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Specific Substantial Dysconnectivity in Schizophrenia: A Transdiagnostic Multimodal Meta-analysis of Resting-State Functional and Structural Magnetic Resonance Imaging Studies

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ABSTRACT

BACKGROUND: This study investigated characteristic large-scale brain changes in schizophrenia. Numerous imaging studies have demonstrated brain changes in schizophrenia, particularly aberrant intrinsic functional connectivity (iFC) of ongoing brain activity, measured by resting-state functional magnetic resonance imaging, and aberrant gray matter volume (GMV) of distributed brain regions, measured by structural magnetic resonance imaging. It is unclear, however, which iFC changes are specific to schizophrenia compared with those of other disorders and whether such specific iFC changes converge with GMV changes. To address this question of specific substantial dysconnectivity in schizophrenia, we performed a transdiagnostic multimodal meta-analysis of resting-state functional and structural magnetic resonance imaging studies in schizophrenia and other psychiatric disorders.

METHODS: Multiple databases were searched up to June 2017 for whole-brain seed-based iFC studies and voxel-based morphometry studies in schizophrenia, major depressive disorder, bipolar disorder, addiction, and anxiety. Coordinate-based meta-analyses were performed to detect 1) schizophrenia-specific hyperconnectivity or hypoconnectivity of intrinsic brain networks (compared with hyperconnectivity or hypoconnectivity of each other disorder both separately and combined across comparisons) and 2) the overlap between dysconnectivity and GMV changes (via multimodal conjunction analysis).

RESULTS: For iFC meta-analysis, 173 publications comprising 4962 patients and 4575 control subjects were included, and for GMV meta-analysis, 127 publications comprising 6311 patients and 6745 control subjects were included. Disorder-specific iFC dysconnectivity in schizophrenia (consistent across comparisons with other disorders) was found for limbic, frontoparietal executive, default mode, and salience networks. Disorder-specific dysconnectivity and GMV reductions converged in insula, lateral postcentral cortex, striatum, and thalamus.

CONCLUSIONS: Results demonstrated specific substantial dysconnectivity in schizophrenia in insula, lateral postcentral cortex, striatum, and thalamus. Data suggest that these regions are characteristic targets of schizophrenia.

Keywords: Functional connectivity, Functional magnetic resonance imaging, Gray matter volume, Meta-analysis, Schizophrenia, Specific brain changes

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Brain imaging and neuropathological studies have demonstrated structural and functional brain changes in schizophrenia (1–3). Such changes affect large-scale brain systems (4–6) defined by distinct brain regions, their interregional connectivity, and their specific function and/or physiology. Alterations of large-scale systems in schizophrenia are of special interest for two reasons: large-scale changes reflect changes at microscopic levels, and changes in large-scale systems are thought to mediate behavioral phenotypes (7). In vivo brain imaging enables detection of large-scale systems; for example, voxel-based morphometry (VBM) of structural magnetic resonance imaging (MRI) data allows estimation of regional gray matter volume (GMV), whereas correlations among blood oxygenation fluctuations of resting-state functional MRI enable measuring between regions intrinsic functional connectivity (iFC) of ongoing brain activity. iFC organizes brain activity into so-called intrinsic brain networks of coherent ongoing activity (8,9), with high consistency across individuals (10), development (11), states of consciousness (12), and species (13). This qualifies intrinsic networks as distinct large-scale brain systems. Thus, changes in large-scale systems in schizophrenia are reflected by intrinsic network changes,

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which, in turn, have been demonstrated for several modalities (14,15). For example, concerning network connectivity, within-network and between-network iFC is impaired, preferentially in networks covering prefrontal and limbic [i.e., agranular or dysgranular (16)] cortices, such as default mode network (DMN) (17,18) and salience network (SAL) (18,19). Concerning network structure, regional GMV changes focus on regions such as insula, anterior cingulate cortex, or superior temporal gyrus, which are parts of DMN and SAL (20–22).

Recent meta-analyses of imaging studies integrated sometimes inconsistent findings across iFC studies (23,24) and GMV studies (25–28) in schizophrenia. Concerning iFC changes, consistent hypoconnectivity was found within and across SAL, DMN, and frontoparietal executive network (FPN), whereas hyperconnectivity was observed between SAL and limbic network (LIM) (23). Concerning GMV changes, consistent volume reductions were reported for thalamus, striatum, insula, anterior cingulate cortex, and medial prefrontal cortex (25,26). Whereas these studies greatly clarified our picture of aberrant intrinsic connectivity and gray matter in schizophrenia, two important questions remain unanswered. 1) To which degree are network iFC changes specific to schizophrenia compared with iFC changes in other psychiatric disorders, such as major depressive disorder (MDD) or bipolar disorder? Analogously to disorder-specific task hypoactivation or GMV decrease (26,29,30), we define disorder-specific hypoconnectivity in schizophrenia as significantly stronger or weaker hypoconnectivity in schizophrenia compared with hypoconnectivity of another disorder (correspondingly for hyperconnectivity). Thus, specificity in this sense does not necessarily mean that schizophrenia-specific changes are present only in schizophrenia; they just have to be significantly more pronounced in schizophrenia [for the same use of the term "specific" in recent meta-analyses contrasting psychiatric disorders, see (26,29,30)]. 2) How do disorder-specific network iFC changes in schizophrenia link with regional structural changes, such as GMV alterations? We use the term "substantial brain dysconnectivity" to refer to the concept underlying this question. iFC changes reflect dysconnectivity; when iFC changes converge with changes in underlying brain structure, dysconnectivity becomes substantial. Based on previous resting-state functional and structural MRI studies (23,26), we expected specific substantial dysconnectivity in schizophrenia, particularly for cortical and subcortical regions of prefrontal limbic networks.

To address this hypothesis, we performed coordinate-based meta-analyses of both resting-state functional and structural MRI studies. Meta-analysis is a powerful tool for 1) synthesizing inconsistent results by accounting for between-study heterogeneities, such as methodological variations; 2) detecting diagnosis-specific abnormalities by contrasting one disorder (e.g., schizophrenia) with other disorders; and 3) combining unimodal results, e.g., from functional and structural meta-analyses, via multimodal conjunction. Therefore, to investigate aberrant network iFC specific to schizophrenia, we conducted a coordinate-based meta-analysis of seed-to-whole-brain iFC studies in schizophrenia and other psychiatric disorders using multilevel kernel density analysis (MKDA) (31,32). This meta-analytic approach was introduced by Kaiser *et al.* (32), who analyzed seed-to-whole-brain iFC changes in MDD as changes of intrinsic network iFC, and was recently extended to schizophrenia and other disorders (23,33). In this framework, the location of a given iFC seed defines the intrinsic seed network, and locations of iFC changes determine within-network and between-network iFC changes of seed-network connectivity (23,32,33). Disorder-specific network iFC changes of schizophrenia, in turn, were then defined as stronger (or weaker) iFC hyperconnectivity or hypoconnectivity in schizophrenia relative to hyperconnectivity or hypoconnectivity in another disorder (first compared with each disorder separately, then combined across all comparisons). To identify substantial iFC dysconnectivity in schizophrenia, we additionally performed MKDA meta-analysis of VBM studies in schizophrenia and linked results with the results of the iFC meta-analysis via conjunction (34).

METHODS AND MATERIALS

Meta-analysis of Network iFC Changes Specific to Schizophrenia

Literature Search and Study Selection. Publications were searched in PubMed, Web of Science, EMBASE, and reference lists of reviews and eligible articles using the keywords "rest* OR intrinsic AND connect* AND [disorder name]" up to June 12, 2017 (Figure 1A; see Supplemental Table S1 for detailed keywords and Supplemental Figures S1–S5 for details on single disorders). Five psychiatric disorders were investigated based on high prevalence in adulthood relative to other disorders (26,35,36): schizophrenia, MDD, bipolar disorder, addiction, and anxiety. Addiction comprised the DSM-5 category substance-related and addictive disorders. Studies of seed-based whole-brain resting-state FC comparing patients with one of these disorders with healthy control (HC) subjects were selected (32). Studies were included in line with MOOSE guidelines for meta-analyses of observational studies (Figure 1A) (37). Study quality was systematically checked concerning data precision, study design, demographic and clinical characteristics, dropout rates, and reliability of seed regions of interest. Publications using identical patient and HC samples were treated as one single study to control for possible confounds (32); therefore, the number of included publications exceeded the number of included studies. If a study compared multiple patient samples (e.g., hallucinating and nonhallucinating) with the same HC sample, these comparisons were treated as separate contrasts. Only studies including patients with explicit diagnosis of the respective disorder (e.g., using DSM-IV) were selected; concerning schizophrenia, studies comprising patients without explicit diagnosis of schizophrenia, e.g., patients with first-episode psychosis or at high risk for psychosis, were excluded. For details on single disorders, see Supplemental Methods and Supplemental Figures S1–S5. Further exclusion criteria were 1) methods other than seed-based iFC (e.g., independent component analysis or graph analysis), as these distinct methodological approaches do not yield identical iFC measures (Supplemental Table S18 shows a list of these excluded studies); 2) analysis restriction to prespecified regions of interest (not whole-brain); 3) neurological or medical comorbidity; 4) no baseline comparison for longitudinal or intervention studies; and 5) no significant group differences or no peak

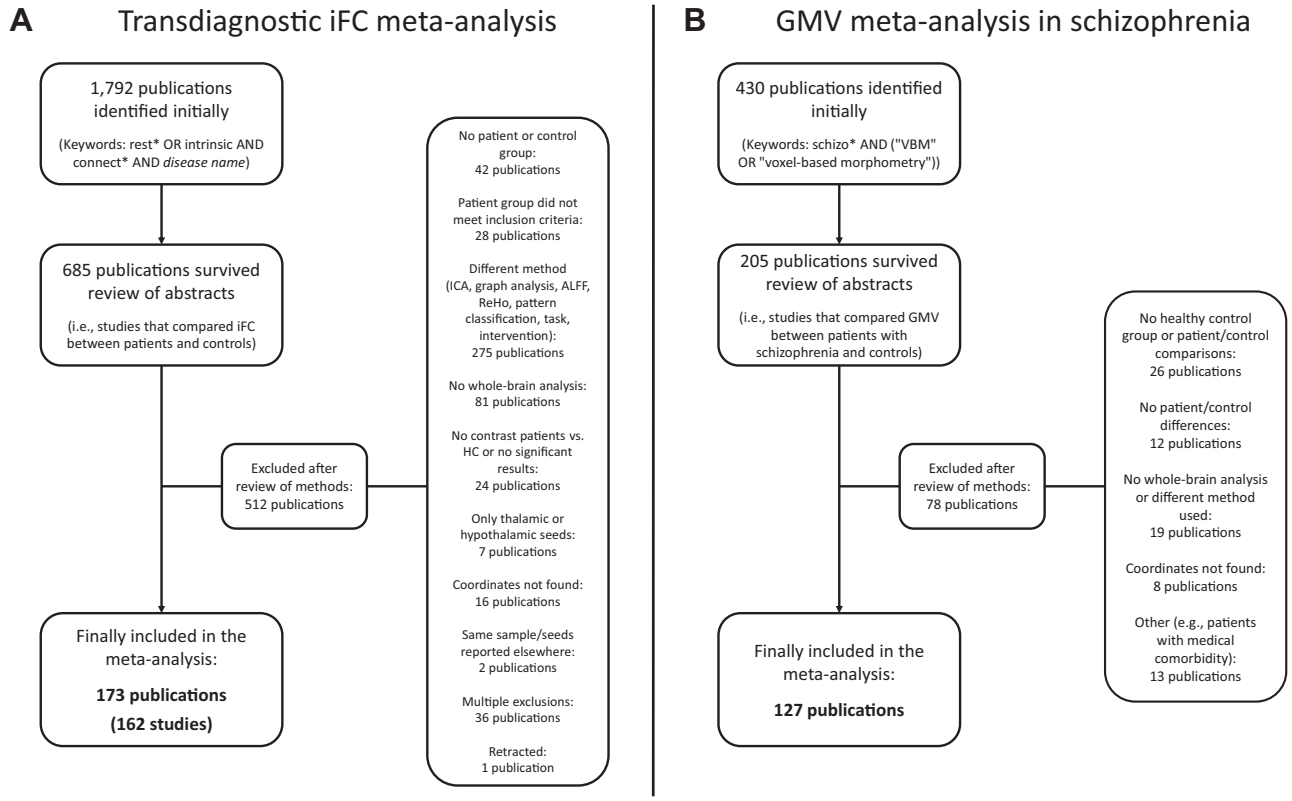

Figure 1. Flow diagram of study selection for transdiagnostic intrinsic functional connectivity (iFC) **(A)** and schizophrenia gray matter volume (GMV) **(B)** meta-analyses. Note that the number of publications exceeded the number of studies in the transdiagnostic iFC meta-analysis, as publications using the same patient and control samples were counted as one single study. ALFF, amplitude of low frequency fluctuations; HC, healthy control; ICA, independent component analysis; ReHo, regional homogeneity; VBM, voxel-based morphometry.

coordinates reported in stereotactic space. No restrictions were made regarding age, illness duration, symptom severity (current episode or remission), or medication status to ensure maximal coverage of studies.

Data Extraction. Seed center coordinates and peak coordinates of between-group effects were extracted from included whole-brain seed-based iFC studies and converted to Montreal Neurological Institute standard space if necessary. If the seed region of interest was an anatomical region from a standard brain atlas or mask, the center of mass was calculated to obtain a representative coordinate (32). Based on the location of their center coordinate within the network mask, seeds were categorized into one of the following seven predefined seed networks from Yeo *et al.*'s clustering approach on resting-state FC of 1000 healthy subjects, covering cortex (8), striatum (38), and cerebellum (39): LIM, FPN, DMN, SAL, auditory sensorimotor (ASM) network, dorsal attention network, and visual network (Supplemental Figure S6). SAL refers to Yeo *et al.*'s ventral attention network (renamed because SAL is more commonly used in schizophrenia research). As a similar network parcellation was not available for thalamus, studies using only thalamus seeds were excluded (33). Peak effects were categorized according to the network assignment of their corresponding seed, reflecting aberrant iFC with the respective seed network, and grouped by hyperconnectivity (increased positive or reduced negative connectivity) and hypoconnectivity (increased negative or reduced positive connectivity) in patients compared with HC subjects (32).

Meta-analysis and Conjunction Analysis. Coordinate-based meta-analysis was performed separately for each seed network if at least three independent studies per disorder were available (32,33). The meta-analysis was conducted via MKDA, a well-established toolbox used in multiple coordinate-based meta-analyses (23,31–33) (for technical details, see Supplemental Methods). Briefly, MKDA convolves peak coordinates with spherical kernels (radius = 15 mm) and weights and synthesizes studies into density maps, which show for each voxel the weighted proportion of studies reporting aberrant iFC within 15 mm of this voxel (= density statistic). Notably, for each meta-analytic contrast, one density map is produced (see below for specific meta-analytic contrast definitions).

Density maps were then statistically evaluated using Monte Carlo simulations (15,000 iterations), identifying clusters significant for $p < .05$, familywise error rate–corrected for multiple comparisons, at height-based (density statistic) or extent-based (cluster size) threshold (31). Both thresholds were reported, as they provide complementary information (32). Result clusters overlapping with the seed network indicated within-

network hyperconnectivity or hypoconnectivity, whereas clusters outside the seed network indicated between-network (i.e., overlapping with another network) or outside-network (e.g., with thalamus) hyperconnectivity or hypoconnectivity.

The following analyses were conducted (for clarity, we describe only hyperconnectivity contrasts here; hypoconnectivity was investigated analogously):

1. Disorder versus HC subjects: e.g., SZP > HC, detecting consistent hyperconnectivity with the respective seed network in schizophrenia compared with HC subjects via MKDA (analogously for each other disorder). These contrasts replicate previous meta-analyses [e.g., in schizophrenia (23) or depression (32)]. Owing to our focus on schizophrenia, only results for schizophrenia are reported and discussed in detail.
2. Network dysconnectivity specific to schizophrenia:
   i. Single-disorder–specific hyperconnectivity in schizophrenia: e.g., (SZP > HC) > (MDD > HC) or (SZP > HC) < (MDD > HC), detecting brain regions with significantly stronger or weaker hyperconnectivity with the respective seed network in schizophrenia (vs. HC subjects) compared with hyperconnectivity in another disorder (vs. HC subjects). To restrict disorder-specific hyperconnectivity results to true changes in schizophrenia (i.e., hyperconnectivity also present when comparing schizophrenia with HC subjects), these results were overlapped with SZP > HC results via conjunction analysis, using a method commonly applied in meta-analyses. Briefly, we intersected meta-analytic p value maps and adjusted the significance threshold, accounting for potential noise in p value estimation ($p < .005$) (Supplemental Methods) (34).
   ii. Four-disorder–specific hyperconnectivity in schizophrenia: to reveal consistent hyperconnectivity across single-disorder comparisons, we performed conjunction across all four single-disorder–specific hyperconnectivity result maps ($p < .00001$) (Supplemental Methods) (34). This conjunction approach was chosen over contrasting schizophrenia with a pooled average of other disorders to avoid reducing single-disorder abnormalities or canceling out opposing effects during averaging.

Control Analyses. Using jackknife and other post hoc analyses, we tested for disproportionate influences on results by single studies, overlapping subject samples, seed regions, and demographic or clinical variables (age, illness duration, symptom severity, medication). To address methodological heterogeneity within the included studies, we tested for the influence of factors such as global signal regression, eyes open or closed during scanning, and duration of resting-state fMRI scanning (for details, see Supplemental Methods).

Meta-analysis of GMV Changes in Schizophrenia

To study substantial dysorganization of intrinsic connectivity, we additionally performed a meta-analysis of structural MRI studies in schizophrenia, following previous meta-analyses (25,26). PubMed, Web of Science, EMBASE, and reference lists of reviews and eligible articles were searched through January 1, 2017, using the keywords "schizo* AND (VBM OR voxel-based morphometry)" (Figure 1B). All structural MRI studies performing whole-brain VBM and comparing patients with schizophrenia with HC subjects were included according to MOOSE guidelines (for details, see Supplemental Methods) (37). Peak coordinates of significantly increased or decreased GMV in patients were extracted from each study and converted to Montreal Neurological Institute space if necessary. MKDA meta-analysis of peak effects was conducted as described above (contrasts: SZP > HC, SZP < HC), identifying brain regions of consistently increased or decreased regional GMV in schizophrenia (significance threshold $p < .05$ family-wise error rate–corrected, height-based and extent-based). Jackknife and post hoc analyses tested for disproportionate influences of single studies and methodological issues, such as modulation during VBM (Supplemental Methods). As a control analysis, we also conducted a transdiagnostic GMV meta-analysis comprising schizophrenia, MDD, bipolar disorder, addiction, and anxiety to identify GMV changes specific to schizophrenia (Supplemental Methods).

Multimodal Conjunction of Four-Disorder–Specific Dysconnectivity and Abnormal GMV in Schizophrenia

For each seed network, we investigated the overlap of four-disorder–specific hyperconnectivity or hypoconnectivity in schizophrenia with GMV increase or decrease in schizophrenia via conjunction of thresholded meta-analytic result maps ($p < .00064$ accounting for four-tailed testing) (Supplemental Methods) (34,40). As control analysis, we also overlapped four-disorder–specific hyperconnectivity or hypoconnectivity with four-disorder–specific GMV increase or decrease in schizophrenia via conjunction (Supplemental Methods).

RESULTS

For the iFC meta-analysis, 162 studies from 173 publications comprising 4962 patients across five psychiatric disorders and 4575 HC subjects were selected (Supplemental Table S1), including 59 schizophrenia studies with 2069 patients and 2106 HC subjects (Supplemental Tables S2–S6 show characteristics of included studies for each disorder). The number of studies per seed network and disorder is shown in Supplemental Table S7. IFC seeds used by schizophrenia studies are shown in Supplemental Table S8 and Figure S7. For the GMV meta-analysis, 127 studies with 6311 patients with schizophrenia and 6745 HC subjects were included (Supplemental Table S9).

Network Dysconnectivity in Schizophrenia

We identified significant within-network and between-network hyperconnectivity and hypoconnectivity of prefrontal limbic networks (LIM, FPN, DMN, SAL) and ASM in patients with schizophrenia compared with HC subjects, largely replicating results of a recent meta-analysis (23) (Supplemental Figure S8A and Table S10; detailed description in Supplemental Results). Control analyses showed no significant influence of any study; subject sample; seed region; age; illness duration; symptom severity; medication; or methodological factors, such as global signal regression, eyes open or closed, or scan duration (Supplemental Results).

Single-Disorder–Specific Network Dysconnectivity in Schizophrenia

This analysis and subsequent analyses were conducted only for LIM, FPN, DMN, and SAL, as for other networks, not all disorders provided at least three studies per network (Supplemental Table S7). We observed only hyperconnectivity or hypoconnectivity in schizophrenia (vs. HC subjects) that was significantly stronger than hyperconnectivity or hypoconnectivity in another disorder (vs. HC subjects). For all networks and across-disorder comparisons, no weaker single-disorder–specific hyperconnectivity or hypoconnectivity was found in schizophrenia.

Single-Disorder–Specific Hyperconnectivity. For LIM, hyperconnectivity with DMN (cluster in pons and cerebellum) was specifically stronger in schizophrenia compared with MDD, bipolar disorder, and addiction (but not anxiety), and hyperconnectivity with FPN (cluster covering right caudate and putamen) was stronger compared with MDD and bipolar disorder (Figure 2 and Supplemental Tables S11–S14). For FPN, we found stronger hyperconnectivity with ASM in left lateral postcentral gyrus compared with MDD, bipolar disorder, addiction, and anxiety. Concerning DMN, within-network hyperconnectivity was stronger in the left ventrolateral prefrontal cortex and frontal operculum in schizophrenia compared with MDD and bipolar disorder. For SAL, no single-disorder–specific hyperconnectivity was observed in schizophrenia compared with any disorder.

Single-Disorder–Specific Hypoconnectivity. For LIM, hypoconnectivity with SAL was specifically stronger in right insula in schizophrenia compared with MDD, bipolar disorder, addiction, and anxiety, and hypoconnectivity with DMN was stronger in right superior temporal gyrus, amygdala, bilateral anterior cingulate, and medial prefrontal cortex compared with bipolar disorder (Figure 3 and Supplemental Tables S11–S14). For FPN, we found stronger hypoconnectivity with bilateral thalamus [peaking in mediodorsal nucleus according to

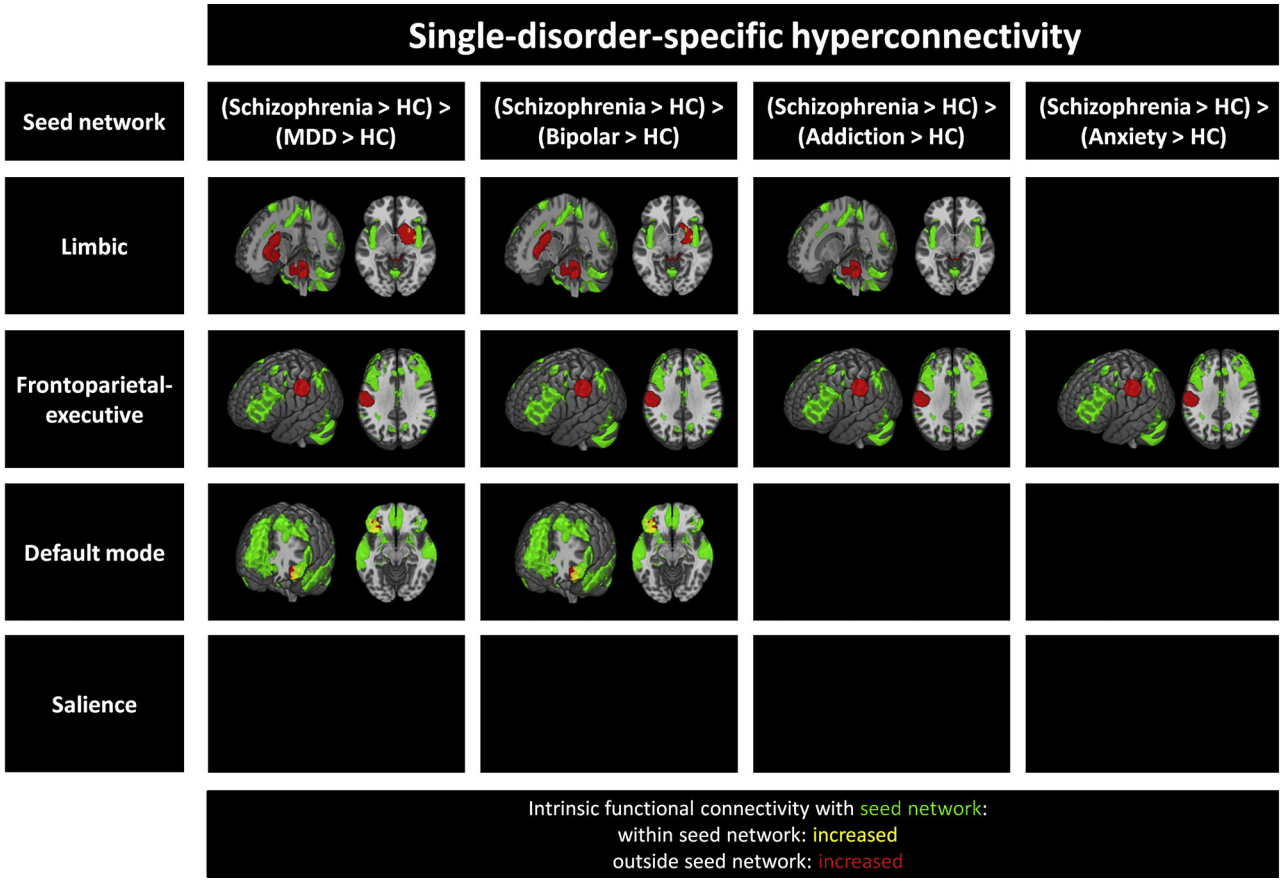

Figure 2. Single-disorder–specific hyperconnectivity: stronger intrinsic functional connectivity hyperconnectivity in schizophrenia versus other psychiatric disorders. Meta-analytic result clusters of single-disorder–specific intrinsic functional connectivity hyperconnectivity in schizophrenia (vs. healthy control [HC] subjects) compared with hyperconnectivity of other psychiatric disorders, i.e., major depressive disorder (MDD), bipolar disorder, addiction, and anxiety (vs. HC). Result clusters reflect brain regions of stronger within-network hyperconnectivity (yellow) or between-network or outside-network hyperconnectivity (red) with the respective seed network in schizophrenia compared with consistent hyperconnectivity of other disorders. Note that we did not observe weaker hyperconnectivity in schizophrenia compared with other disorders. Disorder-specific intrinsic functional connectivity changes were restricted to changes in patients with schizophrenia compared with HC subjects via conjunction analysis. Reported results are significant for $p < .005$. Note that correction for multiple testing (familywise error correction for significance threshold $p < .05$) was performed for the two input maps (i.e., the meta-analytic result maps) to conjunction analysis. Results are overlaid on the corresponding seed network (green).

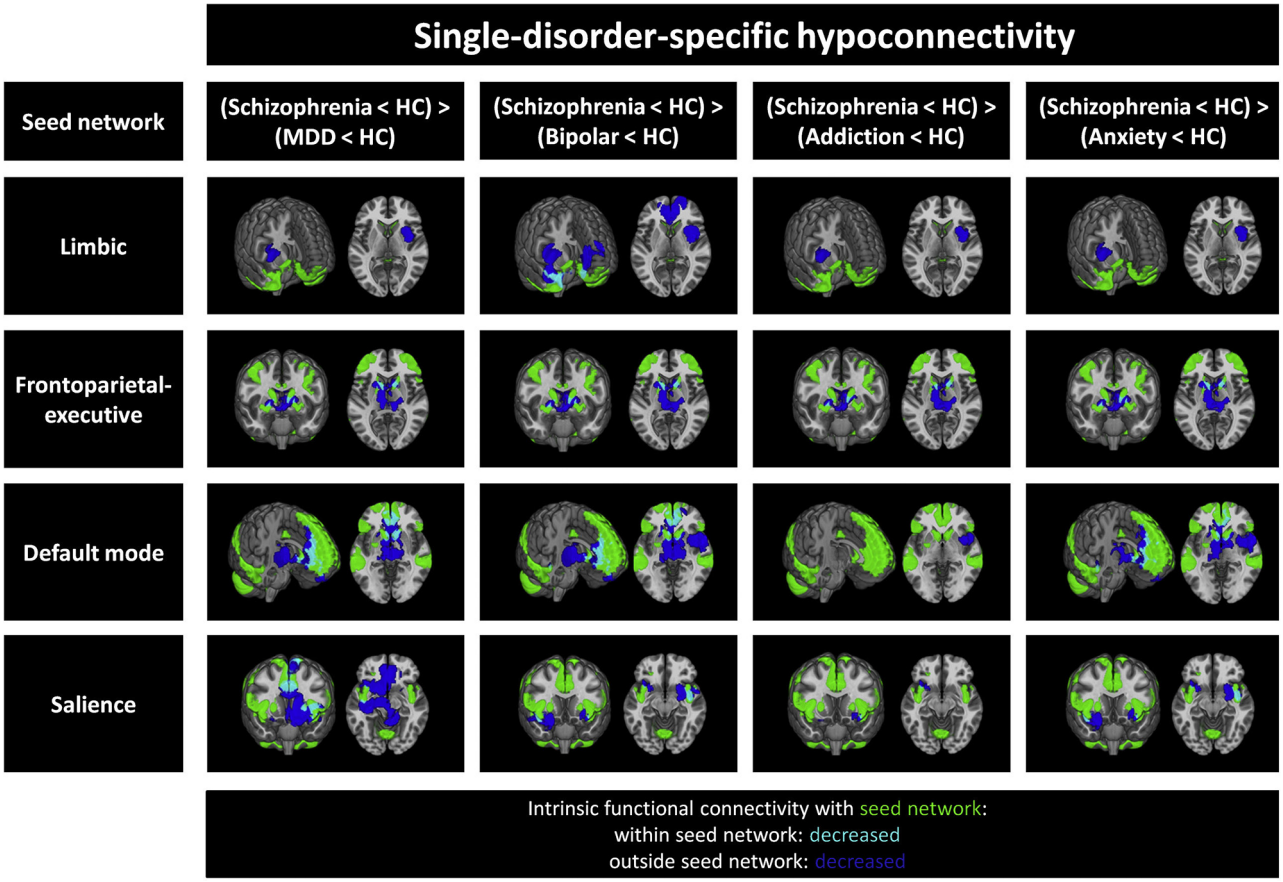

Figure 3. Single-disorder–specific hypoconnectivity: stronger intrinsic functional connectivity hypoconnectivity in schizophrenia versus other psychiatric disorders. Meta-analytic result clusters of single-disorder–specific intrinsic functional connectivity hypoconnectivity in schizophrenia (vs. healthy control [HC] subjects) compared with hypoconnectivity of other psychiatric disorders, i.e., major depressive disorder (MDD), bipolar disorder, addiction, and anxiety (vs. HC). Result clusters reflect brain regions of stronger within-network hypoconnectivity (cyan) or between-network or outside-network hypoconnectivity (blue) with the respective seed network in schizophrenia compared with consistent hypoconnectivity of other disorders. Note that we did not observe weaker hypoconnectivity in schizophrenia compared with other disorders. Disorder-specific intrinsic functional connectivity changes were restricted to changes in patients with schizophrenia compared with HC subjects via conjunction analysis. Reported results are significant for $p < .005$. Note that correction for multiple testing (familywise error correction for significance threshold $p < .05$) was performed for the two input maps (i.e., the meta-analytic result maps) to conjunction analysis. Results are overlaid on the corresponding seed network (green).

WFU_PickAtlas (41)] and caudate compared with MDD, bipolar disorder, addiction, and anxiety. Concerning DMN, stronger hypoconnectivity was observed with SAL in right insula and anterior cingulate compared with bipolar disorder, addiction, and anxiety (but not MDD); with LIM in left frontal pole compared with anxiety disorder; and with thalamus (outside the network mask) and caudate in MDD, bipolar disorder, and anxiety (but not addiction). SAL showed stronger hypoconnectivity with DMN and LIM, covering left anterior insula and putamen, right orbitofrontal cortex, and superior temporal gyrus compared with MDD, bipolar disorder, addiction, and anxiety (for MDD, clusters extended more into striatum, anterior cingulate, and brainstem).

Four-Disorder–Specific Network Dysconnectivity in Schizophrenia

Four-disorder–specific hyperconnectivity or hypoconnectivity in schizophrenia was investigated by conjunction across all four single-disorder–specific hyperconnectivity or hypoconnectivity maps.

Four-Disorder–Specific Hyperconnectivity. For FPN, four-disorder–specific hyperconnectivity in schizophrenia was found with ASM in left lateral postcentral gyrus (Figure 4 and Supplemental Table S15). For LIM, DMN, and SAL, no four-disorder–specific hyperconnectivity was found.

Four-Disorder–Specific Hypoconnectivity. For LIM, four-disorder–specific hypoconnectivity in schizophrenia was found with SAL in right insula (Figure 4 and Supplemental Table S15). For FPN, we found four-disorder–specific hypoconnectivity with bilateral thalamus and caudate (mainly outside the network mask). SAL showed four-disorder–specific hypoconnectivity with DMN in left anterior insula and putamen. For DMN, no four-disorder–specific hypoconnectivity was found.

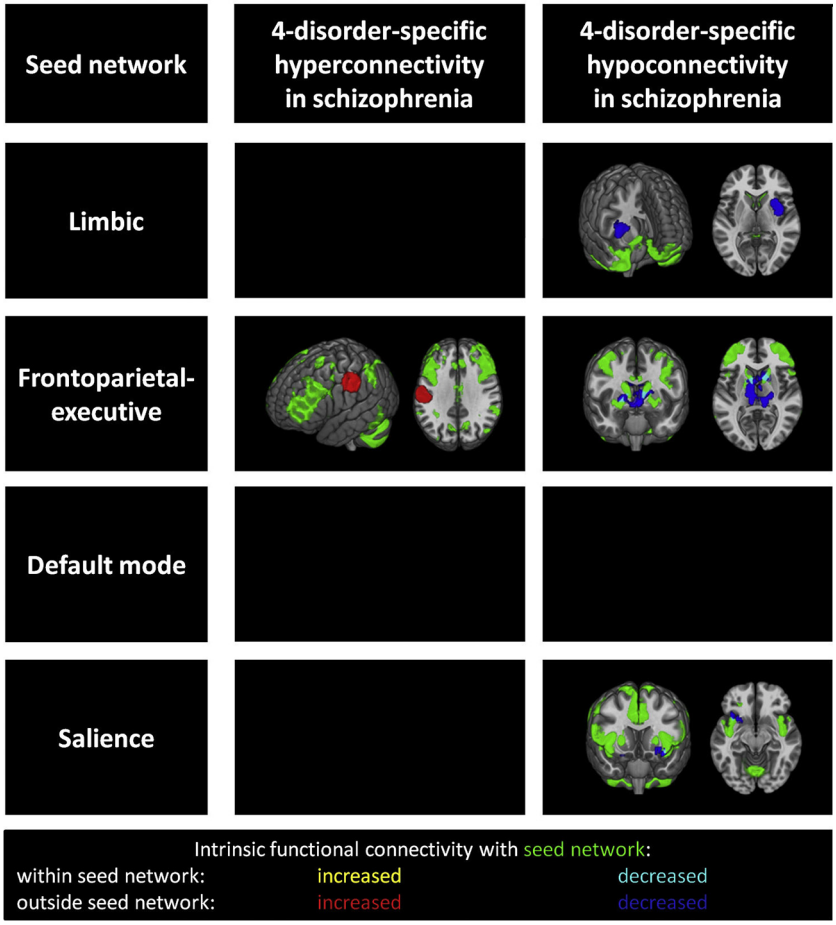

Figure 4. Four-disorder–specific dysconnectivity in schizophrenia. Result of conjunction across all four single-disorder–specific hyperconnectivity or hypoconnectivity maps (schizophrenia vs. major depressive disorder, bipolar disorder, addiction, and anxiety). Result clusters reflect brain regions of stronger within-network hyperconnectivity (yellow), between-network or outside-network hyperconnectivity (red), within-network hypoconnectivity (cyan), or between-network or outside-network hypoconnectivity (blue) with the respective seed network in schizophrenia compared with other disorders. Reported results are significant for $p < .00001$. Results are overlaid on the corresponding seed network (green).

Regional GMV Changes in Schizophrenia

Decreased GMV in schizophrenia was found for bilateral insula, superior temporal gyrus, anterior cingulate and medial prefrontal cortices, lateral postcentral gyrus, medial thalamus, striatum, and amygdala, replicating previous meta-analyses (Supplemental Figure S8B and Table S16) (26). Increased GMV was observed for bilateral cerebellum and pons (more pronounced in right hemisphere). Control analyses showed no significant influence of any study or methodological factors such as modulation during VBM (Supplemental Results). A further control analysis revealed four-disorder–specific GMV increase in cerebellum and pons and four-disorder–specific GMV decrease in insula, superior temporal gyrus, medial prefrontal cortex, mediodorsal thalamus, caudate, and amygdala (Supplemental Results).

Conjunction of Four-Disorder–Specific Dysconnectivity and Abnormal GMV in Schizophrenia—Specific Substantial Dysconnectivity

GMV decrease converged with four-disorder–specific hyperconnectivity in left lateral postcentral gyrus (for FPN) and with four-disorder–specific hypoconnectivity on bilateral insula (for SAL and LIM), bilateral caudate and left putamen (for SAL and FPN), and bilateral medial thalamus (for FPN) (Figure 5 and Supplemental Table S17). No overlap of GMV increase and four-disorder–specific hyperconnectivity or hypoconnectivity was found. As control, conjunction of four-disorder–specific dysconnectivity with four-disorder–specific GMV changes in schizophrenia showed convergence of GMV decrease and hypoconnectivity on anterior insula (for SAL and LIM) and mediodorsal thalamus (for FPN) (Supplemental Results and Supplemental Discussion).

DISCUSSION

To identify characteristic changes in intrinsic brain networks in schizophrenia, we performed a transdiagnostic multimodal meta-analysis of resting-state functional and structural MRI studies in schizophrenia, MDD, bipolar disorder, addiction, and anxiety. We found specifically aberrant FC for intrinsic prefrontal limbic networks in schizophrenia, where aberrant connectivity converged with reduced brain volume in insula, lateral postcentral cortex, striatum, and thalamus. This result provides, to our knowledge, first-time evidence for specific substantial dysconnectivity of intrinsic brain networks in schizophrenia. Integrating both specificity and multimodality

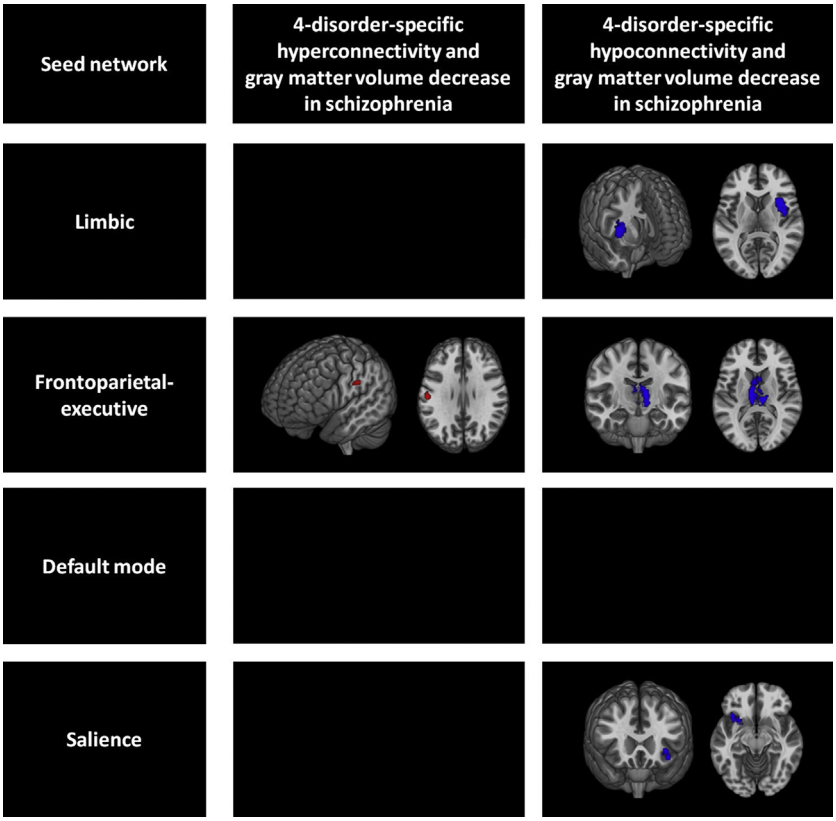

Figure 5. Specific substantial dysconnectivity in schizophrenia. Results of conjunction between four-disorder–specific hyperconnectivity or hypoconnectivity in schizophrenia (Figure 4) and gray matter volume (GMV) decrease or increase in schizophrenia (Supplemental Figure S8B). Red color represents overlap of GMV decrease and four-disorder–specific hyperconnectivity, blue color represents overlap of GMV decrease and four-disorder–specific hypoconnectivity; no overlap of GMV increase and four-disorder–specific hyperconnectivity or hypoconnectivity was observed. Reported results are significant for $p < .00064$. Note that correction for multiple testing (familywise error correction for significance threshold $p < .05$) was performed for the GMV meta-analytic result map as input to the conjunction analysis.

of imaging results based on a large number of patients, findings suggest insula, lateral postcentral cortex, striatum, and thalamus as characteristic targets of schizophrenia.

Specific Substantial Dysconnectivity in Schizophrenia

Our main result of specific substantial dysconnectivity in insula, lateral postcentral cortex, striatum, and thalamus in patients with schizophrenia (Figure 5) is based on three single results:

1. Dysconnectivity in schizophrenia. Based on resting-state fMRI studies comparing patients with schizophrenia and HC subjects, we observed extended iFC changes in patients (Supplemental Figure S8A). When compared with results of a recent meta-analysis with similar methodology (23), dysconnectivity patterns were largely identical for hypoconnectivity but more extended for hyperconnectivity; this is possibly due to the larger number of studies included in our meta-analysis. Post hoc analyses showed that dysconnectivity patterns were not disproportionately influenced either by clinical or demographic factors (age, illness duration, symptom severity, medication) or by methodological factors (global signal regression, eyes open or closed, scan duration), indicating the robustness of our results. Both consistency with previous studies and robustness of results support the valid basis of our approach on dysconnectivity.
2. Specific dysconnectivity. Comparing dysconnectivity of schizophrenia with that of other disorders, we found specific hyperconnectivity between FPN and ASM in lateral postcentral cortex and specific hypoconnectivity among LIM, SAL, FPN, and DMN in insula, thalamus, and striatum (Figure 4). Specificity here does not imply that observed brain changes are not present in other disorders. Rather, it means that these iFC changes are more pronounced in schizophrenia than in other disorders. The findings were based on single comparisons of schizophrenia hyperconnectivity or hypoconnectivity with MDD, bipolar disorder, addiction, and anxiety disorder (Figures 2 and 3), plus subsequent conjunction across comparisons (Figure 4). Single-disorder–specific dysconnectivity demonstrates that both hyperconnectivity and hypoconnectivity were consistently stronger in schizophrenia independent of network or across-disorder contrast, indicating a general pattern of increased dysconnectivity in schizophrenia (detailed discussion of single-disorder contrasts is provided in Supplemental Discussion). Furthermore, specific dysconnectivity that is consistent across comparisons with other disorders indicates that increased dysconnectivity in schizophrenia converges on selected regions within distinct intrinsic networks, such as thalamus with regard to FPN or striatum with regard to SAL and FPN (Figure 4).
3. Specific substantial dysconnectivity. Our GMV meta-analysis revealed aberrant regional brain volumes in schizophrenia for prefrontal limbic regions, lateral

postcentral and superior temporal gyrus, striatum, thalamus, and pons and cerebellum (Supplemental Figure S8B). Control analyses showed that methodological issues such as modulation during VBM did not influence results. GMV changes were consistent with findings of previous meta-analyses (25,26) and mega-analysis (20). Notably, results were more circumscribed than findings of region of interest–based GMV meta-analyses (27,28), which can detect GMV changes in focused regions that are not detectable via whole-brain approaches owing to lower statistical power.

Putting results 2 and 3 together via multimodal conjunction analysis, we found that four-disorder–specific dysconnectivity in schizophrenia converged with reduced gray matter volume in insula, lateral postcentral cortex, striatum, and thalamus (Figure 5), meaning that specific dysconnectivity was substantial in these regions. Three observations are remarkable. First, all clusters of four-disorder–specific hyperconnectivity or hypoconnectivity were located in areas of abnormal GMV and thus survived conjunction; second, disorder-specific hyperconnectivity or hypoconnectivity overlapped only with reduced GMV; third, reduced GMV overlapped with both hyperconnectivity and hypoconnectivity, implying a general link between GMV decrease and hyperconnectivity or hypoconnectivity rather than a unidirectional association between reduced GMV and reduced iFC. Specific substantial dysconnectivity suggests insula, lateral postcentral cortex, striatum, and thalamus as specific targets of schizophrenia. Implications of these findings for distinct microscopic pathophysiologies (e.g., striatum and dopamine dysfunction) and behavioral impairments (e.g., medial thalamus and corticocortical communication in domain-general prefrontal networks) are discussed in detail in Supplemental Discussion.

Our finding integrates previous large-scale models of schizophrenia, most notably models of aberrant corticostriatopallidothalamocortical circuits (4,6,42,43), thalamocortical dysconnectivity (44,45), and insular dysfunction (46–48). With respect to these system-based models of schizophrenia, the current study integrates distinct models by providing direct statistical evidence that different large-scale brain systems are characteristically altered in schizophrenia. In contrast, our approach allows no conclusions regarding whether common or distinct microscopic mechanisms underlie large-scale changes. Notably, the output map in Figure 5, representing statistical summary across multiple studies, should not be interpreted such that all patients with schizophrenia exhibit all observed alterations. Like each statistical summary map, this map is an abstraction of brain changes in schizophrenia that does not really exist (as a kind of essence); it rather characterizes a population of heterogeneous instances (i.e., patients) that are similar to this abstract map, but to variable degrees. Likewise, changes in both investigated modalities (iFC and GMV) need not necessarily coincide in one patient. In this sense and with respect to previous system-based models, the widespread and multimodal spatial pattern of specific substantial dysconnectivity implies a remarkable heterogeneity of the schizophrenia spectrum for distinct pathophysiological pathways.

Clinical Implications—Developing Diagnostic Tools for Schizophrenia

Specific substantial dysconnectivity in distinct target regions has important clinical implications. Recent transdiagnostic meta-analyses mostly searched for common structural or functional abnormalities across psychiatric disorders (26,36), whereas we looked for specific changes separating schizophrenia from other disorders. This approach is consistent with a recent line of research using multivariate pattern classification of neuroimaging markers for differential diagnosis of psychiatric diseases (49,50). Schizophrenia was discriminated from bipolar disorder using structural MRI (51) and task fMRI (52) and from MDD using structural and diffusion MRI (53). To enable the transfer of our statistical summary maps into single-subject–level biomarkers, several approaches are possible: 1) improving reliability of MRI measures within and across subjects and scanners; 2) establishing differential diagnostic thresholds of large-scale system-level scalar markers (e.g., weighted multisystems sum scores) based on large subject samples—we would speculate that schizophrenia, although itself a heterogeneous spectrum, is located at one end of the spectrum of psychiatric disorders (e.g., always stronger hypoconnectivity compared with both HC subjects and other disorders); 3) focused or targeted pattern classification studies followed by receiver operating characteristic curve analyses using the multimodal system-level patterns identified by our study (e.g., insular, striatal, and thalamic GMV and network iFC) instead of whole-brain patterns; 4) longitudinal studies testing prognostic capabilities of our findings (e.g., in prodromal stages) or applicability in therapy monitoring.

Limitations

First, this meta-analysis was restricted to seed-based resting-state FC, the most frequently used method investigating iFC. Other methods, such as independent component analysis, Granger causality, or graph analysis, had to be excluded (Supplemental Table S18), as these methodologically different iFC measures would confound the meta-analysis or could not be unambiguously assigned to one specific seed network (e.g., independent component analysis components) (32). Second, the number of included studies differed considerably across disorders and networks, allowing transdiagnostic meta-analyses only for four of seven networks. We controlled for this analysis asymmetry by first synthesizing studies for each disorder separately and then comparing across disorders. Owing to the low number of studies for some disorders and networks (e.g., three bipolar disorder studies for FPN), single studies could bias or inflate meta-analytic effects. We controlled for such possible disproportionate influences via jackknife-analyses. Third, we included studies covering a broad range of age, illness duration, and symptom severity to ensure maximal coverage. Furthermore, imaging parameters (eyes open or closed, scan duration) and preprocessing (global signal regression yes or no), which are still debated topics, varied across studies. Post hoc analyses showed that no demographic or clinical or methodological variable disproportionately influenced results. Fourth, partially overlapping subject samples across studies may bias results. We controlled for partial nonindependence via jackknife analyses,

showing no disproportionate influence of any study (54). Fifth, we used VBM-based regional GMV to describe structural abnormalities. Future studies should consider structural connectivity or, particularly concerning development of prognostic markers, cortical thickness and gyrification (55). Further studies could focus iFC analyses on brain regions with GMV abnormalities, thus investigating the effect of impaired structure on supported functions.

Conclusions

We provide evidence for specific substantial dysconnectivity in schizophrenia in insula, lateral postcentral cortex, striatum, and thalamus.

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