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Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia
A Meta-analysis

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IMPORTANCE Schizophrenia is associated with alterations in mean regional brain volumes. However, it is not known whether the clinical heterogeneity seen in the disorder is reflected at the neurobiological level, for example, in differences in the interindividual variability of these brain volumes relative to control individuals.

OBJECTIVE To investigate whether patients with first-episode schizophrenia exhibit greater variability of regional brain volumes in addition to mean volume differences.

DATA SOURCES Studies that reported regional brain volumetric measures in patients and controls by using magnetic resonance imaging in the MEDLINE, EMBASE, and PsycINFO databases from inception to October 1, 2016, were examined.

STUDY SELECTION Case-control studies that reported regional brain volumes in patients with first-episode schizophrenia and healthy controls by using magnetic resonance imaging were selected.

DATA EXTRACTION AND SYNTHESIS Means and variances (SDs) were extracted for each measure to calculate effect sizes, which were combined using multivariate meta-analysis.

MAIN OUTCOMES AND MEASURES Relative variability of regional brain volumetric measurements in patients compared with control groups as indexed by the variability ratio (VR) and coefficient of variation ratio (CVR). Hedges *g* was used to quantify mean differences.

RESULTS A total of 108 studies that reported measurements from 3901 patients (1272 [32.6%] female) with first-episode schizophrenia and 4040 controls (1613 [39.9%] female) were included in the analyses. Variability of putamen (VR, 1.13; 95% CI, 1.03-1.24; $P = .01$), temporal lobe (VR, 1.12; 95% CI, 1.04-1.21; $P = .004$), thalamus (VR, 1.16; 95% CI, 1.07-1.26; $P < .001$), and third ventricle (VR, 1.43; 95% CI, 1.20-1.71; $P < 1 \times 10^{-5}$) volume was significantly greater in patients, whereas variability of anterior cingulate cortex volume was lower (VR, 0.89; 95% CI, 0.81-0.98; $P = .02$). These findings were robust to choice of outcome measure. There was no evidence of altered variability of caudate nucleus or frontal lobe volumes. Mean volumes of the lateral ($g = 0.40$; 95% CI, 0.29-0.51; $P < .001$) and third ventricles ($g = 0.43$; 95% CI, 0.26-0.59; $P < .001$) were greater, whereas mean volumes of the amygdala ($g = -0.46$; −0.65 to −0.26; $P < .001$), anterior cingulate cortex ($g = -0.26$; 95% CI, −0.43 to −0.10; $P = .005$), frontal lobe ($g = -0.31$; 95% CI, −0.44 to −0.19; $P = .001$), hippocampus ($g = -0.66$; 95% CI, −0.84 to −0.47; $P < .001$), temporal lobe ($g = -0.22$; 95% CI, −0.36 to −0.09; $P = .001$), and thalamus ($g = -0.36$; 95% CI, −0.57 to −0.15; $P = .001$) were lower in patients. There was no evidence of altered mean volume of caudate nucleus or putamen.

CONCLUSIONS AND RELEVANCE In addition to altered mean volume of many brain structures, schizophrenia is associated with significantly greater variability of temporal cortex, thalamus, putamen, and third ventricle volumes, consistent with biological heterogeneity in these regions, but lower variability of anterior cingulate cortex volume. This finding indicates greater homogeneity of anterior cingulate volume and, considered with the significantly lower mean volume of this region, suggests that this is a core region affected by the disorder.

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Supplemental content

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Schizophrenia is a complex mental disorder with a lifetime prevalence of approximately 1%. It remains a leading contributor to the global burden of disease,[1,2] partly because current treatments have limited efficacy for many patients.[3] There is thus a need to understand the neurobiological processes underlying the disorder to guide treatment development and aid diagnosis and prognostication.[4,5] Ventricular enlargement and lower gray matter volume are among the best established neurobiological findings in schizophrenia, with strong evidence of significant group-level differences between patients and control individuals in the mean volumes of a range of brain structures.[6-10] However, at the individual patient level, there is emerging evidence that these structural differences vary markedly in nature and extent.[11,12] Nevertheless, it remains to be determined whether schizophrenia is associated with greater variability in brain structure per se or whether the evidence of subgroup differences is an artifact of selection of individuals from extreme ends of a distribution of similar variance, albeit with shifted mean, to that of healthy controls.

We adopted a meta-analytic approach to examine differences in brain structural variability between groups of patients with schizophrenia and matched healthy controls. Although meta-analysis of differences in mean values of neurobiological (or other) measures is a frequently used technique in schizophrenia research, we are not aware of previous meta-analytic studies that examined differences in measures of variability. We hypothesized that these measures would be greater in patient groups relative to healthy controls. We also conducted an updated meta-analysis of mean volume differences, including recently published studies.

Key Points

Question Do patients with first-episode schizophrenia exhibit greater interindividual variability of regional brain volumes relative to matched healthy control individuals?

Findings Patients with schizophrenia have significantly greater variability in the volumes of the putamen, temporal lobe, and thalamus even after accounting for group differences in the mean volume of these structures. Conversely, patients have significantly lower variability in the volume of the anterior cingulate cortex relative to healthy controls.

Meaning The greater variability in volume seen in a number of brain regions in schizophrenia is consistent with neurobiological heterogeneity; the lower variability of anterior cingulate cortex volume suggests that alterations in this region may represent a core feature of the disorder that is shared across illness subtypes.

Methods

Study Selection

We searched the MEDLINE, EMBASE, and PsychINFO databases from inception to October 1, 2016, for studies that reported measures of regional brain volumes in patients with schizophrenia and healthy controls. To minimize the potential confounding effect of factors associated with chronic illness, such as long-term treatment and prolonged institutionalization, we included only studies of patients in their first episode of schizophrenia. We focused on studies that reported volumetric measures rather than those that used voxel-based morphometry because the latter do not generally report measures of variance (further details of the search, study selection, and inclusion criteria are provided in the eMethods in the Supplement).

Data Extraction and Processing

We extracted means and variance measures (SDs) of volumetric measures for the patient and control groups. Brain structures were included in our analysis if at least 10 studies met the inclusion criteria. In addition, we recorded details of the following potential moderating factors: duration of psychosis, duration of medication treatment, patient diagnoses, segmentation method, and age and sex matching.

Outcome Measures for Variability

Our primary outcome measure was the relative variability of patient compared with control measures, as indexed by the log variability ratio (lnVR), the natural logarithm of the ratio of unbiased estimates of the population SDs for each group,[13] as follows:

$$\ln \mathrm{VR} = \ln\left(\frac{\hat{\sigma}_p}{\hat{\sigma}_c}\right) = \ln\left(\frac{s_p}{s_c}\right) + \frac{1}{2(n_p-1)} - \frac{1}{2(n_c-1)}$$

Where $\hat{\sigma}_p$ and $\hat{\sigma}_c$ are unbiased estimates of population SDs, s_p and s_c are the reported sample SDs, and n_p and n_c are the sample sizes for patient and control groups, respectively, in each case.

It is common in biological systems to find that variance scales with mean, such that larger mean values are associated with greater variance.[14] Thus, a between-group difference in relative variability, although real, may in part reflect between-group differences in mean. We therefore present a further analysis with log coefficient of variation ratio (lnCVR), the natural logarithm of the ratio of unbiased estimates of population coefficients of variation for each group. This relative mean-scaled variability quantifies variability differences after accounting for differences in mean[13] and is a more conservative test of our hypothesis for those structures with greater mean volume in patient groups (attributable to the larger denominator in the equation below), such as lateral and third ventricles. Conversely, for those regions with lower mean volume in patients (ie, most other regions), the lnVR is the more conservative test of our hypothesis. The lnCVR is given by the following:

$$\ln \mathrm{CVR} = \ln\left(\frac{\hat{\sigma}_p/\bar{x}_p}{\hat{\sigma}_c/\bar{x}_c}\right) = \ln\left(\frac{s_p/\bar{x}_p}{s_c/\bar{x}_c}\right) + \frac{1}{2(n_p-1)} - \frac{1}{2(n_c-1)}$$

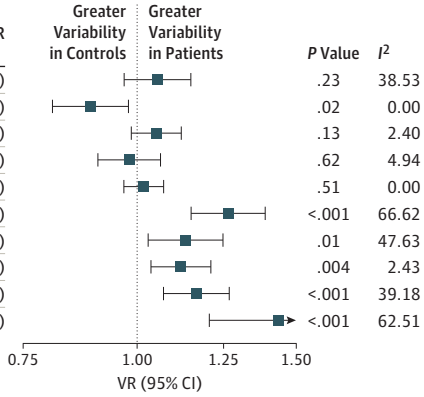
where $\bar{x}_p$ and $\bar{x}_c$ are the reported means for patient and control groups, respectively.

Outcome Measures for Mean Differences in Regional Brain Volumes

We used Hedges g as our effect size measure for the meta-analysis of between-group differences in mean volumes.

Figure 1. Forest Plot Showing Effect Sizes for Variability Ratio (VR) of Regional Brain Volumes in Schizophrenia

Brain Region	No. of Studies	No. of Patients	No. of Controls	Effect Size for VR (95% CI)	*P* Value	I^2
Amygdala	23	1161	1154	1.05 (0.97-1.15)	.23	38.53
ACC	11	443	450	0.89 (0.81-0.98)	.02	0.00
Caudate	22	1106	990	1.05 (0.99-1.12)	.13	2.40
Frontal lobe	22	693	698	0.98 (0.91-1.06)	.62	4.94
Hippocampus	36	1615	1683	1.02 (0.97-1.07)	.51	0.00
Lateral ventricle	31	1416	1382	1.26 (1.15-1.39)	<.001	66.62
Putamen	15	964	845	1.13 (1.03-1.24)	.01	47.63
Temporal lobe	22	733	725	1.12 (1.04-1.21)	.004	2.43
Thalamus	21	1102	1023	1.16 (1.07-1.26)	<.001	39.18
Third ventricle	13	362	388	1.43 (1.20-1.71)	<.001	62.51



The VR was significantly increased in the lateral and third ventricles, temporal lobe, thalamus, and putamen, indicating greater variability in the volumes of these structures in patient groups relative to controls. In contrast, the VR was significantly reduced in the anterior cingulate cortex (ACC), indicating lower variability in the volume of this region in patient groups.

Statistical Analysis

Because most studies reported volumes for several structures of interest (eTable 1 in Supplement), we conducted meta-analyses using a multivariate approach because this enables simultaneous estimation of summary effect sizes across all regions of interest, reducing multiplicity concerns.[15] Furthermore, this approach incorporates estimation of covariance among outcome measures, improving estimation of summary effect size relative to univariate analysis.[16] We used an omnibus Wald-type χ^2 test to evaluate the significance of model coefficients across regions (see the eMethods, including its Statistical Analysis subsection, and eTable 2 in the Supplement for further details of the multivariate approach). When the omnibus test was significant, we tested the effect separately by region. To aid interpretation of results, summary effect sizes for lnVR and lnCVR were transformed back to a linear scale as follows:

$$\mathrm{VR} = e^{\ln \mathrm{VR}} = \frac{\hat{\sigma}_p}{\hat{\sigma}_c}$$

$$\mathrm{CVR} = e^{\ln \mathrm{CVR}} = \frac{\hat{\sigma}_p/\bar{x}_p}{\hat{\sigma}_c/\bar{x}_c}$$

Thus, a variability ratio (VR) (or coefficient of variation ratio [CVR]) of 1 indicates equal variability in patient and control groups, a VR (or CVR) greater than 1 indicates greater relative variability in patient groups, and a VR (or CVR) less than 1 indicates lower variability in patient groups. We used an omnibus test to assess whether lnVR or lnCVR differed among regions, with post hoc tests to assess interregional differences on a pairwise basis. Given the large number of such tests (45 pairwise comparisons per measure), false discovery rate adjustment of the probability threshold was used to control the expected proportion of type I error to 5% of rejected null hypotheses.

Meta-regression

We tested the effects of potentially moderating factors on variability and mean differences by using multivariate mixed-effects meta-regression. We used an omnibus test to assess the significance of these effects across all regions simultaneously. Because these meta-regression analyses were exploratory, we did not apply correction for multiple comparisons when assessing effects at the level of the individual region.

Publication Bias and Inconsistency

Publication bias was assessed across all regions simultaneously by visual inspection of funnel plots of SEs against regional residuals and by using the excess significance test,[17] the *P* curve method,[18,19] and a multivariate analogue of the Egger regression test.[20] Inconsistency was assessed using the I^2 statistic (with >50% conventionally indicating moderate-high inconsistency and <50% indicating low-moderate inconsistency[21]), an approach that generalizes straightforwardly to the multivariate setting.[22]

Meta-analyses were conducted using the metafor package[23] in the R statistical programming language.[24] *P* curve analyses were conducted using the online *P* curve app, version 4.052 (http://www.p-curve.com/app4/).

Results

Study Selection

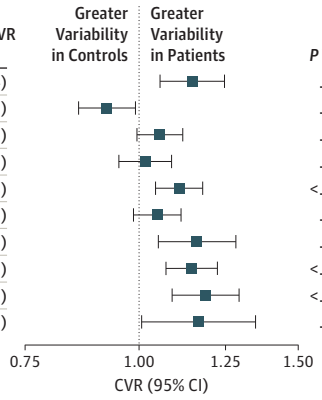
A total of 108 studies that reported data from 3901 patients and 4040 controls were included (eResults, eTable 1, and eFigure 1 in the Supplement). Sufficient studies were found to conduct analyses for the following regions: temporal lobe, frontal (or prefrontal) lobe, anterior cingulate cortex, hippocampus, thalamus, amygdala, caudate nucleus, and putamen.

Variability Ratio

We found a significant overall effect of group on VR across all regions of interest (χ^2 = 53.02, *P* < .001). **Figure 1** shows that the variability of patient groups was significantly greater for the lateral ventricle (VR, 1.26; 95% CI, 1.15-1.39; *P* < .001), third ventricle (VR, 1.43; 95% CI, 1.20-1.71; *P* < .001), putamen (VR, 1.13; 95% CI, 1.03-1.24; *P* = .01), temporal lobe (VR, 1.12; 95% CI, 1.04-1.21; *P* = .004), and thalamus (VR, 1.16; 95% CI, 1.07-1.26; *P* < .001) volumes. Anterior cingulate cortex was the only region with significantly lower variability in patient groups

Figure 2. Forest Plot Showing Effect Sizes for Mean-Scaled Variability in Regional Brain Volumes in Schizophrenia

Brain Region	No. of Studies	No. of Patients	No. of Controls	Effect Size for CVR (95% CI)	P Value	I^2
Amygdala	23	1161	1154	1.14 (1.05-1.24)	.001	54.00
ACC	11	443	450	0.92 (0.86-0.99)	.03	0.00
Caudate	22	1106	990	1.05 (0.99-1.12)	.08	3.21
Frontal lobe	22	693	698	1.02 (0.95-1.09)	.65	2.62
Hippocampus	36	1615	1683	1.11 (1.04-1.18)	<.001	28.97
Lateral ventricle	31	1416	1382	1.05 (0.99-1.11)	.13	36.07
Putamen	15	964	845	1.16 (1.05-1.28)	.003	50.88
Temporal lobe	22	733	725	1.14 (1.07-1.22)	<.001	2.14
Thalamus	21	1102	1023	1.18 (1.09-1.29)	<.001	49.55
Third ventricle	13	362	388	1.16 (1.01-1.35)	.04	63.98



The coefficient of variation ratio (CVR) was significantly increased in the amygdala, hippocampus, putamen, temporal lobe, thalamus, and third ventricle, indicating greater variability in the volumes of these structures in patient groups relative to controls, after accounting for group differences in the mean volumes. ACC indicates anterior cingulate cortex.

(VR, 0.89; 95% CI, 0.81-0.98; P = .02). Variability was not significantly altered in the amygdala (VR, 1.05; 95% CI, 0.97-1.15; P = .23), caudate (VR, 1.05; 95% CI, 0.99-1.12; P = .13), frontal lobe (VR, 0.98; 95% CI, 0.91-1.06; P = .62), or hippocampus (VR, 1.02; 95% CI, 0.97-1.07; P = .51) (see eTables 5-14 in the Supplement for effect size estimates for individual studies).

Coefficient of Variation Ratio

We found a significant overall effect of group on CVR across all regions of interest (χ^2 = 48.90, P < .001). **Figure 2** shows that significant variability differences found with VR remained present using CVR for the putamen (CVR, 1.16; 95% CI, 1.05-1.28; P = .005), temporal lobe (CVR, 1.14; 95% CI, 1.07-1.22; P = .003), thalamus (CVR, 1.18; 95% CI, 1.09-1.29; P < .001), third ventricle (CVR, 1.16; 95% CI, 1.01-1.35; P = .04), and anterior cingulate cortex (CVR, 0.92; 95% CI, 0.86-0.99; P = .03) volumes. No significant difference was found in variability of frontal lobe (CVR, 1.02; 95% CI, 0.95-1.09; P = .65) and caudate (CVR, 1.05; 95% CI, 0.99-1.12; P = .08) volumes using the CVR, consistent with the VR results. However, variability of the hippocampus (CVR, 1.11; 95% CI, 1.04-1.18; P < .001) and amygdala (CVR, 1.14; 95% CI, 1.07-1.22; P = .001) volumes was significantly increased in patients using CVR, inconsistent with the findings using the VR (see eTables 5-14 in the Supplement for effect size estimates for individual studies).

Comparison of Regional Differences in Variability

We found a significant overall effect of region on variability differences between the patient and control groups, as measured by lnVR (χ^2 = 42.49, P < .001) and lnCVR (χ^2 = 32.34, P < .001). For brevity, we record only those pairwise interregional comparisons for which between-region differences were significant (adjusted for multiple comparisons with a false discovery rate–adjusted P = .05) for lnVR and lnCVR (see eTable 3 in the Supplement for details of all comparisons). Variability effect sizes for the anterior cingulate cortex were significantly lower than for caudate nucleus (ΔlnVR = 0.17, adjusted P = .01; ΔlnCVR = 0.13, adjusted P = .03), hippocampus (ΔlnVR = 0.14, adjusted P = .03; ΔlnCVR = 0.18, adjusted P = .001), lateral ventricle (ΔlnVR = 0.35, adjusted P < .001; ΔlnCVR = 0.13, adjusted P = .04), putamen (ΔlnVR = 0.24, adjusted P = .002; ΔlnCVR = 0.23, adjusted P = .002), temporal lobe (ΔlnVR = 0.23, adjusted P = .001; ΔlnCVR = 0.22, adjusted P < .001), thalamus (ΔlnVR = 0.27, adjusted P < .001; ΔlnCVR = 0.25, adjusted P < .001), and third ventricle (ΔlnVR = 0.48, adjusted P < .001; ΔlnCVR = 0.23, adjusted P = .03). In addition, variability effect sizes for the thalamus were significantly greater than for the frontal lobe (ΔlnVR = 0.17, adjusted P = .01; and ΔlnCVR = 0.15, adjusted P = .03).

Mean Differences

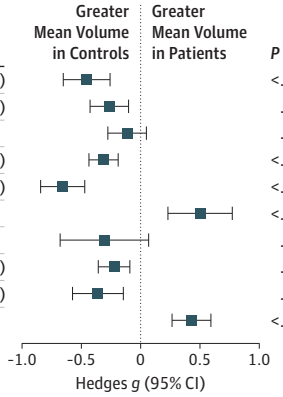
We found a significant overall effect of group on mean volume across all regions of interest (χ^2 = 198.53, P < .001). Most regional mean volumes were significantly lower in patients, including the amygdala (g = −0.46; 95% CI, −0.65 to −0.26; P < .001), anterior cingulate cortex (g = −0.26; 95% CI, −0.43 to −0.10; P = .001), frontal lobe (g = −0.31; 95% CI, −0.44 to −0.19; P < .001), hippocampus (g = −0.66; 95% CI, −0.84 to −0.47; P < .001), temporal lobe (g = −0.22; 95% CI, −0.36 to −0.09; P = .001), and thalamus (g = −0.36; 95% CI, −0.57 to −0.15; P = .001). Lateral (g = 0.40; 95% CI, 0.29-0.51; $P < 1 \times 10^{-5}$) and third ventricle (g = 0.43; 95% CI, 0.26-0.59; P < .001) volumes were significantly greater in patients. Significant mean differences between patients and controls were not found for the caudate nucleus (g = −0.11; 95% CI, −0.28 to 0.05; P = .23) or putamen (g = −0.31; 95% CI, −0.68 to 0.07; P = .11) (**Figure 3**) (see eTables 5-14 in the Supplement for effect size estimates for individual studies).

Meta-regression

We found a significant effect of the proportion of the patient sample with a diagnosis of schizoaffective disorder on lnVR (χ^2 = 21.01, P = .02) and lnCVR (χ^2 = 25.92, P = .004). Significant effects at the individual region level were found for hippocampus for lnVR (z = 2.13, P = .03) and lnCVR (z = 2.33, P = .02) and for anterior cingulate cortex for lnVR (z = 2.28, P = .02), with a higher proportion of schizoaffective disorder diagnoses associated in all 3 cases with lower variability in patients relative to controls. No significant effect of the propor-

Figure 3. Forest Plot Showing Effect Sizes for Mean Differences in Regional Brain Volumes in Schizophrenia

Brain Region	No. of Studies	No. of Patients	No. of Controls	Effect Size for VR (95% CI)	P Value	I^2
Amygdala	23	1161	1154	-0.46 (-0.65 to -0.26)	<.001	78.01
ACC	11	443	450	-0.26 (-0.43 to -0.10)	.006	48.44
Caudate	22	1106	990	-0.11 (-0.28 to 0.05)	.23	78.53
Frontal lobe	22	693	698	-0.31 (-0.44 to -0.19)	<.001	28.66
Hippocampus	36	1615	1683	-0.66 (-0.84 to -0.47)	<.001	74.14
Lateral ventricle	31	1416	1382	0.40 (0.29 to 0.51)	<.001	55.51
Putamen	15	964	845	-0.31 (-0.68 to 0.07)	.11	78.66
Temporal lobe	22	733	725	-0.22 (-0.36 to -0.09)	.001	43.67
Thalamus	21	1102	1023	-0.36 (-0.57 to -0.15)	.001	76.03
Third ventricle	13	362	388	0.43 (0.26 to 0.59)	<.001	15.15



Mean volumes of the third and lateral ventricles were significantly increased, whereas mean volumes were significantly reduced for the thalamus, temporal lobe, hippocampus, frontal lobe, anterior cingulate cortex (ACC), and amygdala in schizophrenia.

tion of patients with a diagnosis of schizophreniform disorder on either variability measure was found. No significant effect of duration of psychosis or treatment (mean [SD]) was found on either variability measure. Further details of the results of the meta-regression analyses are given in eTable 4 in the Supplement.

Publication Bias and Inconsistency

Regression tests for funnel plot asymmetry were not significant for VR (z = 0.49, P = .63) (eFigure 2 in the Supplement) or CVR (z = 0.07, P = .94) (eFigure 3 in the Supplement). Although the regression test for mean volume differences was not significant (z = 0.60, P = .55) (eFigure 4 in the Supplement), visual inspection suggested asymmetry. We therefore repeated this analysis, omitting the 4 outlying estimates. The outcome of the analysis was not significantly altered by these omissions (eFigure 5 in the Supplement).

The expected number of significant results did not differ from the observed number of significant results for VR (expected, 22.52, observed, 33; χ^2 = 0.46, P = .50) or for mean differences (expected, 93.37, observed, 92; χ^2 = 0.03, P = .86). However, a greater than expected number of significant results was observed for CVR (expected, 22.01, observed, 43; χ^2 = 21.81, P < .001). P curve analysis indicated evidential value for all measures (VR: z_{full} = −6.15, P < .001; z_{half} = −4.24, P < .001; CVR: z_{full} = −3.25, P < .001; z_{half} = −4.15, P < .001; mean difference: z_{full} = −13.62, P < .001; z_{half} = −13.80, P < .001) (eFigures 6, 7, and 8 in the Supplement).

Inconsistency (between-study heterogeneity), as measured by I^2, ranged from zero (anterior cingulate cortex, both variability measures, hippocampus, VR) to 93.24 (putamen, Hedges g) (Figures 1, 2, and 3).

Discussion

Our first main finding is that the variability in volume of several brain regions (third ventricle, putamen, temporal lobe, and thalamus) was significantly greater in patients with first-episode schizophrenia than in controls. Our second main finding is that the variability of anterior cingulate cortex volume was significantly lower in patients with first-episode schizophrenia than in controls. These findings were robust to choice of variability measure. Because all variability differences were calculated on a within-study basis, these findings cannot be accounted for by methodologic differences among studies. These findings are broadly consistent with our hypothesis of higher variability in patients but demonstrate that the effect is not uniform across brain regions.

We also found lower mean amygdala, frontal lobe, hippocampal, temporal lobe, thalamus, and anterior cingulate volumes and greater mean lateral and third ventricular volumes in patients, with no significant between-group difference in mean caudate and putamen volumes. These results are broadly in line with previous meta-analyses.[6,9]

Recently, there has been increasing interest in subtypes of schizophrenia,[5,25] and a number of studies have reported structural differences between groups of patients defined on the basis of putative illness subtypes, for example, based on symptom dimensions,[11,26-29] cognitive features,[12,30] treatment response,[31-33] or illness progression.[34] However, these studies did not address whether there is greater brain structural variability in schizophrenia per se, in excess of that which might be expected because of normal individual differences. Another potential limitation of such studies is that by selecting by subtype, generally in chronically ill patients, differences may reflect sampling extreme ends of a distribution of similar variance to that seen in controls or may be secondary to differences in other factors linked to the subtype, such as treatment. Our meta-analysis addresses these issues and extends our understanding of schizophrenia as a heterogeneous disorder by showing, for the first time to our knowledge, altered structural variability across a number of brain regions. Patients were not selected on the basis of a theoretical classification into a putative subtype, indicating that brain structural heterogeneity may be a general feature of the disorder from the first episode.

Interpretation

Our findings systematically demonstrate greater structural variability in groups of patients with schizophrenia compared with healthy controls in 4 brain regions: putamen,

thalamus, temporal lobe, and third ventricle. We found unaltered variability of frontal lobe and caudate nucleus volumes and lower variability of anterior cingulate cortex volumes. There are a number of potential explanations for our findings.

Greater variability in patient groups may be related to increased movement artifact found in clinical populations or other measurement artifact. Although images contaminated by gross movement artifact are usually discarded, this does not guarantee that all motion artifacts are removed from the data. The extent of residual artifact has been associated with lower mean values of certain automated morphometric measurements in patient groups (eDiscussion in Supplement),[35] although the association between artifact and the variability of such measurements is unclear, and we did not find an association between variability and segmentation method (manual vs automatic) in our meta-regression analyses.

Another possibility is that our findings are attributable to factors secondary to the illness, such as medication, recreational substance exposure, or mental and physical comorbidities (including subclinical abnormalities[36]). Healthy controls, in contrast, may be unusually healthy compared with the general population,[37] such that the variability differences that we report may in part be attributable to the homogeneity of control groups. Although this is a concern for all patient studies, it is of greater relevance in our meta-analysis because of the direct comparison of interindividual variability between groups, whereas in other contexts, the variability to which the present report pertains is considered to be noise and factored into the analysis. To reduce potential confounding sources of variability, we restricted our analyses to studies of patients with a first episode of schizophrenia and found no effect of mean (SD) duration of psychosis or treatment on either variability measure. Nevertheless, we cannot exclude a contribution of these or other factors to the findings. This lack of influence of duration of psychosis or treatment on variability could be confirmed by repeating this analysis to include samples of patients with chronic conditions or examining changes in brain volume variability over time from longitudinal studies, but this is beyond the scope of the present study. Additional studies are needed to examine whether such variability is present in other psychiatric disorders with similarly heterogeneous populations and to compare the extent of such variability among disorders.

Finally, differences in variability could reflect heterogeneity in the biological processes underlying the disorder, indicating that some brain regions are affected in all patients, whereas other regions are affected only in some patients or to varying degrees across patients. This finding could be attributable to the inclusion of patients with different biological subtypes in which the biological processes underlying the illness do not extend to involve all regions uniformly in patients. The results of the meta-regressions suggest that such subtypes are unlikely to reflect the schizophrenia/schizoaffective disorder diagnostic categories because greater heterogeneity of patient samples with respect to this feature was associated with lower rather than greater variability. Although this finding suggests that these diagnostic categories do not underlie the variability that we found, studies that directly compare variability among diagnostic groups are needed to definitively test this. In contrast, the robust findings of unaltered variability of frontal lobe and caudate volumes and lower variability in the anterior cingulate cortex suggest that illness effects in these regions are consistent across patients. In particular, the finding of lower variability in the anterior cingulate cortex could indicate that this region is most uniformly affected in the disorder (although not necessarily most severely affected because the effect size for mean differences is small), suggesting that lower volume in this region may reflect a core component of the biological processes underlying schizophrenia shared across subtypes of the disorder. Alternatively, this finding may reflect a core component of the biological processes underlying mental disorders more generally. Recent evidence that morphometric abnormalities in this region are seen across psychiatric disorders[38,39] raises the possibility that the reduction in variability that we report in this region may reflect the biological processes of a common factor seen in all these disorders, such as psychological stress.[40] Finally, because the lower variability in anterior cingulate cortex was unexpected, the finding should be treated with caution pending confirmation in new samples.

Implications

The key implication of our findings is that important aspects of the biological processes underlying schizophrenia may be missed by focusing solely on between-group differences in means. For example, in line with previous findings, our updated meta-analysis of mean volume differences found no evidence of alteration in mean putamen volume in patients. However, we found a robust effect of schizophrenia on the variability of putamen volume. Understanding of the determinants of structural variability and potential associations with clinical outcomes could provide new insights into the neurobiological process(es) underlying schizophrenia, with implications for precision medicine. In contrast, because schizophrenia has considerable heterogeneity in symptomatic,[41] cognitive,[42] genetic,[43] and treatment-response[44] domains, it is surprising that some regions have unaltered or even lower variability, which identifies these regions as potentially central to the neurobiological processes underlying the disorder.

Limitations

Most of our analyses did not find significant publication bias, and exclusion of potential outliers seen on the funnel plot did not change the findings. Of interest, a greater than expected number of significant results were found for CVR but neither of the other measures. The reason for this finding is not clear because, to our knowledge, the present study is the first to apply a statistical significance threshold to group differences in variability for this literature; thus, a selective publication incentive for such measures is unlikely to exist. Moderate to high inconsistency of effect size estimates for mean volume differences were seen for many regions (Figure 3). This finding could reflect methodologic factors, such as differences in scanner resolution or recruitment strategies among studies. However, the random-effects model that we used is robust to such

inconsistency, which would not explain our variability findings because these reflect within-study variation (methodologic factors are common to patient and control groups in a given study). Effect size estimates for the variability measures, particularly VR, were more consistent across studies. However, moderate to high inconsistency was found for some regions, specifically lateral (VR) and third ventricles (VR, CVR), putamen (CVR), thalamus, and amygdala (CVR). This finding suggests that findings for these regions may be influenced by methodologic differences among studies, and further confirmatory work is required. In contrast, the low to moderate inconsistency in the remaining analyses suggests that these findings are generalizable across settings. Because there were too few studies for us to conduct variability analyses in some other brain regions implicated in schizophrenia, such as the insula,[45] an important future direction when more data become available will be to determine whether variability is also altered in these regions. Given the problems associated with underpowered studies, the effect sizes that we present can be used to ensure that future studies in these and other regions are adequately powered to detect group differences.

Conclusions

We found evidence that the Anna Karenina principle[46,47] holds for aspects of the neurobiological processes of schizophrenia by demonstrating that, in some brain regions, patients with schizophrenia have significantly greater structural variability relative to controls. These findings not only provide evidence of the existence of significant neurobiological heterogeneity in the disorder but also identify volume changes in the anterior cingulate cortex as a uniform aspect of the neurobiological mechanisms of schizophrenia.

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