

Large-scale analysis of structural brain asymmetries in schizophrenia via the ENIGMA consortium

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Abstract

BACKGROUND: Left-right asymmetry is an important organizing feature of the healthy brain that may be altered in schizophrenia, but most studies have used relatively small samples and heterogeneous approaches, resulting in equivocal findings. We carried out the largest case-control study of structural brain asymmetries in schizophrenia ($N = 11,095$), using a single image analysis protocol.

METHODS: We included T1-weighted data from 46 datasets (5,080 affected individuals and 6,015 controls) from the ENIGMA Consortium. Asymmetry indexes were calculated for global and regional cortical thickness, surface area, and subcortical volume measures. Differences of asymmetry were calculated between affected individuals and controls per dataset, and effect sizes were meta-analyzed across datasets. Analyses were also performed with respect to the use of antipsychotic medication and other clinical variables, as well as age and sex. Case-control differences in a multivariate context were assessed in a subset of the data ($N = 2,029$).

RESULTS: Small average differences between cases and controls were observed for asymmetries in cortical thickness, specifically of the rostral anterior cingulate ($d = -0.08$, $p_{\text{FDR}} = 0.047$) and the middle temporal gyrus ($d = -0.07$, $p_{\text{FDR}} = 0.048$), both driven primarily by thinner cortices in the left hemisphere in schizophrenia. These asymmetries were not significantly associated with the use of antipsychotic medication or other clinical variables. Older individuals with schizophrenia showed a stronger average leftward asymmetry of pallidum volume than older controls ($d = 0.08$, $p_{\text{FDR}} = 9.0 \times 10^{-3}$). The multivariate analysis revealed that 7% of the variance across all structural asymmetries was explained by case-control status ($F = 1.87$, $p = 1.25 \times 10^{-5}$).

CONCLUSIONS: Altered trajectories of asymmetrical brain development and/or lifespan asymmetry may contribute to schizophrenia pathophysiology. Small case-control differences of brain macro-structural asymmetry may manifest due to more substantial differences at the molecular, cytoarchitectonic or circuit levels, with functional relevance for lateralized cognitive processes.

Introduction

Schizophrenia is a serious mental illness characterized by various combinations of symptoms that may include delusions, hallucinations, disorganized speech, affective flattening, avolition, and executive function deficits¹. Left-right asymmetry is an important feature of human brain organization for diverse cognitive functions – for example, roughly 90% of people present with a left-hemisphere dominance for language and right-handedness²⁻⁵. A possible role of altered structural and functional brain asymmetry in schizophrenia has been studied for several decades⁶⁻¹⁰. Theoretical work has especially focused on disrupted laterality for language in relation to disorganized speech and auditory hallucinations¹¹⁻¹³. Individuals with schizophrenia have been reported to show a decreased left-lateralized language dominance^{14,15}, as well as an absence or even reversal of structural asymmetries of language-related regions around the Sylvian fissure (which divides the temporal lobe from the frontal and parietal lobes)^{13,16-18}. Furthermore, the rate of non-right-handedness in schizophrenia is elevated compared to the general population^{13,19-23}. Interestingly, some genomic loci that influence aspects of structural brain asymmetry or hand preference overlap with those associated with schizophrenia²⁴⁻²⁷. Thus, there might be an etiological link between altered brain asymmetry and schizophrenia.

However, alterations in structural brain asymmetry in schizophrenia have so far only been reported in studies with relatively small samples^{13,16-18,28-34}, to our knowledge, the largest case-control sample consisted of 167 affected individuals and 159 controls³¹. Many of the existing findings are inconsistent and/or remain unreplicated, which is possibly due to the low statistical power which limits the sensitivity to detect true effects, and also increases the risk of overestimating effect sizes^{35,36}. The reproducibility of findings may be further affected by the heterogeneity of clinical and demographic characteristics across studies. Moreover, varying approaches to process and analyze magnetic resonance imaging (MRI) data limit the possibility to reproduce results and/or to perform meta-analyses. For example, in studies targeting specific regions of interest, regions have been inconsistently defined, while studies that involved cortex-wide mapping used different image analysis protocols. Studies of subcortical volumetric asymmetries in schizophrenia have generally suffered from similar issues³⁷⁻³⁹, with the notable exception of a study in 884 affected individuals and 1,680 controls that used a single image analysis pipeline⁴⁰. This study found an increased leftward asymmetry of the pallidum in schizophrenia (driven by a larger pallidum volume in the left hemisphere) compared to controls, which was also detectable in adolescents with subclinical psychotic experiences^{40,41}.

The Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA, <http://enigma.ini.usc.edu>) consortium aims to perform large-scale analyses by combining imaging data from research groups

across the world, processed with standardized protocols^{42,43}. Previously, this consortium reported large-scale cortical thinning, smaller surface area, and altered subcortical volume in individuals with schizophrenia compared to controls^{44,45}. However, asymmetry was not measured in these previous ENIGMA studies, and no tests were performed to assess whether case-control effects were different in the two hemispheres. The ENIGMA consortium has investigated structural brain asymmetries in other disorders⁴⁶: major depressive disorder (MDD)⁴⁷, autism spectrum disorder (ASD)⁴⁸, obsessive compulsive disorder (OCD)⁴⁹, and attention deficit/hyperactivity disorder (ADHD)⁵⁰, but not schizophrenia to date. Case-control group-level effects were small for all of these disorders, with ASD showing the most widespread asymmetry differences – mostly involving regional cortical thickness measures – with a maximum Cohen’s *d* of 0.13⁴⁸. Similar effect sizes may be anticipated for schizophrenia. Therefore, a large sample size is likely required to detect and accurately measure any effects. Although small group-average differences of brain macro-anatomy are unlikely to have clinical uses by themselves, they may help to identify brain regions and networks that have clinically relevant disruptions at other neurobiological levels – for example molecular or cytoarchitectonic – which can be investigated in future studies. Of note, the ENIGMA consortium has recently reported on asymmetry alterations with respect to subcortical *shape* (2,833 individuals with schizophrenia versus 3,929 controls), based on an automated approach quantifying local concave versus convex surface curvature⁵¹, but this study did not address subcortical *volume* asymmetries, and omitted the cerebral cortex.

Therefore, we designed the current study focusing on cortical and subcortical structural asymmetries in schizophrenia using the largest sample to date, containing 5,080 affected individuals and 6,015 controls from 46 separate datasets. The datasets were collected originally as distinct studies over approximately 25 years, using different recruitment schemes, MRI scanning equipment and parameters. Importantly, for the current study, all primary MRI data were processed through a single pipeline for cortical atlas-based segmentation/subcortical parcellation and quality control. Case-control differences were tested separately for each regional asymmetry index (AI) within each dataset, and effects were then combined across datasets using meta-analysis methodology. This approach was taken due to restrictions on sharing individual-level data for many of the primary datasets. We also explored possible associations of structural brain asymmetries with medication use and other disorder-specific measures: age at onset, duration of illness, as well as total, positive, and negative symptom scores. For 14 datasets, for which individual-level data were available, we tested for a multivariate association of case-control status simultaneously with regional AIs across the brain. Together, these analyses aimed to provide novel insights into the extent and mapping of structural brain asymmetry alterations in schizophrenia, and how they relate to key clinical variables.

Methods

Datasets

Structural MRI data were derived from 46 separate datasets (45 case-control and one case-only) via researcher participation in the ENIGMA schizophrenia working group, totaling 11,095 individuals. Of these, 5,080 were affected with schizophrenia and 6,015 were unaffected controls (Table 1, Supplementary Table 1A). The datasets came from various countries around the world (Fig. 1). Data collection was performed after written informed consent and was approved by local institutional review boards. Sample size-weighted mean age across datasets was 33.3 (range 16.2-44.0) years for individuals with schizophrenia and 33.0 (11.8-43.6) years for controls. Affected individuals and controls were 67% and 52% male, respectively. Diagnostic interviews were conducted by registered clinical research staff using different diagnostic criteria (either the Diagnostic and Statistical Manual of Mental Disorders [DSM]-III, DSM-IV, DSM-5 or International Classification of Diseases [ICD]-10), and hand preference was obtained through assessment scales (mainly the Edinburgh Handedness Inventory and Annett Handedness Scale) or self-report (Supplementary Table 2). No controls had present or past indications of schizophrenia.

Image acquisition, processing and quality control

T1-weighted structural brain MRI scans were acquired at each study site. Site-specific scanner information, field strengths (1 T, 1.5 T, and 3 T), and image acquisition parameters are provided in Supplementary Table 2. For data from all sites, image processing and segmentation were performed using FreeSurfer (see Supplementary Table 2 for software versions)⁵². For each individual, using the ‘recon-all’ pipeline, cerebral cortical thickness and surface area measures were derived for 34 bilaterally paired Desikan-Killiany (DK) atlas regions, as well as whole hemisphere-level average cortical thickness and surface area measures⁵³. Volumes for 8 bilaterally paired regions from a neuroanatomical atlas of brain subcortical structures⁵⁴ were derived using the ‘aseg’ segmentation command in FreeSurfer. A standardized ENIGMA quality control procedure was applied at each participating site (described in full here: <http://enigma.ini.usc.edu/protocols/imaging-protocols/>). Briefly, this included outlier detection in the derived cortical and subcortical measures and visual inspection of segmentations projected onto the T1-weighted image of each individual. For cortical measures, predefined guidelines for visual inspection were followed. Measurements from regions with poor segmentation were excluded, as well as individuals whose data failed overall quality checks. Data sharing limitations did not allow the central analysis group to have access to individual-level data for the majority of participating study sites. For further processing and analyses of the data, a script running in R software (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org)⁵⁵ was prepared and distributed among participating sites, to ensure coordinated collection of descriptive and summary statistics for subsequent meta-analysis by the central analysis team.

Asymmetry index calculation

For each bilaterally paired brain regional measure, we used the left (L) and right (R) hemispheric measurements to calculate an asymmetry index (AI), $= \frac{L-R}{(L+R)/2}$, where the denominator corrects for automatic scaling of the index with the magnitude of the bilateral measure. This formula for AI calculation has been widely used^{2,49,56-58}. A negative value of the AI reflects a larger right hemispheric measurement ($R > L$), and a positive value a larger left hemispheric measurement ($L > R$). Distributions of AIs were plotted using histograms to allow for visual inspection. Left or right measurements equal to 0 were set to missing, as these most likely reflected data entry errors. Furthermore, when a left or right measurement was missing, the corresponding measurement in the opposite hemisphere was also set to missing. The standardized pipeline from raw image data through FreeSurfer does not introduce left-right flipping errors, but to ensure that such errors were not introduced during processing of raw imaging data by non-standard processes (e.g. during the conversion of DICOM to NIFTI files with bespoke scripts), we compared mean regional asymmetries for all datasets against grand sample-size adjusted means. If we noticed a large proportion of reversed average asymmetries for a dataset, we contacted the relevant site to re-check and correct their process (Supplementary Table 3).

Asymmetry differences between individuals with schizophrenia and unaffected controls

Group differences were examined separately for each brain regional AI and each case-control dataset, using univariate linear regression implemented in R. Our primary analysis model included diagnosis (case-control status) as the main binary predictor, and sex and age as covariates (model 1 in Supplementary Note 1). For ten datasets where more than one scanner had been used (Supplementary Table 2), we added $n-1$ binary dummy covariates (where n is the number of scanners in a given dataset), to statistically control for scanner effects. Sex was not included as a covariate for the RSCZ dataset, as this dataset included only males. Collinearity between predictor variables was assessed using the R-package *usdm* (v1-1.18)⁵⁹, and high collinearity (variance inflation factor > 5) was not found for any dataset. Linear regression analysis for any structural AI was not performed if the total sample size of a given dataset was lower than ten plus the number of scanner covariates, or if one of the diagnostic groups had a sample size lower than five. For each brain regional AI and each case-control dataset, we extracted the t -statistic for the ‘diagnosis’ term to calculate its corresponding Cohen’s d effect size, standard error and 95% confidence interval, using

$$d = \frac{t(n_1+n_2)}{\sqrt{n_1 n_2 \sqrt{df}}}, se_d = \sqrt{\left(\frac{n_1+n_2-1}{n_1+n_2-3}\right) \left[\left(\frac{4}{n_1+n_2}\right) \left(1 + \frac{d^2}{8}\right)\right]}, \text{ and } 95\% \text{ CI} = [d - 1.96 * se_d, d + 1.96 * se_d]^{60}.$$

In these equations, d is the Cohen’s d effect size, t is the t -statistic, se is the standard error, n_1 is the number of unaffected controls, n_2 is the number of individuals with schizophrenia, and df the degrees of freedom in the linear model.

Random-effects meta-analysis

For each brain regional AI (Supplementary Fig. 1-3), effect sizes for ‘diagnosis’ from each case-control dataset were meta-analyzed in a random-effects model fitted with a restricted maximum likelihood (REML) estimator, using the function ‘rma’ in the R package *metafor* (v3.0-2)⁶¹. Meta-analyzed effect sizes were projected on 3D meshes of inflated cortical or subcortical models from Brainder (www.brainder.org/research/brain-for-blender/), using Matlab R2020a (version 9.8.0.1323502; MathWorks, Natick, MA, USA). We calculated false discovery rate (FDR) corrected p-values using the Benjamini-Hochberg method to account for multiple tests⁶² (i.e., separately for testing 35 cortical thickness AIs, 35 cortical surface area AIs, and eight subcortical volume AIs). Effects with $p_{\text{FDR}} < 0.05$ were considered statistically significant. For AIs that showed significant group differences between cases and controls, the group differences for the corresponding left and right measurements separately were also assessed *post hoc* (again using linear modelling with diagnosis, age and sex as predictors), to help describe the asymmetry differences.

Sensitivity analyses

For any AI that showed a significant case-control group difference in the primary meta-analysis, we identified datasets within which the 95% CI of the diagnosis effect did not overlap with the 95% CI of the meta-analyzed effect – using the ‘find.outliers’ function in the R package *dmetar* (v0.0.9)⁶³ – and then repeated the meta-analysis after excluding such outlier datasets. In addition, for any AI that showed a significant case-control group difference in the primary meta-analysis, we also applied models that included the same covariates as the primary analysis, but also included either handedness (right-handed vs. non-right-handed), intracranial volume (ICV), both handedness and ICV, or age² (models 2-5 in Supplementary Note 1).

Medication group differences

For AIs that showed significant case-control group differences in the primary analysis, we explored associations with antipsychotic medication use at the time of scanning, through between-group comparisons of AIs of unmedicated individuals with schizophrenia, affected individuals taking only first-generation (typical) antipsychotics, affected individuals taking only second-generation (atypical) antipsychotics, and those taking both first- and second-generation antipsychotics. Sex and age were included as covariates (model 6 in Supplementary Note 1) and derived Cohen’s *d* effect sizes were again meta-analyzed across datasets in a random-effects model. Applying a minimum group size threshold of 5 within any given dataset, sufficient data on the presence/absence of antipsychotic medication use for at least one comparison were available for 31 of the datasets (Supplementary Table 1B), and the sample sizes for each between-group comparison are in Supplementary Table 9. We

calculated FDR corrected p-values to correct for all of the multiple subgroup comparisons and structural asymmetries tested.

Correlations of asymmetries with clinical variables

For AIs that showed significant case-control group differences in the primary analysis, we assessed relationships between these AIs and clinical variables within affected individuals only: age at onset, duration of illness, chlorpromazine equivalent medication dose (at the time of scanning), as well as positive, negative, and total symptom severity scores from the Positive and Negative Symptom Scale (PANSS)⁶⁴, or the Scale for the Assessment of Positive Symptoms (SAPS)⁶⁵ and Scale for the Assessment of Negative Symptoms (SANS)⁶⁶ (separately depending on data availability, see Supplementary Table 1A). Partial correlations between brain AIs and these quantitative measures were estimated using the ‘*pcor.test*’ function in the R package *ppcor* (v1.1)⁶⁷. Age and sex were included as covariates (model 7 in Supplementary Note 1). The same minimum sample size requirement for dataset inclusion was applied as in the linear regression analyses (above). Correlation coefficients were meta-analyzed across datasets in a mixed-effects model including dataset as a random effect. We calculated FDR corrected p-values to control for all of the clinical variables and structural asymmetries tested. Sample sizes for each model are shown in Supplementary Table 10.

Secondary analysis of age- or sex-specific effects

For all AIs in all case-control datasets we applied models which were the same as the primary analysis but additionally included either diagnosis-by-age or diagnosis-by-sex interaction terms. We then carried out meta-analyses of the interaction effect estimates across datasets to assess possible AI differences between affected individuals and controls that were relatively specific to either males or females, or differed with age (models 8-9 in Supplementary Note 1). In the same way as our primary analysis, we calculated FDR corrected p-values to account for multiple regional asymmetries tested.

Multivariate analysis of case-control asymmetry differences

To examine case-control group differences across all brain regional AIs simultaneously in one model, we conducted a multivariate analysis based on 14 datasets for which individual-level data were available to the central analysis team. For this analysis, we only retained individuals with complete data for all bilateral measures of cortical and subcortical structures, which were 935 individuals affected with schizophrenia and 1,095 unaffected controls (Supplementary Table 1C). We separately adjusted the left and right measurements using ComBat harmonization (an empirical Bayesian method) to remove dataset effects⁶⁸, where each dataset (and each scanner within multi-scanner datasets) was treated as a distinct ‘batch’. Diagnosis, age and sex were used as covariates when finding the data harmonization parameters in ComBat. After ComBat adjustment, one additional

control individual was removed due to being assigned a negative corrected right hemisphere lateral ventricle volume (Supplementary Fig. 4). AIs for cortical and subcortical measures were then calculated using the same formula as above, and collinearity between AIs was assessed by calculating a correlation matrix. AIs did not show higher pairwise correlations than 0.5 (Supplementary Fig. 5-6). A multivariate analysis of covariance (MANCOVA) using the ‘manova’ function in R was applied, testing all 76 regional structural brain AIs simultaneously against case-control status, with age and sex as covariates. We ran one million label-swapping permutations of case-control labels and calculated a permutation p -value by assessing the number of times the F -statistic of an analysis with permuted data was equal to or larger than the F -statistic of the analysis with real data, divided by the total number of permutations. When permuting case-control labels, we conserved case-control numbers within each dataset (and within scanner for multi-scanner datasets). To help interpret the MANCOVA results, we also derived univariate case-control association statistics for each separate structural AI from the multivariate association analysis output, using ANCOVA (‘summary.aov’ function in R).

Results

Asymmetry differences between individuals with schizophrenia and unaffected controls

In our primary analysis (model 1), total hemispheric average cortical thickness asymmetry ($d = -0.053$, $z = -1.92$, $p = 0.055$) and surface area asymmetry ($d = 0.027$, $z = 1.23$, $p = 0.22$) did not significantly differ between affected individuals and controls. At a regional level (Fig. 2, Supplementary Table 4, Supplementary Fig. 1-3), there was a small but significant case-control difference in cortical thickness asymmetry of the rostral anterior cingulate cortex ($d = -0.083$, $z = -3.21$, $p = 1.3 \times 10^{-3}$, $p_{\text{FDR}} = 0.047$, reversal from leftward average asymmetry in controls to rightward average asymmetry in cases), and also in cortical thickness asymmetry of the middle temporal gyrus ($d = -0.074$, $z = -2.99$, $p = 2.8 \times 10^{-3}$, $p_{\text{FDR}} = 0.048$, increased average rightward asymmetry in cases) (Fig. 3, Supplementary Fig. 7-8, Supplementary Table 5). *Post hoc* analysis of unilateral effects showed that both of these regional asymmetry differences were driven primarily by thinner left than right cortex in individuals with schizophrenia compared to controls (Table 2, Supplementary Table 6). The middle temporal cortex is a core language network region⁶⁹, and left-hemisphere thinning is compatible with disrupted leftward laterality of brain organization for language in schizophrenia^{10,11}.

Nominally significant regional case-control associations (i.e. which did not survive multiple testing correction), were found for the AIs of inferior parietal cortex thickness, cuneus surface area, parahippocampal gyrus surface area, and nucleus accumbens volume (Fig. 3, Supplementary Table 5).

Sensitivity analyses

For rostral anterior cingulate thickness asymmetry, there were three datasets in the primary meta-analysis which had outlier case-control effect sizes when compared to the meta-analyzed effect (see Methods). After excluding these datasets and repeating the meta-analysis for this AI, the case-control difference remained, with the same directionality ($d = -0.073$, $z = -3.51$, $p = 4.5 \times 10^{-4}$) (Supplementary Table 7). For middle temporal gyrus thickness asymmetry, the exclusion of two outlier datasets also yielded a similar result compared to the primary analysis ($d = -0.079$, $z = -3.44$, $p = 5.9 \times 10^{-4}$), again with the same directionality (Supplementary Table 7). In models that included either handedness, ICV, both handedness and ICV, or age² as additional covariates (models 2-5), the results for both of these regional AIs remained nominally significant, although the case-control effect for middle temporal gyrus thickness asymmetry decreased in most of these models, whereas it increased for rostral anterior cingulate thickness asymmetry (Supplementary Table 8).

Medication group differences

Rostral anterior cingulate thickness asymmetry did not differ between affected individuals across medication groups (model 6) (Supplementary Table 9). For the middle temporal gyrus, there was a nominally significant increase in average rightward asymmetry in affected individuals taking first generation versus second generation antipsychotics at the time of scanning ($d = -0.21$, $z = -2.56$, $p = 0.011$, $p_{\text{FDR}} = 0.13$), i.e., this was not significant after multiple testing correction (Supplementary Table 9).

Correlations of asymmetries with clinical variables

We found nominally significant correlations between rostral anterior cingulate thickness asymmetry and negative symptom severity measured with SANS ($r = 0.049$, $z = 2.08$, $p = 0.038$, $p_{\text{FDR}} = 0.32$, decreased rightward asymmetry with higher negative symptom rate) (Supplementary Table 10A) and between middle temporal gyrus thickness asymmetry and duration of illness ($r = -0.048$, $z = -1.97$, $p = 0.049$, $p_{\text{FDR}} = 0.32$, increased rightward asymmetry with longer duration of illness) (Supplementary Table 10B), but these correlations did not remain significant when correcting for multiple testing. No correlations with chlorpromazine-equivalent medication dose, age at onset, PANSS scores (total or positive and negative subscales), or SAPS or SANS scores, were found for either the rostral anterior cingulate thickness asymmetry or middle temporal gyrus thickness asymmetry (Supplementary Table 10).

Age- and sex-specific effects

In secondary analyses across all AIs using models with interaction terms, we found a significant diagnosis-by-age interaction (model 8) for pallidum volume asymmetry ($d = 0.081$, $z = 3.26$,

$p = 1.1 \times 10^{-3}$, $p_{\text{FDR}} = 9.0 \times 10^{-3}$, stronger leftward asymmetry with higher age in cases)

(Supplementary Table 11-12A, Supplementary Fig. 9). This association was driven by a significantly decreased average leftward asymmetry with increasing age in controls ($r = -0.077$, $p = 1.1 \times 10^{-3}$) that was not present in affected individuals (Supplementary Table 12B; Supplementary Fig. 10). In terms of the corresponding unilateral effects, left and right pallidum volume decreased with increasing age in individuals with schizophrenia (L: $r = -0.17$, $p = 4.7 \times 10^{-9}$; R: $r = -0.20$, $p = 4.7 \times 10^{-21}$) and unaffected controls (L: $r = -0.27$, $p = 2.1 \times 10^{-22}$; R: $r = -0.24$, $p = 6.2 \times 10^{-17}$), but the two groups differed with respect to the side showing the stronger effect (Supplementary Table 12B). No significant sex-by-diagnosis interactions were found (model 9) (Supplementary Table 13).

Multivariate analysis of case-control asymmetry differences

Considering all 76 regional structural brain AIs simultaneously in a multivariate model, applied to the 14 datasets for which individual-level data were available to the central analysis team (935 affected individuals and 1,094 controls), there was a significant multivariate structural brain asymmetry difference between cases and controls that accounted for roughly 7% of the variance considered across all 76 AIs (Wilks' $\Lambda = 0.932$, approximate $F(76, 1950) = 1.87$, $p = 1.25 \times 10^{-5}$). Only three of the F -statistics resulting from one million label-swapping permutations (see Methods) were larger than the F -statistic from the true analysis, resulting in a permutation $p = 3.0 \times 10^{-6}$. We also derived univariate (ANCOVA) association statistics from the multivariate model to understand which AIs contributed most to the significant multivariate association. The structural AIs that showed nominally significant, univariate case-control differences in the 14 datasets available for this analysis were those for pallidum volume, nucleus accumbens volume, and eight regional surface area or thickness measures distributed widely over the cerebral cortex (Table 3). These did not include the two cortical regional AIs that showed significant case-control differences in the meta-analysis over all 45 case-control datasets, but did include AIs of other language-related regions of the temporal lobe: superior temporal sulcus surface area asymmetry and transverse temporal gyrus thickness asymmetry (Table 3).

Discussion

In this study, we investigated group differences in structural brain asymmetries between individuals with schizophrenia and unaffected controls, in the largest sample to date. The large sample size offered unprecedented statistical power to identify group differences, and to measure their effect sizes³⁵. Subtle differences of regional asymmetry were found for rostral anterior cingulate thickness, middle temporal gyrus thickness, and pallidum volume (the latter in older individuals). The Cohen's d effect sizes were less than 0.1; i.e., very small⁷⁰. In light of previous large-scale analyses of bilateral

cortical and subcortical alterations in schizophrenia^{44,45}, our results suggest that morphometric alterations in this disorder are largely the same for the left and right hemispheres, involving only subtle asymmetrical effects at the group average level. This suggests that effect sizes of brain asymmetry differences in schizophrenia reported in earlier, much smaller studies (see Introduction), are likely to have been overestimated. Nonetheless, in a multivariate context, 7% of the total variance across all regional asymmetries was explained by case-control status.

Subtle group differences of asymmetry in terms of macro-anatomic features, such as those studied here, may reflect substantial effects at other neurobiological levels with more functional relevance for disorder symptoms – for example molecular, cytoarchitectonic and/or circuit levels⁷¹⁻⁷³. The middle temporal gyrus is prominently involved in the brain’s language network⁶⁹, so that our univariate finding of lower left-sided cortical thickness in schizophrenia in this region is broadly consistent with a prominent theory in the literature: that left-hemisphere language dominance may be affected in this disorder^{10,11}. Cortical thinning of the left-hemispheric middle temporal gyrus has been associated with auditory verbal hallucinations in schizophrenia⁷⁴, and reported to be present also in individuals with first-episode schizophrenia and high familial risk for the disorder^{75,76}. In terms of grey matter volume, an opposite pattern (reduced right, increased left) has been reported for the middle temporal gyrus in putatively at-risk children compared to typically developing children⁷⁷. However, volume measures confound cortical thickness and surface area, and since these two aspects of cortical anatomy are known to vary substantially independently^{26,78,79}, it is unclear how these earlier volume-based findings may relate to the present findings based on cortical thickness asymmetry. Again, earlier findings in smaller samples may have been false positives with over-estimated effect sizes.

The rostral anterior cingulate cortex is an important hub in emotional and cognitive control⁸⁰, both of which are often affected in schizophrenia. In this region we observed a thinner left-sided cortex in affected individuals than controls on average, which was more pronounced than on the right side. This may be consistent with a previous study where adolescent/young adult relatives of individuals with schizophrenia showed a longitudinal decline of gray matter volume in the left rostral anterior cingulate cortex compared to controls⁸¹. It is therefore possible that asymmetrical differences in this region emerge before schizophrenia onset, although the previous study included only 23 relatives, so its reported effects remain equivocal, and it used volume rather than thickness measures. In the present study, we saw no evidence for an age*diagnosis interaction effect for this regional thickness asymmetry, which is consistent with a pre-onset alteration that subsequently remains stable through adulthood.

Multivariate analysis in 14 of the datasets, for which individual-level data were available, resulted in a highly significant case-control difference. Various regional asymmetries contributed to this

multivariate association, with pallidum volume asymmetry showing the largest individual contribution. Pallidum volume asymmetry was especially associated with schizophrenia in older individuals, as observed in secondary testing of univariate interaction models across all 45 case-control datasets. Larger pallidum volume in schizophrenia compared to controls – with a stronger effect in the left hemisphere – has been reported before^{40,41,45,82}, although some datasets in our analysis partly overlapped with three of these studies^{40,41,45}. An age-dependent relationship between familial risk for schizophrenia and larger left pallidum volume has also been described in a small study of young adults⁸³ – this suggests that alterations of pallidum asymmetry might already be present in a prodromal stage of the disease. However, in the present study, the group difference in pallidum volume was absent in younger individuals and became more apparent in older adults. This also explains why the association was not significant in the primary univariate meta-analysis of all datasets together, i.e. it was driven by a subset of datasets that included older individuals, and that were also available for multivariate analysis (Supplementary Fig. 10). The pallidum is prominently involved in reward and motivation⁸⁴, and impaired reward anticipation and a loss of motivation are well-known negative symptoms of schizophrenia⁸⁵. However, how pallidum structural asymmetry may relate to functional disorder-relevant changes remains unknown.

We found a tentative difference of middle temporal gyrus thickness asymmetry between individuals who were taking first-generation versus second-generation antipsychotics, with a relatively larger effect size ($d = -0.21$) than any case-control differences from the primary analysis. This result suggests that first-generation antipsychotics have a stronger effect on left middle temporal gyrus thickness than second-generation antipsychotics, which could relate to molecular or cellular hemispheric differences. Alternatively, this regional asymmetry may relate to clinical differences of disorder presentation which affect treatment choices. Indeed, we saw nominally significant evidence that this same asymmetry relates to illness duration. However, the medication subgroup analyses were limited by relatively small sample sizes compared to the primary case-control analysis, and this particular association did not survive multiple testing correction. Also, medication status was based on medication use at the time of scanning, and did not include information on previously used antipsychotics. This association therefore remains tentative until replicated.

Various brain regional asymmetries have shown significant heritability in a recent genome-wide analysis of general population data²⁶, including rostral anterior cingulate thickness asymmetry and pallidum volume asymmetry (but not middle temporal gyrus thickness asymmetry). When polygenic risk for schizophrenia was assessed with respect to these heritable asymmetries in a multivariate analysis²⁷, one of the strongest associations was with rostral anterior cingulate thickness asymmetry. The direction of that effect was consistent with the present study, i.e. a rightward shift of asymmetry with increased polygenic risk for schizophrenia. In contrast, pallidum volume asymmetry showed

little relation to schizophrenia polygenic risk²⁷, suggesting non-heritable contributions to this association. These genetic findings were established with adult general population data (UK Biobank)²⁷, but together with the current case-control findings, they indicate that altered rostral anterior cingulate thickness asymmetry may be a link between genetic susceptibility and disorder presentation. Left-right asymmetry of the brain originates during development *in utero*^{71,86-91}, and specific genomic loci that affect brain asymmetry have recently been identified^{26,92}. Some of the implicated genes may be involved in patterning the left-right axis of the embryonic or fetal brain, and genes expressed at different levels on the left and right sides of the embryonic central nervous system were found to be particularly likely to affect schizophrenia susceptibility⁸⁶. However, other genes may affect brain asymmetry as it changes throughout the lifespan^{2,93} and therefore may affect susceptibility to asymmetry-associated disorders later in life.

This was the largest study of structural brain asymmetries in schizophrenia to date, and made use of a single image processing and analysis pipeline to support analysis across multiple datasets. However, several limitations also apply. First, schizophrenia is a highly heterogeneous disorder covering a range of possible symptoms, which may correspond to differing underlying disease mechanisms. Our primary analysis only considered case-control group average differences, and in secondary analyses, we did not find significant correlations of asymmetries with major clinical variables within cases after adjusting for multiple testing - including age at onset, duration of illness, and symptom scores. More detailed clinical data would be useful to gather in future large-scale studies of structural asymmetries. Second, we used cross-sectional datasets, limiting the possible interpretation with respect to cause-effect relations or longitudinal changes. Third, we used macro-anatomical brain atlases for both the cortical and subcortical structures, which is the most feasible approach for large-scale analysis across multiple datasets, but limits spatial resolution. With higher resolution mapping, regions that showed negative results in our study may harbor more focal case-control asymmetry differences, which could be revealed for example through vertex-wise cortical mapping^{58,92,94}, or subcortical partitioning into subfields or nuclei. Fourth, data for several variables were only available from a limited number of study sites (medication, handedness, clinical variables), reducing the sample size and thus statistical power in these secondary analyses. Fifth, this study focused on group average differences, but individual-level deviations in affected individuals may be highly heterogeneous and not well captured by group-average approaches⁹⁵. Future studies may investigate individual or patient subgroup asymmetry deviations from a normative range or structural pattern, which may deliver clinical utility, for example through contributing to diagnosis or prognosis. This concept has shown promising results in recent studies even in smaller samples^{95,96}. The small group-average effects that we identified in the present study are unlikely to have clinical utility when considered in isolation, although they may contribute to multivariate prediction models in future research, for example when considering brain features across multiple imaging modalities.

In summary, we performed the largest study of asymmetry differences between individuals with schizophrenia and unaffected controls to date. Effect sizes were small, but several regional case-control asymmetry differences in cortical thickness and subcortical volume were suggested, and multivariate analysis indicated that 7% of variation across all regional asymmetries could be explained by the case-control group difference. Our findings therefore support a long-standing theory that the brain's asymmetry can be different in schizophrenia^{10,11}, even if earlier studies in smaller samples were likely to have over-estimated the effect sizes in relation to structural asymmetry. Altered asymmetry in schizophrenia may conceivably occur during development through disruption of a genetically regulated program of asymmetrical brain development, and/or through different trajectories of lifespan-related changes in brain asymmetries. The specific regions implicated here provide targets for future research on the molecular and cellular basis of altered lateralized cognitive functions in schizophrenia, which may ultimately help to identify pathophysiological mechanisms.

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Competing interests

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Author contributions

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Data availability

This study made use of 46 separate data sets collected around the world, under a variety of different consent procedures and regulatory bodies, during recent decades. Requests to access the data sets will be considered in relation to the relevant consents, rules and regulations, and can be made via the schizophrenia working group of the ENIGMA consortium: <http://enigma.ini.usc.edu/ongoing/enigma-schizophrenia-working-group/>.

Figures and tables

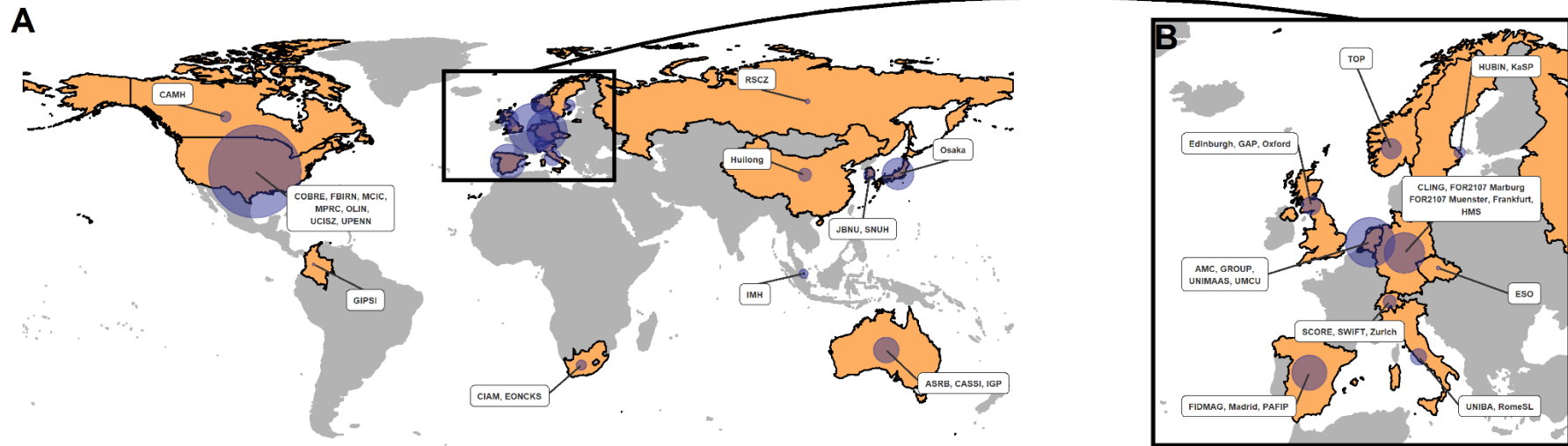
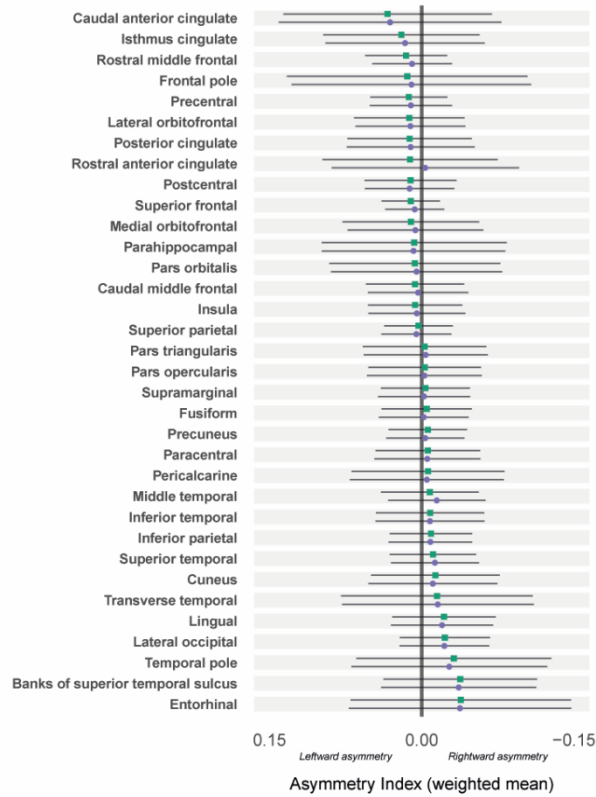
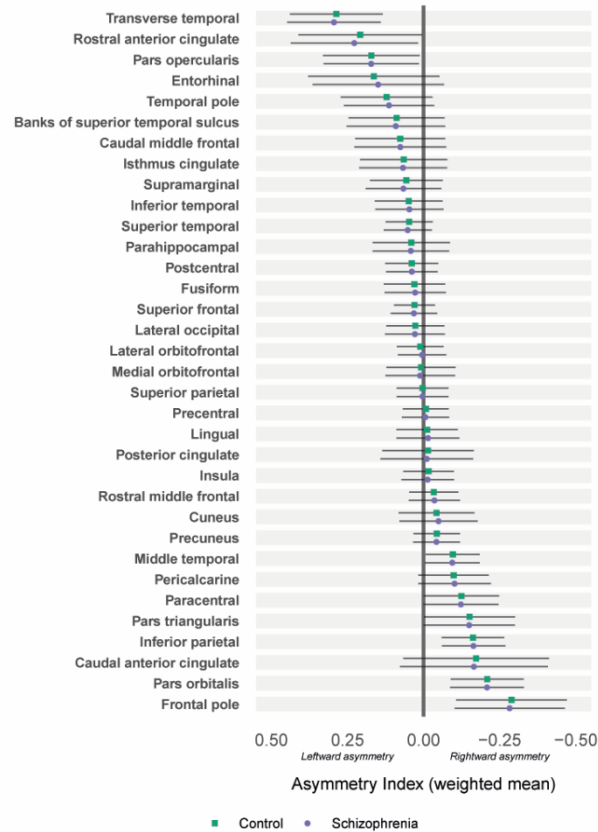


Fig. 1. Geographic origin of included datasets. **A)** Countries from which one or more datasets originate are highlighted in the world map, with dataset names included in labels. The relative sample size of datasets per country is indicated by blue circles. **B)** Zoomed map of Europe. For more details, see Table 1. Figure generated in R using packages *rnaturalearth*, *ggrepel*, and *sf*.

Cortical Thickness Asymmetry



Cortical Surface Area Asymmetry



Subcortical Volume Asymmetry

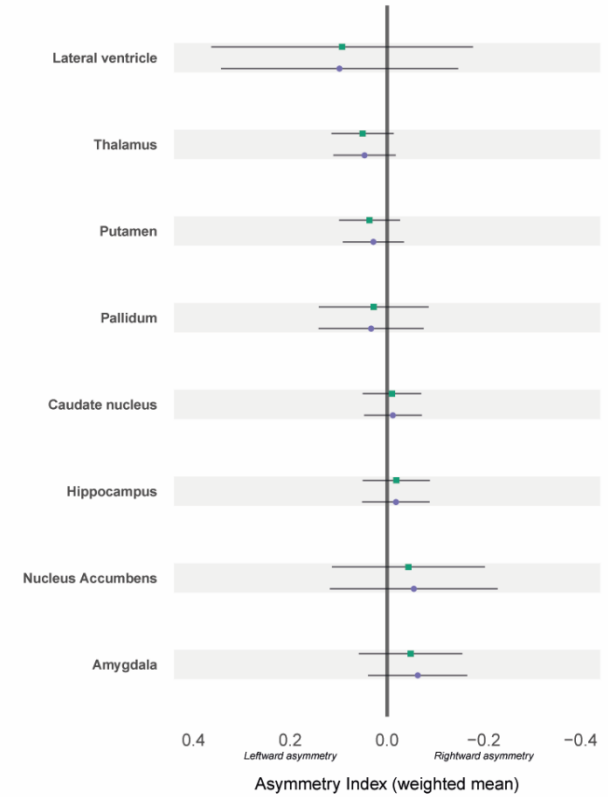


Fig. 2. Average structural asymmetries of the brain in individuals with schizophrenia and unaffected controls. For each bilaterally paired structural measure, the mean asymmetry index (AI) across datasets, weighted by sample size, is shown for individuals with schizophrenia (purple) and unaffected controls (green). A positive AI indicates left > right asymmetry, whereas a negative AI indicates right > left asymmetry. Error bars show pooled standard deviations.

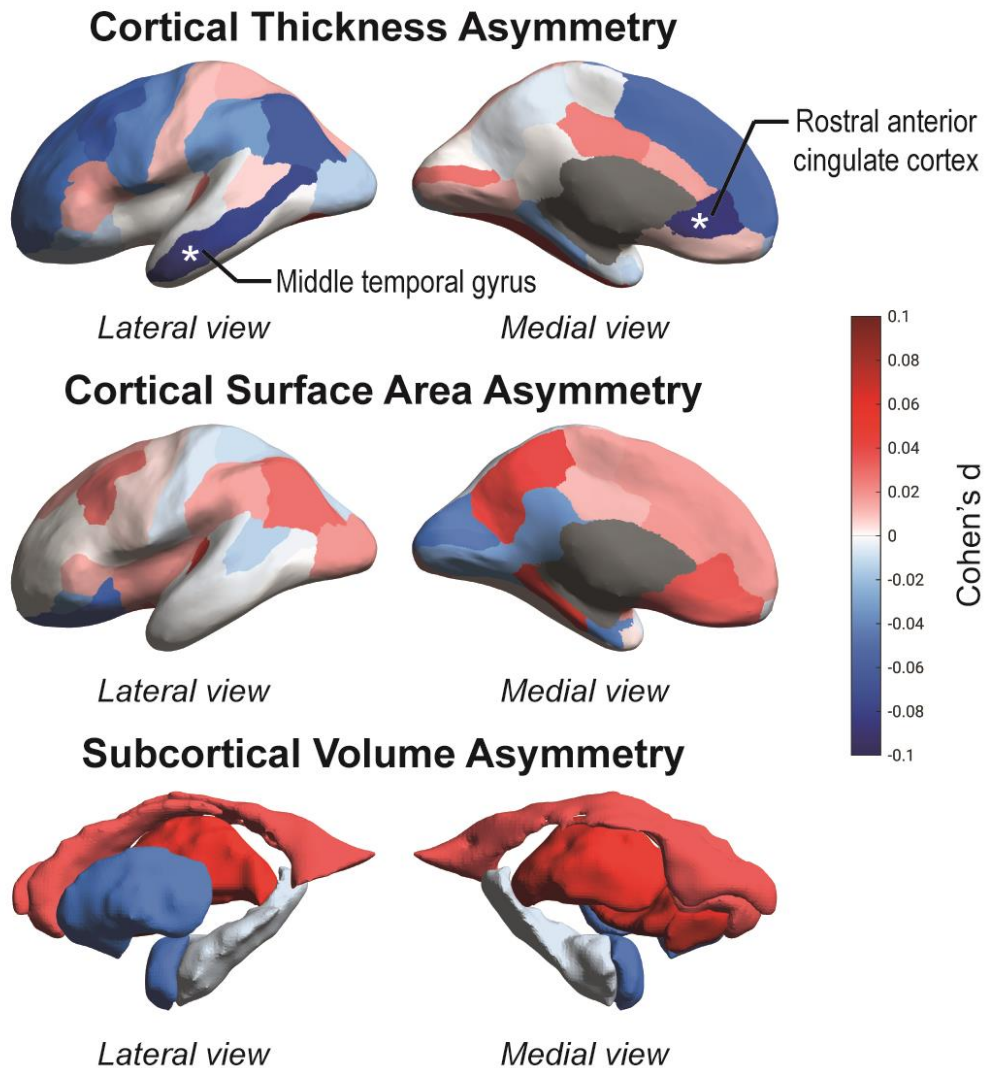


Fig. 3. Map of cortical and subcortical asymmetry differences between individuals with schizophrenia and unaffected controls. Cohen's d effect sizes from random-effects meta-analysis are projected on inflated left hemisphere cortical surface models (for cortical thickness and surface area) or subcortical structures (for subcortical volumes). Positive effects are shown in red shades (larger leftward or smaller rightward asymmetry in cases versus controls), while negative effects are shown in blue shades (smaller leftward or larger rightward asymmetry in cases versus controls). Gray shades indicate masked out structures. See also Fig. 2 and Supplementary Table 4 for directions of effects. Regions significant at $p_{\text{FDR}} < 0.05$ are labelled and marked with asterisks.

Table 1. Overview of the ENIGMA-Schizophrenia datasets.

Dataset	Country	N Total	Individuals with Schizophrenia		Unaffected Controls	
			N M/F	Mean age (years)	N M/F	Mean age (years)
AMC	Netherlands	405	180 / 26	22.2	130 / 69	23.5
ASRB*	Australia	429	177 / 86	38.6	79 / 87	39.3
CAMH	Canada	264	70 / 48	44.0	77 / 69	43.6
CASSI*	Australia	116	35 / 18	35.2	33 / 30	30.5
CIAM	South Africa	51	13 / 8	31.1	16 / 14	26.6
CLING	Germany	371	35 / 13	32.4	132 / 191	25.2
COBRE*	United States	143	60 / 13	37.4	50 / 20	35.7
EdinburghEHRS	United Kingdom	67	19 / 12	21.8	17 / 19	21.2
EdinburghFunc	United Kingdom	60	11 / 14	37.2	18 / 17	37.5
EdinburghSFMH	United Kingdom	76	23 / 12	37.5	23 / 18	38.2
EONCKS*	South Africa	200	74 / 34	34.2	51 / 41	31.9
ESO*	Czech Republic	80	20 / 20	29.5	20 / 20	29.1
FBIRN	United States	359	139 / 46	39.0	124 / 50	37.5
FIDMAG	Spain	283	124 / 36	39.6	54 / 69	37.5
FOR2107 Marburg*	Germany	403	23 / 14	37.2	143 / 223	34.0
FOR2107 Muenster*	Germany	163	4 / 4	33.4	60 / 95	27.0
Frankfurt	Germany	59	20 / 9	38.1	13 / 17	35.2
GAP	United Kingdom	209	85 / 37	27.5	32 / 55	25.9
GIPSI	Colombia	43	35 / 8	33.5	-	-
GROUP	Netherlands	271	59 / 29	28.2	83 / 100	30.1
HMS	Germany	101	32 / 14	28.4	28 / 27	35.4
HUBIN	Sweden	196	70 / 24	41.7	69 / 33	42.0
Huilong	China	333	133 / 112	25.5	49 / 39	27.7
IGP*	Australia	138	40 / 28	41.7	38 / 32	36.0
IMH*	Singapore	227	105 / 46	33.1	47 / 29	31.8
JBNU	South Korea	208	57 / 37	39.3	48 / 66	41.4
KaSP	Sweden	88	34 / 22	30.3	15 / 17	27.5
Madrid	Spain	105	17 / 4	16.2	59 / 25	11.8
MCIC	United States	311	113 / 35	32.9	101 / 62	31.4
MPRC*	United States	437	128 / 78	35.4	96 / 135	37.1
OLIN*	United States	868	174 / 138	37.7	310 / 246	37.6
Osaka	Japan	855	118 / 98	36.1	318 / 321	34.1
Oxford	United Kingdom	74	24 / 17	16.3	15 / 18	16.1
PAFIP	Spain	556	214 / 138	29.9	127 / 77	29.2
RomeSL	Italy	280	110 / 54	39.4	73 / 43	37.5
RSCZ	Russia	98	46 / 0	22.2	52 / 0	22.3
SCORE	Switzerland	205	117 / 44	25.5	17 / 27	25.5
SNUH	South Korea	80	18 / 22	22.9	20 / 20	22.6
SWIFT	Switzerland	37	17 / 7	34.2	5 / 8	29.3
TOP	Norway	522	130 / 89	32.0	159 / 144	35.4
UCISZ*	United States	57	22 / 5	42.9	23 / 7	41.4
UMCU	Netherlands	600	236 / 79	30.9	165 / 120	32.9
UNIBA*	Italy	143	54 / 19	33.5	28 / 42	26.6
UNIMAAS	Netherlands	66	21 / 10	28.3	24 / 11	28.1
UPENN	United States	370	105 / 72	38.9	90 / 103	36.4
Zurich*	Switzerland	88	45 / 15	30.5	18 / 10	32.5
Total/Mean		11,095	3,386 / 1,694	33.3	3,149 / 2,866	33.0

All datasets are shown with their total sample sizes and the numbers of male (M) and female (F) individuals with and without schizophrenia, as well as mean ages. For datasets marked with *, we had access to the individual-level data for the multivariate analysis. Exact sample sizes in the multivariate analysis are shown in Supplementary Table 1C.

Table 2. Significant brain regional asymmetry differences between individuals with schizophrenia and unaffected controls.

Structural AI	Sample size (N)		Mean AI (SD)		Cohen's <i>d</i> effect size [95% CI]			Average asymmetry	
	Control	Schizophrenia	Control	Schizophrenia	Left	Right	AI	Control	Schizophrenia
Rostral anterior cingulate cortex (cortical thickness asymmetry)	5,811	4,851	0.012 (0.086)	-0.0035 (0.092)	-0.20 [-0.28, -0.11]	-0.094 [-0.15, -0.036]	-0.083 [-0.13, -0.032]	Leftward	Reversed to rightward
Middle temporal gyrus (cortical thickness asymmetry)	5,673	4,684	-0.0080 (0.048)	-0.015 (0.048)	-0.41 [-0.50, -0.32]	-0.36 [-0.44, -0.27]	-0.074 [-0.12, -0.026]	Rightward	Increased rightward

Mean AI = weighted mean asymmetry index across datasets. SD = pooled standard deviation across datasets (positive mean indicates average leftward asymmetry, negative mean indicates average rightward asymmetry). Cohen's *d* effect sizes are shown from separate meta-analysis of left-hemisphere, right-hemisphere and asymmetry index differences between cases and controls. No regional measures of cortical surface area asymmetry or subcortical volume asymmetry showed significant case-control differences after false discovery rate correction.

Table 3. Multivariate analysis of case-control brain asymmetry differences between 935 individuals with schizophrenia and 1,094 controls for which individual-level data were available (14 datasets).

Structural asymmetry	<i>Approximate F</i>	<i>p</i>
Multivariate test (all regional cortical and subcortical asymmetries)	1.87	Nominal $p = 1.25 \times 10^{-5}$ Permutation $p = 3.0 \times 10^{-6}$
Most significant univariate effects:		
	<i>F</i>	<i>p</i>
Pallidum (volume asymmetry)	29.1	7.8×10^{-8}
Nucleus accumbens (volume asymmetry)	9.3	2.3×10^{-3}
Rostral middle frontal gyrus (surface area asymmetry)	7.7	5.5×10^{-3}
Parahippocampal gyrus (surface area asymmetry)	7.2	7.4×10^{-3}
Parahippocampal gyrus (thickness asymmetry)	5.5	0.019
Transverse temporal gyrus (thickness asymmetry)	5.4	0.021
Cuneus (surface area asymmetry)	5.4	0.021
Banks of superior temporal sulcus (surface area asymmetry)	4.9	0.027
Insula (surface area asymmetry)	4.6	0.031
Medial orbitofrontal cortex (thickness asymmetry)	3.9	0.048

Results are shown for the multivariate MANCOVA over all asymmetries, and the specific asymmetries with nominal significance ($p < 0.05$) in the corresponding univariate ANCOVAs, with their F statistics (*F*) and p-values (*p*).

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