Estimating multimodal brain variability in schizophrenia spectrum disorders: A worldwide ENIGMA study

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Abstract

Schizophrenia is a multifaceted disorder associated with structural brain heterogeneity. Recent research underscored that profound understanding of structural brain heterogeneity is relevant to identify illness subtypes as well as informative biomarkers. However, our understanding of structural heterogeneity in schizophrenia is still limited. This comprehensive meta-analysis therefore investigated and compared the variability of multimodal structural brain measures for white and gray matter in individuals with schizophrenia and healthy controls. Using the ENIGMA dataset of MRI-based brain measures from 22 sites, we examined variability in cortical thickness, surface area, folding index, subcortical volume and fractional anisotropy, both at regional and global level. At the regional level, we found that schizophrenia patients are distinguished by higher heterogeneity in the frontotemporal network with regard to multimodal structural measures. Multimodal heterogeneity in these regions potentially implies different subtypes that share impaired frontotemporal interaction as a core feature of schizophrenia. At the global level, the Person-Based Similarity Index (PBSI) analysis surprisingly revealed that schizophrenia patients are distinguished by a significantly higher homogeneity of the folding index, implying that certain gyrification attributes represent a uniform aspect of schizophrenia across subtypes. These findings underscore the importance of studying structural brain variability for a more holistic understanding of schizophrenia's neurobiology, potentially facilitating the identification of illness subtypes and informative biomarkers. These findings could guide future investigations and tailor precision medicine approaches for schizophrenia.

Introduction

Schizophrenia is characterized by an array of biological and symptomatic heterogeneity that remains incompletely understood[1–3]. Notably, the biological heterogeneity of schizophrenia is reflected in structural irregularities of the brain[4–8] as well as functional abnormalities[9,10]. Historically, neuroimaging studies including meta-analyses have predominantly focused on evaluating mean differences in structural brain measures between individuals with psychosis and healthy controls[11–13]. However, recent studies also emphasized that individuals with or at clinical high risk for psychosis exhibit differences in variability of structural brain measures compared to healthy controls[7,14–18]: While higher variability of selective brain structures is potentially associated with schizophrenia subtypes, lower variability argues for a more stable feature of the disorder that is shared across illness subtypes[7].
Therefore, a shift in perspective towards the analysis of variability, above and beyond mean differences, promotes a more nuanced neurobiological understanding of schizophrenia, with clinical relevance for the identification of illness subtypes and biomarkers as well as for the analysis of effects of confounding variables such as medications[19–21]. In addition to regional structural measures, global measures such as the Person-Based-Similarity-Index (PBSI)[15,22] have been applied for example to reveal higher divergence of general cortical thickness, surface area and subcortical volume in individuals at high risk for psychosis[17]. Against this backdrop, our meta-analysis study investigated a variety of MRI-based brain measures, both for gray and white matter structures and both at global and regional levels, to enable a comprehensive, multimodal assessment of neuroanatomical heterogeneity in schizophrenia. To attenuate limitations of individual studies with small sample size and to support the replicability of our findings, multimodal variability was explored using Meta- and Mega-analysis of a large dataset from the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium[13,23].

Methods

Participants

The ENIGMA dataset comprised neuroimaging data from 22 sites, including 15 sites with individual-level data and 7 sites with group-level data. Sites with individual-level data provided cortical, subcortical and white matter measures for individual schizophrenia patients (SZ) and healthy controls (HC), while sites with group-level data provided mean and standard deviation of respective measures across SZ and HC. The dataset included 6138 individuals for cortical thickness (CT), 6138 for cortical surface area (SA), 5701 for cortical folding index (FI), 6139 for subcortical volume (SV) and 2636 individuals for white matter measure fractional anisotropy (FA). Prior to data collection, each site obtained ethics committee approval, and participants provided informed consent or assent prior to participation.

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MRI processing

Neuroimaging data were processed according to the standardised ENIGMA protocol(http://enigma.ini.usc.edu/protocols/imaging-protocols/). Motion correction (DTI analysis), automated Talairach transformation, skull stripping, segmentation of the subcortical white and gray matter volumetric structures as well as intensity normalisation were incorporated by automated Freesurfer pipelines[24–31]. Preprocessing procedures generated values of fractional anisotropy (FA) for white matter labels, values of subcortical volumes (SV) as well as values of cortical thickness (CT), surface area (SA) and folding index (FI) for cortical regions according to the Desikan-Killiany atlas[32]. As part of the ENIGMA quality control procedure, outliers (± 2 SD from the mean) were identified and all images were visually inspected to remove poorly segmented regions. These quality control procedures led to minor fluctuation in sample size for each region of interest (ROI). The application of this protocol finally yielded 68 cortical ROIs, 18 subcortical ROIs and 63 DTI ROIs. Subjects younger than 18 years or older than 65 years were discarded from further analysis.

Statistical analysis

Variability ratio: Statistical analyses were performed in R version 4.2.0 and Python version 3.9.16. Variability ratio (VR) was computed and visualized as forest plots in R using the packages metafor and tidyverse. In order to compare variability in regional neuroanatomical measures between schizophrenia patients and healthy controls, the natural logarithm of VR was calculated for each region of interest (ROI) according to the following formula:

$$ln(\frac{\sigma_{SZ}}{\sigma_{HC}}) = ln(\frac{SD_{SZ}}{SD_{HC}}) + \frac{1}{2(n_{SZ}-1)} - \frac{1}{2(n_{HC}-1)}$$

where σ is the unbiased estimate of the standard deviation, SD the reported sample standard deviation and n the sample size for the respective group. The results of the variability ratio analysis were summarized in forest plots which exhibit the VR with 95% confidence intervals across all ROIs for a given measure (CT, SA, FI, FA and SV). For the forest plots, ln(VR) values were back-transformed into a linear scale (VR) to facilitate interpretation: VR of 1 indicates equal variability in neuroanatomical measures between schizophrenia patients and healthy controls, while VR > 1 indicates greater and VR < 1 lower variability in schizophrenia patients compared to controls, respectively. Brain surface plots in which the variability ratio for CT, SA, FI, FA and SV is illustrated with color-coded z-values were generated in Python, using the libraries mayavi, nibabel, surfer and matplotlib.

Coefficient of variation ratio: In biological systems, variance usually scales with mean such that larger mean values are coupled with larger variance[33]. For a given structure and measure, a between-group difference in variability could be therefore driven by a between-group difference in mean. For each measure, we therefore also investigated how mean and standard deviation (SD) differences between patients and controls vary across sites. While the majority of cortical, subcortical and white matter regions showed correlations between mean and SD differences close to zero, some regions showed moderate positive correlations (**Supplementary Fig. 1**). Even though there were also a few regions with negative correlations between mean and SD differences, the magnitude of these negative correlations were comparably low (**Supplementary Fig. 2**). To assess a potential impact of correlations between mean and SD on our variability ratio results, we additionally computed the coefficient of variation ratio (CVR) which incorporates between-group differences in mean to quantify between-group differences in variability[7]:

$$ln(\frac{\frac{\sigma_{SZ}}{\bar{x}_{SZ}}}{\frac{\sigma_{HC}}{\bar{x}_{HC}}}) = ln(\frac{\frac{SD_{SZ}}{\bar{x}_{SZ}}}{\frac{SD_{HC}}{\bar{x}_{HC}}}) + \frac{1}{2(n_{SZ}-1)} - \frac{1}{2(n_{HC}-1)}$$

where $\bar{x}$ is the mean for the respective group. As for VR, the CVR analysis was illustrated in forest plots, ln(CVR) values in the forest plots were back-transformed into a linear scale and brain surface plots with color-coded CVR-z-values were generated.

Person-based similarity index: In addition to the region-specific VR and CVR analyses, we calculated the person-based similarity index (PBSI) to explore between-group differences of variability for a given measure across brain regions[16,22]. Separately for the brain measures CT, SA, FI, FA and SV, the PBSI was computed for the patient and control group according to the following formula:

$$PBSI_i = \frac{1}{N-1} \sum_{i \neq j} cor(y_i, y_j)$$

For $j \neq i$, the PBSI of the ith participant is the mean Spearman correlation between their brain measure y_i and the brain measure y_j of any other participant of the same group with N individuals. For a given participant i, y_i represents a vector in which all of their values for a given measure (e.g. CT) are concatenated. With regard to a given brain measure, the PBSI score of each participant therefore indicates their similarity to all other members of the same group (PBSI scores closer to 1 indicate higher similarity). The PBSI scores for CT, SA,

FI, SV and FA were then compared between schizophrenia patients and controls using a Mann-Whitney *U* test with Bonferroni correction.

Results

Cortical thickness

Compared with controls, the schizophrenia group exhibited greater variability in bilateral inferior, middle and superior temporal regions as well as in bilateral superiorfrontal regions. From these frontotemporal regions, the largest effect sizes were found in the right middle (VR = 1.19, 95% CI: 1.08 - 1.30) and left superior temporal areas (VR = 1.16, 95% CI: 1.10 - 1.22). Unilaterally, the schizophrenia group demonstrated greater variability in the left supramarginal region (VR = 1.11, 95% CI: 1.03 - 1.19), in the right pars orbitalis region (VR = 1.07, 95% CI: 1.01 - 1.13), in the left fusiform region (VR = 1.09, 95% CI: 1.01 - 1.17) as well as in the right precentral region (VR = 1.10, 95% CI: 1.01 - 1.21). In comparison to individuals with schizophrenia, healthy controls did not show significantly higher variability in cortical thickness for any cortical region (**Fig. 1**). When the coefficient of variation ratio was computed instead of the variability ratio, all regions with higher heterogeneity in schizophrenia remained significantly different from controls, and there were still no regions with higher heterogeneity in controls (**Supplementary Fig. 3**).

Cortical surface area

Compared with controls, greater variability in the schizophrenia group was particularly evident in the following regions: Right superiortemporal region (VR = 1.12, 95% CI: 1.02 - 1.23), cortical areas around the right superior temporal sulcus (VR = 1.11, 95% CI: 1.03 - 1.20) and right supramarginal region (VR = 1.11, 95% CI: 1.04 - 1.18). Moreover, greater variability in the schizophrenia group was found in the left postcentral region (VR = 1.09, 95% CI: 1.01 - 1.17), in the right medial orbitofrontal region (VR = 1.09, 95% CI: 1.02 - 1.15), in the left superiorparietal region (VR = 1.07, 95% CI: 1.01 - 1.14), in the right middle temporal region (VR = 1.09, 95% CI: 1.01 - 1.17) as well as in the left precuneus (VR = 1.06, 95% CI: 1.01 - 1.11) and right lingual region (VR = 1.10, 95% CI: 1.01 - 1.19). Bilaterally, the superior frontal and transverse temporal areas showed higher variability in comparison to healthy controls (left superior frontal region: VR = 1.07, 95% CI: 1.01 - 1.12; right superior frontal region: VR = 1.06, 95% CI: 1.01 - 1.12; left transverse temporal region: VR = 1.07, 95% CI: 1.02 - 1.13; right transverse temporal region: VR = 1.08, 95% CI: 1.01 - 1.16 (**Fig. 2**). When compared to the schizophrenia group, the control group did not exhibit higher variability of the cortical surface area in any cortical region (**Fig. 2**). When we computed the coefficient of variation instead of the variability ratio, all regions with higher variability in schizophrenia remained significantly different from controls, and again no regions

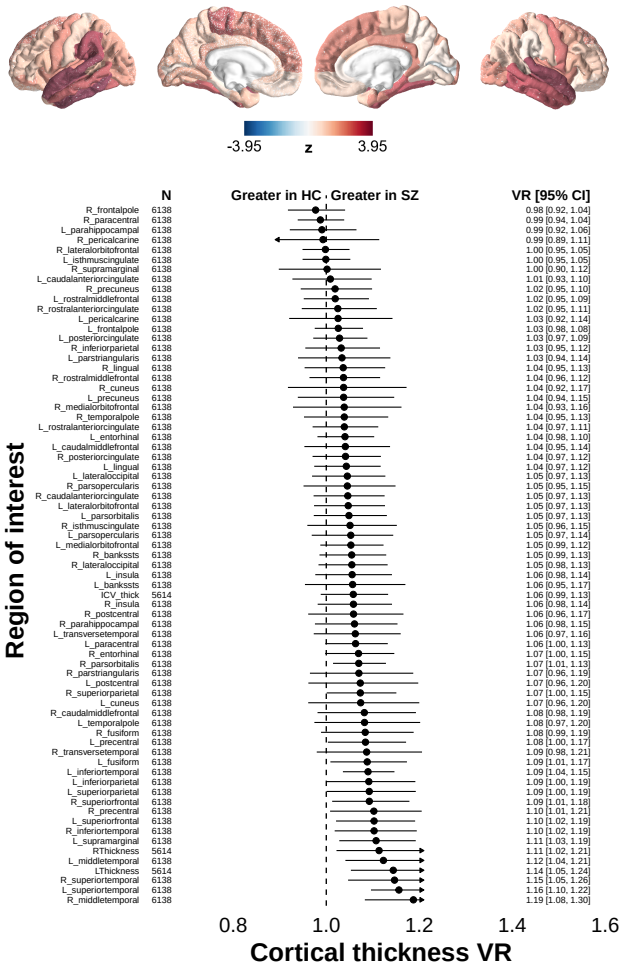

Figure 1. Variability ratio of cortical thickness. Lower panel: Variability ratio (VR) effect sizes for individuals with schizophrenia (SZ) vs. healthy controls (HC) are shown for different cortical regions and on a linear scale, statistically controlling for age and gender. Upper panel: VR effect sizes are projected onto the brain surface and color-coded as z-values. In these cortical maps, areas with higher VRs in patients appear in gradients of red, and areas with higher VRs in controls appear in gradients of blue. CI: Confidence Interval. Independent of the applied variability measure (variability ratio vs. coefficient of variation ratio), higher heterogeneity in schizophrenia was observed for the following regions: Bilateral superior, middle and inferior temporal region, bilateral superior frontal region, left supramarginal and fusiform region as well as right pars orbitalis and precentral region.

showed higher variability in controls (**Supplementary Fig. 4**).

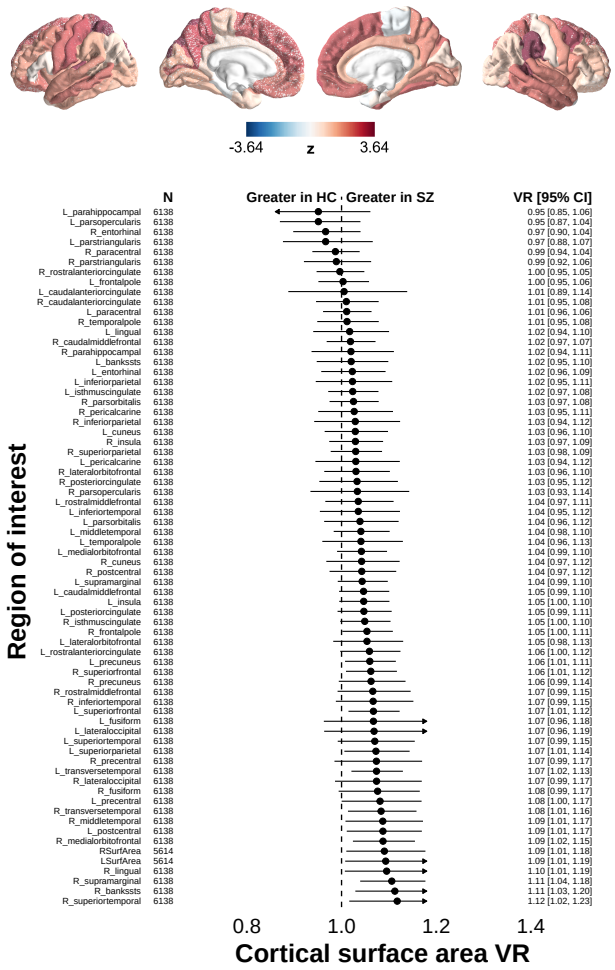

Figure 2. Variability ratio for cortical surface area. Same conventions as for Fig. 1. Higher heterogeneity in schizophrenia was observed for the following regions, irrespective of the deployed variability measure: Bilateral superiorfrontal and transverse temporal regions, cortical areas around the right superior temporal sulcus, right superiortemporal region, right supramarginal region, left postcentral region, right medialorbitofrontal region, left superiorparietal region, left precuneus, right middle temporal region and right lingual region.

Cortical folding index

The schizophrenia group exhibited higher heterogeneity than controls in the right inferiortemporal region (VR = 1.33, 95% CI: 1.10 - 1.60) and lower heterogeneity in the left parahippocampal region (VR = 0.72, 95% CI: 0.56 - 0.91, **Fig. 3**). Higher heterogeneity of the right inferiortemporal region as well as higher homogeneity in the left parahippocampal region in schizophrenia were preserved when the coefficient of variation ratio was examined instead of the variability ratio (**Supplementary Fig. 5**). Of all gray matter measures, only the cortical folding index showed higher regional homogeneity in addition to higher regional heterogeneity in individuals with schizophrenia compared to healthy controls.

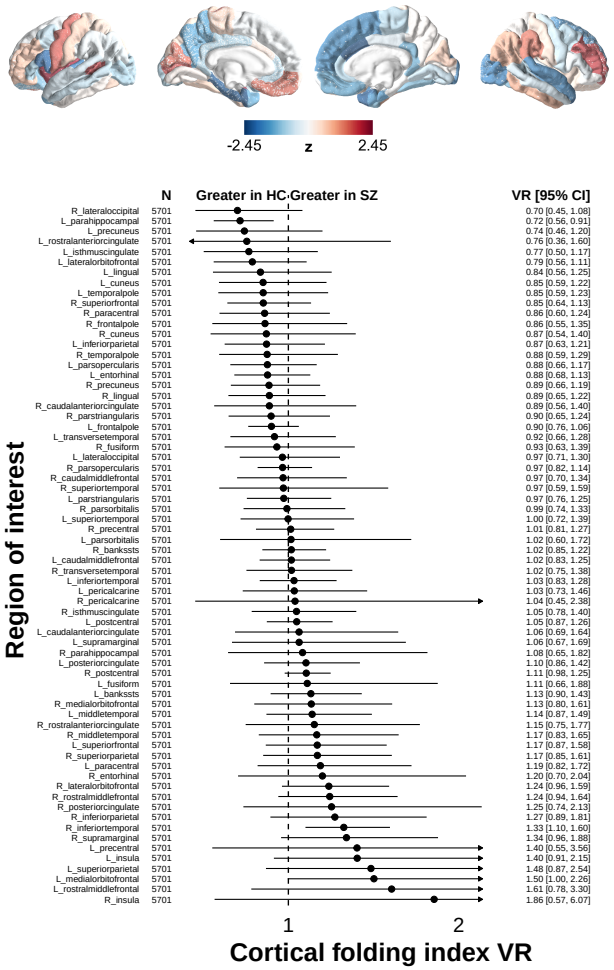

Figure 3. Variability ratio for cortical folding index. Same conventions as for Fig. 1. Irrespective of the applied variability measure, schizophrenia patients exhibited higher heterogeneity in the right inferiortemporal region, but lower heterogeneity in the left parahippocampal area.

Subcortical volume

Bilaterally, the variability of the lateral ventricle and of the inferior lateral ventricle was distinctly higher in the schizophrenia group than in the control group. Among the ventricle measurements, the highest effect size was found in the left inferior lateral ventricle (VR = 1.43, 95% CI: 1.26 - 1.61, **Fig. 4**). Additionally, higher vari-

ability in the bilateral pallidum and putamen, and in the left nucleus accumbens, left caudate and right hippocampus were evident in the schizophrenia compared to the control group. Among these brain regions, the highest effect sizes were found for the left nucleus accumbens (VR = 1.13, 95% CI: 1.04 - 1.22) and the left pallidum (VR = 1.10, 95% CI: 1.04 - 1.17, **Fig. 4**). No subcortical region showed significantly higher heterogeneity in the control group (**Fig. 4**). When the coefficient of variation ratio was computed instead of the variability ratio, higher heterogeneity in schizophrenia was confirmed for all regions except for bilateral pallidum and putamen (**Supplementary Fig. 6**). As for the variability ratio, no subcortical region exhibited higher heterogeneity in controls when the coefficient of variation ratio was examined (**Supplementary Fig. 6**).

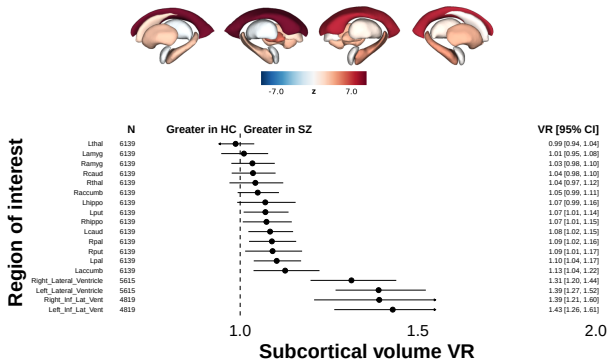

Figure 4. Variability ratio for subcortical volume. Same conventions as for Fig. 1. Lower panel: Variability ratio (VR) effect sizes are shown for subcortical volumes. Upper panel: VR effect sizes are projected onto respective subcortical structures and color-coded as z-values. In these subcortical maps, areas with higher VRs in patients appear in gradients of red, and areas with higher VRs in controls appear in gradients of blue. Independent of the applied variability measure, schizophrenia patients showed higher heterogeneity for lateral ventricles, left nucleus accumbens, left caudate and right hippocampus.

Fractional anisotropy

Variability of the superior fronto-occipital fasciculus was lower in the schizophrenia compared to the control group, on both the left (VR = 0.86, 95% CI: 0.78 - 0.94) and right side (VR = 0.85, 95% CI: 0.75 - 0.95, **Fig. 5**). In contrast, no white matter tract showed greater heterogeneity in variability ratio in individuals with schizophrenia compared to controls. When the coefficient of variation ratio was examined instead of the variability ratio lower bilateral heterogeneity of the superior fronto-occipital fasciculus in the schizophrenia compared to the control group remained significant (**Supplementary Fig. 7**), and several regions including the left uncinate fasciculus exhibited greater heterogeneity in the schizophrenia compared to the control group (CVR = 1.16, 95% CI: 1.01 - 1.33, **Supplementary Fig. 7**).

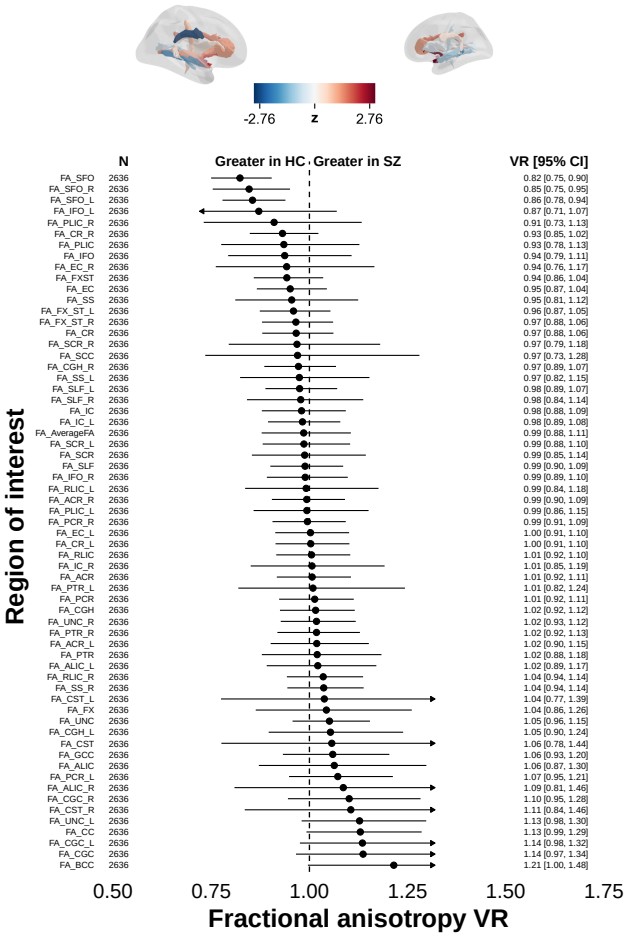

Figure 5. Variability ratio for fractional anisotropy. Same conventions as for Fig. 1. Lower panel: Variability ratio (VR) effect sizes are shown for fractional anisotropy (FA) of white matter structures. Upper panel: VR effect sizes are projected onto respective white matter structures and color-coded as z-values. In these maps, areas with higher VRs in patients appear in gradients of red, and areas with higher VRs in controls appear in gradients of blue. Irrespective of the deployed variability measure, higher homogeneity in schizophrenia was observed for the superior fronto-occipital fasciculus in both hemisperes.

Person-Based Similarity Index

At a global level, the Person-Based Similarity Index (PBSI) analysis revealed that heterogeneity of cortical thickness is similar for schizophrenia patients and

healthy controls (p = 4.891e-01, Mann-Whitney U test, Bonferroni-corrected). However, schizophrenia patients showed less heterogeneity (higher PBSI) in cortical surface area, subcortical volume and especially in the folding index compared to healthy controls (folding index: p = 2.123e-16; surface area: p = 4.972e-06; subcortical volume: p = 8.33e-06, Mann-Whitney U test, Bonferroni-corrected). On the other hand, individuals with schizophrenia exhibited higher heterogeneity (lower PBSI) in fractional anisotropy (p = 2.649e-09, Mann-Whitney U test, Bonferroni-corrected).

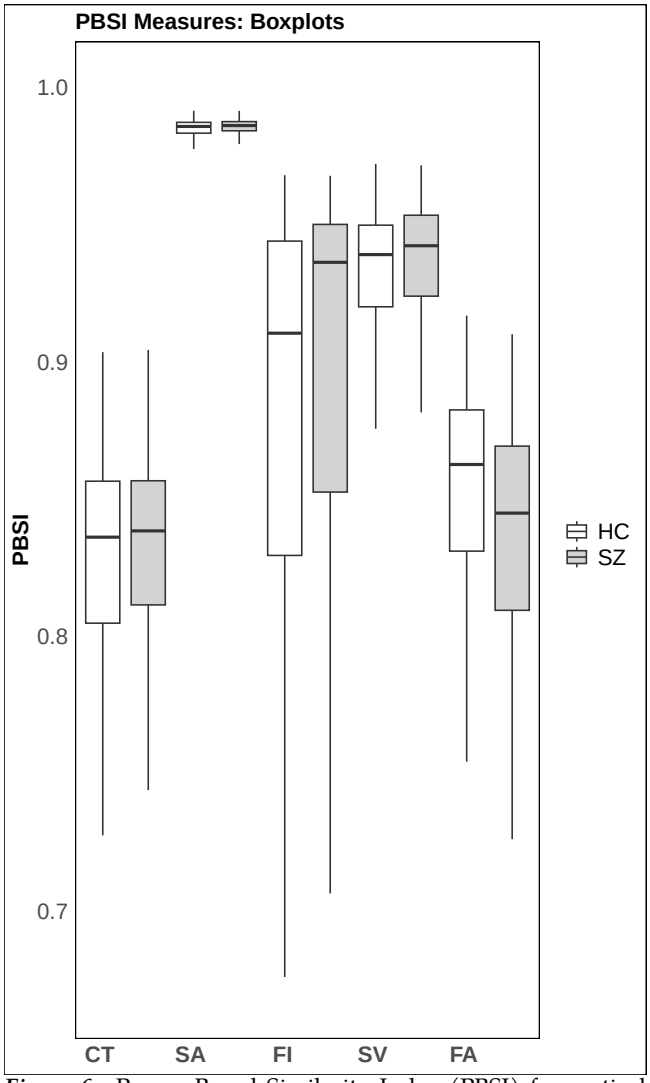

Figure 6. Person-Based Similarity Index (PBSI) for cortical thickness (CT), cortical surface area (SA), cortical folding Index (FI), subcortical volume (SV) and fractional anisotropy (FA).

Discussion

The results of this comprehensive meta-analysis afford an advance in the understanding of structural brain heterogeneity in schizophrenia, an aspect that has been insufficiently studied to date, yet holds significant implications for the identification of illness subtypes and informative biomarkers[7]. A strength of this study was the comprehensive heterogeneity assessment of multiple structural brain measures based on an ENIGMA Schizophrenia Working Group dataset, a substantial repository of MRI-based brain measures collected from various sites globally[11,12,23]. Different structural brain measures are thought to be influenced by separate sets of genes during different stages of development[34–39], and the multimodal assessment and comparison of structural brain measures is instrumental to disentangle their potentially different alteration in schizophrenia[13]. This study therefore explored and compared variability in cortical thickness, surface area, folding index, subcortical volume, and fractional anisotropy, allowing for a thorough assessment of regional and global variability. Moreover, the framework of the large ENIGMA dataset increases the robustness of the results and therefore the replicability of findings in psychiatry and neuroscience[23,40–44].

One of the key findings at the regional level is greater multimodal variability in schizophrenia for frontotemporal structures. While cortical surface area and folding index were more heterogeneous in a few temporal and frontal regions, higher variability of cortical thickness comprised widespread bilateral temporal areas in addition to some frontal regions. Thus, these results suggest that schizophrenia is associated with multimodal structural variability in different components of a frontotemporal network, thereby extending previous findings according to which schizophrenia patients show on average thinning of frontal and temporal regions[12,13,45,46]. A possibility would be that different subgroups exist that can be distinguished by different neuroanatomical correlates: While one subgroup may have structural irregularities in temporal rather than frontal regions, be it cortical thinning, folding abnormalities or a combination thereof, another subgroup may be characterized by the inverse structural pattern. In all cases, the result would likely be impaired frontotemporal interaction, a hallmark of psychotic disorders. At least with regard to mean-scaled variability, schizophrenia patients also showed more heterogeneity of fractional anisotropy in the left uncinate fasciculus which connects temporal with frontal regions. Structural deficits of the left uncinate fasciculus may therefore also contribute to aberrant frontotemporal interaction in a subset of patients. On the other hand, our

study also showed that gyrification of the left parahippocampal region is more homogeneous in schizophrenia compared to controls. Gyrification characteristics of the left parahippocampal region may therefore occur uniformly across potential subtypes and represent a central attribute of the disorder. Interestingly, a part of the left parahippocampal region has been recently shown to be thinner and associated with hallucinations in schizophrenia spectrum individuals[47]. In our study, greater variability was also observed with regard to the volume of the left nucleus accumbens and caudate, regions implicated in reward processing and goal-directed motor control, respectively[48,49]. Variability in these subcortical structures may be linked to the heterogeneity of negative and catatonic symptoms that differ substantially across schizophrenia individuals[50,51]. Overall, the largest effect sizes with regard to greater variability ratio were observed for the lateral ventricles in both hemispheres. Since ventricular enlargement is among the best established neurobiological findings in schizophrenia patients[7,11,52–55], it is notable that higher variability in schizophrenia remained robust when the coefficient of variation with accounting for group differences in mean was used instead of the variability ratio. In contrast, a previous study comparing first-episode schizophrenia with healthy controls showed higher variability of lateral ventricles only for the variability ratio, but not for the coefficient of variation[7]. This difference with our study could be related to the longer illness duration in our study, which included individuals with chronic schizophrenia.

Notably, at a global level, a part of our findings challenges the prevailing view of greater brain heterogeneity in schizophrenia in comparison to healthy individuals[7,14,15,18]. The Person-Based Similarity Index (PBSI) analysis[16,17] surprisingly revealed that individuals with schizophrenia are characterized by a significantly higher homogeneity of especially the folding index, a measure related to the gyrification of the brain. This observation supports the view that certain gyrification characteristics could represent a potential core feature of schizophrenia[39]. Previous studies demonstrated that adolescent and young adult individuals with schizophrenia typically feature stronger gyrification in widespread regions compared with healthy controls[56–66], possibly related to overexpression of fibroblast growth factor-2 gene in the dorsolateral prefrontal cortex and further molecular-level aberrations in schizophrenia[39,67]. While gyrification patterns are determined early in development[68], it is plausible that certain folding characteristics might render the brain more susceptible to the later development of schizophrenia, thus presenting a potential predictive biomarker for the disorder. In line with this view, previous studies with limited sample size have shown that schizophrenia is associated with aberrant gyrification characteristics in specific cortical regions which are in part related to particular symptoms and deficits of the disorder[58,59,62,63,65,69–73]. For instance, the severity of positive symptoms in schizophrenia has been associated with gyrification in the right frontal and temporolimbic region[63,64]. Similarly, fronto-temporolimbic disconnectivity in schizophrenia, which is related to delusions, hallucinations and disorganization symptoms[74,75], has been proposed to be linked with local gyrification patterns[39]. Previous studies also compared PBSI scores for cortical thickness, subcortical volume and cortical surface area between schizophrenia or first episode psychosis patients and healthy controls[15,16]. While some results are in line with ours, e.g. higher cortical surface area PBSI scores in psychosis patients[16], others differ, e.g. higher cortical thickness PBSI scores in controls[15,16] instead of no significant difference in our study. Potential reasons for deviations from our results are the far more limited sample size in both studies as well as the shorter illness duration of first-episode psychosis patients in Antoniades et al[16]. However, the PBSI analysis also revealed that individuals with schizophrenia exhibit greater global heterogeneity than controls with regard to fractional anisotropy, suggesting that different white matter abnormalities contribute to schizophrenia subtypes. White matter pathology has been associated with functional dysconnectivity in schizophrenia[76], and resulting impairment of neural network synchrony may underlie schizophrenia symptoms[77,78].

Despite the findings, this study is not without limitations. Not all data were individual-level data, which could potentially introduce bias. Moreover, not all measures were collected at all sites, and in particular the amount of fractional anisotropy data was lower in comparison to other measures. In addition, the parcellation of gray and white matter networks was coarse, and a more fine-grained parcellation in future studies may lead to more differentiated insights of structural variability.

In conclusion, this study provides novel insights into the heterogeneity of structural brain measures in schizophrenia. In light of increasing interest in schizophrenia subtypes and corresponding neurobiological characteristics[79–91], high variability in certain neuroanatomical structures may point to potential avenues for the development of more targeted treatment strategies. On the other hand, low variability of structural features such as gyrification may substantiate core features of schizophrenia that are shared across illness

subtypes.
Our results hold potential to guide future research efforts and pave the way for precision medicine approaches in schizophrenia. Ultimately, this study underscores the critical role of variability in our understanding of complex disorders like schizophrenia, a perspective that is essential for a more holistic approach to its neurobiology.

Acknowledgements

More information will follow.

Funding/Support

PH is supported by a NARSAD grant from the Brain & Behavior Research Foundation (28445) and by a Research Grant from the Novartis Foundation (20A058). The Australian Schizophrenia Research Bank (ASRB) was supported by the Australian National Health and Medical Research Council (NHMRC; Enabling Grant, ID 386500), the Pratt Foundation, Ramsay Health Care, the Viertel Charitable Foundation and the Schizophrenia Research Institute. Chief Investigators for ASRB were V. Carr, U. Schall, R. Scott, A. Jablensky, B. Mowry, P. Michie, S. Catts, F. Henskens, C. Pantelis. We would like to acknowledge Carmel Loughland, Kathryn McCabe, and Jason Bridge for management and quality control of data obtained from the ASRB. The Imaging Genetics in Psychosis (IGP) study was supported by Project Grants from the Australian National Health and Medical research Council (NHMRC; APP630471 and APP1081603), and the Macquarie University's ARC Centre of Excellence in Cognition and its Disorders (CE110001021).

Conflict of interest

No disclosures were reported.

Author contributions

WO co-analyzed and interpreted the data, co-performed the statistical analysis, wrote the first draft of the manuscript and revised the manuscript. SF and FR co-analyzed the data, and SF additionally took care of data reception and management. PH initiated, conceptualized and supervised the study, co-analyzed the data and co-performed the statistical analysis. All other authors provided a part of the dataset and refined the manuscript. All authors approved the final version of the manuscript.

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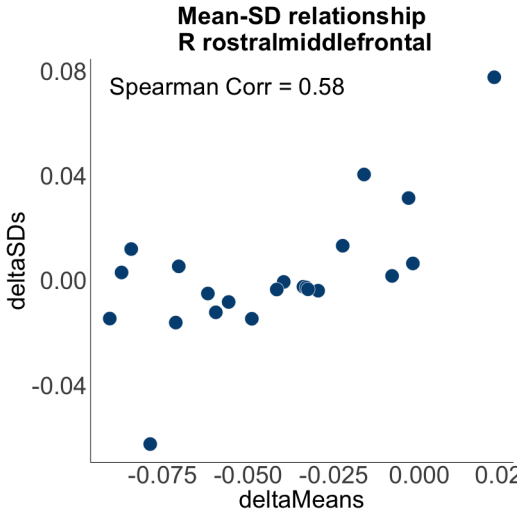
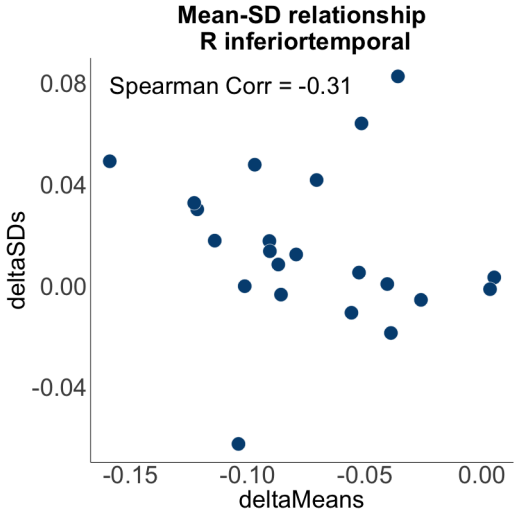
Supplementary Information

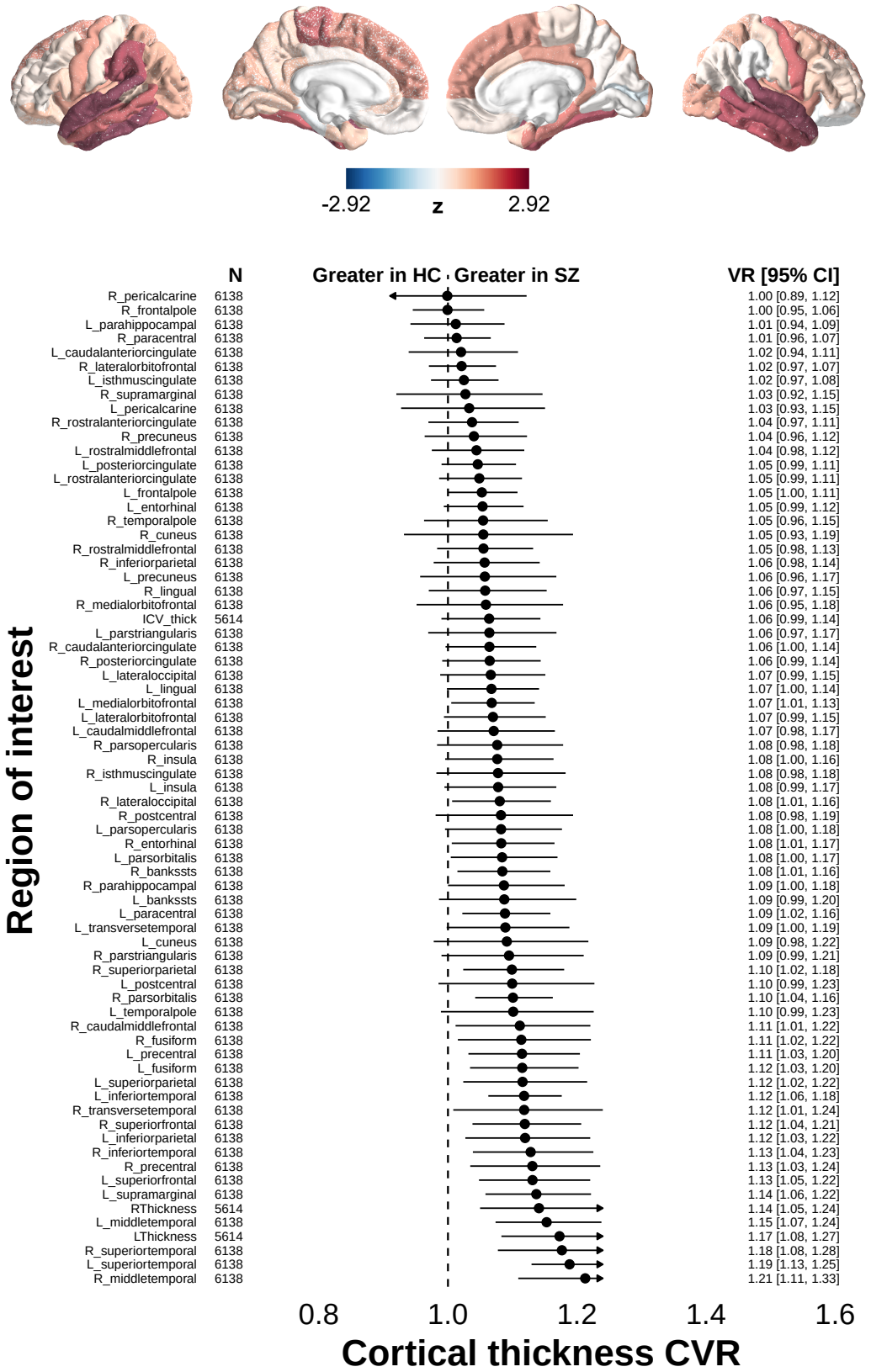
Supplementary Figures



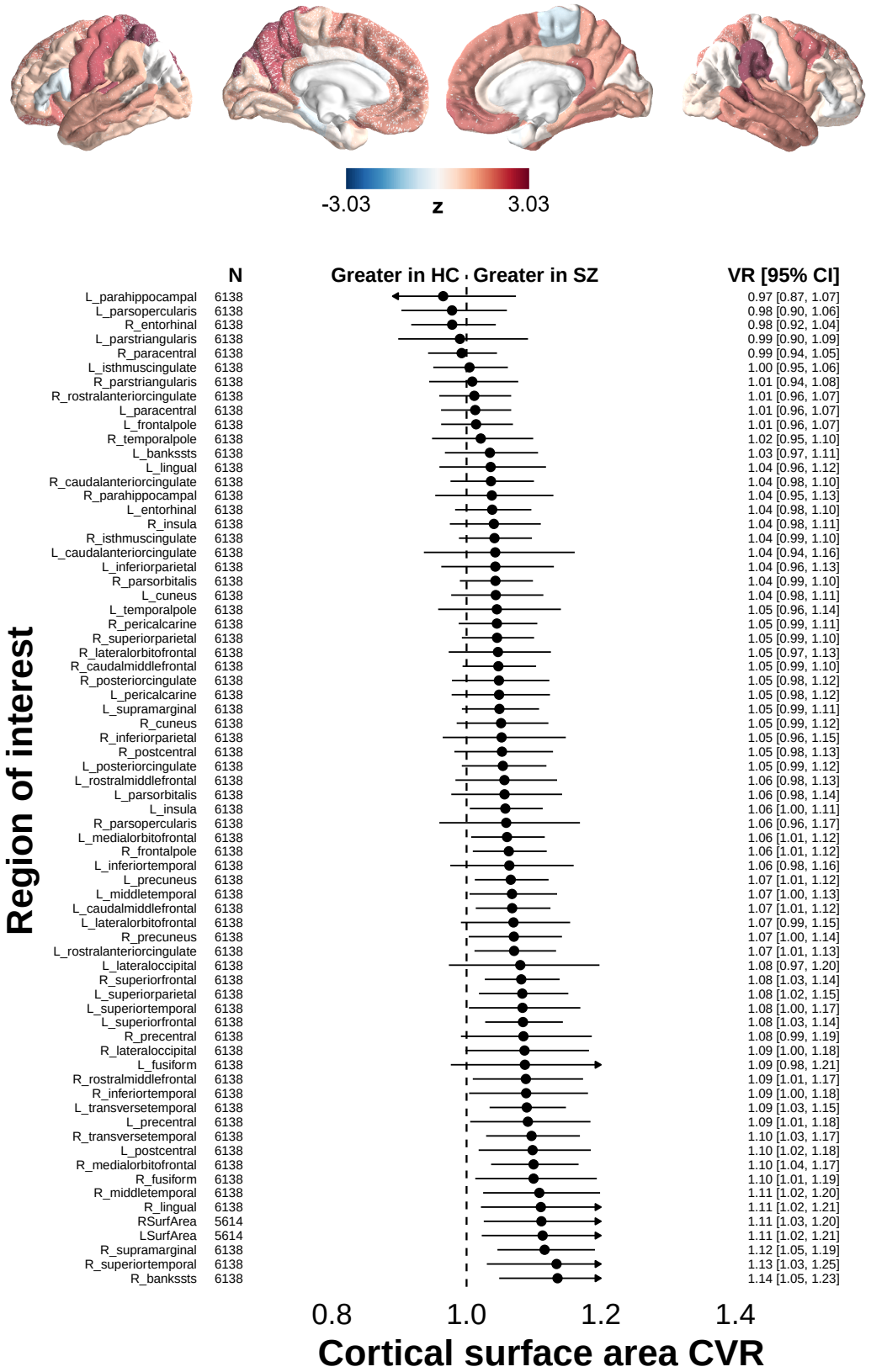
Supplementary Figure 1. Relationship between mean and standard deviation across sites - cortical thickness of the right rostral middle frontal cortex (R rostralmiddlefrontal). Differences of standard deviations (deltaSDs) are plotted against differences of means (deltaMeans). Difference values were obtained by substracting Mean/SD of controls from Mean/SD of patients. For cortical thickness, the right rostral middle frontal cortex showed the highest positive correlation between deltaMeans and deltaSDs.



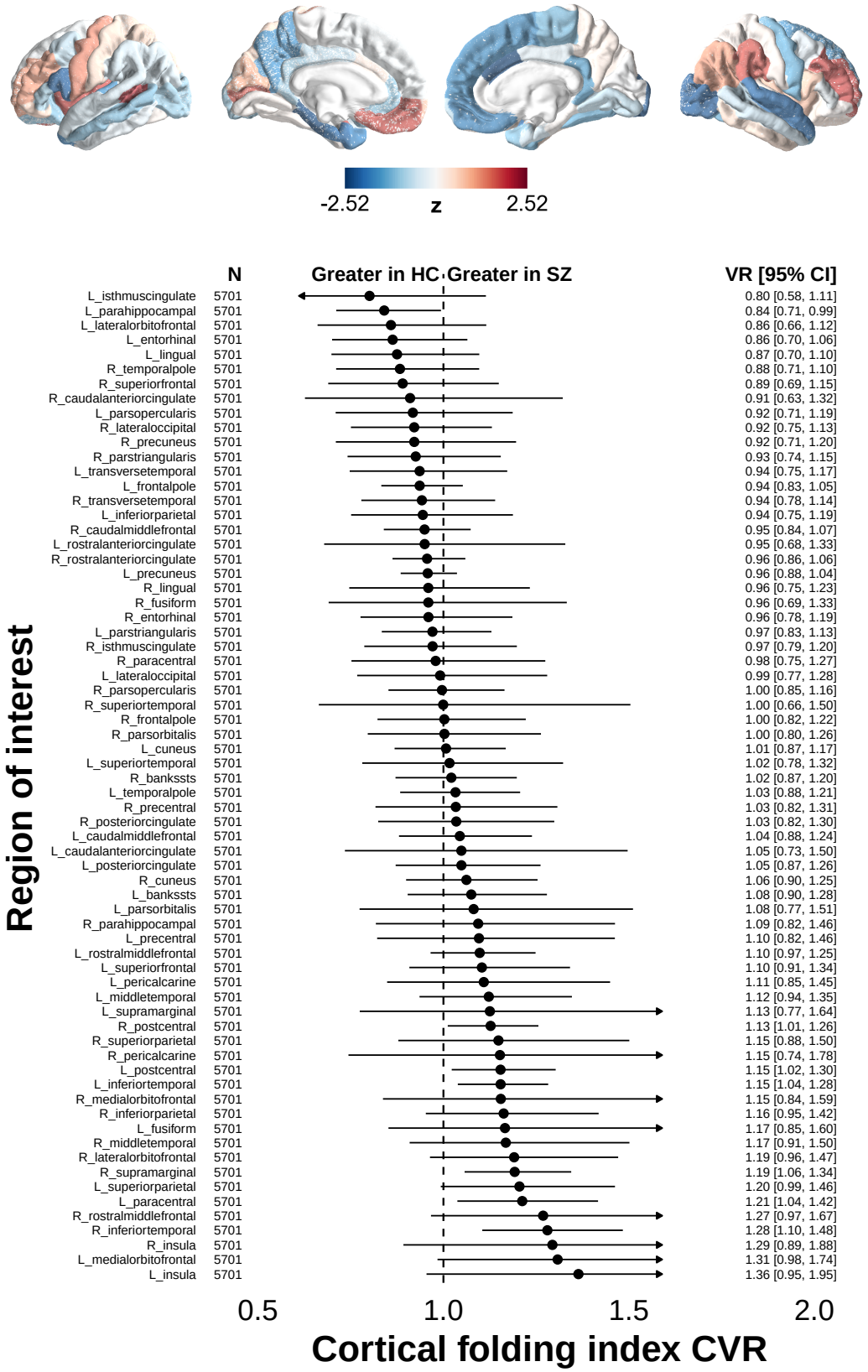
Supplementary Figure 2. Relationship between mean and standard deviation across sites - cortical thickness of the right inferior temporal cortex (R inferiortemporal). Same conventions as for Supplementary Figure 1. For cortical thickness, the right inferior temporal cortex showed the highest negative correlation between deltaMeans and delta SDs.



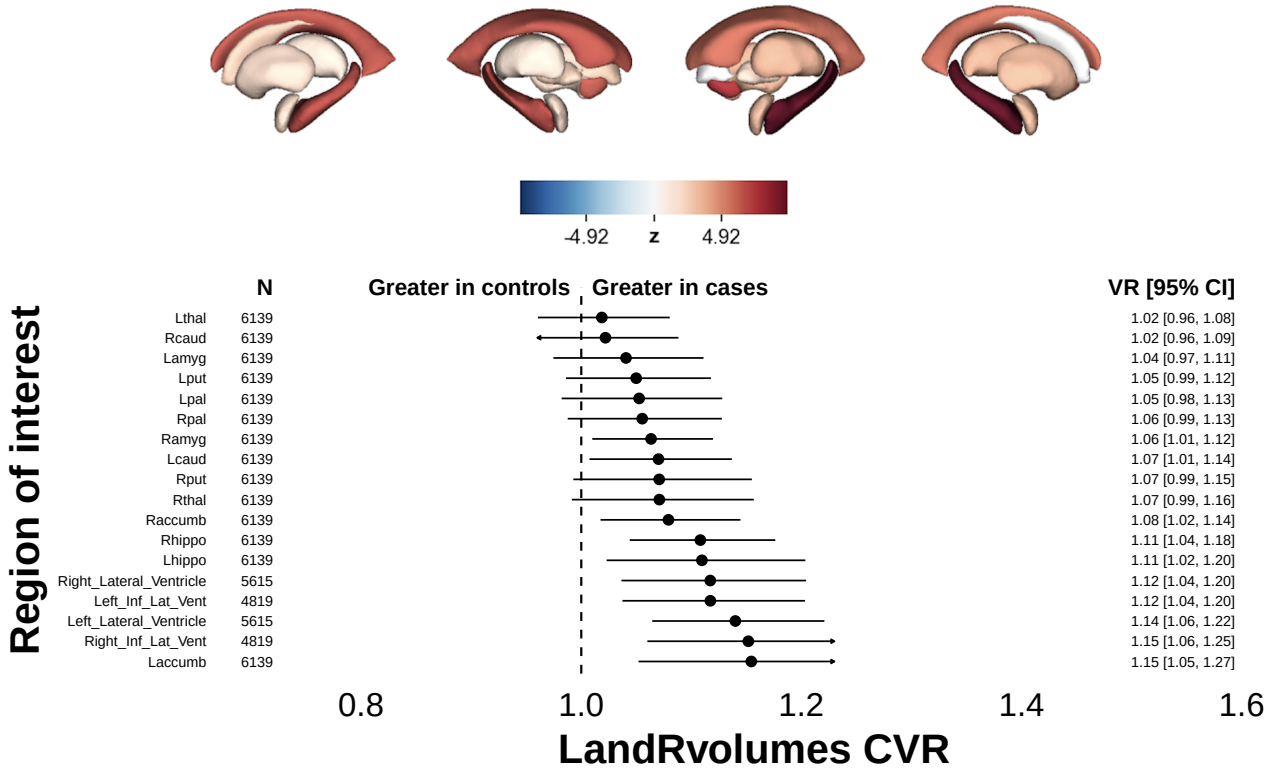
Supplementary Figure 3. Coefficient of Variation ratio for cortical thickness. Lower panel: Coefficient of variation ratio (CVR) effect sizes for schizophrenia patients (SZ) vs. healthy controls (HC) are shown for different cortical regions and on a linear scale, statistically controlling for age and gender. Upper panel: CVR effect sizes are projected onto the brain surface and color-coded as z-values. In these cortical maps, areas with higher CVRs in patients appear in gradients of red, and areas with higher CVRs in controls appear in gradients of blue. CI: Confidence Interval.



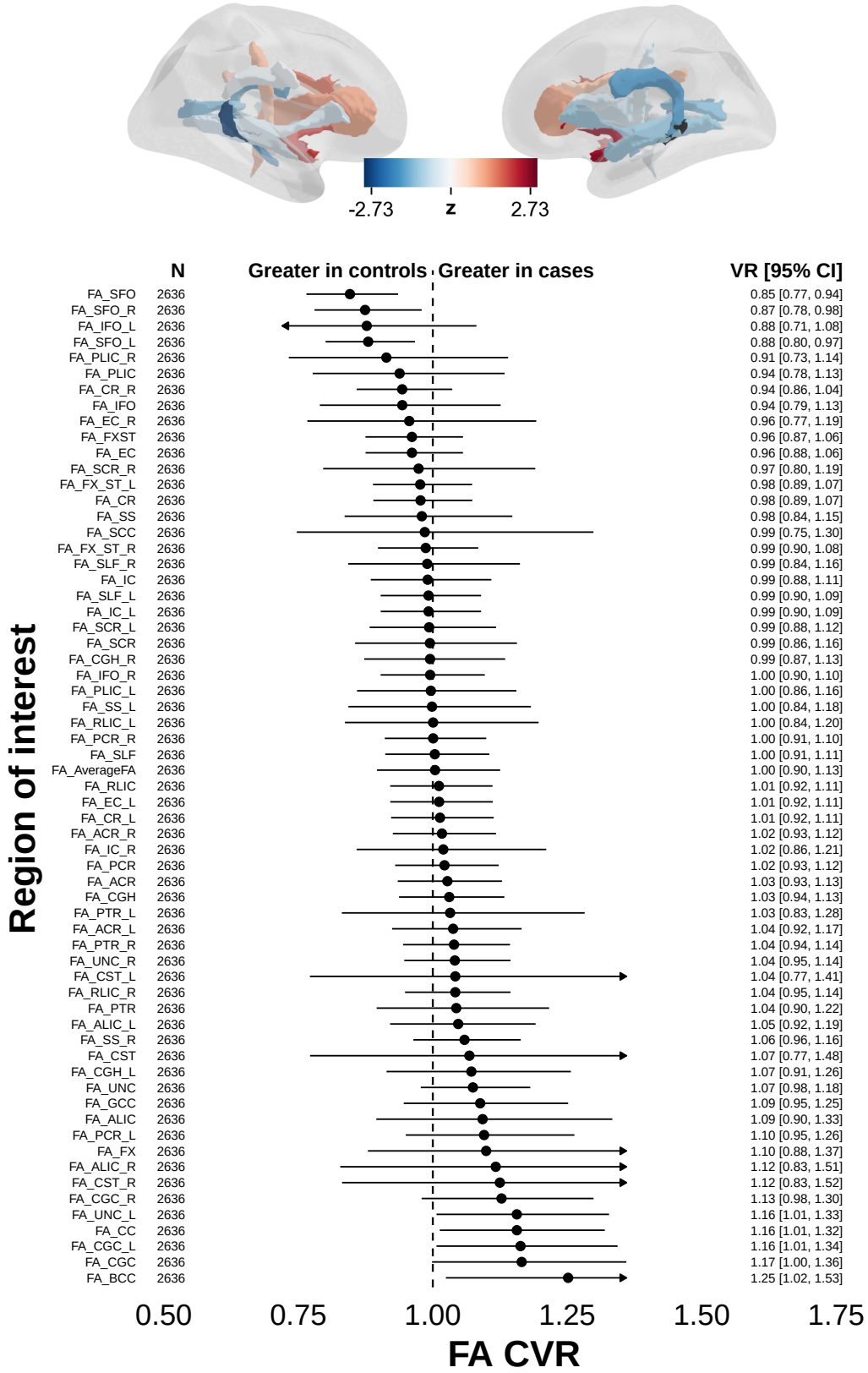
Supplementary Figure 4. Coefficient of Variation ratio for cortical surface area. Same conventions as for Supplementary Fig. 3.



Supplementary Figure 5. Coefficient of Variation ratio for cortical folding index. Same conventions as for supplementary Fig. 3.



Supplementary Figure 6. Coefficient of Variation ratio for subcortical volume. Same conventions as for supplementary Fig. 3. Lower panel: Coefficient of Variation ratio (CVR) effect sizes are shown for subcortical volumes on the left and right side (LandRvolumes). Upper panel: CVR effect sizes are projected onto respective subcortical structures and color-coded as z-values. In these subcortical maps, areas with higher CVRs in patients appear in gradients of red, and areas with higher CVRs in controls appear in gradients of blue.



Supplementary Figure 7. Coefficient of Variation ratio for fractional anisotropy. Same conventions as for supplementary Fig. 3. Lower panel: Coefficient of Variation ratio (CVR) effect sizes are shown for fractional anisotropy (FA) of white matter structures. Upper panel: CVR effect sizes are projected onto respective white matter structures and color-coded as z-values. In these maps, areas with higher CVRs in patients appear in gradients of red, and areas with higher CVRs in controls appear in gradients of blue.

Supplementary Table 1: Sample demographics

Site	Level	Patients (T1)	Controls (T1)	Patients (DTI)	Controls (DTI)
ASRB	Group	263	166	326	197
CASSI	Individual	58	65	0	0
CIAM	Individual	19	31	12	25
COBRE	Individual	73	70	73	70
ESO	Individual	40	40	0	0
FBIRN	Group	184	174	145	144
FIDMAG	Individual	57	57	57	57
HIULONG	Individual	245	88	245	88
IGP	Group	68	71	0	0
IMH	Individual	178	111	0	0
IRCCS	Individual	172	116	78	144
MPRC	Individual	230	270	0	0
OLIN	Individual	135	389	0	0
OSAKA1	Group	142	402	0	0
OSAKA2	Group	76	237	63	229
OSAKA3	Group	82	413	82	327
PUK	Individual	60	28	0	0
SWIFT	Individual	24	14	0	0
TOP	Individual	352	756	170	582
UCISZ	Individual	26	29	0	0
UNINA	Individual	49	55	49	55
Paris	Group	33	55	0	0