Research Paper

Global brain connectivity alterations in patients with schizophrenia and bipolar spectrum disorders

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Background: The human brain is organized into functionally distinct modules of which interactions constitute the human functional connectome. Accumulating evidence has implicated perturbations in the patterns of brain connectivity across a range of neurologic and neuropsychiatric disorders, but little is known about diagnostic specificity. Schizophrenia and bipolar disorders are severe mental disorders with partly overlapping symptomatology. Neuroimaging has demonstrated brain network disintegration in the pathophysiologies; however, to which degree the 2 diagnoses present with overlapping abnormalities remains unclear. **Methods:** We collected resting-state fMRI data from patients with schizophrenia or bipolar disorder and from healthy controls. Aiming to characterize connectivity differences across 2 severe mental disorders, we derived global functional connectivity using eigenvector centrality mapping, which allows for regional inference of centrality or importance in the brain network. **Results:** Seventy-one patients with schizophrenia, 43 with bipolar disorder and 196 healthy controls participated in our study. We found significant effects of diagnosis in 12 clusters, where pairwise comparisons showed decreased global connectivity in high-centrality clusters: sensory regions in patients with schizophrenia and subcortical regions in both patient groups. Increased connectivity occurred in frontal and parietal clusters in patients with schizophrenia, with intermediate effects in those with bipolar disorder. Patient groups differed in most cortical clusters, with the strongest effects in sensory regions. **Limitations:** Methodological concerns of in-scanner motion and the use of full correlation measures may make analyses more vulnerable to noise. **Conclusion:** Our results show decreased eigenvector centrality of limbic structures in both patient groups and in sensory regions in patients with schizophrenia as well as increased centrality in frontal and parietal regions in both groups, with stronger effects in patients with schizophrenia.

Introduction

Schizophrenia and bipolar-spectrum disorders (BD) are severe mental disorders that are leading causes of morbidity.[1] Although schizophrenia and BD are separate diagnostic entities, converging evidence suggests that the 2 disorders reflect different parts along the same continuum.[2,3] Schizophrenia has been conceptualized as a disorder of brain connectivity since the early 1900s,[4] and recent efforts enabled by in vivo neuroimaging approaches for delineating and exploring brain network abnormalities support the dysconnectivity hypothesis.[5–8] However, despite extensive research, sensitive and specific intermediate neuroimaging phenotypes have yet to be identified.

Resting-state fMRI (rs-fMRI) enables inference about the dynamics and correlates of functional brain networks.[9,10] Methods based on principles from graph theory, targeting the correlation patterns between brain regions (nodes) and their connections (edges), characterize global features of network organization.[11] Centrality measures probe the relative importance of nodes,[12,13] allowing for delineation of brain regions exhibiting hub-like properties, reflecting critical modules in the processing systems of the brain. Imaging studies applying centrality indices have identified regions of high centrality (hubs) overlapping with the default mode network (DMN).[14] Previous studies converge on frontoparietal and limbic dysfunction in individuals with schizophrenia and BD, respectively,[7,15,16] and have demonstrated

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reduced connectivity of high-degree hubs in those with schizophrenia.[16–18] Decreased centrality of critical hubs may point to less centralized and coordinated brain network functioning in individuals with schizophrenia.[18] However, the degree to which individuals with schizophrenia and BD present with unique and common global brain network alterations is unclear.

The question pertaining to clinical specificity is particularly relevant in light of recent work implicating high-centrality regions in a range of disorders,[19] demonstrating that perturbations to hub regions are more likely to be symptomatic than alterations in nonhub regions. Further, the results support that the spatial distribution of hub reductions yields an associated set of symptoms and corresponding diagnosis (i.e., specific clusters of symptoms are associated with specific subsets of hubs).[19] It is therefore conceivable that schizophrenia and BD are characterized by alterations in functional brain connectivity in high-centrality regions and, further, that the specific symptom profiles may reflect the specific hub regions involved. Indices of brain connectivity and its spatial distribution may thus provide novel information about the shared and unique brain network alterations and inform models of the pathogenic mechanisms of severe mental illness.

To this end our primary aim was to identify common and unique global brain connectivity differences in patients with BD and schizophrenia as well as patterns distinguishing the 2 patient groups from each other. Our secondary aim was to explore associations between brain connectivity and burden of different symptom domains. We assessed global brain functional connectivity using voxel-wise eigenvector centrality mapping (ECM) calculated from rs-fMRI data obtained from patients with schizophrenia and BD and healthy controls. We anticipated centrality reductions in hub regions across patient groups, with stronger reductions associated with more severe symptoms. Further, we hypothesized altered centrality of regions involved in sensorimotor and perceptual processing;[20–22] centrality decreases in frontal, anterior cingulate, precuneus and parietal regions in patients with schizophrenia;[18] and aberrant limbic centrality in patients with BD.[15] In order to address questions pertaining to regional specificity, we performed full-brain analyses with stringent corrections for multiple comparisons using permutation testing.

Methods

Participants

We recruited in- and outpatients from psychiatric hospital units in the Oslo, Norway, area. Healthy controls aged 18–40 years were invited to participate based on a random selection from the Norwegian National Population Register. Individuals with a history of head trauma, neurologic disorders, or pathological neuroradiological findings were excluded.

To be included in the patient samples, patients had to fully understand all the information given to them, including the fact that the study was voluntary and that they could withdraw at any time, and be able to provide informed consent. This ability was judged by a clinical psychologist or by a physician trained in psychiatry. Patients completed a clinical interview with a trained clinician that included history of illness and symptom measures. Diagnostic criteria were assessed using the Structured Clinical Interview for DSM-IV (SCID), and symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS).[24] We included patients with a range of schizophrenia-spectrum disorders (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, and psychosis not otherwise specified [NOS]); for simplicity, these disorders will be referred to collectively as schizophrenia throughout the paper unless otherwise specified. We also included patients with a bipolar spectrum-disorder (i.e., BDI, BDII, and BD NOS). Both the patient and control samples overlap with that of Kaufmann and colleagues,[22] although the present study includes an additional sample of patients with BD and the methods and objectives do not overlap.

We interviewed healthy controls using general questions about symptoms of severe mental illness as well the Primary Care Evaluation of Mental Disorders (PRIME-MD)[23] to ensure there was no history of a severe psychiatric disorder in controls themselves or in any of their close relatives, no diagnosis of drug abuse/dependency, and no somatic conditions interfering with brain functioning.

Written informed consent was obtained from all participants, and the Regional Committee for Medical Research Ethics South East Norway and the Norwegian Data Inspectorate approved our study protocol.

MRI acquisition

We obtained MRI scans using a General Electric (Signa HDxt) 3 T scanner with an 8-channel head coil at Oslo University Hospital, Ullevål, Norway. To reduce motion, participants were instructed to lie still, and their heads were fixed with foam pads.

Axial resting-state fMRI images were collected using a T_2*-weighted 2-dimensional gradient echo planar imaging (EPI) sequence with 203 volumes (repetition time [TR] 2638 ms, echo time [TE] 30 ms, flip angle 90°, acquisition matrix 64 × 64, in-plane resolution 4 × 4 mm, 45 slices, slice thickness 3 mm). The 3 first volumes were discarded in addition to 5 dummy volumes. Participants were instructed to relax with their eyes open.

We also collected a sagittal fast spoiled gradient echo T_1-weighted sequence (TR 7800 ms, TE 2.956 ms, inversion time [TI] 450 ms, flip angle 12°, in-plane resolution 1 × 1 mm, 166 slices, slice thickness 1.2 mm, acquisition time 7 min, 8 s).

MRI processing and analysis

T_1-weighted data were processed using FreeSurfer.[25] We used automated full brain segmentation[26] to provide brain masks for coregistration of fMRI volumes. Brain extracted data sets were visually inspected and manually edited if required.

The fMRI data were preprosessed using FEAT, part of the FMRIB Software Library,[27] including motion correction, brain extraction, spatial smoothing using a 6 mm full-width at half-maximum (FWHM) Gaussian kernel, and high-pass filter of

100 s. To minimize the influence of noise (e.g., related to participant motion and vascular artifacts) we applied FMRIB's independent component analysis (ICA)–based Xnoiseifier (FIX),[28,29] which uses single-session multivariate exploratory linear optimized decomposition into independent components (MELODIC) to decompose the individual fMRI data sets. Using default options, components were classified as noise and nonnoise variability, respectively, using a standard training set supplied with FIX. Components identified as noise and the estimated participant motion parameters were regressed out of the data, and we manually inspected the resulting cleaned fMRI data sets. Also, we calculated the number and proportion of noise components and the total and relative proportion of variance removed by FIX and compared this between groups. It has been shown that ICA-based denoising is more effective for removing motion artifacts than spike regression and scrubbing.[30,31]

The fMRI volumes were registered to the participants' structural scans using the FMRIB linear image registration tool (FLIRT)[32] implementing boundary-based registration.[33] The T_1-weighted volume was nonlinearly warped to the Montreal Neurological Institute MNI152 template[34] using FMRIB's nonlinear image registration tool (FNIRT[27]), and we applied the same warping to the fMRI data.

Eigenvector centrality mapping

Eigenvector centrality mapping provides a weighted centrality index, taking into account degree centrality (the number of edges to a node), while favouring connections to high-centrality nodes.[35] Defining voxels as nodes, ECM enables data-driven analysis of functional connectivity based on the voxel-wise correlation structure.[35,12]

Preprocessed, cleaned and normalized functional data sets were processed in Lipsia,[36] and we calculated voxel-wise ECM volumes considering the absolute value of the correlation coefficient (i.e., assigning equal weights to positive and negative correlations). We used a common mask excluding voxels not represented in all participants to ensure that individual centrality maps were computed based on the same brain mask, and we calculated a 1-sample t test of ECM across healthy controls.

Statistical analyses

Main effects of diagnosis on centrality were tested using general linear models (GLM) with the 3 diagnostic groups coded as dummy variables in addition to age and sex. To correct for multiple comparisons, statistical inference was done using permutation testing across 5000 iterations and threshold-free cluster enhancement (TFCE).[37] An F test evaluated any differences among the 3 groups, and additional t contrasts assessed pairwise group differences. Individual mean ECM values in clusters showing main effects of diagnosis were submitted to further analysis in SPSS software version 21.0. We performed analyses of covariance (ANCOVA) with ECM values in each cluster as the dependent variable, sex as the fixed factor, diagnosis as the random factor and age as the covariate in order to estimate commonly reported effect sizes. As these clusters were already significant at the voxel level after TFCE correction, we did not do any further corrections for multiple comparisons. In order to evaluate whether clusters with increased/decreased ECM in patients were regions with high or low centrality, we ran paired t tests between means of each cluster and the ECM mean across the entire brain.

To address our secondary objective, we tested for associations with PANSS positive, negative, general psychopathology, and total scores[24] within each patient group with age and sex as covariates in each cluster. Nominal p values were adjusted using Bonferroni correction to control the family-wise error (FWE) rate. Because symptom-connectivity associations do not necessarily comply with the clusters showing case–control differences, we also performed full-brain voxel-wise analyses testing for associations between symptoms and centrality within each patient group, with age and sex as covariates.

In order to test for medication effects, we used ANCOVA to compare ECM values between the patients with BD who were treated with antipsychotic medication and those who were not. Likewise, we tested for differences between the schizophrenia and BD groups after excluding patients who were not treated with antipsychotics.

Dual regression

Effects on ECM reflect altered global voxel centrality, but do not reveal the origins (e.g., the degree to which the alterations are due to spatially distributed or specific alterations). In line with previous studies,[38,39] we used clusters with significant diagnostic effects on ECM as seeds in dual regression (DR)[40,41] in order to investigate the regional contribution. Briefly, the first step in the DR analysis uses the clusters as seeds or spatial regressors to estimate the seed time course for each individual. Next, the time courses are normalized by their variance and used as temporal regressors against the fMRI data set to find the individual spatial maps reflecting the functional connectivity maps specific for the relevant seed for each participant. In order to explore the regional sources of the diagnostic effects on functional connectivity patterns as revealed by ECM, these connectivity maps were concatenated across participants and submitted to permutation testing across 5000 iterations using the randomize tool in FSL and TFCE.

Effects of motion and subgroups

To test for effects of motion, we calculated mean relative motion per individual (defined as the average root mean square of the frame-to-frame displacement). Although we went to great lengths to minimize the influence of participant motion using FIX and aggressively regressing the motion parameters out of the data, some residual effects could remain. Thus, to test the influence on the main effects of diagnosis, we conducted an ANCOVA to test for differences in motion between groups, and each ECM model was rerun including average motion as an additional covariate.

As we included a broad psychosis spectrum, the ECM ANCOVAs were rerun after excluding patients with psychosis NOS, and then after excluding patients with schizoaffective and schizophreniform disorders. We conducted an ANCOVA with age and sex as covariates to test for differences between schizophrenia and schizoaffective and schizophreniform disorders and psychosis NOS. As the BD group was too small to estimate reliable subgroup effects, we tested only for differences between BDI and BDII/BD NOS.

Results

Sample characteristics

We included 310 individuals in our study: 71 patients with schizophrenia-spectrum disorders (34 with schizophrenia, 11 with schizoaffective disorder, 2 with schizophreniform disorder and 23 with psychosis NOS), 43 patients with BD (25 with BDI, 15 with BDII and 3 with BD NOS), and 196 healthy controls. Table 1 summarizes the demographic and clinical characteristics of the sample. The mean age of patients with schizophrenia (28.2 yr) was younger than those with BD (31.2 yr) and healthy controls (31.3 yr). Patients with schizophrenia also had lower IQ and fewer years of education than those with BD and healthy controls. Compared with patients with BD, those with schizophrenia scored higher on all symptom domains. At the time of investigation, 59 patients with schizophrenia-spectrum disorders (30 with schizophrenia, 3 with schizophreniform disorder, 9 with schizoaffective disorder, and 17 with psychosis NOS) and 22 patients with BD (16 with BDI, 5 with BD2 and 1 with BD NOS) were taking antipsychotic medication.

Group differences on ECM

The 1-sample t test across healthy controls showed highest centrality in the thalamus, hippocampus, insula, cingulate gyrus, precuneus and primary sensory regions. The voxelwise F-test evaluating ECM differences among the 3 groups identified 12 significant clusters (all $p < 0.05$, corrected; Fig. 1A). Four subcortical clusters were observed bilaterally in the putamen and hippocampus/amygdala. In addition, we identified 8 cortical clusters, including the bilateral dorsolateral and dorsomedial frontal lobes, bilateral occipital cortex, bilateral posterior parietal lobe and somatosensory cortex. Table 2 shows the statistics for the effects of group in each cluster. The strongest effects of group were found in the right ($\eta^2_p = 0.170$) and left ($\eta^2_p = 0.148$) hippocampus/amygdala, right posterior parietal lobe ($\eta^2_p = 0.148$) and left occipital lobe ($\eta^2_p = 0.144$).

Pairwise comparisons among the groups

Table 2 shows pairwise group comparisons in each cluster. Compared with healthy controls, patients with schizophrenia exhibited decreased and increased EC in 7 and 5 clusters,

Table 1: Demographic and clinical characteristics of study participants

Characteristic	Group; mean ± SD*			Statistical test	p value	Post hoc
	Schizophrenia, n = 71	Bipolar disorder, n = 43	Healthy controls, n = 196			
Age, yr	28.2 ± 7.8	31.3 ± 11.3	31.5 ± 7.8	$F = 4.22$	0.016	1 < 2,3
Male sex, no. (%)	44 (62)	19 (43.2)	113 (57.7)	$\chi^2 = 4.15$	0.13	
Education, yr†	12.2 ± 2.8	13.8 ± 2.3	14.5 ± 2.2	$F = 21$	< 0.001	1 < 2,3
IQ†‡	98.5 ± 15.4	110.5 ± 11	112.8 ± 10.6	$F = 32.7$	< 0.001	1 < 2,3
Age at onset, yr†§	22.7 ± 6.1	20.7 ± 8.2	—	$t = 1.45$	0.15	—
Duration of illness, yr†¶	5.3 ± 5.3	10.7 ± 9.4	—	$t = –3.81$	< 0.001	—
Symptom rating†						
PANSS total	58.1 ± 13.7	41.3 ± 7.4	—	$t = 7.4$	< 0.001	—
PANSS positive	13.3 ± 4.9	8.3 ± 2.2	—	$t = 6$	< 0.001	—
PANSS negative	14.8 ± 5	9.2 ± 2.7	—	$t = 6.7$	< 0.001	—
PANSS general	30 ± 6.8	23.5 ± 4.6	—	$t = 6$	< 0.001	—
GAF symptom	46.1 ± 14	60.2 ± 10.1	—	$t = –5.7$	< 0.001	—
GAF function	47 ± 12.4	57.9 ± 11.8	—	$t = –4.6$	< 0.001	—
Medication, no. (%); defined daily dose†**						
Antipsychotics	59 (93.7); 1.33 ± 1.25	22 (51.2); 0.88 ± 0.58	—	$t = 1.87$	0.07	—
Lithium	5 (7.9); 0.65 ± 0.23	10 (27); 1.07 ± 0.44	—	$t = –1.98$	0.07	—
Antiepileptic	3 (4.8); 0.34 ± 0.33	8 (21.2); 1.07 ± 0.33	—	$t = –3.52$	0.008	—
Antidepressants	21 (33.3); 2.51 ± 4.19	13 (35.1); 1.34 ± 0.88	—	$t = 1.01$	0.32	—

BD = bipolar disorder; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.
*Unless indicated otherwise.
†Data missing in the following categories: education (15 schizophrenia, 5 BD, 11 controls), IQ (12 schizophrenia, 4 BD, 11 controls), age at onset and duration of illness (6 schizophrenia), symptom rating (4 schizophrenia) and medication (8 schizophrenia, 6 BD).
‡Measured using the Wechsler Abbreviated Scale of Intelligence.
§Defined as age at first symptom of psychosis for patients with schizophrenia and depression/mania/hypomania for patients with BD.
¶Defined as the number of years between age at onset and age at MRI scanning.
**Some patients were taking more than 1 medication.

respectively (Fig. 2). We found decreases in all subcortical clusters and the occipital and somatosensory cortices, whereas increases were found in the remaining 5 cortical clusters (frontal and parietal lobe clusters). Similarly, compared with healthy controls, patients with BD showed decreases in subcortical clusters and increases in the left parietal and right frontal lobe. Compared with patients with BD, those with schizophrenia showed increases in 4 clusters (3 frontal lobe clusters and the right parietal lobe) and decreases in 4 clusters (bilateral occipital lobe, somatosensory cortex and left hippocampus/amygdala). Pairwise comparisons of the voxel-wise analysis showed large significant effects in various clusters in patients with schizophrenia, a small decrease in the putamen in patients with BD, and decreased EC in patients with schizophrenia compared with those with BD in the somatosensory cortex and left occipital lobe (all $p < 0.05$, corrected; Fig. 1B).

Associations between mean centrality and cluster statistics

Paired t tests showed that EC in the left frontal lobe ($t = –5.49$, $p < 0.001$) and parietal lobe clusters (right: $t = –2.62$, $p < 0.001$; left: $t = –10.49$, $p < 0.001$) in patients was lower than the whole brain mean, while all 7 clusters with reduced EC in patients were higher than the mean ($t > 15$ and $p < 0.001$ for all clusters). Eigenvector centrality in the right dorsolateral frontal lobe was above the mean ($t = 6.32$, $p < 0.001$), while EC in the dorsomedial frontal lobe was not significantly different ($t = –1.68$, $p = 0.10$).

Seed-based connectivity analysis

Compared with healthy controls, patients with schizophrenia showed widely distributed increases in connectivity with the seed of increased EC clusters and widely

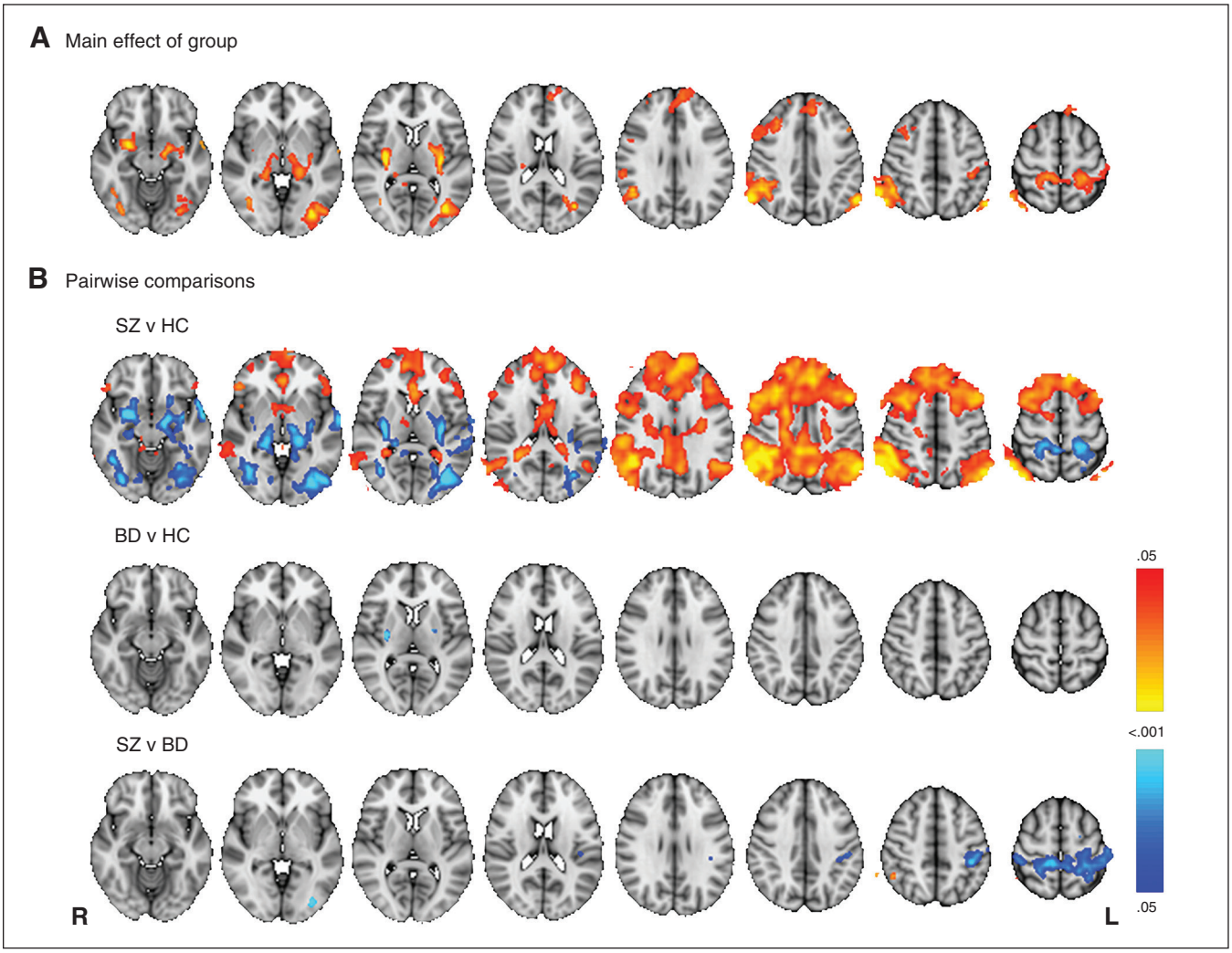

Fig. 1: Voxelwise analysis showing significant main effects of group on centrality. (**A**) Results from the *F*-test showing a main effect of diagnosis on eigenvector centrality. (**B**) Pairwise comparisons (*t* tests) among the 3 groups. Red and blue colours show regions with centrality increase and decrease, respectively, in patients compared with healthy controls (HC), and in patients with schizophrenia (SZ) compared with those with bipolar disorder (BD). Effects shown are significant at $p < 0.05$, corrected for multiple comparisons using nonparametric permutation testing across 5000 iterations and threshold-free cluster enhancement.

distributed decreased connectivity with the seed of decreased EC clusters ($p < 0.05$, corrected; Fig. 3). Though effects were widespread, both distributions showed strongest connectivity differences with the seeds in the somatomotor and occipital regions, insula and thalamus. No effect was seen in patients with BD. Using voxels showing differences between patient groups as seed, mainly in somatosensory regions, revealed reduced global connectivity in patients with schizophrenia compared with those with BD, with strongest effects in the bilateral occipital cortex ($p < 0.05$, corrected; Fig. 3B).

Clinical correlates and medication

Whole-brain analysis revealed no significant associations between PANSS symptom scores and centrality within the patient groups. Likewise, associations between PANSS scores and centrality of the 12 clusters were modest, and no effects survived Bonferroni correction (Table 3). We observed trend associations with negative (right parietal lobe and hippocampus/amygdala), positive (dorsal frontal lobe, right occipital lobe, and left hippocampus/amygdala) and general (right parietal lobe) symptom domains in patients with schizophrenia and in

Table 2: Brain clusters showing significant effect of diagnosis on centrality

			MNI			Diagnosis*		SZ–control		BD–control		SZ–BD	
Cluster	Anatomic region	Voxels	*x*	*y*	*z*	*F* (η^2_p)	*p* value	*t*†	*p* value	*t*†	*p* value	*t*†	*p* value
rdlFL	r dl frontal lobe	642	28	76	54	24.18 (0.137)	< 0.001	6.91	< 0.001	2.39	0.017	2.89	0.004
ldlFL	l dl frontal lobe	63	70	72	56	11.68 (0.071)	< 0.001	4.80	< 0.001	1.53	0.13	2.13	0.034
dmFL	dm frontal lobe	1100	50	83	54	14.53 (0.087)	< 0.001	5.35	< 0.001	1.79	0.07	2.29	0.023
rpPL	r p parietal/angular gyrus	1770	21	34	49	26.45 (0.148)	< 0.001	7.27	< 0.001	1.48	0.14	3.94	< 0.001
lpPL	l p parietal/angular gyrus	140	74	32	55	13.49 (0.081)	< 0.001	4.72	< 0.001	3.13	0.002	0.69	0.49
rOC	r occipital cortex	381	23	37	28	21.23 (0.122)	< 0.001	–6.25	< 0.001	0.49	0.62	–4.91	< 0.001
lOC	l occipital cortex	2014	63	26	40	25.74 (0.144)	< 0.001	–7.16	< 0.001	–1.01	0.32	–4.27	< 0.001
SS	somatosensory	1719	42	41	74	19.90 (0.115)	< 0.001	–5.50	< 0.001	1.87	0.06	–5.56	< 0.001
rHPC	r hippocampus/amygdala	838	31	63	29	31.16 (0.170)	< 0.001	–7.50	< 0.001	–4.00	< 0.001	–1.93	0.06
lHPC	l hippocampus/amygdala	750	55	48	33	26.51 (0.148)	< 0.001	–7.03	< 0.001	–3.36	0.001	–2.14	0.033
rPUT	r putamen	399	29	55	39	14.45 (0.087)	< 0.001	–3.90	< 0.001	–4.44	< 0.001	1.04	0.30
lPUT	l putamen	628	60	53	38	15.50 (0.092)	< 0.001	–4.34	< 0.001	–4.27	< 0.001	0.530	0.59

ANCOVA = analysis of covariance; BD = bipolar disorder; dl = dorsolateral; dm = dorsomedial; FL = frontal lobe; HPC = hippocampus; l = left; MNI = Montreal Neurological Institute; OC = occipital cortex; p = posterior; PL = parietal lobe; PUT = putamen; r = right; SS = somatosensory; SZ = schizophrenia.
*An ANCOVA *F*-test was run for effect of diagnosis in each cluster, with 2 degrees of freedom, with pairwise comparisons distinguishing among the 3 groups.
†Positive *t* values show an increase in patients with schizophrenia and BD compared with healthy controls, and in patients with schizophrenia compared with patients with BD.

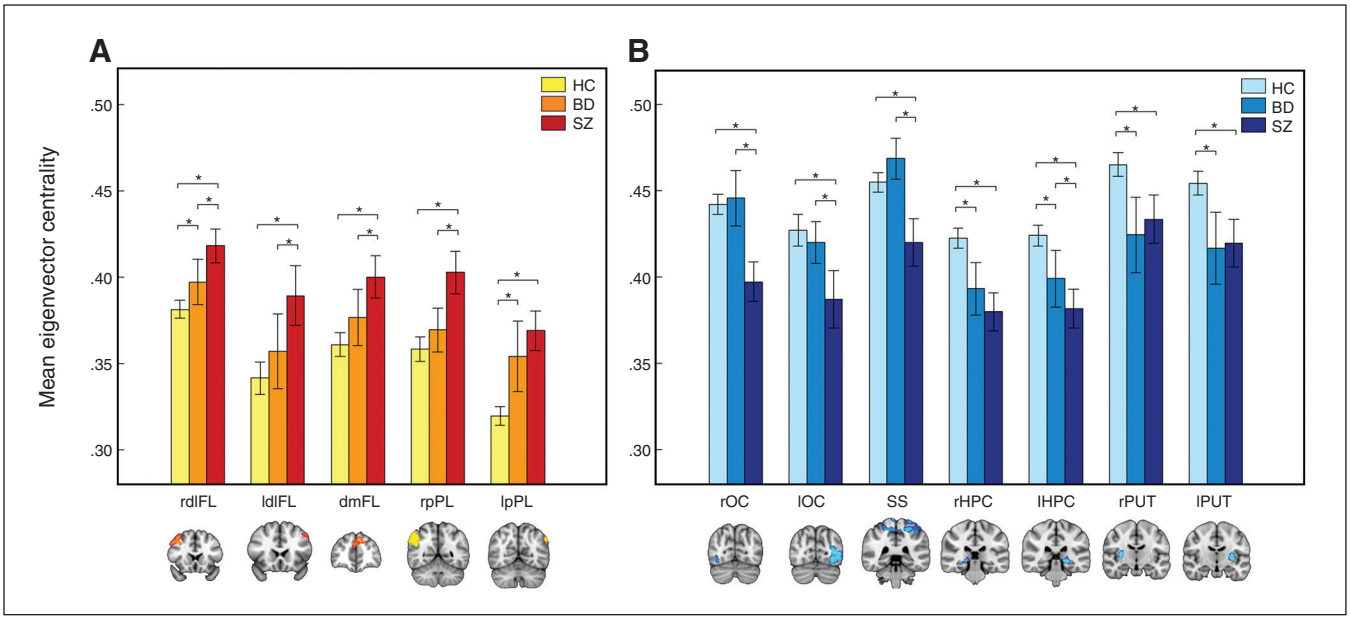

Fig. 2: Mean eigenvector centrality in each diagnostic group for clusters with (**A**) increased and (**B**) decreased centrality in patients with schizophrenia (SZ). Error bars show 95% confidence intervals. *$p < 0.05$. BD = bipolar disorder; DL = dorsolateral; DM = dorsomedial; FL = frontal lobe; HC = healthy controls; HPC = hippocampus; L = left; OC = occipital cortex; p = posterior; PL = parietal lobe; PUT = putamen; R = right; SS = somatosensory cortex.

the general symptom domain (right frontal lobe cluster) in patients with BD.

There were no significant differences between patients with BD who were or were not taking antipsychotics in any of the clusters. Effects on centrality between patients with schizophrenia and BD who were treated with antipsychotics revealed largely overlapping results, as seen for the full sample (results not shown).

Effects of motion and subgroups

Adding motion as an additional covariate in the ANCOVA revealed a significant main effect of motion on ECM in 6 of the 12 clusters, indicating decreasing EC with increasing motion in 3 clusters (right and left occipital lobe and somatosensory cluster) and increasing EC with increasing motion in 3 clusters (right dorsolateral frontal lobe, dorsomedial frontal lobe, and left putamen; Table 4).

Controlling for relative motion did not remove any of the group effects on centrality. We observed a significant effect of group in relative motion ($F = 8.51$, $p < 0.001$), with pairwise comparisons indicating increased motion in patients with schizophrenia compared with healthy controls ($t = 4.13$, $p < 0.001$) and patients with BD ($t = 2.14$, $p = 0.033$), but no difference between healthy controls and patients with BD ($t = 0.95$, $p = 0.34$). Main effects of diagnosis on EC remained significant in all clusters when rerunning the ANCOVA with motion as an additional covariate ($p < 0.001$).

The proportional ($F = 3.43$, $p = 0.034$) and total ($F = 3.44$, $p = 0.033$) variance removed by FIX was higher in patients than healthy controls. Pairwise comparisons showed significantly higher proportional ($t = 2.15$, $p = 0.032$) and total ($t = 2.34$, $p = 0.020$) variance removed in patients with schizophrenia than in controls, and a trend-level difference between patients with BD and controls for proportional and total variance, respectively ($t = 1.92$, $p = 0.06$ and $t = 1.68$, $p = 0.09$).

Subgroup analysis showed that main effects of diagnosis remained in all clusters when excluding patients with psychosis NOS, schizophreniform disorder and schizoaffective disorder (Table 4). The ANCOVA between patients with psychosis NOS, schizophreniform disorder and schizoaffective disorder ($n = 37$) and schizophrenia ($n = 34$) did not reveal any significant differences, nor did the ANCOVA between patients with BDI ($n = 25$) and those with BDII and BD NOS ($n = 18$).

Discussion

We have demonstrated regional differences in global resting-state brain connectivity in patients with schizophrenia and BD compared with healthy controls, with the strongest effects observed in those with schizophrenia. The main effects yielded a pattern of increased centrality in cortical clusters encompassing parts of the DMN, suggesting a system-level dedifferentiation of parts of the DMN in patients with severe mental illness during rest. Decreased centrality occurred predominantly in subcortical structures, the occipital lobe and somatosensory regions, implicating reduced connectivity and poorer functioning in sensory and limbic structures in patients than in controls. We found no significant associations with symptom domains.

Pairwise comparisons among patients with schizophrenia, BD and healthy controls

Compared with healthy controls, decreased centrality was found in the occipital lobe and somatosensory cortex in patients with schizophrenia and in the putamen and hippocampus/amygdala in both patients with schizophrenia and BD. Specifically, the hippocampus/amygdala and putamen are limbic regions involved in the processing and regulation of memory functions and emotions, and are often implicated in both BD[42,43] and schizophrenia.[44,45] Somatosensory and occipital cortices are critical for visual and sensory processing and

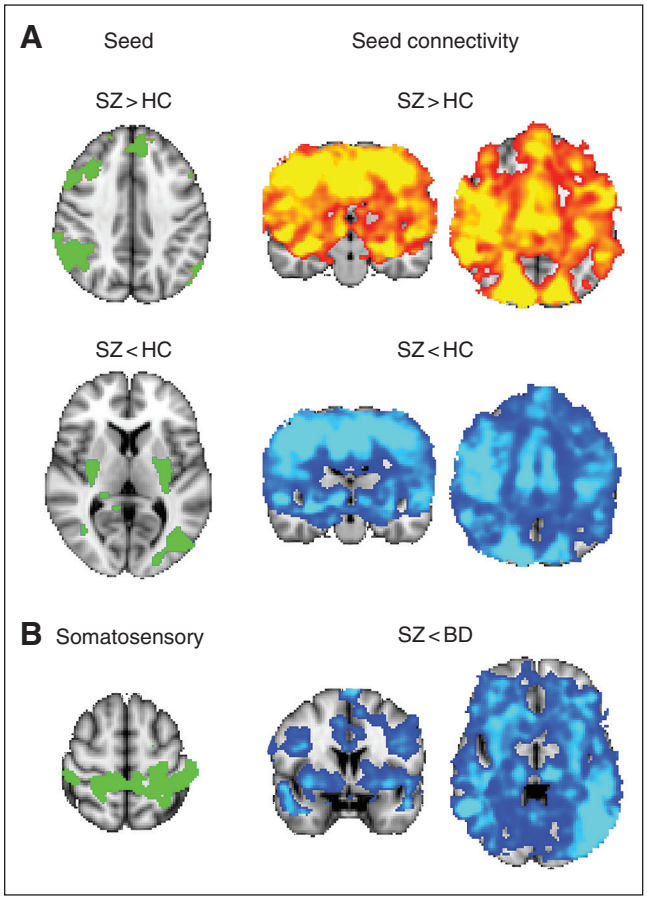

Fig. 3: Seed-based functional brain connectivity. The 3 defined seeds are shown in green: namely, (**A**) the cluster from the *F*-test with increased and decreased centrality in patients with schizophrenia (SZ) compared with healthy controls (HC), and (**B**) a somatosensory seed with significantly different centrality between patients with schizophrenia and those with bipolar disorder (BD). Seed connectivity maps for the group contrast of interest are shown in yellow or blue, referring to (**A**) increased or decreased connectivity with the seed in patients with schizophrenia compared with healthy controls, respectively, and (**B**) decreased connectivity with the somatosensory seed in patients with schizophrenia compared with those with BD ($p < 0.05$, corrected).

are known to be affected in patients with schizophrenia.[20,46] In a previous study with an overlapping schizophrenia sample,[22] lower level sensory regions were shown to have reduced signal amplitude and aberrant functional network connectivity, indicating that different methodological approaches point to dysfunction in these regions. Decreased centrality in these regions suggests less coordinated sensory processing, which may be related to the range of cognitive and emotional symptoms through various downstream mechanisms.[21,47] Patients with schizophrenia had decreased occipital and somatosensory centrality compared with patients with BD, a finding also supported by the voxel-wise brain analysis, suggesting stronger implications of sensory and visual circuits in patients with schizophrenia. The putamen and right hippocampus/amygdala were affected in both groups, highlighting disruption in mood circuits, which is a characteristic feature of both disorders.

Increased centrality in patients with schizophrenia was found in the frontal and posterior parietal lobes, largely overlapping with DMN regions. Patients with BD showed intermediate connectivity in these clusters, exhibiting significant increases compared with healthy controls in the left parietal and right frontal lobe and decreases compared with patients with schizophrenia in frontal clusters and the right parietal lobe. Differential frontoparietal centrality may reflect reduced executive functioning, planning and DMN-associated introspection and self-referential thought in patients with schizophrenia compared with those with BD.[18,48] Findings of intermediate EC in patients with BD in these clusters suggest that the patient groups may indeed reflect different parts along the same continuum,[49,50] though also with distinguishing features as seen with differential decreases in sensory clusters.

Associations between mean centrality and cluster statistics

We found that all clusters with decreased centrality in patients had a high average centrality compared with the whole brain mean across participants, supporting the notion of reductions of hub regions in patients.[18,19,51] Hubs are essential for efficient information flow and integration and are more likely to be symptomatic if affected.[14,19] Likewise, being more biologically costly to maintain makes hubs vulnerable to pathology.[14,19] Although high-centrality clusters were decreased, not all high-centrality regions in the brain were affected, suggesting specific targeting of hub regions in patients with schizophrenia and BD.

In line with previous studies,[14] the precuneus, which is a core DMN hub, showed high centrality. However, most

Table 3: Associations between centrality and symptom domains*

	Positive			Negative			General			Total		
Cluster; group	*t*	*p* value	η^2_p	*t*	*p* value	η^2_p	*t*	*p* value	η^2_p	*t*	*p* value	η^2_p
Schizophrenia												
rdlFL	–0.07	0.94	0	0.03	0.97	0	0.79	0.43	0.010	0.38	0.71	0.002
ldlFL	–0.16	0.63	0	0.14	0.89	0	0.78	0.44	0.009	0.38	0.71	0.002
dmFL	2.1	0.039	0.066	1.40	0.17	0.030	1.45	0.15	0.032	1.98	0.05	0.059
rpPL	1.27	0.21	0.025	2.35	0.022	0.080	2.35	0.022	0.081	2.49	0.016	0.089
lpPL	–0.05	0.96	0	1.18	0.24	0.022	1.07	0.29	0.018	0.94	0.35	0.014
rOC	–2.1	0.048	0.061	–0.59	0.56	0.006	–1.66	0.10	0.042	–1.75	0.09	0.046
lOC	–0.62	0.54	0.006	0.04	0.97	0	–0.67	0.51	0.007	–0.53	0.60	0.005
SS	0.9	0.37	0.013	–0.06	0.95	0	0.38	0.71	0.002	0.48	0.63	0.004
rHPC	–1.54	0.13	0.036	–3.32	0.002	0.149	–1.57	0.12	0.037	–2.52	0.014	0.092
lHPC	–2.14	0.036	0.068	–2.59	0.012	0.096	–1.82	0.07	0.050	–2.63	0.011	0.099
rPUT	0.56	0.58	0.005	–0.72	0.47	0.008	0.21	0.84	0.001	0.04	0.97	0
lPUT	0.19	0.85	0.001	–0.55	0.58	0.005	0.13	0.90	0	–0.07	0.94	0
Bipolar disorder												
rdlFL	0.49	0.63	0.006	–0.81	0.42	0.017	9.22	< 0.001	0.055	–1.06	0.30	0.028
ldlFL	1.79	0.08	0.076	–0.65	0.52	0.011	0.32	0.75	0.003	0.5	0.62	0.006
dmFL	–0.19	0.85	0.001	–0.84	0.41	0.018	0.71	0.48	0.013	0.06	0.96	0
rpPL	–0.36	0.72	0.003	–0.44	0.66	0.005	–0.57	0.57	0.008	–0.64	0.53	0.010
lpPL	0.23	0.82	0.001	–0.04	0.97	0	0.45	0.66	0.005	0.33	0.74	0.003
rOC	0.78	0.44	0.015	–1.61	0.12	0.062	0	> 0.99	0	–0.34	0.74	0.003
lOC	0.3	0.77	0.002	–1.34	0.19	0.044	–0.5	0.62	0.006	–0.71	0.48	0.013
SS	–0.03	0.98	0	–0.1	0.92	0	0.36	0.72	0.003	0.18	0.86	0.001
rHPC	–0.49	0.63	0.006	0.53	0.60	0.007	0.47	0.64	0.006	0.33	0.74	0.003
lHPC	0.75	0.46	0.014	1.39	0.17	0.047	1.56	0.13	0.059	1.74	0.09	0.072
rPUT	0.08	0.42	0.017	–0.01	0.99	0	0.64	0.53	0.010	0.64	0.52	0.011
lPUT	1.56	0.13	0.059	0.31	0.76	0.003	0.98	0.33	0.024	1.22	0.23	0.037

dl = dorsolateral; dm = dorsomedial; FL = frontal lobe; HPC = hippocampus; l = left; OC = occipital cortex; p = posterior; PL = parietal lobe; PUT = putamen; r = right; SS = somatosensory.
*Associations between eigenvector centrality score in each cluster and Positive and Negative Syndrome Scale scores within each patient group.

significant clusters encompassing other DMN regions showed relatively low average centrality across participants. The reason for this is unclear, but it could point to differential patterns of centrality in the various canonical DMN regions. Low average centrality in the respective DMN clusters indicates global desynchronization, whereas the centrality increases observed in patients indicate that these DMN regions show stronger global functional integration during rest. This suggests a system-level dedifferentiation of parts of the DMN in patients with severe mental illness.

This pattern of a relative decrease in the centrality of select hub-like regions and an increase in low-centrality clusters suggests a smaller range in centrality values in schizophrenia, as seen in other studies,[17] indicating less functional specialization or brain network differentiation. A distribution of low centrality regions with some high-degree hubs has been shown to be an optimal network configuration,[14] and a more uniform distribution of EC in patients would be indicative of a less efficient network.

Seed-based connectivity analysis

We probed the regional sources of the centrality differences by means of seed-based analyses. Using clusters showing either increased or decreased EC as separate seeds revealed that both were explained by globally altered connectivity in patients with schizophrenia, in whom the DMN regions showed increased connectivity and sensory/limbic regions showed reduced connectivity. No effects were apparent in patients with BD, indicating that altered global connectivity is more characteristic of schizophrenia. Seeding from voxels with decreased EC in patients with schizophrenia compared with those with BD, largely comprising the somatosensory cortex, showed a global connectivity decrease in patients with schizophrenia.

Clinical correlates

Within-group region of interest and voxel-wise analyses showed no significant associations between symptom scores and centrality in either patient group. However, some trends were seen, and further studies are needed to assess their reliability and clinical significance.

Limitations

The present approach has some limitations. Artifacts related to in-scanner participant motion reflect a challenge in neuroimaging, particularly when targeting the covariance structure of the time series. We used advanced methods for data cleaning and regressed out motion parameters from the fMRI data before computing EC maps; however, we still cannot be certain to have removed all motion-related effects. The EC map across participants showed a network of high-centrality regions similar to other ECM studies, supporting the reliability of the method.[35,39,52] However, relying on measures of full correlations when assessing the structure of the brain network, which is the case for the current implementation of ECM,[36] may be less reliable and more vulnerable to noise than estimates of partial correlations.[53] Further studies using alternative definitions of the connectivity matrices are needed.

Other limitations were that many patients were medicated, and groups were unevenly matched on IQ, education and duration of illness. Caution is needed when assessing effects of medication and cognitive functions as they are extremely difficult to disentangle using the present study design because of the inherent collinearity between medication type, dose, diagnosis and clinical variables. Ideally, this should be assessed in a properly designed randomized controlled trial. However, we tested for centrality differences between patients with BD who were and were not being treated with

Table 4: Subgroup analyses and effects of relative motion*

	SZ subgroups		BD subgroups		Dx without other SZ		Effect of motion			Dx with motion	
Cluster	*t*	*p* value	*t*	*p* value	*F* (η^2_p)	*p* value	*F* (η^2_p)	*t*	*p* value	*F* (η^2_p)	*p* value
rdlFL	–0.68	0.50	0.07	0.94	12.41 (0.085)	< 0.001	13.75 (0.943)	3.71	< 0.001	18.52 (0.109)	< 0.001
ldlFL	0.11	0.91	–0.69	0.49	6.36 (0.045)	0.002	3.72 (0.012)	1.93	0.06	9.17 (0.057)	< 0.001
dmFL	1.83	0.07	–0.61	0.54	14.58 (0.098)	< 0.001	11.16 (0.035)	3.34	0.001	10.45 (0.064)	< 0.001
rpPL	1.01	0.32	0.02	0.98	18.91 (0.124)	< 0.001	0.8 (0.003)	0.89	0.37	23.6 (0.134)	< 0.001
lpPL	1.36	0.18	0.37	0.72	13.02 (0.089)	< 0.001	3.36 (0.011)	–1.83	0.07	15.05 (0.09)	< 0.001
rOC	–0.62	0.54	0.32	0.75	14.76 (0.099)	< 0.001	23.98 (0.073)	–4.9	< 0.001	15.31 (0.091)	< 0.001
lOC	–1.79	0.08	0.34	0.73	25.34 (0.159)	< 0.001	10.83 (0.034)	–3.29	0.001	20.12 (0.117)	< 0.001
SS	0.69	0.49	–0.41	0.68	11.02 (0.076)	< 0.001	27.44 (0.083)	–5.24	< 0.001	14.86 (0.089)	< 0.001
rHPC	–1.14	0.26	1.77	0.08	26.41 (0.165)	< 0.001	0.03 (0)	0.17	0.87	29.85 (0.164)	< 0.001
lHPC	–1.39	0.17	0.46	0.65	23.00 (0.146)	< 0.001	0.021 (0)	–0.15	0.89	24.88 (0.141)	< 0.001
rPUT	0.38	0.70	0.28	0.78	11.96 (0.082)	< 0.001	3.55 (0.012)	1.88	0.06	15.93 (0.095)	< 0.001
lPUT	–0.30	0.77	0.35	0.73	12.78 (0.087)	< 0.001	6.5 (0.021)	2.55	0.011	17.98 (0.106)	< 0.001

BD = bipolar disorder; dl = dorsolateral; dm = dorsomedial; FL = frontal lobe; HPC = hippocampus; l = left; OC = occipital cortex; p = posterior; PL = parietal lobe; PUT = putamen; r = right; RM = relative motion; SS = somatosensory; SZ = schizophrenia.

*Subgroup analyses show results of the *t* test between centrality means of patients with schizophrenia (*n* = 34) and the other patients in the schizophrenia group (i.e., those with schizoaffective disorder, schizophreniform disorder and psychosis not otherwise specified, *n* = 37), patients with BDI (*n* = 25) and other patients in the BD group (i.e., those with BDII/BD not otherwise specified, *n* = 18), and the effect of diagnosis on centrality with other schizophrenia patients excluded. Positive *t* values shows higher mean centrality in patients with schizophrenia and BDI compared with the other subgroups. The main effect of motion is shown in each cluster (positive and negative *t* values show an increased or decreased centrality with increasing motion, respectively, and the effect of diagnosis with motion added as an additional covariate to the model.

antipsychotics, which revealed no differences. Testing for centrality differences between patients with schizophrenia and those with BD who were treated with antipsychotics showed similar effects as when including all patients. This finding supports the notion that effects observed in the present study were not purely a result of medication status.

Conclusion

We have demonstrated aberrant and partially overlapping network configuration in the resting state in patients with schizophrenia and BD, including subcortical and sensory regions and frontal and parietal lobes. No significant associations were found with symptom burden. Patient groups were significantly different in almost all cortical clusters, with the strongest effects in sensory regions. In general, our results are not contradictory with the continuum hypothesis of severe mental illness, but suggest that the centrality of sensory and DMN regions during rest may provide a novel phenotype for distinguishing between schizophrenia and BD, which needs to be replicated in independent samples.

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