Connectome architecture shapes large-scale cortical reorganization in schizophrenia: a worldwide ENIGMA study

Foivos Georgiadis[1]^, Sara Larivière[2],David Glahn[3], L. Elliot Hong[4], Peter Kochunov[4], Bryan Mowry[5], Carmel Loughland[6], Christos Pantelis[7], Frans A. Henskens[8], Melissa J. Green[9], Murray J. Cairns[10], Patricia T Michie[11], Paul E. Rasser[12], Paul Tooney[10], Rodney J. Scott[10], Stanley Catts[13], Ulrich Schall[14], Vaughan Carr[15], Yann Quidé[9], Axel Krug[16], Frederike Stein[17], Igor Nenadić[18], Katharina Brosch[17], Tilo Kircher[17], Raquel Gur[19], Ruben Gur[19], Theodore D. Satterthwaite[19], Andriana Karuk[20], Edith Pomarol-Clotet[20], Joaquim Radua[21], Paola Fuentes-Claramonte[20], Raymond Salvador[20], Gianfranco Spalletta[22], Aristotle Voineskos[10], Kang Sim[23], Benedicto Crespo-Facorro[24], Diana Tordesillas Gutiérrez[25], Stefan Ehrlich[26], Nicolas Crossley[27], Dominik Grotegerd[28], Jonathan Repple[28], Rebekka Lencer[28], Udo Dannlowski[28], Vince Calhoun[29], Caroline Demro[30], Ian S. Ramsay[31], Scott R. Sponheim[32], Andre Schmidt[33], Stefan Borgwardt[34], Alexander S. Tomyshev[35], Irina Lebedeva[35], Cyril Hoschl[36], Filip Spaniel[36], Adrian Preda[37], Dana Nguyen[38], Anne Uhlmann[39], Dan J Stein[40], Fleur M Howells[40], Henk S. Temmingh[40], Scott . Sponheim[32], Ana M. Diaz Zuluaga[41], Carlos López Jaramillo[41], Felice Iasevoli[42], Ellen Ji[1], Stephanie Homan[1], Wolfgang Omlor[1], Philipp Homan[1], Stefan Kaiser[43], Erich Seifritz[1], Bratislav Misic[2], Paul Thompson[44], Theo G.M. van Erp[37], Jessica Turner[29], Boris Bernhardt[2]*, Matthias Kirschner[43]*^

^Corresponding authors

*These authors contributed equally to the work

1. Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital University of Zurich, Switzerland
2. McGill University, Montreal Neurological Institute
3. Department of Psychiatry, Harvard Medical School, Boston, MA USA
4. Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine
5. Queensland Brain Institute, The University of Queensland, QLD Australia
6. School of Medicine and Public Health, University of Newcastle
7. Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne, Carlton South, Victoria, Australia
8. School of Medicine and Public Health, University of Newcastle, Australia

9. School of Clinical Medicine, Discipline of Psychiatry and Mental Health, UNSW Sydney, Sydney, NSW, Australia

10. School of Biomedical Science and Pharmacy, University of Newcastle, NSW Australia

11. School of Psychological Sciences, University of Newcastle, NSW Australia

12. School of Medicine and Public Health, College of Health, Medicine, and Wellbeing, The University of Newcastle, Callaghan, NSW, Australia

13. Faculty of Medicine, University of Queensland, QLD Australia

14. Hunter Medical Research Institute, Newcastle, Australia

15. School of Clinical Medicine, Discipline of Psychiatry, UNSW Sydney, Sydney, NSW, Australia

16. University Hospital Bonn, Department of Psychiatry and Psychotherapy, Venusberg-Campus 1, 53127 Bonn, Germany

17. Department of Psychiatry, University of Marburg, Rudolf Bultmann Str. 8, 35039 Marburg, Germany

18. Dept. of Psychiatry and Psychotherapy, Philipps-University Marburg, Marburg, Germany

19. University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

20. FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain

21. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

22. Santa Lucia Foundation IRCCS, Rome

23. West Region, Institute of Mental Health, Singapore

24. Hospital Universitario Virgen del Rocío, IBiS-CSIC, Universidad de Sevilla, Seville, Spain

25. Department of Radiology, Marqués de Valdecilla University Hospital, Valdecilla Biomedical Research Institute IDIVAL, Santander, Spain.

26. Division of Psychological & Social Medicine and Developmental Neurosciences, Technischen Universität Dresden, Faculty of Medicine, University Hospital C.G. Carus, Germany

27. Department of Psychiatry, Pontificia Universidad Católica de Chile

28. Institute for Translational Psychiatry, University of Münster, Germany

29. Tri-Institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State, Georgia Tech, Emory, Atlanta, GA, USA
30. University of Minnesota Department of Psychology
31. University of Minnesota Department of Psychiatry & Behavioral Sciences
32. Minneapolis VA Health Care System
33. University of Basel, Department of Psychiatry, Basel, Switzerland
34. Department of Psychiatr, University of Lübeck. Germany
35. Mental Health Research Center, Moscow, Russian Federation
36. National Institute of Mental Health, Topolova 748, 250 67 Klecany, Czech Republic.
37. Department of Psychiatry and Human Behavior, University of California Irvine, CA, USA
38. Department of Pediatric Neurology University of California Irvine, CA, USA
39. Department of child and adolescent psychiatry, TU Dresden, Germany
40. Department of Psychiatry and Mental Health, University of Cape Town, South Africa
41. Research Group in Psychiatry, Department of Psychiatry, School of Medicine, Universidad de Antioquia, Medellin, Colombia
42. University of Naples, Department of Neuroscience
43. Division of Adult Psychiatry, Department of Psychiatry, Geneva University Hospitals, Geneva, Switzerland
44. Imaging Genetics Center, Stevens Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Corresponding Authors: Foivos Georgiadis, e-mail: foivos.georgiadis@pukzh.ch; Matthias Kirschner, e-mail: matthias.kirschner@unige.ch

Abstract

Objective: Schizophrenia is associated with widespread brain-morphological alterations, believed to be shaped by the underlying connectome architecture. This study tests whether large-scale structural reorganization in schizophrenia relates to normative network architecture, in particular regional centrality/hubness and connectivity patterns. We examine network effects in schizophrenia across different disease stages, and transdiagnostically explore consistency of such relationships in patients with bipolar and major depressive disorder.

Methods: We studied anatomical MRI scans from 2,439 adults with schizophrenia and 2,867 healthy controls from 26 ENIGMA sites. Case-control patterns of structural alterations were evaluated against two network susceptibility models: 1) hub vulnerability, which examines associations between regional network centrality and magnitude of disease-related alterations; 2) epicenter models, which identify regions whose typical connectivity profile most closely resembles the disease-related morphological alteration patterns. Both susceptibility models were tested across schizophrenia disease stages and compared to meta-analytic bipolar and major depressive disorder case-control maps.

Results: In schizophrenia, regional gray matter reductions co-localized with interconnected hubs, in both the functional ($r=0.58$, $p_{spin}<0.0001$) and structural connectome ($r=0.32$, $p_{spin}=0.01$). Epicenters were identified in temporo-paralimbic regions, extending to frontal areas. We found unique epicenters for first-episode and early stages, and a shift from occipital to temporal-frontal epicenters in chronic stages. Transdiagnostic comparisons revealed shared epicenters in schizophrenia and bipolar, but not major depressive disorders.

Conclusions: Cortical reorganization over the course of schizophrenia closely reflects brain network architecture, emphasizing marked hub susceptibility and temporo-frontal epicenters. The observed overlapping epicenters for schizophrenia and bipolar disorder furthermore suggest shared pathophysiological processes within the schizophrenia-bipolar-spectrum.

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Introduction

Several large-scale studies have confirmed cortical thickness and subcortical volume abnormalities in major psychiatric disorders such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) (1–6). Among these, SCZ has been associated with the most widespread and marked alterations (2, 7), appearing early in the disease course and progressing over time (8). Although cortical reorganization in SCZ is most pronounced in temporal-paralimbic and frontal regions (1, 8, 9), the pattern is not uniformly distributed across the entire brain and cannot solely be explained by spatial proximity of the affected regions (10).

The staggering interconnectedness of neuronal regions in the brain, which gives rise to a multi-level network architecture, suggests that local aberrant functioning may affect synaptically-connected neuronal populations (11, 12). Distributed structural alterations could, thus, arise from, or be influenced by, network architecture and manifest as a diverse set of cognitive and affective symptoms. Recent studies have found that patterns of cortical alterations in SCZ, when compared to controls, reflect distinct functional and cytoarchitectural systems (9, 13), as well as cortical connectivity (10). This suggests that the topography of SCZ-related cortical reorganization is not randomly distributed, but shaped by the underlying network architecture of the cortex.

Testing this hypothesis at a large scale has recently become possible. Collaborative efforts, such as the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) consortium, have aggregated neuroimaging data of disease phenotypes (7) in thousands of patients and controls. Moreover, benchmark datasets such as the Human Connectome Project (HCP) provide rich information on functional and structural brain connectivity (14). Many studies have demonstrated important inter-regional variations in connectivity, with *hub* regions showing denser connectivity patterns to other regions. These regions may serve as central information relays, promoting processing efficiency (15). High centrality of a region, however, could render it more susceptible to metabolic stress, and predispose it to more pronounced structural alterations —the so-called nodal stress or hub vulnerability hypothesis (15–17). Higher vulnerability of hubs to structural damage has been reported across multiple neurological and neurodegenerative disorders (17–22) and more recently in SCZ (9, 10). Disease epicenter models have furthermore highlighted regions whose connectivity profile most closely resembles a disease-related morphological alteration pattern (9, 17, 22-25), providing insights into how connectome architecture may guide pathological processes. Fitting hub vulnerability and epicenter models to large-scale data in SCZ may advance our understanding of how network architecture relates to spatial patterns of morphological alterations in SCZ. Epicenter models may identify disease specific epicenters and provide new information about how SCZ-related cortical alterations are anchored to normative functional and structural networks (15).

In this study, we test the hypotheses that network-central brain regions (i.e., hubs) are more vulnerable to morphometric alterations in SCZ and that individual brain regions' connectivity profiles shape the spatial distribution of cortical reorganization in SCZ. We also sought to investigate how brain network features relate to different stages of SCZ including first-episode, early course, and chronic SCZ (9, 10, 26) as well as individual clinical factors. To this end, we used two network-based models combining MRI-based morphology data of 2,439 adults with SCZ and 2,867 healthy controls from the ENIGMA-Schizophrenia consortium and high definition structural and functional connectivity information from the HCP. First, we applied hub vulnerability models to spatially correlate regional network centrality with the degree of SCZ-related cortical thickness and subcortical volume alterations derived from case-control comparisons. Second, we used epicenter models to relate nodal connectivity profiles to the spatial distribution of cortical thickness alterations. Finally, given that psychiatric disorders are increasingly conceptualized as dimensional rather than strictly categorical disorders (27, 28), we examined whether our network models would reflect SCZ-specific features or rather represent a shared signature across other major psychiatric conditions (29) such as has been shown for subcortical volume, cortical thickness and surface area measures (30, 31), as well as for structural connectome properties (32). Therefore, we extended our analysis to meta-analytic case-control alterations in BD and MDD. Both disorders show various degrees of clinical, genetic, and neuroanatomic proximity to SCZ, with BD being more proximal (29, 33–36) and MDD being more distant with respect to the genetic, clinical, and morphometric patterns of SCZ (30, 31, 37).

Methods

ENIGMA participants

We analyzed subject-level data from 26 international centers of the ENIGMA-Schizophrenia Working Group including 2,439 adults with schizophrenia (786 females, mean age ± SD = 35.5 ± 12.4 years) and 2,867 healthy controls (1,408 females, mean age ± SD = 35.0 ± 13.4 years). Diagnosis of schizophrenia or schizoaffective disorder was confirmed at each center according to international diagnostic criteria of the ICD-10 (or DSM-IV). Details on subject inclusion criteria and site-specific demographic information are provided in Tables S1-2. Local institutional review boards and ethics committees approved each cohort study included, and written informed consent was provided according to local requirements.

Image acquisition and processing

Following published ENIGMA pipelines (1, 2), all 26 participating sites processed 3D T1-weighted structural brain MRI scans using FreeSurfer (38, 39) and extracted cortical thickness (CT) from 68 Desikan-Killiany (DK) atlas regions (40) as well as subcortical volume (SV) data from 16 brain structures. Number of scanners, vendor, strength, sequence, acquisition parameters, and FreeSurfer

versions are provided in Table S3. Quality control followed standard ENIGMA protocols at each site before subsequent mega-analysis (http://enigma.usc.edu/protocols/imaging-protocols).

Statistical mega-analysis

We analyzed CT measures from 68 cortical regions and SV measures from 12 subcortical gray matter regions (bilateral amygdala, caudate, nucleus accumbens, pallidum, putamen, and thalamus) and bilateral hippocampi. Data were first harmonized across scanners and sites using ComBat, a batch effect correction tool that uses a Bayesian framework to improve the stability of the parameter estimates (41, 42). Surface-based linear models were used to compare morphometric difference profiles of CT and SV in patients relative to controls, correcting for age and sex, using SurfStat, available at (https://mica-mni.github.io/surfstat/). Findings were corrected for multiple comparisons using the false discovery rate (FDR) procedure (43).

Functional and structural connectivity matrix generation from HCP data

Resting-state fMRI, and diffusion MRI of unrelated healthy adults (n = 207, 83 males, mean age ± SD = 28.73 ± 3.73 years, range = 22 to 36 years) from the HCP were used and underwent the initiative's minimal preprocessing (44, 45). High-resolution functional and structural data were parcellated according to the Desikan-Killiany atlas to align with the ENIGMA-Schizophrenia dataset. Functional and structural connectivity matrices were generated following previous work and are described in detail in the see supplementary methods.

Hub vulnerability model

To test the hub vulnerability hypothesis, *i.e.*, that nodes with higher normative network centrality, established based on an independent sample of healthy individuals, would display higher levels of disease-specific morphometric alterations in SCZ, we performed spatial correlations between the cortical and subcortical SCZ-related morphometric profile and normative weighted degree centrality maps (Fig.1 A-B). Weighted degree centrality, defined as the sum of the weights of edges (connections) connecting each node to all neighboring nodes, was used here to identify structural and functional hub regions; higher degree centrality denotes a hub region. Node centrality was defined as the weighted sum of cortico-cortical and subcortico-cortical edges for every region, respectively. Since correlations between brain maps are known to be inflated due to spatial autocorrelation, we generated a null distribution using 10,000 rotated maps based on the spin permutation test (46). In the case of the subcortical map we used a similar approach, with the exception that subcortical labels were randomly shuffled as opposed to being projected onto spheres, such as in the spin test procedure (22).

Mapping disease epicenters

To identify disorder-specific cortical and subcortical epicenters, we spatially correlated every region's healthy functional and structural cortical connectivity profile to the whole-brain patterns of cortical

alterations in SCZ (Fig.2A) (22, 47). We repeated this approach systematically for each parcellated region and for functional and structural cortical connectivity separately. Statistical significance of spatial similarity between an individual brain regions functional and structural connectivity profile and schizophrenia-related cortical alterations was determined through correlation analyses correcting for spatial autocorrelation with permutation test as described above. Regions were ranked in descending order based on the strength of their correlation coefficients, with the highest-ranked regions being considered the most significant disease epicenters. A region can be considered an epicenter regardless of its cortical abnormality level (effect-size of case-control differences), as long as it is strongly connected to other regions with high abnormality and weakly connected to regions with low abnormality. Additionally, it is important to note that disease epicenters do not necessarily have to be hub regions, but may rather be feeder nodes that directly connect peripheral nodes to hubs. To account for multiple testing (n=80), epicenters were only considered significant if spin-test p-values (p_{spin}) survived Bonferroni correction ($p<0.05$).

Robustness and confirmation analyses

To assess the robustness and reproducibility of our mega-analytic findings, we repeated the hub vulnerability models and disease epicenter analyses using previously published ENIGMA summary statistics of case-control differences in SCZ (1). For details, see supplementary methods.

Hub vulnerability and epicenters across different stages of SCZ

In a next step, we examined whether the link between network features and structural alterations differed between early (<2 years) and late (>20 years) disease stages of SCZ. These subgroup analyses aimed to investigate extreme ends of early and late disease stages that differ from the mean duration of illness (DURILL) of 11.6 (SD=7.0) years of the total sample (n=2,439) included in the main analysis. To this end the following subgroups were defined based on available data time of scanning: first-episode psychosis (<=1 month of DURILL, n=214, mean age=25 (15-50)), early course (>1 month but <2 years DURILL, n=503, mean age=27 (15-72) and late chronic disease stage (>20 years DURILL, n=457, mean age=35 (35-77). The hub vulnerability and epicenter models were re-computed for each disease stage and compared accordingly.

Subject-level cortical abnormality modeling

We next sought to examine whether our network-based models can be translated to individual schizophrenia patients' data and how they are influenced by individual clinical factors. Batch-corrected cortical thickness data in patients were first adjusted for age and sex and subsequently z-scored relative to healthy controls to generate individualized cortical abnormality z-score maps. To test the hub vulnerability hypothesis, we correlated the derived patient-specific cortical abnormality z-score maps with the normative functional and structural centrality metrics (derived from HCP. Fig. 1B). The derived patient-specific correlation coefficients describe the individual scores of hub vulnerability.

Subsequently, we determined each patient's structural and functional disease epicenters by identifying brain regions whose healthy connectivity profiles were significantly correlated with the patient's brain abnormality map. Having established both network-based models in subject-level data (see results below), we next examined the association between individual clinical factors and patient's hub vulnerability and epicenters respectively. To this end, we correlated the subject-level hub vulnerability scores and the most relevant epicenters with antipsychotic medication, duration of illness and symptom severity (measured with the PANSS). For details, see supplementary methods.

Cross-disorder comparison with ENIGMA BD and MDD

Finally, we tested whether the associations between network modeling features and brain morphometric alterations are specific for SCZ, or reflect a shared signature across other psychiatric disorders. Summary statistics from the latest cortical morphometry meta-analyses of case-control differences in BD and MDD including, in total, 4,595 patients and 12,013 controls were derived from the ENIGMA Toolbox (47). The extracted regional Cohen's *d* values were then used to analyze the BD and MDD data using the hub vulnerability model and epicenter mapping approaches described above. To analyze the overlap between the disease-specific epicenter maps of SCZ, BD and MDD, we compared the magnitude to which a region serves as an epicenter for a specific disease, as captured by the Pearson's correlation coefficient *r*, to the corresponding *r* magnitude for the other two diseases. This was achieved by pairwise comparisons of the correlation coefficient of the normative connectivity profile with pairs of disorder morphological alteration patterns. The differences between correlation coefficients were compared for statistical significance with an *r*-to-*z* transform, using R package *cocor* and Zou's CIs.

Results

Cortical and subcortical alterations in SCZ

Using a mega-analytic approach, widespread cortico-subcortical morphological alteration patterns were observed in people with SCZ relative to HCPs, closely mirroring the cortical and subcortical meta-analytic case-control maps previously reported (1, 2). Specifically, patients with SCZ showed strongest cortical thickness reduction in fronto-temporal regions including the bilateral supramarginal, temporal, and fusiform gyri, the bilateral insula, and frontal regions including the bilateral superior frontal as well as the bilateral caudal middle frontal gyri (all *t*-values > 11, FDR p< 2.2e-16, Fig. 1A, Table S4). In addition, people with SCZ showed strongest volume deficiencies in the bilateral hippocampus followed by bilateral amygdala, and thalamus (all *t*-values > 11, FDR p<1e-11; Fig. 1A, Table S5).

Functional and structural degree centrality predict regional susceptibility

To test the hub vulnerability hypothesis in SCZ, we compared the spatial patterns of normative nodal degree centrality (Fig 1B) and SCZ-related morphological alterations (Fig 1A). We found that cortical thickness deficiencies in SCZ were most pronounced in functional ($r = 0.58$, $p_{spin} < 0.0001$), as well as

structural (r = 0.32, p_{spin}= 0.01) cortico-cortical hubs compared to non-hub regions (Fig. 1C). In other words, functional and structural degree centrality predicted susceptibility to SCZ-related cortical thickness alterations. Lower subcortical volume showed moderate non-significant associations with functional subcortico-cortical hubs (r = 0.44, p_{spin}= 0.11), while no relationship was observed between subcortical volume abnormalities and structural subcortico-cortical hubs (r = 0.03, p_{spin}= 0.92; Fig. 2C). Robustness of the observed hub vulnerability in SCZ was confirmed using meta-analytic morphological summary statistics (1, 2) (Fig. S1).

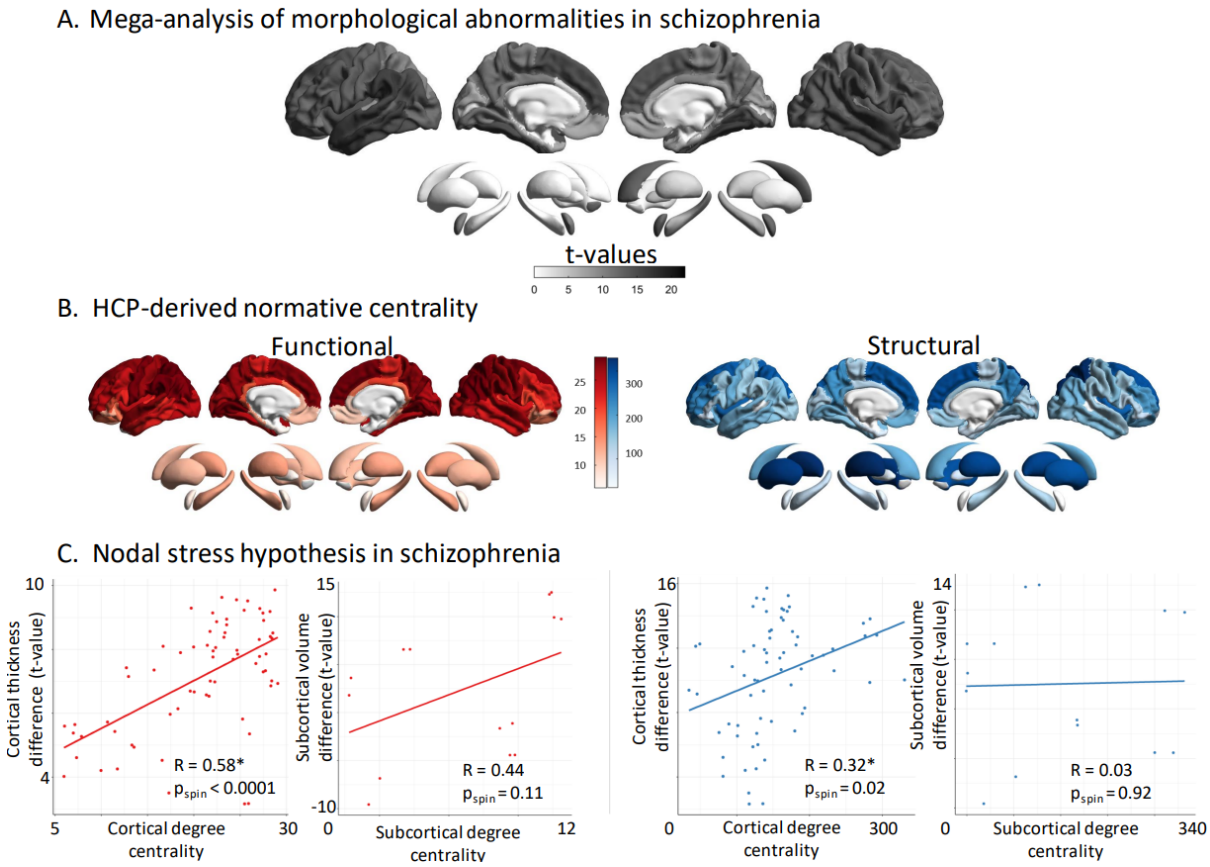

Figure 1. Hub vulnerability mapping. (A) Unthresholded *t*-maps of cortical thickness and subcortical volume deficiencies in SCZ (n = 2,439), compared to HCP (n = 2,867). **(B)** Normative functional and structural network organization, derived from the HCP dataset, was used to identify hubs (*i.e.*, regions with greater degree centrality). **(C)** Correlation of gray matter morphological alterations with node-level functional (*left*) and structural (*right*) maps of degree centrality. In SCZ, regions with high functional or structural centrality are significantly more likely to display morphological alterations in the cortex. Subcortical functional subcortico-cortical degree centrality showed a moderate non-significant correlation with morphometric alterations, while no correlation was observed for structural subcortico-cortical degree centrality. HCP: Healthy control participants; SCZ: Schizophrenia.

Disease epicenters of schizophrenia

Having identified that cortico-cortical hubs are more susceptible to cortical alterations in SCZ, we next examined whether SCZ-related cortical thickness alterations are reflected in the connectivity profile of

one or more brain regions. This would indicate that these regions likely serve as network-level epicenters of the disease. We systematically compared the functional and structural connectivity profile of each cortical region to whole-brain patterns of cortical alterations in SCZ (Fig. 2A). This approach identified several temporo-paralimbic regions - including the entorhinal cortices, banks of superior temporal sulci, inferior temporal, and additionally frontal gyri (bilateral *pars triangularis*, left *pars opercularis*) - as the most significant functional and structural epicenters (all $p_{spin} < 0.05$; Table S6, Fig. 2B). In the subcortex, the bilateral amygdala, caudate, putamen and the left pallidum emerged as significant functional epicenters (all $p_{spin} < 0.05$; Table S7, Fig. 2B), whereby no structural subcortical epicenters were identified. Overall, highest-ranked disease epicenters were not themselves hub regions, but were rather feeder nodes, ranking on average (median) at the 40th percentile of nodal centrality distribution. Robustness of the derived epicenters was confirmed using meta-analytic morphological summary statistics (1, 2) (Fig. S2).

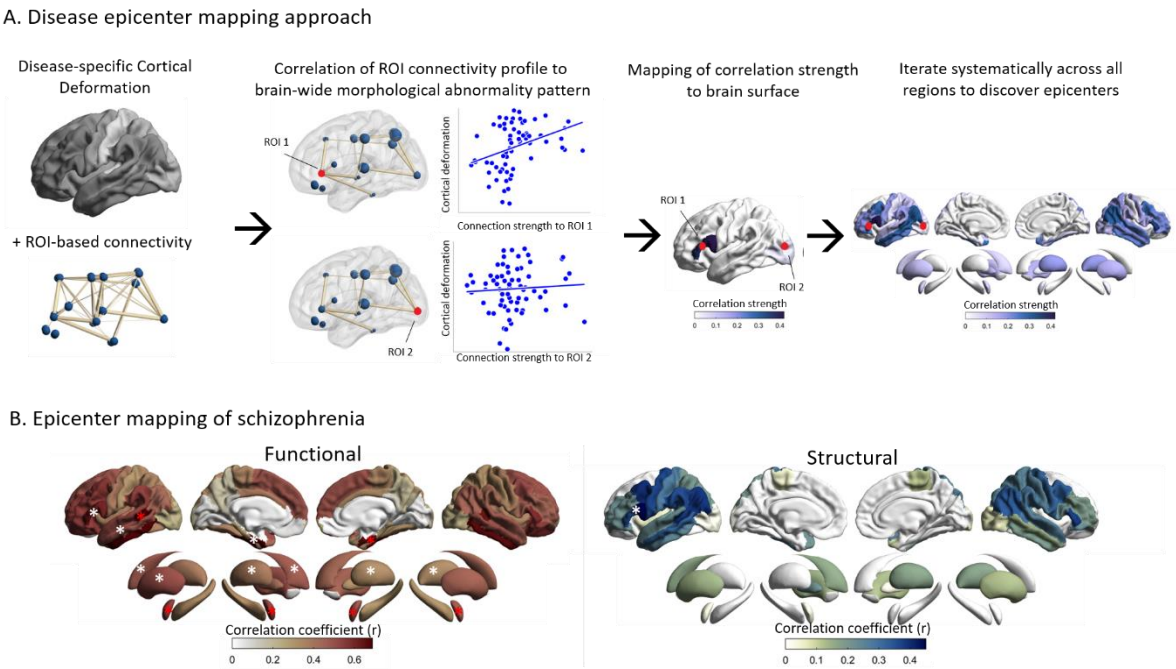

Figure 2. Disease epicenters. (A) Disease epicenter mapping schematic: Combining morphological abnormality patterns with ROI-based connectivity, we systematically computed the degree of correlation of each region to the disease-specific morphological alterations. Epicenters are regions whose connectivity profiles significantly correlated with the syndrome-specific morphological alterations; significance was assessed using spin permutation tests. This procedure was repeated systematically to assess the epicenter value of every cortical and subcortical region, as well as for both functional and structural connectivity matrices. **(B)** Correlation coefficient maps depicting the strength of association between the normative region-based functional (*left*) and structural (*right*) connectivity and the SCZ-specific morphological abnormality maps. Disease epicenters are regions more strongly connected with morphologically altered regions - and, inversely, more weakly connected with regions with less pronounced alterations. Asterisks denote the top five significant epicenters. Red asterisks denote epicenters unique to SCZ compared to BD, specifically the right entorhinal cortex, the left banks of the superior temporal sulcus, and bilateral amygdala (for more details on cross-disorder comparison, see Fig. 4).

Hub vulnerability and epicenter mapping across different disease stages

Building on the significant associations of functional and structural degree centrality and cortical alterations across the complete sample, we next asked how this association might relate to first-episode, early (< 2 years) and late (> 20 years) stages of SCZ. We found that both functional and structural degree centrality to be correlated with thinner cortex in individuals with first-episode (r_{func} = 0.35, p_{spin} = 0.01, r_{struc} = 0.28, p_{spin} = 0.04), early disease stage (r_{func} = 0.37, p_{spin} = 0.04, r_{struc} = 0.24, p_{spin} = 0.09), and late chronic disease stages (r_{func} = 0.44, p_{spin} =0.003, r_{struc} = 0.28, p_{spin} = 0.04) (Fig. 3A). In other words, across all disease stages, cortical alterations were significantly linked to cortico-cortical hubs compared to non-hub regions. Epicenter mapping of cortical alterations across disease stages revealed unique occipital and parieto-temporo-frontal epicenters in first-episode and early disease stage, while no unique epicenters were found in chronic disease stages (Fig. 3B, Table S8). Across disease stages, convergent functional and structural epicenters were identified in temporo-frontal and parieto-frontal regions, respectively (Fig 3B). Overall, these findings suggest an occipital to temporo-frontal shift of epicenters from early to chronic disease stages.

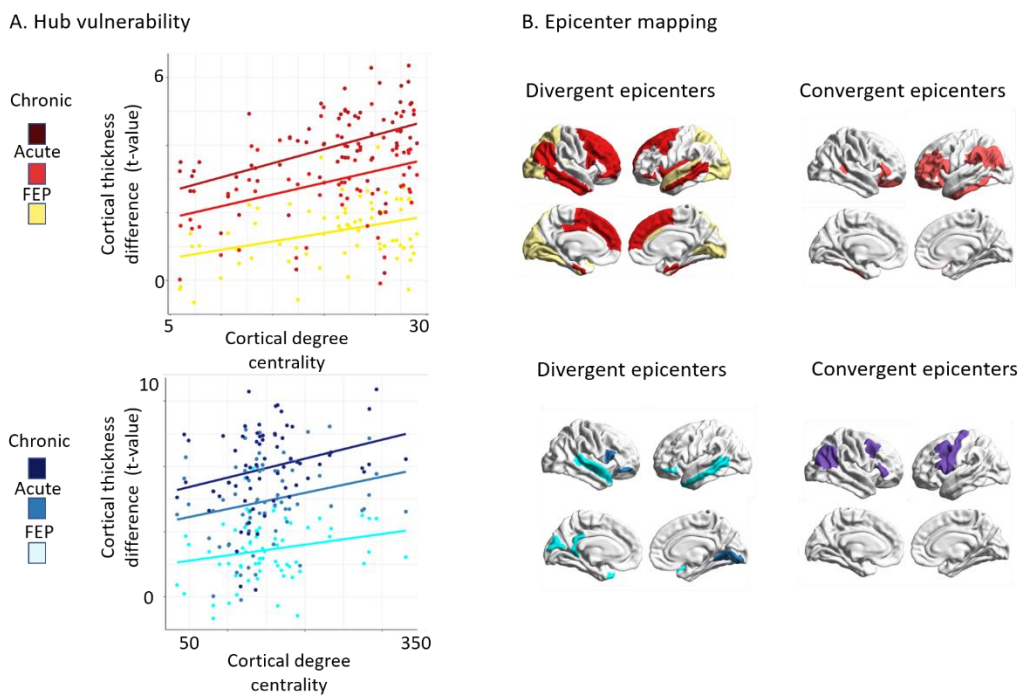

Figure 3. Disease stage comparison of network modeling. (A) Correlation of cortical thickness abnormality in SCZ to node-level functional (*upper*) and structural (*lower*) maps of degree centrality (all r>0.23, pspin<0.05). Color code indicates first-episode, early disease stage, and chronic disease stage from brighter to darker colors. (B) SCZ epicenter mapping (for details, see Fig. 2). Divergent (unique) epicenters are only significant in one of three disease stages with color indicating the corresponding disease stage. Convergent epicenters are significant in all three disease stages (p_{spin} <0.05). Subgroups of disease stages are defined by duration of illness: first-episode psychosis <1 month; early disease stage (>1 month but < 2 years); chronic disease stage (>20 years). FEP: First episode psychosis.

Subject-level cortical abnormality modeling

We next assessed whether our network-based susceptibility models also relate to brain abnormality patterns in individual patients. Although the individual subject-level data displayed overall lower sensitivity, due to the increased heterogeneity in cortical abnormality patterns, the results closely mirrored our group-level analysis (Fig. S2). We observed similar associations between patient-specific cortical abnormality maps and functional as well as structural cortico-cortical hubs (Fig. S2). Individual level of hub vulnerability indicated by subject-level higher positive correlation coefficients was aassociated with duration of illness (r_{func}=0.16, p_{Bonf}<0.001, r_{struc}=0.2, p_{Bonf}<0.001), PANSS total scores (r_{func}=0.12, p_{Bonf}=0.016, r_{struc}=0.12, p_{Bonf}=0.016) and PANSS general scores (r_{func}=0.21, p_{Bonf}=0.004). No significant association was observed with either positive symptoms, negative symptoms or antipsychotic medication (Table S9). Correlating the individual 10 top ranked epicenters with clinical scores we found a significant positive correlation between antipsychotics dose and epicenter likelihood of the left inferior frontal gyrus (pars triangularis) (r_{func}=0.1, p=0.033), and a negative correlation between general PANSS Symptoms and left banks of superior temporal sulcus (r_{struc}=-0.22, p_{Bonf}=0.002). None of the other epicenters were significantly associated with the clinical scores tested (Table S10-11).

Cross-disorder comparison of hub vulnerability and epicenter mapping

To test whether our network models are specific to SCZ or rather reflect transdiagnostic features, we applied both network-based susceptibility models to meta-analytic cortical maps of BD and MDD. The hub vulnerability model revealed that cortical thickness alterations in BD were correlated with cortico-cortical hubs (r_{struc} = 0.35, p_{spin} = 0.01; r_{func} = 0.32, p_{spin} = 0.07) as well as marginally with functional subcortico-cortical hubs (r_{func} = 0.52, p_{spin} = 0.06). No associations were found in MDD (all p_{spin} > 0.05, Fig 4A). In BD, epicenter modeling identified functional and structural disease epicenters predominantly in the frontal cortices specifically, the bilateral orbitofrontal cortex, the middle frontal gyrus, and the left inferior frontal gyrus (all p_{spin} < 0.05, Fig 4b). By contrast, no significant cortical epicenters were observed in MDD (all p_{spin} >0.05, Fig 4b). In the subcortex, the caudate nucleus emerged as the only functional and structural epicenter in BD, and the nucleus accumbens as sole structural epicenter in MDD (all p_{spin} <0.05, Fig 4b). Correlating the epicenter maps of SCZ and BD revealed a significant overlap both cortically (r_{func} = 0.88, p_{spin} < 0.05, r_{struc}= 0.74, p_{spin} < 0.05) and to a lesser extent subcortically (r_{func} = 0.63, p= 0.007, r_{struc}= 0.41, p= 0.07). However, distinct localized disease epicenters were also identified for each disorder. Specifically, in SCZ the right entorhinal cortex (diff = 0.23, CI: 0.10 - 0.39) and the left banks of the superior temporal sulcus (diff = 0.15, CI: 0.01 - 0.30) emerged as unique epicenters, whereas the BD group had the left rostral middle frontal gyrus as its unique epicenter (diff = 0.30, CI: 0.45, 0.15). Altogether, these findings suggest some convergence of the hub vulnerability and epicenter models in SCZ and BD - but not MDD - and reveal distinct temporo-limbic epicenters in SCZ and frontal epicenters in BD.

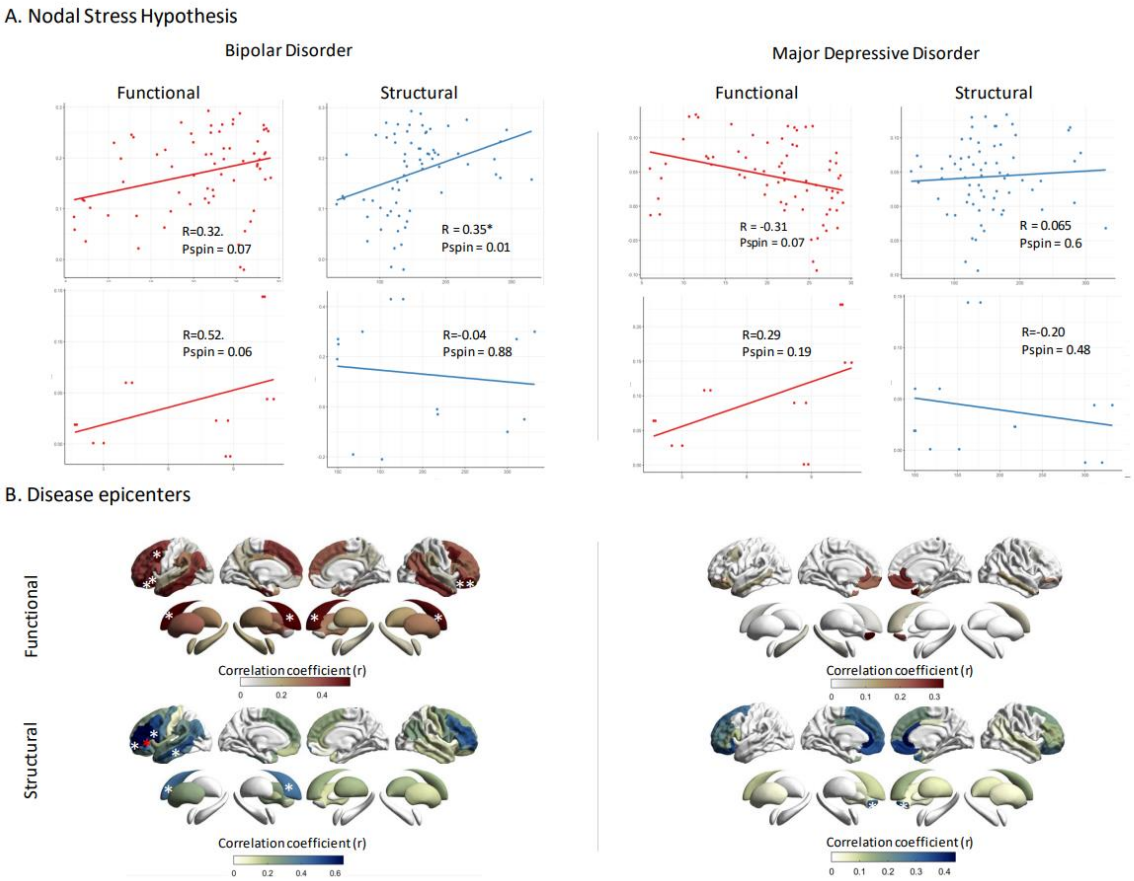

Figure 4. Cross-disorder comparison of network modeling. (**A**) Correlation of SCZ-related gray matter alteration to node-level functional (left) and structural (right) maps of degree centrality in BD and MDD. In BD, cortical regions with high structural centrality are significantly more likely to display higher morphological alterations; this trend is also observed for functional centrality. No such relationship is observed in MDD. (**B**) Correlation coefficient maps depicting strength of association between the normative region-based functional (top) and structural (bottom) connectivity and the BD- (left) and MDD-specific (right) morphological alteration maps. Asterisks denote the significant epicenters, whereby a red asterisk denotes a uniquely significant epicenter for the disorder. Functional BD epicenters: pars orbitalis of inferior frontal gyrus (L), lateral orbitofrontal cortex (L), caudal middle frontal gyrus (L), inferior and middle temporal gyrus (L) cortically and the caudate nucleus in the subcortex (func: bilateral, struc: left). Structural BD epicenters: *pars opercularis* (L) and *pars triangularis* (L) of inferior frontal gyrus, rostral middle frontal gyrus (L), middle temporal gyrus (L) cortically and the caudate nucleus (L), subcortically. In MDD, no functional epicenters were detected. Structural MDD epicenters: nucleus accumbens (R). BD: Bipolar disorder; MDD: Major depressive disorder; SCZ: Schizophrenia

Discussion

Our study explored spatial associations between brain network architecture with morphometric alterations of SCZ, leveraging the largest multisite curated neuroimaging dataset to date. We found that cortical regions with higher cortical network centrality were, on average, more vulnerable to SCZ-related cortical thickness alterations in all stages of the disease, while subcortical regions with high subcortico-cortical centrality did not share this property. Examining the degree to which each brain region's network connections match the morphological alteration patterns of SCZ, we identified temporo-paralimbic regions extending to the inferior frontal gyrus as the most probable disease epicenters. Across disease stages, we observed unique epicenters for first-episode and early stages (<2years), and a shift from occipital to temporal-frontal epicenters in chronic stages (>20years). Translating our network models to subject-level data, we found that individual hub vulnerability was associated with duration of illness and overall symptom severity. Functional and structural connectivity-based models generally converged, with however functional connectivity emerging as more sensitive for detecting vulnerable nodes and epicenters in SCZ. Finally, cross-disorder comparison revealed similar associations of cortical node centrality and cortical alterations in BD and SCZ, but not in MDD and SCZ - as well as shared and distinct epicenters in SCZ and BD.

By combining our findings of SCZ-related cortical thickness alterations with normative brain connectivity information, we provide evidence for the hub vulnerability hypothesis in SCZ, i.e., the centrality of a cortical region - in terms of its position in both the functional and the structural connectome - is well correlated with the degree of its deformation. Wannan *et al.* (10) previously found that cortical deformation tends to cluster in regions with high normative structural covariance, and Shafiei *et al.* (9) have shown that the deformation of a cortical region correlates with the collective deformation of its network-neighboring regions, weighted by their respective connection strength. Prior studies further observed that network-central cortical nodes (48, 49) and the neuroanatomical tracts connecting them to other regions (50) are disproportionately affected in SCZ. Our findings confirm and extend these observations in a mega-analytic approach, using a simple measure of hub centrality, supporting a network organization of cortical alterations in SCZ. We found that relationships between regional cortical thickness deficiencies and regional node centrality were present in first-episode, early, and late disease stages. Individual hub vulnerability further correlated with longer duration of illness and clinical profiles of higher general symptom severity. These findings suggest that network organization may be guiding cortical alterations throughout the disease process of SCZ. The vulnerability of cortical hub regions to deficiencies in cortical thickness was originally examined in neurological disorders, including Parkinson's disease (18), Alzheimer's disease (19, 20), and other neurodegenerative conditions (21), as well as epilepsy (22). Several biological mechanisms could lead to a marked susceptibility of hub regions. According to the stress-threshold model, centrally located neuronal populations are especially vulnerable to pathophysiological perturbations due to their higher

neuronal activity and concomitant metabolic demands (49, 51). In addition, hub regions are more likely to be part of the association cortices which, partly due to their prolonged window of developmental plasticity, have been shown to be especially vulnerable to developmental insults (52) - tying into the known neurodevelopmental aspects of SCZ pathogenesis (53).

Having identified the relevance of brain connectivity as a factor potentially contributing morphological alteration in SCZ, we tested if the underlying connectivity of specific regions – or epicenters – constrains the SCZ-related cortical abnormality pattern. We identified temporo-paralimbic brain regions extending to the frontal gyrus as the most probable SCZ epicenters. The bilateral entorhinal cortex was most consistently the top-ranked epicenter. This is in line with recent reports in first-episode psychosis (26) and chronic SCZ (19), while also mirroring epicenters of cortical atrophy in neurodegenerative disorders (54). Our epicenter mapping across first-episode, early, and late disease stages revealed a shift from the occipital to the temporo-frontal epicenter - confirming recent longitudinal observations in first-episode psychosis (26). The consistent involvement of temporo-paralimbic and frontal cortical regions, as potential epicenters across all disease stages, aligns with a series of studies implicating these regions in SCZ pathophysiology. Cortical thickness deficits in these regions emerge early in the disease (8, 55), are predictors for conversion (55) and are most strongly affected in chronic SCZ (1). More generally, aggregation of epicenters in the temporo-paralimbic cortex could be explained by regional cellular and molecular features that promote brain plasticity, higher metabolic activity, making the paralimbic cortex more vulnerable to developmental disruptions (56, 57). In terms of their positioning in the network, the most significant epicenters were not themselves hubs, but rather regions with centrality slightly above the median. If they are indeed active in the pathophysiological process, epicenters could represent regions affected earlier in the disease process, and serve as a gateway through which hub nodes are affected downstream due to their connections to these nodes.

Our cross-disorder comparison showed that the hub vulnerability models were also implicated in cortical alterations in BD, while cortical findings in MDD did not share this property. Epicenter mapping revealed some convergence of SCZ and BD along a temporo-limbic to frontal gradient, with an accentuation of temporo-paralimbic and frontal regions in schizophrenia and BD respectively. Overall, the magnitude of observed cortical and subcortical disease epicenters was most pronounced in SCZ, intermediate in BD and relatively lacking in MDD, resembling a phenotypic continuum rather than categorical diseases. Both, the hub susceptibility and epicenter models further revealed differential aspects of functional and structural connectivity to SCZ and BD-specific pathophysiology. Specifically, hubs and epicenters of SCZ and BD were more sensitive to detection with the functional and structural connectome, respectively. This finding could reflect the inherent differential sensitivity of diffusion MRI to long-range fiber bundles and that of resting-state functional MRI to short-range intracortical spatially distributed polysynaptic cortical systems (58). Disease epicenters in SCZ preferentially

appeared in polysynaptic temporo-limbic regions, making them more amenable to detection through the functionally-derived connectome. Conversely, disease epicenters in BD appeared more stable across modalities, with an accentuation in frontal regions, thus lending structural connectivity an increased sensitivity to their detection. Collectively, our findings suggest that shared network architecture features across SCZ and BD reflect the high biological proximity of these two disorders (1–4, 30, 34), while the unique epicenters could reflect biological differences driving their differential clinical manifestations. By contrast, cortical abnormalities in MDD seem to lack a straightforward network influence - consistent with its more different structural brain signature compared to SCZ. However, given that we used meta-analytic data, the lack of findings in MDD could reflect heterogeneity in the study samples included, whereby specific cohorts with psychotic depression could potentially display more similarities to SCZ and BD.

Several implications could arise from the associations between hub vulnerability, epicenter mapping, and morphometric signatures of SCZ. According to our network models, epicenters emerging early in the disease process might be further characterized by distinct alterations in genetic activity, macro- or micromorphology and/or activity. Aberrant signaling of cortical development involving myelination, branching, and synaptic pruning (30, 59, 60) might propagate from focal epicenters to connected regions in a network-spreading pattern leading to the characteristic pattern of cortical alteration. Applying multi-omic approaches longitudinally across neurodevelopment and early SCZ stages are of interest to test this hypothesis and examine the role of the derived epicenters in aberrant developmental processes. In SCZ such network-spreading phenomenon might not be limited to neurodevelopmental processes but additionally involves neurodegeneration later in life. Trans-neuronal spread of misfolded proteins reflecting brain network organization have been documented in several neurodegenerative disorders (17, 18, 61, 62). In this regard, hub regions would be expected to be progressively affected during the disease process of SCZ. Insights from neurological disorders with a similar pattern could be informative, in terms of recognizing potentially common upstream pathways to better understand potential neurodegenerative processes of cortical thickness deficiencies in SCZ.

The present study is limited by its cross-sectional nature and cannot provide definitive answers pertaining to the temporal unfolding of the pathophysiological processes. With the increasing availability of longitudinal studies, future studies could test a “spreading” model, whereby the pathophysiology could originate from disease-specific epicenter regions, and then, through these, propagate to the vulnerable hub regions. Finally, although HCP is a current benchmark dataset to obtain normative structural and functional brain connectivity information, the use of individualized structural and functional connectivity information in patients might further improve the accuracy of network modeling of schizophrenia.

Conclusion

Leveraging a large-scale, multisite, neuroimaging dataset from the ENIGMA-Schizophrenia working group, this study provides robust evidence that brain network architecture is intricately linked to altered cortical reorganization in SCZ. Nodal centrality and temporo-paralimbic to frontal epicenters emerge as fundamental components of this relationship. We further demonstrated that network organization may guide cortical alteration patterns throughout the disease stages of SCZ. Finally, we identified overlapping and specific epicenters of SCZ and BD, suggesting shared and unique network-spreading processes across the psychosis spectrum.

Acknowledgments

See Supplement

Disclosures

The authors declare that they have no competing interests.

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