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Common Dysfunction of Large-Scale Neurocognitive Networks Across Psychiatric Disorders

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ABSTRACT

BACKGROUND: Cognitive dysfunction is one of the most prominent characteristics of psychiatric disorders. Currently, the neural correlates of cognitive dysfunction across psychiatric disorders are poorly understood. The aim of this study was to investigate functional connectivity and structural perturbations across psychiatric diagnoses in three neurocognitive networks of interest: the default mode network (DMN), the frontoparietal network (FPN), and the salience network (SN).

METHODS: We performed meta-analyses of resting-state functional magnetic resonance imaging whole-brain seed-based functional connectivity in 8298 patients (involving eight disorders) and 8165 healthy control subjects and a voxel-based morphometry analysis of structural magnetic resonance imaging data in 14,027 patients (involving eight disorders) and 14,504 healthy control subjects. To aid the interpretation of the results, we examined neurocognitive function in 776 healthy participants from the Human Connectome Project.

RESULTS: We found that the three neurocognitive networks of interest were characterized by shared alterations of functional connectivity architecture across psychiatric disorders. More specifically, hypoconnectivity was expressed between the DMN and ventral SN and between the SN and FPN, whereas hyperconnectivity was evident between the DMN and FPN and between the DMN and dorsal SN. This pattern of network alterations was associated with gray matter reductions in patients and was localized in regions that subserve general cognitive performance.

CONCLUSIONS: This study is the first to provide meta-analytic evidence of common alterations of functional connectivity within and between neurocognitive networks. The findings suggest a shared mechanism of network interactions that may associate with the generalized cognitive deficits observed in psychiatric disorders.

Keywords: Connectomics, Default mode network, Frontoparietal network, Meta-analysis, Resting-state fMRI, Salience network

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Contemporary psychiatry is rooted in the notion that psychiatric disorders are distinct independent categories with unique clinical presentations. However, in everyday clinical practice, psychiatric disorders tend to have heterogeneous clinical presentations with high co-occurrence (1–3). A common feature of multiple psychiatric disorders is the presence of cognitive deficits, particularly in executive control, working memory, and salience processing (4–6). Moreover, the presence of cognitive dysfunction has been found to have common neurobiological correlates in the dorsolateral prefrontal cortex (dlPFC), insula, and dorsal anterior cingulate cortex (dACC) across different psychiatric disorders (7,8). Collectively, these findings suggest that cognitive impairment may be a transdiagnostic feature of psychiatric disorders (9). Such cognitive dysfunction cannot be explained by localized changes in a small number of regions (10–12); instead, this dysfunction appears to arise from functional alterations within and between large-scale neural networks, consistent with the notion of psychiatric disorders as disconnection syndromes. Thus, studying the pathoconnectome associated with cognitive deficits across multiple psychiatric disorders may allow the identification of transdiagnostic neurobiological mechanisms that underlie multiple forms of psychopathology (13–15).

Menon proposed that, among the functional networks identified in the human brain, there are three core neurocognitive networks that may be affected in multiple psychiatric disorders: the default mode network (DMN), the frontoparietal network (FPN), and the salience network (SN) (16). The DMN, which is mainly composed of the medial PFC (mPFC), posterior cingulate cortex (PCC), and lateral temporal cortex, supports internally oriented attention and self-monitoring, among other functions (17). The FPN, including the dlPFC, dorsomedial PFC, and dorsolateral parietal cortex, is implicated in executive control (18,19). Finally, the SN, consisting of the dACC, insula, and caudate, is involved in orienting toward salient external stimuli and internal events (16,20). A number of recent studies have demonstrated that functional connectivity within

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and between these neurocognitive networks is closely related to cognitive deficits in most psychiatric disorders (15,21,22).

Currently, however, our understanding of the patho-connectomics of cognitive dysfunction across psychiatric disorders is hampered by several limitations in the existing literature such as small sample sizes, inconsistent recruitment criteria, and heterogeneous results. Meta-analyses can be used to test for homogeneous and reliable patterns in the existing literature (23,24). Our recent meta-connectomic analysis across 182 whole-brain resting-state functional magnetic resonance imaging (R-fMRI) studies, which included 13,375 individuals (6683 patients and 6692 healthy control subjects), revealed several regions, including the ventromedial PFC, dlPFC, and motor cortex, with functional alterations across disorders (25). However, this meta-analysis did not consider the functional connectivity between large-scale neurocognitive networks and was therefore unable to reveal the neural basis of transdiagnostic cognitive dysfunction. In addition, this meta-analysis used R-fMRI data without considering possible alterations in gray matter volume. Therefore, whether functional architecture between large-scale neurocognitive networks across disorders is associated with structural perturbations remains unclear. Collectively, the identification of multimodal alterations of large-scale neurocognitive networks across disorders could help elucidate transdiagnostic functional and structural mechanisms underlying cognitive dysfunction.

To address these issues, we conducted whole-brain meta-analyses of 242 R-fMRI and 363 structural MRI studies to examine multimodal alterations of large-scale neurocognitive networks across psychiatric diagnoses, followed by graph-based analysis of R-fMRI data in 766 healthy subjects to explore the cognitive function of network connectivity. First, we hypothesized altered functional connectivity within and between the three neurocognitive networks of interest across psychiatric disorders. Second, we hypothesized multimodal disruption of these neurocognitive networks, with regions showing functional alterations also showing gray matter loss. Third, functional connectivity alterations across psychiatric disorders would be localized in regions that subserve distinct aspects of cognitive performance in healthy participants.

METHODS AND MATERIALS

Dataset Overview

This study included three large datasets (Table 1). Dataset 1, which comprised 242 whole-brain seed-based functional connectivity (SB-FC) R-fMRI studies, was used to detect common network alterations across psychiatric disorders. Dataset 2, which included studies of 363 whole-brain voxel-based morphometry (VBM) analyses with structural MRI data, was used to test for gray matter volumetric changes across psychiatric disorders. Dataset 3, which included R-fMRI data from 766 healthy participants from the Human Connectome Project, was used to determine whether this network connectivity identified in patients was associated with cognitive performance on behavioral tests.

SB-FC Meta-analysis (Dataset 1)

Study Selection. A stepwise procedure was used to search the relevant studies by adopting the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org). Studies published in English before February 2017 were identified by searching five online public datasets: PubMed, Neurosynth, ScienceDirect, Web of Science, and BrainMap. Studies including patients with Axis I psychiatric diagnoses were selected for further analysis. The selected studies were restricted to whole-brain R-fMRI studies using voxelwise SB-FC to compare differences between patients and healthy control groups (see Supplement). These criteria led to the inclusion of 242 SB-FC studies of eight psychiatric disorders with 8298 patients and 8165 healthy control subjects (Supplemental Figures S1 and S2 and Supplemental Table S1). The eight psychiatric disorders include attention-deficit/hyperactivity disorder, anxiety disorders, autism spectrum disorder, bipolar affective disorder, major depressive disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and schizophrenia.

Data Extraction. To identify alterations in functional connectivity in case-control studies, we extracted information reflecting the locations of the seeds and the peak coordinates of significant between-group SB-FC differences, which reflect group-level differences between patients and healthy control subjects. Seeds were categorized into three seed networks defined by our previous voxelwise modular detection (25): the DMN, FPN, and SN (Figure 1A and details in the Supplement). The effects of SB-FC were categorized into two groups: hypoconnectivity (patients $<$ healthy control subjects) and hyperconnectivity (patients $>$ healthy control subjects).

Multilevel Kernel Density Analysis. SB-FC meta-analysis (26,27) was performed using the multilevel kernel density analysis (MKDA) toolbox (https://github.com/canlab/Canlab_MKDA_MetaAnalysis). We first converted the

Table 1. Datasets and Demographics Included in This Study

	Dataset 1		Dataset 2		Dataset 3
	Patients	Healthy Control Subjects	Patients	Healthy Control Subjects	Healthy Subjects
Subjects, *n*	8298	8165	14,027	14,504	766
Gender, Male/Female, *n*	4809/3247[a]	4594/3328[a]	8083/5693[a]	8085/6172[a]	331/435
Age, Years, Mean ± SD	28.89 ± 11.79[b]	28.63 ± 11.35[b]	31.87 ± 12.42[b]	31.12 ± 12.08[b]	22–36+[c]

[a]Gender information was extracted from 237 and 352 available studies by summing the exact numbers in each study of datasets 1 and 2, respectively.
[b]Age information was extracted by averaging the mean and SD values across 235 and 355 studies in datasets 1 and 2, respectively.
[c]The symbol (+) represents that 5 of the included subjects in Human Connectome Project dataset were over 36 years old.

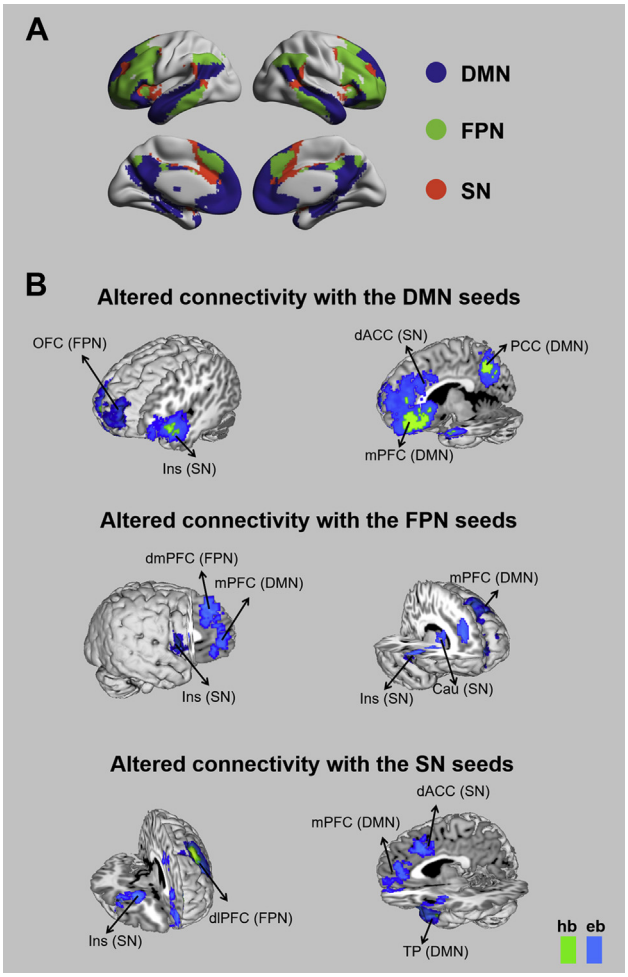

Figure 1. Functional connectivity differences between psychiatric disorders and healthy control subjects. **(A)** Spatial distribution of our three neurocognitive networks of interest. **(B)** Regions showing functional alterations with seeds in the default mode network (DMN), frontoparietal network (FPN), and salience network (SN), respectively, with pooling across patients with hypo- and hyperconnectivity. The three neurocognitive networks were mapped on the cortical surface using BrainNet Viewer (68). Cau, caudate; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; eb, extent-based threshold; hb, height-based threshold; Ins, insula; mPFC, medial prefrontal cortex; OFC, orbital frontal cortex; PCC, posterior cingulate cortex; TP, temporal pole.

coordinates reported in Talairach space to Montreal Neurological Institute standard space (26,28). Then, peak coordinates for seed–network comparisons in each study were convolved with a proposed spherical kernel between 10 and 15 mm (r = 15 mm) (29) thresholded at a maximum value of 1, resulting in an indicator map for each study. We repeated this using another spherical kernel radius (r = 13 mm) to assess the robustness of the findings. In each indicator map, a value of 1 suggested a significant effect in the neighborhood and a value of 0 indicated the absence of a peak in the local vicinity. Subsequently, a weighted average of all the indicator maps was computed to assess the density of effects. We then performed Monte Carlo simulation (10,000 iterations) with the weighted average density maps to establish a familywise error threshold for multiple comparisons. Density maps can be thresholded by two approaches: height-based and extent-based thresholding. The former indicates that the density at a given voxel is above the maximum expected over the whole brain by chance ($p < .05$), and the latter indicates that the density at that cluster exceeds the maximum expected in a cluster of a certain size by chance ($p < .001$) (see Supplement). In this study, we refer to within-network and between-network alterations to indicate that the effects fall within and beyond the functional network where the seeds are located, respectively.

Post Hoc Analyses. Four kinds of post hoc analysis were performed to validate the outcomes of our meta-analysis. First, to test whether the results were affected by head motion (30,31) and global signal (32,33), we separately repeated the meta-analysis with studies that did and did not remove head movement or global signal, and we compared the effect sizes for the different preprocessing strategies. Second, to assess whether the results were independent of the inclusion of a specific study, we performed a series of additional meta-analyses with leave-one-study-out (jackknife) validation (34) (see Supplement). Third, to evaluate whether the results for the DMN were biased by the fact that most of the studies focused on major depressive disorder and schizophrenia and that altered patterns within the neurocognitive networks were frequently reported in both disorders (27,35), we separately repeated the SB-FC meta-analysis of the DMN after excluding studies on depression and schizophrenia. Finally, Fisher's exact test was used to investigate the moderation of effects by clinical and demographic factors, including comorbidity, medication status, age, and gender (see Supplement).

VBM Meta-analysis (Dataset 2)

Whole-brain VBM meta-analysis of structural imaging studies was used to determine the structural substrates of altered functional connectivity across psychiatric disorders. Consistent with the meta-analysis of SB-FC studies, a similar procedure was performed to select studies related to VBM analysis. A total of 363 VBM studies of the same psychiatric disorders with 14,027 patients and 14,504 healthy control subjects were included (Supplemental Table S2 and Supplemental Figures S3 and S4). Peak coordinates with decreased and increased volumes for each study were separately extracted. VBM meta-analysis was also performed with the above-mentioned multilevel kernel density analysis algorithm. To reduce the effects of varying numbers of studies across disorders, maps of decreased and increased gray matter were separately created by performing a meta-analysis of the studies in which an equal number of VBM studies (decreased: 19; increased: 3) was randomly (N = 100) extracted for each disorder and further pooled. Finally, we separately performed cross-voxel Pearson correlation analysis between the average of the hypo- and hyperconnectivity maps and gray matter values to examine the structural substrates of altered functional connectivity.

Correlation Analysis Between Network Connectivity and Cognitive Performance (Datasets 1 and 3)

Next, we used the SB-FC meta-dataset and the Human Connectome Project dataset to examine which aspects of

cognitive function are associated with the neural networks that show altered functional connectivity across psychiatric disorders. This procedure involved the following three steps.

First, using dataset 1, we separately constructed binary networks of hypo- and hyperconnectivity based on the seed regions, referred to as seed nodes, within the neurocognitive networks and the regions showing between-group differences, referred to as target nodes, in the included studies (Supplemental Figure S5). Each seed coordinate from an individual study was smoothed with a 1-cm^3 sphere and compared with the high-resolution 1024-region template (36) (see Supplement). In each of the contrasts, an edge was defined as a pair of seed and target nodes. To assess whether a certain edge had a significantly greater frequency than expected by chance across the included contrasts, a nonparametric permutation test (N = 10,000) was performed with network-based statistic correction (37) (Supplemental Figure S6 and Supplement). The result was a pattern of hypo- and hyperconnectivity that significantly appeared across psychiatric disorders. Next, we divided this hypo- and hyperconnectivity pattern into within- and between-network patterns for each of our three cognitive networks of interest, namely the DMN, FPN, and SN.

Second, to test whether this pattern of hypo- and hyperconnectivity was associated with cognitive performance on behavioral tests, we used dataset 3, derived from the R-fMRI and broad cognitive assessment data of 766 healthy participants. For each subject, based on a 1024 high-resolution parcelation (36), a symmetric 1024 $\times$ 1024 functional connectivity matrix was constructed from the Pearson correlations between the time courses of each pair of regions. For each individual, we extracted the corresponding behavioral scores of 12 items involved in general cognitive function (see Supplement).

Third, for each of the 766 healthy subjects and for each group of edges, we computed the average correlation coefficients from the correlation matrix. Then, we calculated Spearman correlations between the average correlation coefficient of the edges and each of the 12 behavior scores across subjects (see Supplement); statistical inferences for each group of edges were made at $p < .05$ after Bonferroni correction (i.e., uncorrected $p < .05/6$, where 6 represents the number of groups among network connectivity).

RESULTS

Altered Functional Connectivity Within and Between Neurocognitive Networks

The SB-FC meta-analysis revealed common alterations in functional connectivity within and between our three neurocognitive networks (the DMN, FPN, and SN) (Figure 1A and Supplemental Table S3).

Within-Network Alterations. Psychiatric disorders showed functional alterations between the DMN seeds and regions of the mPFC and PCC, between the FPN seeds and the dorsomedial PFC, and between the SN seeds and regions of the dACC and right insula (Figure 1B and Supplemental Table S4). These alterations were not moderated by age, gender, comorbidity, or medication status ($p > .05$).

Between-Network Alterations. For the DMN, psychiatric disorders were characterized by functional alterations between the DMN seeds and the orbital frontal cortex in the FPN as well as regions of the dACC and left insula in the SN (Figure 1B and Supplemental Table S4). For the FPN, psychiatric disorders were associated with functional alterations between the FPN seeds and the rostromedial PFC in the DMN as well as regions of the right insula and caudate in the SN (Figure 1B and Supplemental Table S4). For the SN, psychiatric disorders were characterized by functional alterations between the SN seeds and the dlPFC in the FPN as well as regions of the rostromedial PFC and left temporal pole within the DMN (Figure 1B and Supplemental Table S4). Moreover, additional meta-analyses of studies that had removed head movement and global signal did not change our main findings (Supplemental Figures S7 and S8). These alterations were not moderated by age, gender, comorbidity, or medication status ($p > .05$).

Hypoconnectivity Versus Hyperconnectivity Across Psychiatric Disorders

Network alterations were further characterized in terms of hypoconnectivity versus hyperconnectivity in patients relative to healthy control subjects (Supplemental Table S5).

Within- and Between-Network Hypoconnectivity. Hypoconnectivity was observed within both the ventral DMN (e.g., the mPFC, vACC, and PCC) and the SN (e.g., the dACC and left insula) (Figure 2 and Supplemental Table S6). Moreover, hypoconnectivity was expressed between the DMN seeds and regions of the dACC and ventral insula in the SN as well as between the FPN seeds and the putamen in the SN (Figure 2A, B and Supplemental Table S6). The SN seeds revealed hypoconnectivity with regions of the PCC and left temporal pole in the DMN as well as with regions of the dlPFC and temporoparietal junction in the FPN (Figure 2C and Supplemental Table S6). Thus, the SN showed hypoconnectivity with the DMN as well as with the FPN.

Within- and Between-Network Hyperconnectivity. Hyperconnectivity was observed within both the dorsal DMN (e.g., the rostromedial PFC and precuneus) and the FPN (e.g., the dorsomedial PFC) (Figure 2 and Supplemental Table S6). Moreover, the DMN seeds showed hyperconnectivity with the dlPFC in the FPN and with the dorsal insula in the SN (Figure 2A and Supplemental Table S6). Hyperconnectivity was also expressed between the FPN seeds and the mPFC (Brodmann area 9) in the DMN (Figure 2B and Supplemental Table S6) and between the SN seeds and the precentral cortex in the sensorimotor network (Figure 2C and Supplemental Table S6). Thus, the DMN showed hyperconnectivity with the dorsal SN as well as with the FPN. Taken together, these findings indicate that hypo- or hyperconnectivity is most evident in regions implicated in executive control, self-monitoring, and salience orienting (17,19,20). Figure 3 presents a summary of the disrupted neurocognitive networks architecture across psychiatric disorders. These functional

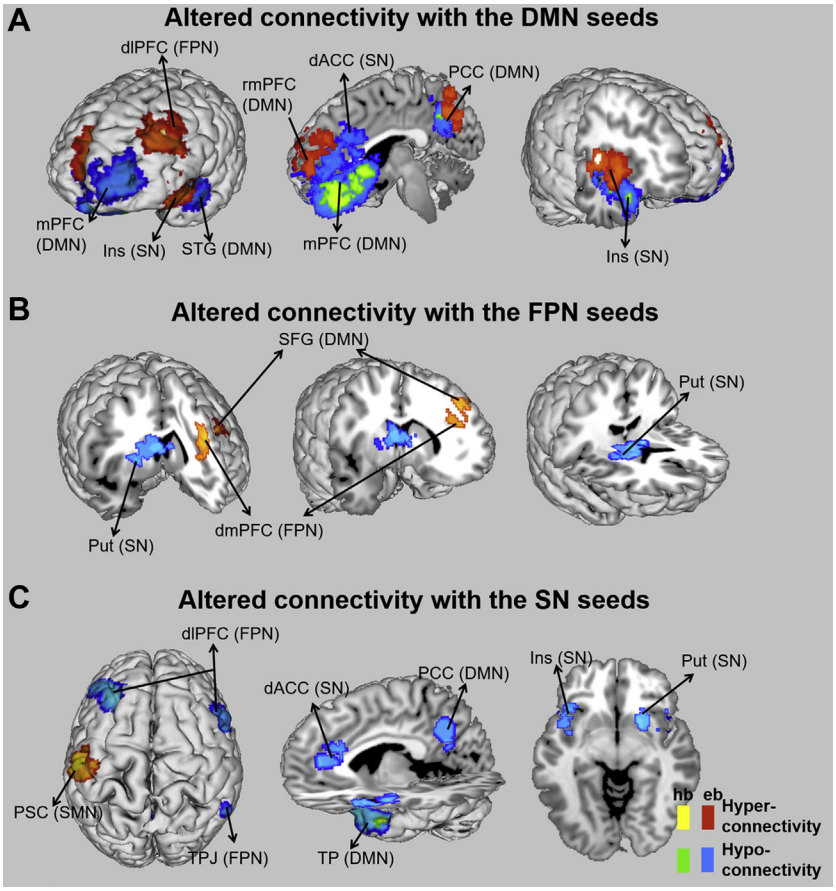

Figure 2. Hypo- and hyperconnectivity across psychiatric disorders. **(A)** Regions showing transdiagnostic default mode network (DMN) hypo- and hyperconnectivity. **(B)** Regions showing transdiagnostic frontoparietal network (FPN) hypo- and hyperconnectivity. **(C)** Regions showing transdiagnostic salience network (SN) hypo- and hyperconnectivity. dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; eb, extent-based threshold; hb, height-based threshold; Ins, insula; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; PSC, precentral cortex; Put, putamen; rmPFC, rostromedial prefrontal cortex; SFG, superior frontal gyrus; SMN, somatomotor network; STG, superior temporal gyrus; TP, temporal pole; TPJ, temporo-parietal junction.

alterations were not moderated by age, gender, comorbidity, or medication status ($p > .05$).

Common Gray Matter Reductions Across Psychiatric Disorders

To investigate whether a potential common anatomical signature underlies the altered network connectivity, we performed a VBM meta-analysis of 363 studies using dataset 2. This analysis revealed decreased gray matter volume in the mPFC, dACC, bilateral insula, dlPFC, and temporoparietal junction, all of which are among the regions showing altered network-level functional connectivity (Figure 4A and Supplemental Table S7). No significant region with increased volume was found across psychiatric disorders. The structural loss was not moderated by age, gender, comorbidity, or medication status ($p > .05$). Moreover, we found significant positive correlations between both the regions showing functional hypo- and hyperconnectivity and the gray matter values ($ps < 1.00 \times 10^{-10}$) (Figure 4A). These findings indicate cross-modality disruptions within the neurocognitive networks.

Behavioral Correlates of Network Connectivity

Finally, we examined which aspects of cognitive function are associated with the neural networks that show altered functional connectivity across psychiatric disorders. To test this hypothesis, we separately identified hypo- and hyperconnectivity that significantly appeared across psychiatric disorders (Supplemental Figure S9 and Supplemental Table S8). Among those connections showing lower values in patients relative to healthy control subjects, within-network DMN–ventral DMN connectivity was positively associated with performance in spatial orientation ($\rho = .10$, $p = .006$) and inhibition control ($\rho = .11$, $p = .002$), and between-network FPN–SN connectivity was positively correlated with fluid intelligence ($\rho = .10$, $p = .008$) (Figure 4B). Among those connections showing higher values in patients relative to healthy control subjects, between-network DMN–FPN connectivity was negatively correlated with behavioral performance in spatial orientation ($\rho = -.12$, $p < .001$), and within-network FPN–FPN connectivity was negatively associated with alertness ($\rho = -.14$, $p < .001$) (Figure 4B).

DISCUSSION

Our study revealed three main findings. First, psychiatric disorders are associated with common alterations of functional connectivity within and between neurocognitive networks. Second, common gray matter reductions within these neurocognitive networks are tightly associated with functional alterations. Third, common network alterations appear to be localized in regions that subserve different

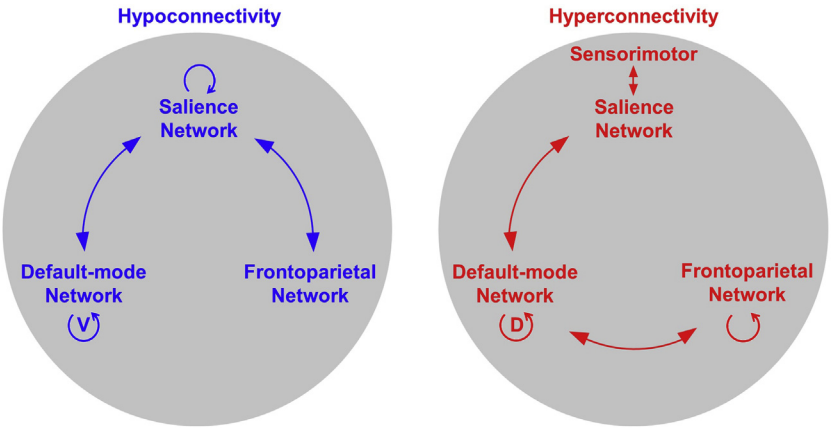

Figure 3. Disrupted functional architecture of neurocognitive networks across psychiatric disorders. A visual representation of the disrupted functional architecture of neurocognitive networks across psychiatric disorders identified in our investigation is shown. The default mode network (DMN) seeds were hypoconnected with the ventral DMN (represented as V in the left panel) and were hyperconnected with the dorsal DMN (represented as D in the right panel). In addition, the salience network exhibited hypoconnectivity with the frontoparietal network and DMN. In contrast, hyperconnectivity was evident between the salience network and DMN, between the frontoparietal network and DMN, and between the salience network and sensorimotor network. The blue and red arrows separately indicate hypoconnectivity and hyperconnectivity, respectively, and the circular arrows indicate within-network connectivity alterations.

aspects of cognitive performance. To our knowledge, this study is the first to provide meta-analytic evidence of shared connectivity alterations within and between networks associated with cognitive function. These findings suggest a shared mechanism of network interactions that contribute to the generalized cognitive deficits observed in psychiatric disorders.

Common Connectivity Alterations Within and Between Neurocognitive Networks

Consistent with our first hypothesis, our findings revealed disrupted functional connectivity within and between neurocognitive networks. There are at least two possible explanations. One is that such reduced functional connectivity is the result of heightened genetic susceptibility to psychiatric disorders (15,38). Consistent with this explanation, several studies have reported transdiagnostic genetic influences on major psychiatric disorders (39–42). A second possible explanation is that disrupted functional connectivity within and between neurocognitive networks is a marker of illness onset and/or progression, consistent with the observation that cognitive function deteriorates around the time an individual develops a mental illness (16,43).

During both the resting state and certain cognitive tasks, the SN plays a crucial role in modulating shifts between internal attention (which is largely subserved by the DMN) and external executive functions (which are largely subserved by the FPN) (16,44–47). This coordination between executive function and internal and external attention is thought to be critically impaired in most psychiatric disorders (16,20). Our findings extend the current literature by revealing that the SN exhibits hypoconnectivity with the FPN, which is involved in the processing of executive control and goal-directed regulation, and with the DMN, which contributes to self-referential processing. In contrast, hyperconnectivity is evident between the dorsal SN and the DMN as well as between the FPN and the DMN (Figure 3). This combination of hypo- and hyperconnectivity between the DMN and the SN is consistent with previous studies showing that distinct parts of the insula exhibit distinct patterns of functional connectivity in healthy subjects (48–50). The dorsal insula (characterized by hyperconnectivity with the DMN) is part of the cingulo-opercular subnetwork, which is critical for cognitive flexibility (51). In contrast, the ventral insula-dACC subnetwork (characterized by hypoconnectivity with the DMN) is part of the SN, which is thought to play a key role in motivational engagement (52). Thus, DMN coupling with different parts of the insula could reflect differential psychopathological presentations. We also found that the SN seeds were hyperconnected with the sensorimotor network, which plays a key role in the perception of external stimuli. A previous coactivation meta-analysis reported that the posterior insula, a component of the SN, is associated with sensorimotor processes (49), suggesting that basic sensory features of the environment have excessive influence on cognitive processing in the diseased brain (48). Thus, imbalanced communication between the SN and the sensorimotor network may help explain sensory processing alterations within a wider psychopathological profile in major psychiatric disorders (53–55).

Relationship Between Functional Connectivity and Structural Perturbations

Consistent with our second hypothesis, our VBM meta-analysis revealed that common gray matter reductions were localized within the neurocognitive networks and tightly associated with functional alterations. This provides support to the notion that neurocognitive networks are susceptible to gray matter loss across multiple psychiatric disorders; in contrast, we detected no common gray matter reductions in regions that were part of other networks (e.g., sensory, visual). Converging neuroimaging evidence suggests that the pattern of connectivity dysfunction among neurocognitive networks corresponds to structural perturbations across psychiatric disorders (8), suggesting that the structural properties of the brain place constraints on functional interactions occurring within and between networks. Notably, the previous structural MRI study found decreased volume in the regions of the mPFC, dACC, and insula and increased volume in the striatum in the psychiatric disorders (8). The pattern of decreased gray matter volumes was similar to our findings, but we did not observe any commonly increased volume across psychiatric disorders. This discrepancy might be caused by several factors, such as differences in included disorders, meta-analytic algorithms, and statistical methods, and the inclusion of

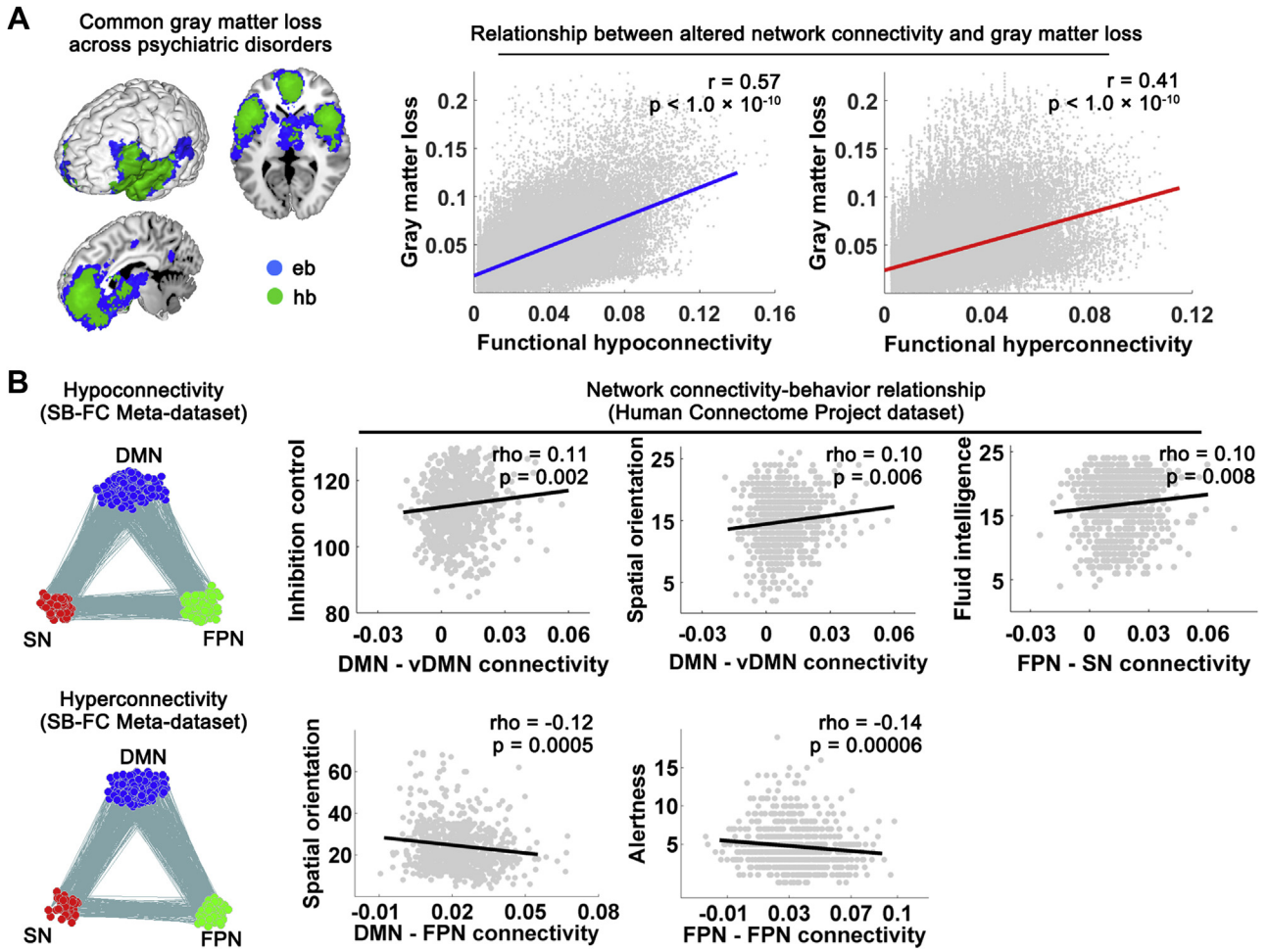

Figure 4. Structural substrates of functional connectivity alterations and its association with cognitive performance. **(A)** Decreased gray matter volume in patients relative to control subjects (left panel) and positive correlation between the regions showing functional alterations and structural perturbations (right panel). **(B)** Relationship between functional connections showing decreases and increases in patients and behavioral cognitive test performance in healthy volunteers. Here, the left panel shows a spring-embedded layout of nodes and edges that significantly decreased (i.e., hypoconnectivity) and increased (i.e., hyperconnectivity) within and between the default mode network (DMN), frontoparietal network (FPN), and salience network (SN) across psychiatric disorders. The right panel shows the relationship between the network connectivity and cognitive performance. eb, extent-based threshold; hb, height-based threshold; HCP, Human Connectome Project; SB-FC, seed-based functional connectivity; vDMN, ventral default mode network.

more up-to-date studies in the current meta-analysis. By combining R-fMRI and structural MRI data, our study extended the previous findings based on single-modality investigations.

Relationship Between Functional Connectivity and Cognitive Performance

Consistent with our third hypothesis, functional connectivity within the DMN was correlated with performance on tasks involving distinct aspects of cognition, including spatial orientation and inhibition control. Owing to the reciprocal relationship between the task-negative network (DMN) and the task-positive networks (FPN and SN), studies have shown that suppression of the DMN is related to improved cognitive control in healthy individuals (56,57). Hence, the current patterns of within-DMN alterations may reflect abnormal communication in internal self-monitoring processing and external cognitive flexibility in psychiatric disorders (16,35,58,59). Next, we observed that the DMN–FPN connectivity is associated with orientation. Previous studies have reported that connectivity between the DMN and FPN is important for the interplay between attention orientation and default mode processing and that mood disorders are associated with disrupted switching between resting and task-context processing (13,60). These studies support our finding that DMN–FPN connectivity is involved in orientation. In contrast, we found that fluid intelligence was associated with FPN–SN connectivity. This observation recapitulates the results of previous studies in which reduced connectivity between the dlPFC and insula was found during cognitive processing in major depression disorder (58,61).

Limitations and Future Work

Several issues need to be further addressed. First, owing to the limited number of studies on specific disorders, we were unable to examine diagnosis-specific network alteration. Even though, when analyzed separately, major depressive disorder and schizophrenia appear to show distinct connectivity patterns (Supplemental Figure S10), additional studies will be required to draw robust conclusions about individual disorders. Second, in our current study, differential weights of individual disorders in the number of included studies and sample size might have a disproportionate influence on the meta-analytic results. Future work with normalizing weights in each disorder might account for the overrepresentation of some disorders in the meta-analytic results. Third, given that only 30 studies reported mean head motion, we were unable to perform meta-regression analysis to remove the effects of head motion on our meta-analytic findings (62). In the future, the availability of more studies will allow the formal evaluation of the effects of head motion on connectivity patterns across psychiatric disorders. Fourth, in the SB-FC studies, the boundaries of the functional networks are dependent on the choice of seed regions. Thus, in our study, anatomical heterogeneity in the seed regions may have had an impact on the anatomical boundaries of canonical functional networks and the associated delineation of the connectivity patterns across psychiatric disorders. Therefore, future studies should test the anatomical effects of seed regions on the meta-analytic results. Fifth, although the current study detected differences in functional connectivity between patients with various psychiatric disorders and healthy control subjects, it is unclear whether these differences reflected deviation from the normal range of functional connectivity; this question would require a larger sample size to estimate normal individual variability across different ages and genders (63–65). Sixth, the orbitofrontal cortex and temporal lobes showed disrupted connectivity with the neurocognitive networks. Although functional image distortions were sensitive in these regions (66,67), the observed gray matter changes in the VBM meta-analysis suggested structural substrates underlying the functional alterations across psychiatric disorders. Finally, we found statistically significant associations between brain connectivity and behavior. However, these associations were relatively modest, and as such they can explain only a fraction of the interindividual variance in network connectivity; other possible explanations for such variance might include individual differences in cognition and behavior that were not modeled in our meta-analysis.

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ARTICLE INFORMATION

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