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Brain Heterogeneity in Schizophrenia and Its Association With Polygenic Risk

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IMPORTANCE Between-individual variability in brain structure is determined by gene-environment interactions, possibly reflecting differential sensitivity to environmental and genetic perturbations. Magnetic resonance imaging (MRI) studies have revealed thinner cortices and smaller subcortical volumes in patients with schizophrenia. However, group-level comparisons may mask considerable within-group heterogeneity, which has largely remained unnoticed in the literature.

OBJECTIVES To compare brain structural variability between individuals with schizophrenia and healthy controls and to test whether respective variability reflects the polygenic risk score (PRS) for schizophrenia in an independent sample of healthy controls.

DESIGN, SETTING, AND PARTICIPANTS This case-control and polygenic risk analysis compared MRI-derived cortical thickness and subcortical volumes between healthy controls and patients with schizophrenia across 16 cohorts and tested for associations between PRS and MRI features in a control cohort from the UK Biobank. Data were collected from October 27, 2004, through April 12, 2018, and analyzed from December 3, 2017, through August 1, 2018.

MAIN OUTCOMES AND MEASURES Mean and dispersion parameters were estimated using double generalized linear models. Vertex-wise analysis was used to assess cortical thickness, and regions-of-interest analyses were used to assess total cortical volume, total surface area, and white matter, subcortical, and hippocampal subfield volumes. Follow-up analyses included within-sample analysis, test of robustness of the PRS threshold, population covariates, outlier removal, and control for image quality.

RESULTS A comparison of 1151 patients with schizophrenia (mean [SD] age, 33.8 [10.6] years; 68.6% male [n = 790] and 31.4% female [n = 361]) with 2010 healthy controls (mean [SD] age, 32.6 [10.4] years; 56.0% male [n = 1126] and 44.0% female [n = 884]) revealed higher heterogeneity in schizophrenia for cortical thickness and area (t = 3.34), cortical (t = 3.24) and ventricle (t range, 3.15-5.78) volumes, and hippocampal subfields (t range, 2.32-3.55). In the UK Biobank sample of 12 490 participants (mean [SD] age, 55.9 [7.5] years; 48.2% male [n = 6025] and 51.8% female [n = 6465]), higher PRS was associated with thinner frontal and temporal cortices and smaller left CA2/3 (t = −3.00) but was not significantly associated with dispersion.

CONCLUSIONS AND RELEVANCE This study suggests that schizophrenia is associated with substantial brain structural heterogeneity beyond the mean differences. These findings may reflect higher sensitivity to environmental and genetic perturbations in patients, supporting the heterogeneous nature of schizophrenia. A higher PRS was associated with thinner frontotemporal cortices and smaller hippocampal subfield volume, but not heterogeneity. This finding suggests that brain variability in schizophrenia results from interactions between environmental and genetic factors that are not captured by the PRS. Factors contributing to heterogeneity in frontotemporal cortices and hippocampus are key to furthering our understanding of how genetic and environmental factors shape brain biology in schizophrenia.

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Editorial
Supplemental content

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Schizophrenia is a severe psychiatric disorder with a lifetime prevalence of about 1%, rendering it a leading cause of disability worldwide, with 26 million people affected.[1] Although genetic and environmental factors contributing to disease risk have been identified, the pathophysiological process remains elusive.[2,3] Patients diagnosed with schizophrenia display substantial heterogeneity in terms of their clinical characteristics and symptoms,[4] treatment response,[5] and long-term prognosis.[6] The notion that the observed heterogeneity stems at least partially from distinct subtypes of patients with differentially affected neurobiology and clinical and cognitive profiles[7-9] has not been fully confirmed to date.[10] Hence, whether a single unifying pathophysiological process is shared across patients or a multitude of partly independent disease processes lead to a similar clinical syndrome remains salient.[11]

Schizophrenia is associated with widespread brain abnormalities, with the most robust group-level mean structural differences being ventricle enlargement, reduced thickness and area of frontotemporal cortices, and reduced hippocampal and amygdala volumes.[12-14] However, substantial variability exists between patients,[7,8,15] presenting a major challenge for achieving imaging-based diagnostic predictions (ie, achieving the goal of precision medicine in psychiatry, and using brain imaging as a clinical tool to guide diagnosis and treatment) with any clinical utility.[16-18] Rather than simply reflecting noise, this interindividual variability in brain structure may possibly carry relevant information regarding gene-environment interactions related to the individual sensitivity to environmental and genetic perturbation. Only a few studies have investigated whether heterogeneity differs between healthy participants and patients with schizophrenia. One functional imaging study[19] reported increased heterogeneity in connectivity and spatial extent of functional brain networks in schizophrenia. Regions with altered spatial variance in functional networks included areas previously implicated in schizophrenia, such as auditory and sensorimotor cortices and basal ganglia, and networks showing increased heterogeneity overlapped with those showing mean volume differences, implying that the mean and variance measures provide complementary but converging results.[20] A recent meta-analysis[15] reported increased interindividual volumetric variability in several cortical and subcortical structures, including the temporal lobe, thalamus, hippocampus, and amygdala in schizophrenia, and lower variability in the anterior cingulate cortex. These results point to the importance of modeling heterogeneity as well as mean changes. Detecting brain regions that are more homogenous in patients could point to a primary role in a shared underlying pathophysiological process of schizophrenia, whereas regions of increased heterogeneity might be informative of putative subtypes of disease or reflect regional differences in the sensitivity to genetic and environmental perturbations.

Schizophrenia is highly heritable,[21] motivating the ongoing efforts to identify intermediate brain phenotypes associated with disease liability to elucidate the pathway from genes to illness manifestation. Several risk loci for schizophrenia have been identified,[22] but the individual contribution of each identified variant is weak, and at present no common variants have been conclusively linked to the disease. The polygenic risk score (PRS) for schizophrenia, which represents a weighted sum of common genetic schizophrenia risk alleles, has been proposed to account for the polygenic nature of disease risk.[23] Beyond being associated with case-control status,[22] PRS has been associated with negative symptoms, anxiety, and lower cognitive ability in adolescents.[24] Polygenic burden has also been linked to a thinner cortex and to prefrontal working memory– and hippocampal encoding–related activation and connectivity in patients and healthy participants.[25-28] This linkage is in line with findings implicating the frontal cortex and hippocampus as core regions in the pathophysiological process of schizophrenia.[29] Polygenic risk for schizophrenia, however, is only weakly associated with subcortical volumes.[30] Risk alleles could also exert their effect by influencing the environmental sensitivity, which could be reflected in the phenotypic variability between individuals.[31]

Thus, revealing brain structures with higher or lower heterogeneity in schizophrenia could facilitate discovery of intermediate brain phenotypes that may serve to identify putative subtypes[8,32] of the disease and phenotypes that are primary or common in the neurobiology of schizophrenia.[15] Further, investigating how the genetic architecture of disease risk is related to brain heterogeneity could reveal regions in which the cumulative burden of common risk alleles influence the phenotypic variance.[33] To this end, we directly compared within-group dispersion in several key brain structural phenotypes, including cortical thickness, as well as cortical, subcortical, and hippocampal subfield volumes between 1151 patients with schizophrenia and 2010 healthy controls. Next, to test whether between-individual variability is associated with the cumulative polygenic risk for schizophrenia in absence of a clinical syndrome, we tested for associations between dispersion in the same brain features and PRS for schizophrenia in 12 490 healthy individuals from the UK Biobank.

Key Points

Question Are schizophrenia and its polygenic risk associated with brain structural heterogeneity in addition to mean changes?

Findings In this case-control analysis of 1151 patients and 2010 controls, schizophrenia was associated with increased heterogeneity in frontotemporal thickness and area and cortical, ventricle, and hippocampal volumes, as well as robust reductions in mean estimates. In an independent sample of 12 490 healthy controls, polygenic risk for schizophrenia was associated with thinner frontotemporal cortices and smaller CA2/3 volume of the left hippocampus, but not with heterogeneity.

Meaning Schizophrenia appears to be associated with increased interindividual differences in brain structure, possibly reflecting clinical heterogeneity, gene-environment interactions, or secondary disease factors.

Methods

Samples

Data were collected from October 27, 2004, through April 12, 2018. Demographic characteristics and clinical information are

presented in eTables 1 and 2 in the Supplement, respectively. The data have been used in previous publications. Details and references are presented in eMethods and eTable 3 in the Supplement, and MRI protocols appear in eTable 4 in the Supplement. Data collection was performed with each participant's written informed consent and with approval by the respective local institutional review boards.

Image Preprocessing and Genetic Data

We processed T1-weighted MRI images using FreeSurfer (version 5.3.0) for cortical reconstruction and volumetric segmentation,[34-37] and FreeSurfer (version 6.0) for hippocampus subfield segmentation[38] (eMethods in the Supplement). We calculated PRS using PRSice (version 1.25),[39] based on the European Caucasian subset of the 2014 Psychiatric Genomics Consortium 2 schizophrenia genome-wide association study[22] (eFigure 1 and eMethods in the Supplement). The PRS based on a threshold of $P < .05$ was used for the main analysis because this threshold has been reported as optimal in terms of explaining case-control differences.[22]

Statistical Analysis

Data were analyzed from December 3, 2017, through August 1, 2018. For all included measures in the case-control sample, we used vertex- or volume-wise generalized additive models to regress out scanner effects while accounting for age, sex, and diagnosis (eMethods in the Supplement). For the case-control comparison and the PRS analysis, we modeled vertex- or volume-wise mean and dispersion using double generalized linear models, which iteratively fit a generalized linear model of the mean parameter and a second generalized linear model of the dispersion parameter on the deviances of the first model (eMethods in the Supplement). We permuted diagnostic labels for the case-control comparison and the PRS UK Biobank analysis by recalculating the mean and dispersion parameters for each iteration. For cortical thickness, the true and permuted statistical maps (t maps) were submitted to the permutation analysis of linear models tool[40] to correct for multiple comparisons using threshold-free cluster enhancement and tail approximation[41] (600 permutations; eMethods in the Supplement). For the region of interest-based measures (eMethods in the Supplement), we performed 5000 permutations per volume and extracted the maximum t value across regions of interest to calculate familywise error.[42] Significance threshold was set at 2-tailed $P < .05$ for all analyses. We also performed a meta-analysis of the multiscanner thickness data. We conducted analyses with and without covarying for estimated intracranial volume (eTIV) for the volumetric measures. We performed follow-up analyses with more stringent exclusion criteria as well, with adding the Euler number as a covariate[43] (eMethods in the Supplement). To assess the robustness to the PRS P value threshold, we performed analyses with PRS threshold selection of 2-sided $P < .001$, the first component from a principal component analysis on PRS (PRS-PC1) calculated across thresholds (eMethods in the Supplement), and exploratory analysis of the second and third components of the principal component analysis (PC2 and PC3) based on their opposite gradient pattern with regard to PRS P value threshold.

Results

Study Samples

The case-control comparison included 1151 patients with schizophrenia (mean [SD] age, 33.8 [10.6] years; 790 male [68.6%] and 361 female [31.4%]) and 2010 healthy controls (mean [SD] age, 32.6 [10.4] years; 1126 male [56.0%] and 884 female [44.0%]). The PRS analysis included 12 490 healthy participants from the UK Biobank (mean [SD] age, 55.9 [7.5] years; 6025 male [48.2%] and 6465 female [51.8%]).

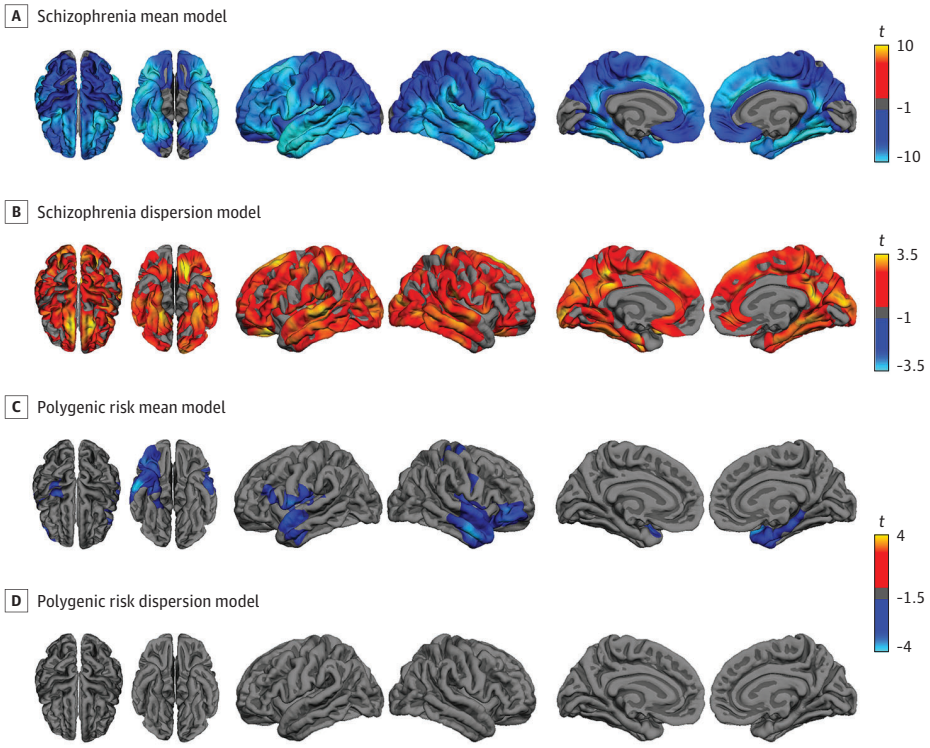
Vertex-Wise Thickness

Schizophrenia was associated with thinner cortex globally, with the exception of the visual cortex, as well as globally higher thickness dispersion (**Figure 1**A and B, **Figure 2**A, and eFigure 2 in the Supplement). Meta-analysis of within-sample effects with more stringent exclusion criteria also revealed and confirmed significantly higher heterogeneity in schizophrenia (left hemisphere, $\beta = 0.31$ [95% CI, 0.16-0.46; $P < .001$]; right hemisphere, $\beta = 0.33$ [95% CI, 0.18-0.48; $P < .001$]) (eFigure 3 in the Supplement), and follow-up multisite analysis (eMethods in the Supplement) did not reveal major interactions between age, sex, or diagnosis and site, indicating that dispersion effects are not simply explained by multisite variability, site by demographic interactions, or a few extreme values. The PRS was associated with lower mean thickness in the right inferior frontal gyrus, the right lateral orbitofrontal cortex, the right precentral gyrus, the right medial temporal cortex, and bilaterally in the middle and superior temporal cortex (Figure 1C and D and eFigure 4 in the Supplement). Converging results were obtained on reanalysis with the addition of the first 4 population components added as covariates (eFigure 5A in the Supplement) or with more stringent exclusion criteria (eFigure 5B in the Supplement). Follow-up analysis using the PRS-PC1 gave close to an identical pattern as the PRS model based on a threshold of $P < .05$ (eFigure 5C in the Supplement; vertex-wise $r = 0.91$), whereas a PRS threshold of $P < .001$ showed weaker association with mean thickness (eFigure 5D in the Supplement). We found no significant association between PRS and thickness dispersion, or between PRS-PC2 or PRS-PC3 and mean or dispersion of cortical thickness. Effects of age and sex are shown in eFigure 6 in the Supplement for case-control comparisons and eFigure 7 in the Supplement for PRS analysis.

Cortical and Subcortical Volumes

Schizophrenia was associated with lower mean cortical volume ($t = -17.05$), mean cortical area ($t = -9.35$), supratentorial volume ($t = -11.43$), total ($t = -18.04$) and subcortical ($t = -4.63$) gray volume, cerebellar cortical volume (left, $t = -11.69$; right, $t = -10.69$), as well as brain stem ($t = -9.64$), amygdala (left, $t = -8.82$; right, $t = -6.16$), thalamus (left, $t = -7.53$; right, $t = -8.35$), and nucleus accumbens (left, $t = -3.26$; right, $t = -5.78$), and several white matter volumes, as well as increased ventricle (t range, 2.29-12.24), caudate

Figure 1. Mean and Dispersion of Cortical Thickness



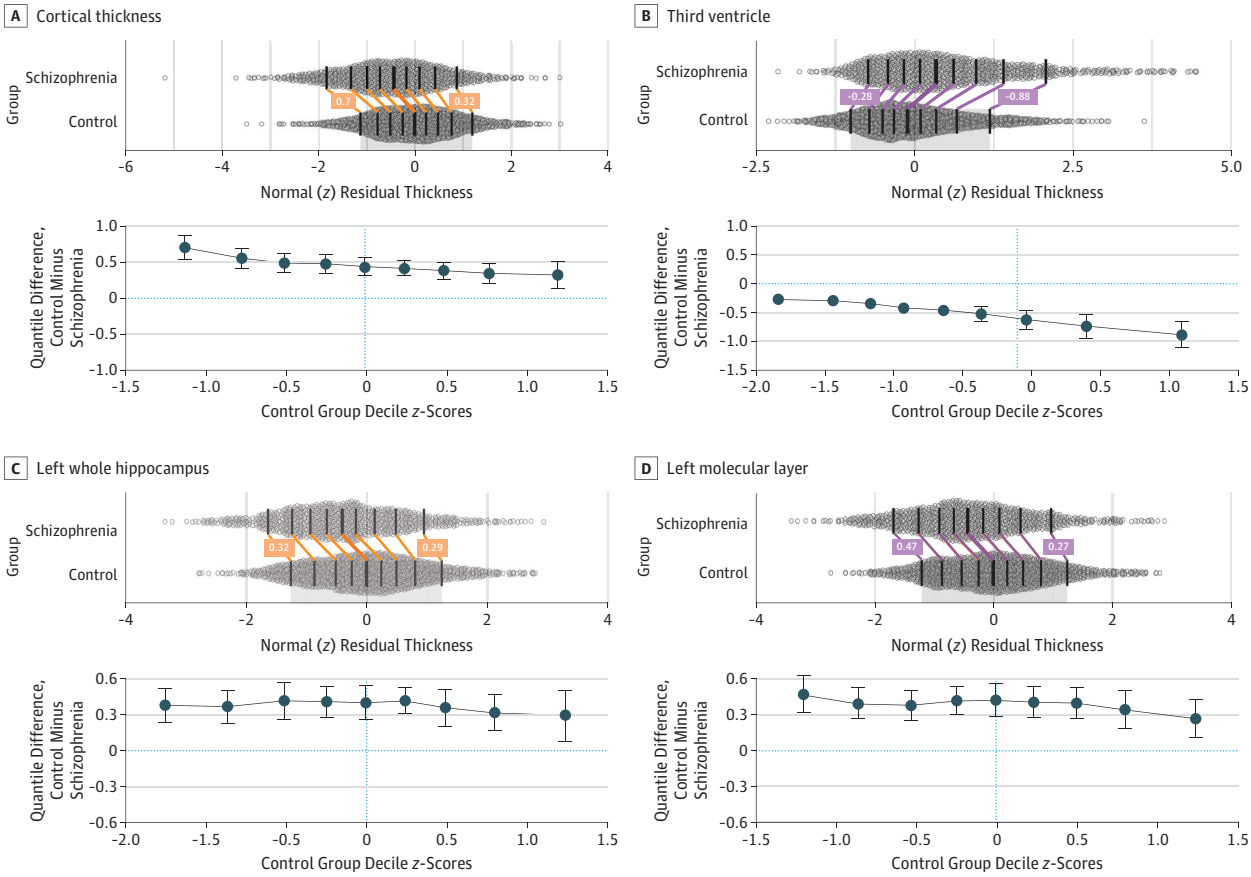
All maps were thresholded using permutation testing, threshold-free cluster enhancement, and fitting the tail of the permutation distribution to a generalized Pareto distribution (500 permutations; $P < .05$, familywise error). A, In the *t* map for the schizophrenia mean model, blue shades represent areas with decreased mean thickness in schizophrenia compared with healthy controls. Schizophrenia was associated with decreased thickness globally, with the exception of the visual cortex, and with strongest effects in frontal and temporal regions, compared with healthy controls. B, In the *t* map for the schizophrenia dispersion model, orange and yellow shades represent areas with increased heterogeneity in schizophrenia compared with healthy controls. Interindividual variability in cortical thickness showed a spatially global increase for the schizophrenia group compared with healthy controls. C, In an independent sample of healthy adults, the mean model showed that higher polygenic risk for schizophrenia was associated with lower cortical thickness, represented by blue shades, in frontal and temporal cortices. D, Polygenic risk was not associated with cortical thickness heterogeneity in any region.

nucleus (left, $t = 4.00$; right, $t = 2.16$), pallidum (left, $t = 9.57$; right, $t = 9.55$), and putamen (left, $t = 5.48$; right, $t = 6.44$) volumes. Schizophrenia was further associated with higher dispersion in mean cortical volume ($t = 3.24$), mean cortical area ($t = 3.34$), total gray volume ($t = 3.41$), and ventricle volumes (t range, 3.18-5.78) (Figure 2B and **Figure 3**). Models without eTIV (eFigure 8A in the Supplement) revealed no significant differences in the mean volumes of caudate nucleus and left putamen and resulted in an additional significant association with dispersion in supratentorial volume ($t = 2.92$). Reanalysis of mean and dispersion models with more stringent exclusion criteria showed converging results (eTable 5 in the Supplement). The PRS was not associated with the mean or the dispersion in any of the subcortical volumes (Figure 3B), which was also true for models without adjustment for eTIV (eFigure 8B in the Supplement).

Hippocampal Subfields

Patients with schizophrenia had lower mean volume in the left ($t = -12.68$) and right ($t = -13.24$) whole hippocampus and in all hippocampal subfields, accompanied with larger right hippocampal fissures. We found higher dispersion in schizophrenia in the left ($t = 3.54$) and right ($t = 2.32$) whole hippocampus and in the left molecular layer ($t = 3.55$), left CA1 (cornu ammonis 1) ($t = 2.32$), left granule cell layer of the dentate gyrus ($t = 3.23$), left CA4 ($t = 3.10$), and left presubiculum ($t = 2.52$) (**Figure 4**A). Models without adjustment for eTIV gave the same results for mean volumes with the exception for the left hippocampal fissure, which did not survive correction, and for dispersion with the exception for the left presubiculum (eFigure 9A in the Supplement). When reanalyzing schizophrenia mean and dispersion models with more stringent exclusion criteria, we obtained similar results (eTable 6 in the Supplement). The PRS was associated with smaller left CA2/3 ($t = -3.00$). None of the subfields showed an association between dispersion and PRS (Figure 4B). Models without adjustment for eTIV revealed smaller left and right CA2/3 ($t = -3.70$), left granule cell layer of the dentate gyrus ($t = -3.20$), and left CA4 ($t = -2.88$) (eFigure 9B in the Supplement) in patients with schizophrenia. Reanalysis with population covariates added to the models, reanalysis with stricter exclusion criteria, and modeling PRS using PRS-PC1 did not alter conclusions (eTable 7 in the Supplement).

Figure 2. Shift Function Plots



Top graphs, Marginal distributions for patients with schizophrenia and healthy controls. Lines show the amount of shift between the 2 distributions. Orange lines and boxes indicate that corresponding deciles are lower in schizophrenia compared with healthy control groups (purple shows the reverse). Bottom graphs, The magnitude of the group difference is plotted as a function of the distribution among healthy controls. A sloped line indicates a difference in the distributions between the groups. Error bars represent bootstrapped 95% CIs. A, Vertex values were extracted by masking the images by the schizophrenia dispersion significance map, and the mean was calculated across vertices and hemispheres and residualized for scanner, sex, and age. Schizophrenia was associated with reduced thickness, with larger differences between groups in the lower deciles. B, Values were residualized for scanner, sex, age, and estimated intracranial volume (eTIV). Schizophrenia was associated with larger volumes compared with controls, with the largest difference between groups in the upper deciles. C and D, Values were residualized for scanner, sex, age, and eTIV. Schizophrenia was associated with smaller volumes compared with controls, with the largest difference between groups in the upper deciles.

Discussion

In the present study we found that schizophrenia is associated with higher brain heterogeneity in cortical thickness and area and cortical, lateral and third ventricle, and hippocampal volumes. The findings, based on harmonized analysis protocols for all included data sets, were robust to strict procedures for removing outliers and quality assessment, and follow-up meta-analysis confirmed that multisite case-control differences cannot be explained by scanning site. These findings are largely in line with those of a recent meta-analysis[15] showing higher volumetric heterogeneity in the temporal lobe and lateral and third ventricles. Our findings also extend this meta-analysis by showing higher heterogeneity in cortical thickness and area as well as in specific hippocampal subfields. Further, higher PRS in healthy individuals was associated with thinner frontal and temporal regions and reduced volume of the left CA2/3, but not with thickness dispersion.

We found widespread reductions in cortical thickness in patients with schizophrenia, with the characteristic pattern of stronger frontotemporal effects, as well as global reductions in cortical volume.[13] In addition to these mean differences, we found that schizophrenia is also associated with higher thickness heterogeneity compared with healthy participants. No cortical region showed the opposite pattern of higher homogeneity among patients. In line with previous studies, we found mean reductions in several brain volumes, with the most robust effects for cortical volume, cerebellum, and hippocampus, as well as ventricle enlargement. These regions additionally showed higher heterogeneity in patients compared with controls, and again no region showed higher homogeneity, as might result if a particular region was similarly affected by a common pathophysiological mechanism.[15] Instead, the re-

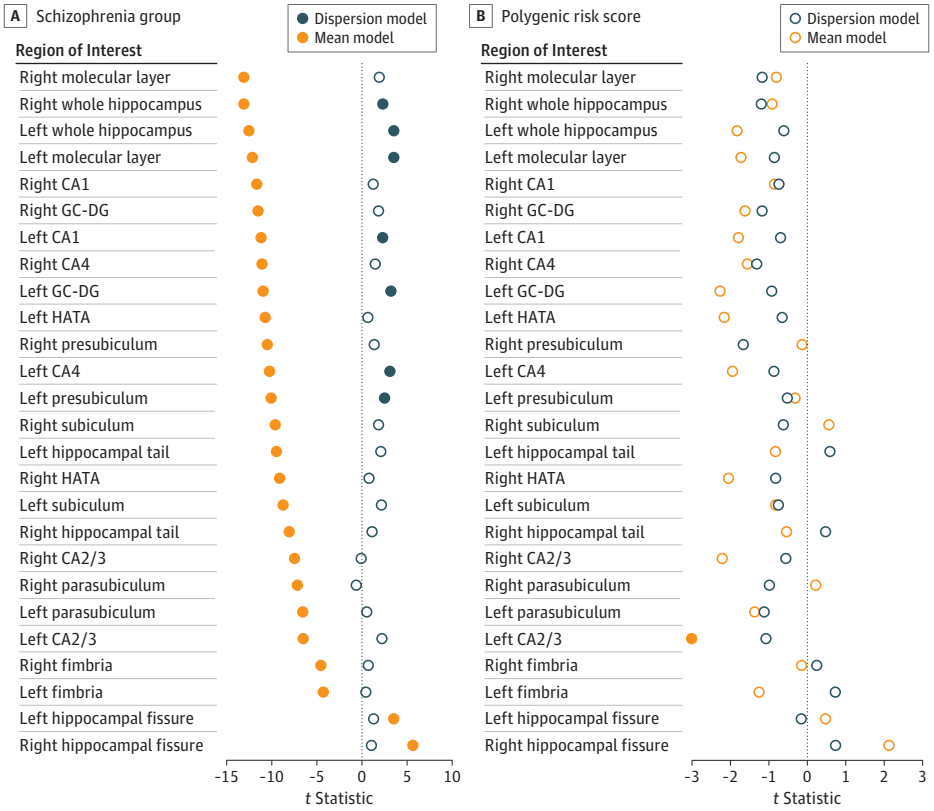
Figure 3. Mean and Dispersion Values of Cortical and Subcortical Volumes

The *t* statistics for mean and dispersion models are shown. Filled dots mark significant effects after correction for multiple comparisons across regions (5000 permutations; permuted $P < .05$, familywise error, adjusted for estimated intracranial volume). A, The schizophrenia group had decreased cortical and subcortical volumes and increased ventricle, putamen, and pallidum volumes. Cortical, hippocampal, and ventricle volumes were more heterogeneous in the schizophrenia group compared with healthy controls. B, Polygenic risk for schizophrenia was not associated with mean changes or dispersion in any of the regions. CC indicates corpus callosum; GM, gray matter; Lh, left hemisphere; Rh, right hemisphere; and WM, white matter.

sults are in line with previous studies suggesting substantial neurobiological heterogeneity in schizophrenia[18] and may reflect putative subtypes[32] and symptom profiles.[44] Results are mostly in line with a recent report[15] of higher volumetric heterogeneity in schizophrenia but contrasts with the finding of higher homogeneity for the anterior cingulate cortex in schizophrenia. One possible explanation is differing sample inclusion criteria, because the previous study[15] included only patients with first-episode psychosis. An earlier disease stage may offer a more direct window into core aspects of the pathophysiological processes, which later shift toward increased interindividual variability as patients vary across different illness stages and degrees of severity, as well as differences in treatment and medication status.

The PRS reflects cumulative risk across multiple genetic loci, and the PRS for schizophrenia has been associated with several phenotypic traits, including liability for psychiatric disease such as bipolar disorder and schizoaffective disorder, negative symptoms, IQ, working memory performance, and brain activation.[25,45,46] The PRS has been associated with cortical gyrification in healthy participants[47] and with global cortical thickness.[27] Our results show that a higher PRS in healthy controls is associated with a mean decrease in thickness in frontotemporal cortex. These shifts in mean thickness were not as-

Figure 4. Mean and Dispersion of Hippocampus Subfield Volumes



The *t* statistics for mean and dispersion models are shown. Filled dots mark significant effects after correction for multiple comparisons across regions (5000 permutations; permuted $P < .05$, familywise error, adjusted for intracranial volume). A, The schizophrenia group had decreased hippocampal volumes. This decrease was also evident in all subfields and accompanied by an increase of the hippocampal fissures. Whole hippocampal volumes were also more heterogeneous in the schizophrenia group, and among the subfields this effect was present in the left molecular layer, left CA1 (cornu ammonis 1), left granule cell layer of the dentate gyrus (GC-DG), left CA4, and left presubiculum. B, Polygenic risk for schizophrenia was associated with mean reductions of left dentate gyrus, left CA4, and bilateral CA2/3. Total hippocampal volumes and subfields showed no significant association between polygenic risk and volume heterogeneity. HATA indicates hippocampus-amygdala transition area.

sociated with brain heterogeneity, as was found for patients, pointing to differential genetic effects on mean thickness and heterogeneity.[48] Risk for schizophrenia is also associated with socioeconomic status and family history of psychiatric disorders, with the latter being partially mediated by the PRS.[49] This finding underscores the importance of investigating environmental risk factors, as well as gene-environment interplay, and their role in explaining the observed clinical and neurobiological heterogeneity.

With regard to hippocampal volumes, we found that a higher PRS was associated with smaller volumes of the left CA2/3, in the absence of an effect on total hippocampal volume and after correcting for total intracranial volume, suggesting a specific effect of genetic risk on this region. The hippocampus has been hypothesized to play a primary role in the pathophysiological processes of schizophrenia, through progressive changes to its neural circuits as the disease evolves.[29] Our results also complement recent studies reporting that polygenic risk for schizophrenia is associated with hippocampal activation during memory encoding[28] and of polygenic overlap between schizophrenia and hippocampus volume,[50] with possible subfield specificity.[51] Also, although the patients showed higher hippocampal heterogeneity, only mean volumes were associated with the PRS, mirroring the findings on cortical thickness. Thus, the CA2/3 emerge as key regions for the manifestation of and the genetic risk for schizophrenia and are potentially informative for the classification of subtypes and degrees of severity.

Despite reliable associations between schizophrenia and brain morphometry,[14] the PRS was only weakly associated with subcortical volumes. The lack of associations between PRS and subcortical volumes in the present study is in line with most previous reports of PRS[30]; however, a recent study[50] found polygenic overlap between schizophrenia and hippocampal, putamen, and intracranial volumes.

Limitations

An important source of heterogeneity in the present case-control sample could be related to different scanning sites. However, in addition to residualizing for scanner site in the main analysis, we also performed within-sample analysis and ran a meta-analysis, which ruled out the scanner as a major contributor. A multivariate approach, such as partial least squares,[52] might be more sensitive to dispersion, and better capture site-related variance.

Heterogeneity could be associated with differences in medication status and duration of illness. Investigation of such effects requires carefully controlled settings and is therefore difficult to address in large-scale multisite studies. Another possible explanation is that the increased variability is caused by movement artifacts, which are typically greater in clinical populations[53]; however, running the analysis in a subset with stricter criteria for data set exclusion did not alter the conclusions, and the results were robust to correction for image quality using the Euler number.[43]

In addition to the concern that clinically defined diagnostic categories do not necessarily comply with biology,[18] an important consideration for case-control studies in general is the possibility that healthy controls are higher functioning compared with the general healthy population owing to selection bias and strict exclusion criteria.[54] Jointly, these concerns underscore the importance of studying the full range of phenotypic variability in the population.

Further, the validity of choosing a given *P* value threshold among several possible thresholds when calculating PRS is uncertain. We addressed this by performing a principal components analysis across PRS calculated across a wide range of thresholds, to derive a more general PRS. This approach yielded results converging with the main analysis using a threshold of $P < .05$. The lack of association between PRS and brain heterogeneity suggests that the current PRS does not strongly reflect variance-controlling variants. However, the PRS might have nonlinear and gene-environment effects that are not detectable in a healthy sample.

As a composite score, PRS likely also hides a substantial genetic heterogeneity. A PRS calculated using a variance-controlling trait loci approach would likely be more sensitive in detecting such effects. Parsing the genetic and clinical contributions to heterogeneity in schizophrenia is an important follow-up, which was not possible herein owing to lack of availability of such data for several of the samples (eTable 2 in the Supplement).

The extent of image smoothing affects sensitivity and anatomical specificity of results,[55] and future studies are needed to determine the influence of analysis pipeline on dispersion effects. Last, schizophrenia is increasingly understood as a neurodevelopmental disorder,[56] and disentangling the sources of heterogeneity in the adult patient population likely requires investigation of the life-span trajectories and aberrant developmental paths.[57,58]

Conclusions

Ongoing efforts are attempting to account for neurobiological and brain heterogeneity by means of delineating patient subtypes,[8,59] as well as characterizing patients by their differential degree of affectedness along one or multiple clinical domains.[11,60] Herein we report that schizophrenia appears to be associated with widespread and increased heterogeneity in cortical thickness and cortical and hippocampal volumes, beyond the known mean differences, compared with controls. The results seem to support the notion that schizophrenia is a highly heterogeneous disorder and suggest that important information may be overlooked when only assessing mean differences between cases and controls.[18] In healthy adults, the PRS was associated with mean differences in brain areas implicated in schizophrenia, but not with brain heterogeneity. Together these findings warrant future longitudinal studies that can disentangle the genetic and environmental factors contributing to diverging trajectories and neurobiological heterogeneity.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: All authors.
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