-6}$	109	0.47	0.821
Pallidum	$<1\times10^{-6}$	117	0.51	0.448
Putamen	$<1\times10^{-6}$	115	0.50	0.552
Thalamus	$<1\times10^{-6}$	115	0.50	0.552
Amygdala	$<1\times10^{-6}$	109	0.47	0.821

The expected proportion under the null is 0.5.