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Brain Network Analysis Reveals Affected Connectome Structure in Bipolar I Disorder

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Abstract: The notion that healthy brain function emerges from coordinated neural activity constrained by the brain's network of anatomical connections—i.e., the connectome—suggests that alterations in the connectome's wiring pattern may underlie brain disorders. Corroborating this hypothesis, studies in schizophrenia are indicative of altered connectome architecture including reduced communication efficiency, disruptions of central brain hubs, and affected "rich club" organization. Whether similar deficits are present in bipolar disorder is currently unknown. This study examines structural connectome topology in 216 bipolar I disorder patients as compared to 144 healthy controls, focusing in particular on central regions (i.e., brain hubs) and connections (i.e., rich club connections, interhemispheric connections) of the brain's network. We find that bipolar I disorder patients exhibit reduced global efficiency (−4.4%, P =0.002) and that this deficit relates (r = 0.56, $P < 0.001$) to reduced connectivity strength of interhemispheric connections (−13.0%, P = 0.001). Bipolar disorder patients were found not to show predominant alterations in the strength of brain hub connections in general, or of connections spanning brain hubs (i.e., "rich club" connections) in particular (all $P > 0.1$). These findings highlight a role for aberrant brain network architecture in bipolar I disorder with reduced global efficiency in association with disruptions in interhemispheric connectivity, while the central "rich club" system appears not to be particularly affected. *Hum Brain Mapp 37:122–134, 2016.*

Key words: connectome; diffusion imaging; bipolar disorder; brain hubs; rich club organization

Additional Supporting Information may be found in the online version of this article.

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INTRODUCTION

Healthy brain function requires effective communication and integration of neural information between distributed brain regions. The anatomical infrastructure to support this interaction are the white matter axonal projections of the brain, together forming a complex network that is known as the human connectome [Hagmann, 2005; Sporns et al., 2005]. This network has been proposed to give rise to, and shape, the collective and coordinated neural phenomena underlying cognitive processes [Sporns, 2011]. Indeed, studies have linked connectome organization to general intelligence [Baggio et al., 2015; Li et al., 2009; Van den Heuvel et al., 2009; Zalesky et al., 2011], working memory performance [Bassett et al., 2009; Cole et al., 2012], executive functioning [Reijmer et al., 2013], major personality traits [Adelstein et al., 2011; Gao et al., 2013], and creativity [Ryman et al., 2014]. The notion that (complex) brain functions are not solely attributable to the properties of individual brain regions but rather emerge from their interplay within the connectome as a whole implies that the pattern of brain wiring may be crucial to healthy brain function and, conversely, brain disease [Fornito et al., 2015; Griffa et al., 2013; Van den Heuvel and Fornito, 2014].

Bipolar disorder is a major psychiatric disorder that affects approximately 1% of the population in its most typical form, "bipolar I disorder" [Belmaker, 2004]. Patients experience recurrent depressive, and (mixed-) manic episodes characterized by increased mood and arousal and reduced sleep [Saunders and Goodwin, 2010]. In addition, the majority of bipolar I disorder patients suffer psychotic symptoms [Dunayevich and Keck, 2000; Goes et al., 2007] and cognitive deficits [Kumar and Frangou, 2010; Martínez-Arán et al., 2000; Martino et al., 2014; Quraishi and Frangou, 2002; Robinson et al., 2006]. Psychiatric symptoms such as these have been suggested to relate to aberrant integration of neural information among functionally specialized brain circuits [Buckholtz and Meyer-Lindenberg, 2012]. If so, the white matter connections linking these systems may be implicated. Indeed, the corpus callosum (CC)—the largest white matter structure in the brain [Fitsiori et al., 2011]—has been proposed to be crucial to cognitive integration [Gazzaniga, 2000], and impaired interhemispheric integration has been shown in bipolar disorder [Leow et al., 2013]. In addition, brain hubs and their mutual connections have been suggested to form a central infrastructure linking dispersed functional communities, thereby enabling integrative brain processing [Collin et al., 2014b; Van den Heuvel and Sporns, 2011; Van den Heuvel and Sporns, 2013a; Van den Heuvel and Sporns, 2013b; Van den Heuvel et al., 2012]. This "rich club" system was shown to be disproportionately affected in schizophrenia patients [Van den Heuvel et al., 2013; Yu et al., 2013] and similar findings in their unaffected siblings suggest that genetic factors may contribute to this deficit [Collin et al., 2014a; Peeters et al., 2015]. Considering the partial overlap in genetic susceptibility for schizophrenia and bipolar disorder [Cardno and Owen, 2014], the disorders might share in some of the white matter deficits [McDonald et al., 2004], but whether hub and rich club connectivity are also affected in bipolar I disorder has not yet been investigated.

The current study explores the structural connectome in bipolar I disorder. We focus on topologically central brain hubs, "rich club" connections spanning hubs, and central interhemispheric connections. If connectivity deficits are identified, their impact on the brain's capacity for global communication, as measured by global network efficiency, is explored, as well as a possible relationship with cognitive performance and clinical symptoms.

MATERIALS AND METHODS

Participants

A total of 360 subjects participated in this study, including 216 bipolar I disorder patients and 144 healthy controls. Subjects were recruited at the University Medical Center Utrecht, the Netherlands, as part of the Bipolar Genetics (BiG) study. BiG is an ongoing case-control study that is part of a collaboration between the University of California Los Angeles and several Dutch health care institutes including the University Medical Center Utrecht (for other participating centers, see Supporting Information). The inclusion criteria for all participants were: (1) Age 18 years or older; (2) At least three Dutch-born grandparents; (3) A good understanding of the Dutch language. Diagnosis of bipolar I disorder was confirmed using the Structured Clinical Interview for DSM-IV (SCID-I) [First et al., 2002]. Patients with a somatic illness that could have influenced diagnosis of bipolar disorder were excluded. The affiliated medical ethics committee approved the investigation and all subjects provided written informed consent prior to participation.

Demographics are described in Table I. Overall IQ was estimated using four subtests (information, arithmetic, block design, and digit symbol coding) of the Wechsler Adult Intelligence Scale-III (WAIS-III) [Stinissen et al., 1970; Wechsler, 1997]. This combination of subtests has been shown to best account for full-scale IQ in schizophrenia patients ($R^2 = 0.90$) and healthy subjects ($R^2 = 0.86$) [Blyler et al., 2000]. In addition, a Dutch version of the National Adult Reading Test (NLV) was administered to estimate premorbid IQ [Schmand et al., 1991]. For patients, the number of manic and depressive episodes was determined using the Questionnaire for Bipolar Disorder [Leverich et al., 2001]; a history of one or more psychotic feature(s) (yes/no) was assessed using section B of the Structured Clinical Interview for DSM Disorders [First et al., 2002] and the Comprehensive Assessment for Symptoms and History [Andreasen et al., 1992]. Handedness (left/right/ambidextrous) and current use of lithium and/or antipsychotic medication (yes/no) were recorded.

TABLE I. Demographic and clinical characteristics

	Bipolar I disorder patients ($N = 216$)	Healthy controls ($N = 144$)	P
Age in years, mean (sd) [range]	47.4 (12.1) [20–79]	46.6 (14.5) [20–81]	0.56
Gender, male/female, No. (%)	114/102 (52.8/47.2)	68/76 (47.2/52.8)	0.30
Current IQ, mean (sd) [range]	99.0 (14.2) [65–136]	108.7 (15.2) [73–144]	<0.01
Premorbid IQ, mean (sd) [range]	106.7 (9.9) [79–130]	107.9 (9.2) [78–130]	0.28
Handedness[#], right/left/ambidextrous (%)	185/21/9 (86.0/9.8/4.2%)	118/21/4 (82.5/14.7/2.8)	0.31
Mood status at inclusion			
Depressive symptoms (IDS-SR_{30}), mean (sd) [range]	16.7 (11.6) [0–58]		
Manic symptoms (ARSM), mean (sd) [range]	2.6 (3.0) [0–13]		
Mood status (eu/mild/dep/man/mix), No. (%)	101/50/36/8/21 (46.8/23.1/16.7/3.7/9.7)		
Psychiatric history			
No. (%) of (hypo-)manic episodes (0/1–4/5–10/11–20/20+/unknown)	0/121/47/17/22/9 (0/55.9/21.8/7.9/10.2/4.2)		
No. (%) of depressive episodes (0/1–4/5–10/11–20/20+/unknown)	20/84/38/29/30/15 (9.3/38.9/17.6/13.4/13.9/6.9)		
No. (%) of patients with history of psychotic features (yes/no/unknown)	162/45/9 (75.0/20.8/4.2)		
Medication			
No. (%) of patients currently on lithium treatment (yes/no)	149/67 (69.0/31.0)		
No. (%) of patients on antipsychotic medication (yes/no/unknown)	93/109/14 (50.5/43.1/6.5)		

Demographic and clinical characteristics per subject group. Group-differences were tested for statistical significance using analysis of variance (ANOVA) for continuous and chi-squared tests for categorical variables. sd = standard deviation; No. = number. [#] missing for two subjects. 30-item Inventory of Depressive Symptoms-Self Report (IDS-SR_{30}); Altman Self-Rating Mania Scale (ASRM). Mood status: eu = euthymic; mild = mild symptoms; dep = moderate–severe depression; man = mania; mix = mixed. Of note, mood status is based on self-report.

Mood status was assessed at inclusion through self-report using the 30-item Inventory of Depressive Symptoms-Self Report (IDS-SR_{30}) [Rush et al., 1996] and the Altman Self-Rating Mania Scale (ASRM) [Altman et al., 1997]. Based on these reports, patients were categorized as either euthymic (IDS-$SR_{30} \leq 13$ and ASRM ≤ 6); or as having mild symptoms (IDS-SR_{30} 14–25 and ASRM ≤ 6); moderate–severe depressive symptoms (IDS-$SR_{30} \geq 26$); (hypo)manic symptoms (ASRM ≥ 6); or mixed symptoms (IDS-$SR_{30} \geq 13$ and ASRM ≥ 6) [Altman et al., 1997; Rush et al., 1996] (Table I).

Image Acquisition and Preprocessing

For each participant, one anatomical (T1-weighted) scan and two diffusion-weighted imaging (DWI) scans were acquired on a 3.0 Tesla Philips clinical MRI scanner at the University Medical Center Utrecht, the Netherlands (for acquisition and preprocessing details see Supporting Information). The cortex was parcellated into 219 roughly equally sized cortical regions (111 in the left and 108 in the right hemisphere, given the on average slightly larger size of the left hemisphere) based on a high-resolution subdivision of FreeSurfer's Desikan-Killiany atlas [Cammoun et al., 2012; de Reus and van den Heuvel, 2014]. White matter pathways were reconstructed using deterministic streamline tractography, based on the Fiber Assignment by Continuous Tracking (FACT) algorithm [Mori and van Zijl, 2002].

Connectome Reconstruction and Analysis

For each participant, the collection of reconstructed fiber tracts and the individual parcellation map was used to create a structural brain network (SI provides further details). A network can be described mathematically as a graph $G = (V, E)$ comprising a set of nodes V (here signifying parcellated cortical regions) and edges E (reflecting reconstructed streamlines) connecting the nodes. Network edges were weighted according to (1) streamline density (SD), computed as the number of streamlines between two regions, divided by their average volume; (2) average mean diffusivity (MD); and (3) fractional anisotropy (FA) along the streamlines linking two regions.

Global Connectivity and Efficiency

Reconstructed white matter pathways were investigated for overall group-differences in diffusion-weighted measures

of structural connectivity (SD, FA, MD). For each individual subject, each of these measures was averaged over all cortico-cortical connections. In addition, to probe the overall communication efficiency of the SD weighted reconstructed brain networks, global efficiency *GE* was computed for each subject as the average inverse shortest path length between each possible pair of brain regions [Rubinov and Sporns, 2010].

Brain Hubs

Brain hubs can be detected using various network measures, including degree (the number of connections of each node or brain region) and betweenness-centrality (the number of shortest paths in the network that pass though a given node) [Rubinov and Sporns, 2010].

Hub detection

For the main hub definition, hubs were identified based on degree-centrality in each subject individually. To this end, degree-centrality was computed for each subject as the number of connections per brain region, by taking the sum over each row of adjacency matrix A. Hubs were defined as the top 20% highest degree brain regions. To ensure that putative effects were not limited to this particular hub definition, alternative definitions were also explored (see Supporting Information).

Hub connectivity

To compute the level of hub connectivity, SD, FA, and MD were averaged over all connections of hub regions.

Node centrality in relation to disease-related connectivity impairments

In addition to dividing brain regions into hubs and nonhubs, we used Pearson's correlations to examine whether putative disease-related changes in connectivity showed an association with nodal centrality. Specifically, we examined whether relative change in connectivity strength (%) of a given region is predicted by its topological centrality (details in Supporting Information).

Rich Club Organization

White matter connections were divided into rich club, feeder, and local connection classes based on the detected brain hubs as defined in the previous section.

Rich club definition

For each subject, links between detected brain hubs were defined as "rich club" connections, links between hubs and nonhubs as "feeder" connections, and links among nonhubs as "local" connections.

Rich club connectivity

Structural connectivity (SD, FA, MD) of each class of links (i.e. "rich club", "feeder", and "local") was computed as the average connectivity value over all connections in that class, and compared between subject groups.

Edge centrality in relation to disease-related change in connectivity

In addition to examining the connection classes, we explored whether the extent of disease-related change in a structural connection was predicted by its topological centrality, computed as binary edge betweenness centrality [Rubinov and Sporns, 2010] (see Supporting Information).

Interhemispheric Connections

Interhemispheric fibers are among the most central connections within the connectome. While under represented in diffusion-weighted network reconstruction because of difficulty tracking fibers through the corpus callosum, particularly towards lateral cortices [Hagmann et al., 2008] they are thought to confer considerable efficiency to the network as a whole.

Interhemispheric connectivity

Measures of white matter connectivity (SD, FA, MD) were averaged over reconstructed connections between the hemispheres (interhemispheric connectivity), as opposed to connections within hemispheres (intrahemispheric connectivity), and compared between subject groups.

Statistical Analysis

Main analyses

Measures of white matter connectivity and network topology were compared between patients and controls using permutation testing (for details see SI). To correct for multiple testing, results were FDR-corrected ($q = 0.05$) over all main analyses (i.e., hub, rich club, and interhemispheric connectivity analyses). Findings surviving FDR-correction indicate a statistically significant effect. Findings at uncorrected $P < 0.05$ (i.e., but not surviving FDR-correction) were interpreted as trend-level effects.

Cognitive and clinical correlates of affected connectivity

Affected connectivity measures in patients (if any) were explored for a relationship with IQ, estimated premorbid IQ, and the number of manic and depressive episodes, using linear regression analyses, with clinical characteristics as dependent and connectivity measures as independent variables. To correct for effects of overall connectivity,

age, and gender, these variables were included as covariates. In addition, bivariate comparisons of patients on or off lithium treatment, and with or without a history of psychotic features, were performed using independent samples *t*-tests.

Validation Analyses

Node definition

It has been shown that organizational parameters of the brain network are consistent across parcellation schemes (i.e., using various templates, or employing random parcellation criteria), but vary substantially across scales of spatial resolution [de Reus and van den Heuvel, 2013; Zalesky et al., 2010]. To explore a potential effect of spatial resolution, two additional node definitions were examined: above and below (in terms of resolution) the original node definition, i.e., comprising a total of 114 and 448 cortical regions respectively [Cammoun et al., 2012]. The main findings were recomputed using these node definitions to assess their validity using different node schemes.

Mood status

To assess a possible influence of mood status on our findings, the main analyses were reran including only patients that, at inclusion, reported either euthymia or mild symptoms at most ($N = 151$).

RESULTS

Global Connectivity and Efficiency

Figure 1 summarizes the findings on overall connectivity and connectome efficiency. Over all reconstructed white matter connections, there was a trend-level reduction in SD connectivity (−2.4%, $P = 0.022$, not surviving FDR-correction) in bipolar I disorder patients as compared to healthy controls. There were no significant differences in FA (−0.4%, $P = 0.392$) or MD (+0.4%, $P = 0.285$). Global efficiency was reduced by 4.4% in patients as compared to controls ($P = 0.002$, FDR-significant). The reduction in *GE* was not solely attributable to the trend-level reduction in SD connectivity in patients, as correction for average SD connectivity using linear regression analysis attenuated but did not erase the effect (−1.7%, $P = 0.037$). Moreover, as previous work has shown that global efficiency is associated with IQ (Li et al., 2009; Van den Heuvel et al., 2009) and the current subjects groups showed a significant difference in IQ ($P < 0.01$), it was assessed whether the reduction in *GE* might be due to an unspecific reduction in intelligence. To this end, *GE* was retested including IQ as a covariate. After correcting for IQ, interhemispheric SD connectivity remained significantly reduced in patients (−11.1%, $P = 0.004$).

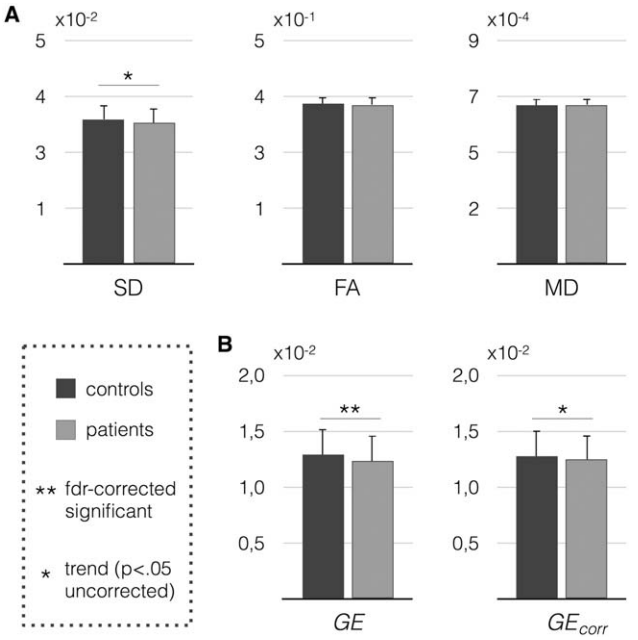

Figure 1.

Global connectivity measures and connectome efficiency. Bar graphs illustrating mean (sd) streamline density (SD), fractional anisotropy (FA) and mean diffusivity (MD) across all reconstructed white matter fibers in bipolar I disorder patients and healthy controls. The lower two bar graphs show global efficiency (*GE*) of the structural connectome, and *GE* corrected for the effects of SD connectivity (GE_{corr}). The patient-control difference in *GE* was statistically significant (i.e., surviving FDR-correction).

Brain Hubs

There was a high correspondence in detected brain hubs between subject groups, with portions of the bilateral cingulate, precuneus, superior frontal, parietal and temporal gyri, pre- and postcentral gyri, and insula constituting the most highly connected brain regions (Fig. 2a). Defining hubs based on betweenness centrality instead of degree resulted in a highly comparable set of brain regions (Supporting Information Table I).

Hub connectivity

There were no group-differences in average SD, FA, or MD over all connections of detected brain hubs (all $P > 0.1$). Defining hubs based on betweenness-centrality (Fig. 2b) or as the top 10% most connected and central brain regions resulted in the same overall findings (Supporting Information provides details).

Node centrality and disease-related change in connectivity

To further explore whether the centrality of a node is a relevant feature in determining whether a brain region

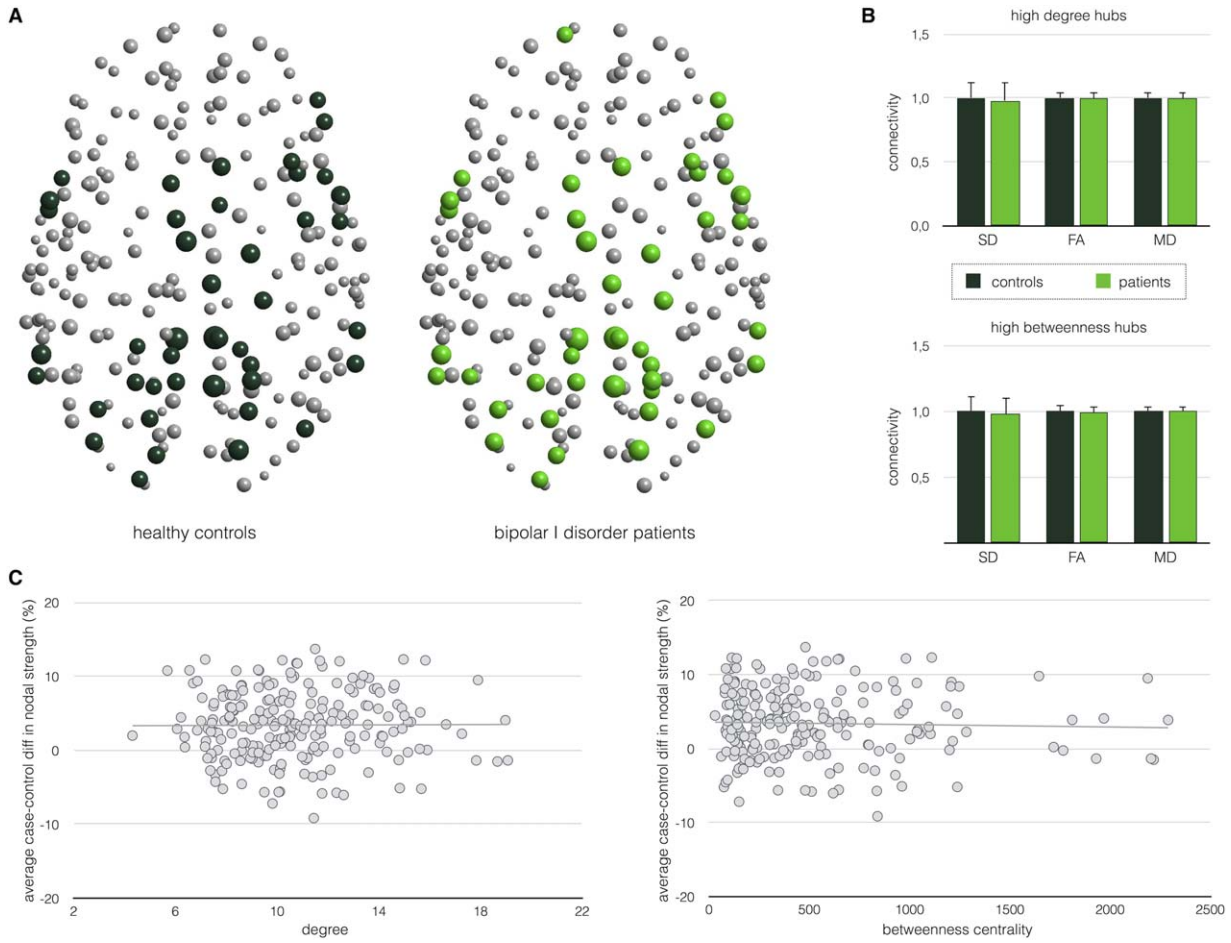

Figure 2.

Brain hub detection and hub connectivity. Panel A depicts the top 20% high-degree brain hubs averaged over healthy controls (left plot) and patients (right plot), in a highly similar fashion across subject groups (Supporting Information Table II lists all detected brain hubs per subject group). Panel B illustrates that there were no significant differences in hub connectivity between patients and controls, irrespective of edge weighting (i.e., SD, FA, MD) or hub definition (i.e., degree- or betweenness based). Of note, to allow visualization of SD, MD and FA connectivity in one chart, connectivity measures in patients are normalized to controls. Corroborating finding no group-differences in hub connectivity, the plots in panel C show that there was no linear association between the average group-difference (%) in connectivity, and nodal degree- and betweenness centrality. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

shows disease-related connectivity change in bipolar I disorder, the correlation between node centrality and the average relative (%) difference in SD connectivity between patients and controls was assessed. Degree ($r = 0.01$, $P = 0.92$) and betweenness centrality ($r = -0.03$, $P = 0.63$) were found not to correlate with group-differences in connectivity (Fig. 2c).

Rich Club Organization

Three connection classes were examined for group-differences: between hubs ("rich club"), from hubs to nonhubs ("feeder") and between nonhubs ("local") connections (Fig. 3a).

Rich club connectivity

There were no significant differences in average SD, FA, or MD of rich club (all $P > 0.2$) or feeder (all $P > 0.05$) connections. Local connections showed a trend-level reduction in SD (−2.8%, $P = 0.009$, not surviving FDR correction), but no changes in FA or MD (both $P > 0.3$) connectivity (Fig. 3b). Examining alternative hub definitions resulted in the same overall findings (supplement).

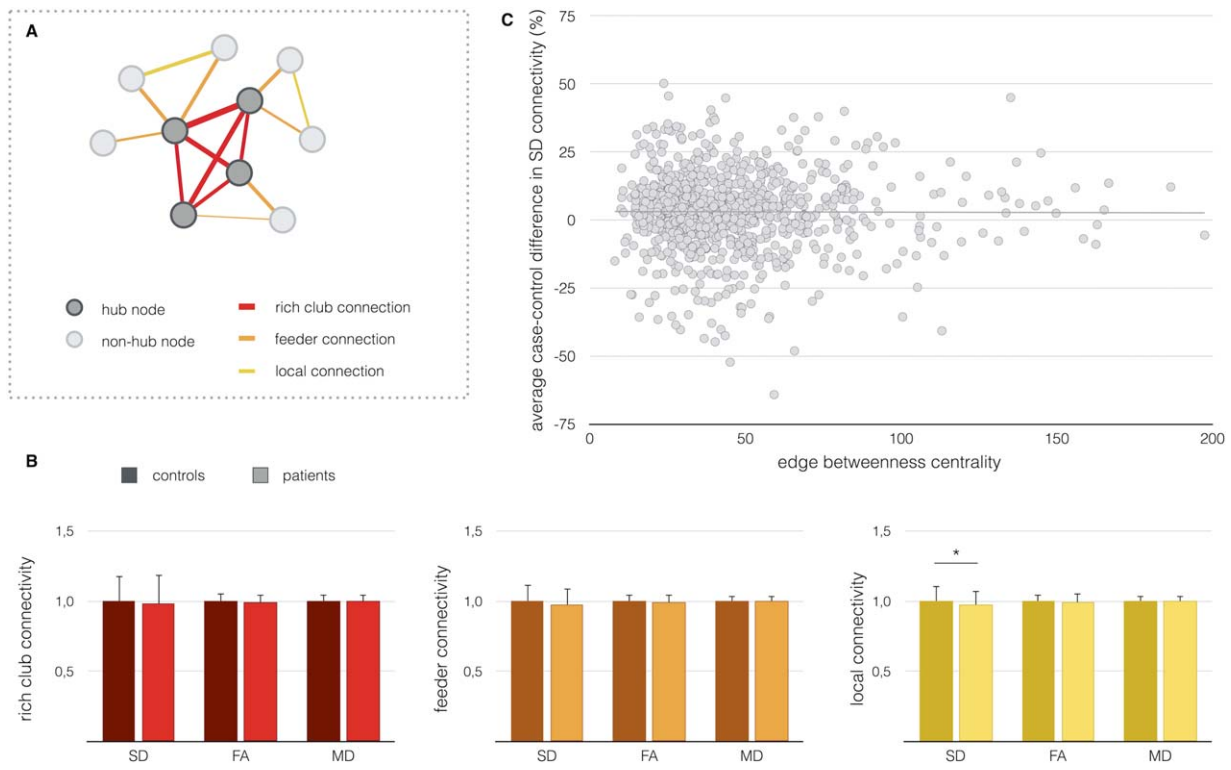

Figure 3.

Rich club organization. Panel A shows a toy network illustrating "rich club" (linking hubs), "feeder" (linking hubs to nonhubs), and "local" (linking nonhubs) connections. There were no significant differences between patients and controls in SD, FA or MD connectivity of either of these connection classes (B). Panel C illustrates that the centrality of an edge was found not to be related to average patient-control differences (%) in structural connectivity (i.e., as evident from the flat trend line; $r = -0.005$, $P = 0.83$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Edge centrality and disease-related change in connectivity

It was examined whether the topological centrality of an edge relates to whether that edge is affected in patients. There was no association between edge centrality and the average percentage of change in SD connectivity in patients as compared to controls ($r = -0.005$, $P = 0.83$) (Fig. 3c).

Interhemispheric Connections

Patients showed marked disruptions of interhemispheric connections (Fig. 4a), including a strong decrease in SD connectivity (−13.0% P =0.001, FDR-corrected significant) and an increase in MD connectivity (+1.7%, $P < 0.001$, FDR-significant) (Fig. 4b). Average FA of interhemispheric connections was not significantly different in patients (P =0.089). Intrahemispheric FA and MD connectivity were similar in patients and controls (both $P > 0.2$) and there was a trend-level reduction in SD connectivity of intrahemispheric connections (−2.1%, $P = 0.045$, not surviving FDR correction) (Fig. 4c). To assess if these differences should be attributed to global connectivity differences, values were normalized to a set of 1000 randomized networks, with preserved degree and weight distribution. While normalization eliminated the group-difference in intrahemispheric SD connectivity ($P = 0.09$), patient-control differences in interhemispheric SD (−11.8%, $P < 0.001$) and MD (+1.3%, $P < 0.001$) connectivity remained statistically significant, suggesting that these effects exceed a global effect and are specific to the white matter tracts connecting the hemispheres.

Impact on global efficiency

To assess the impact of the observed reduction in interhemispheric connectivity on the brain's overall communication capacity, the relationship between interhemispheric connectivity and global efficiency (*GE*) was explored using correlation analyses (see Supporting Information for details). The correlation between *GE* and interhemispheric connectivity was higher in patients ($r = 0.56$, $P < 0.001$) than controls ($r = 0.39$, $P < 0.001$) (Fig. 4d). These correlations remained

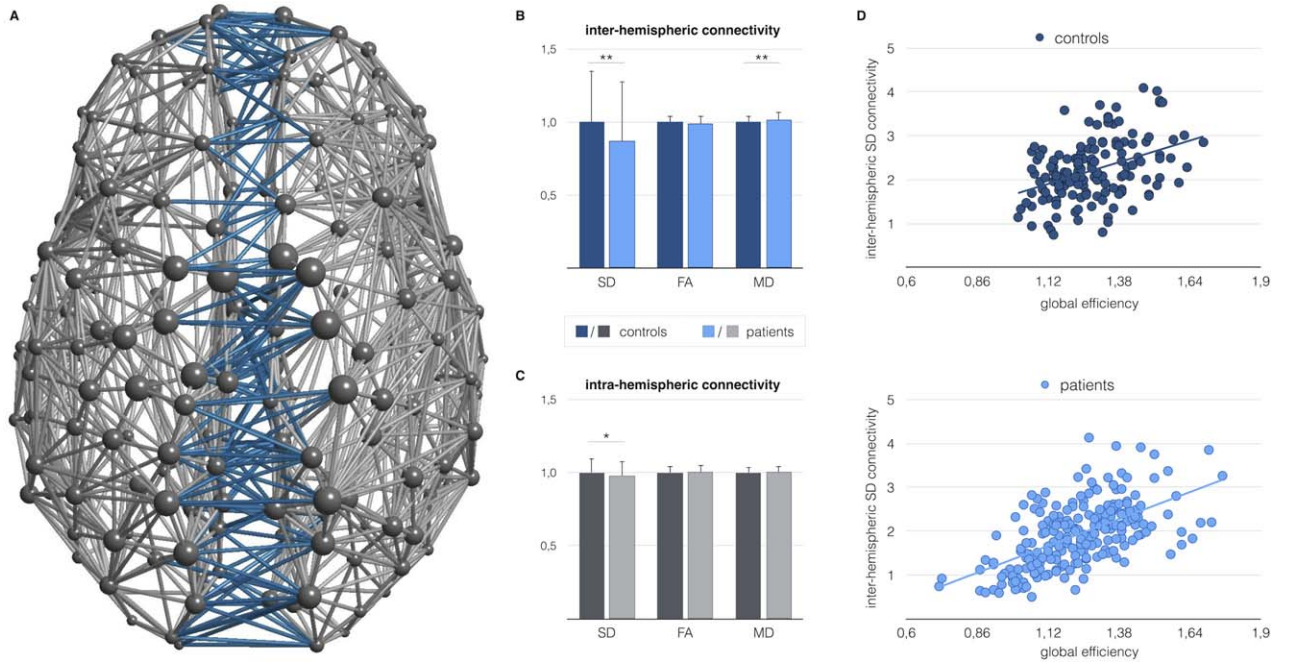

Figure 4.

Inter versus intrahemispheric connectivity. Panel A depicts a group-averaged brain network (group-threshold 30%) with connection coloring indicating intrahemispheric (grey) versus interhemispheric (blue) connections, visualized with the BrainNet Viewer [Xia et al., 2013]. Interhemispheric connections showed marked disruptions in bipolar I disorder patients as compared to controls (B), while intrahemispheric connections were not significantly affected (C). Interhemispheric connectivity was associated with global efficiency in both groups, but this association was significantly stronger in patients than controls (D). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

significant when controlling for overall SD connectivity through normalization (patients: $r = 0.41$, $P < 0.001$; controls: $r = 0.17$, $P = 0.042$), and the case-control differences were statistically significant ($P = 0.038$ and 0.014, respectively, bivariate comparison through Fisher's r-to-z transformation). Together, these findings suggest that the reduction in global efficiency in patients stems (at least in part) from the disruption in interhemispheric connectivity. Indeed, when *GE* was corrected for interhemispheric connectivity using linear regression analysis, the *GE* difference between patients and controls was no longer statistically significant ($P = 0.147$).

Corpus callosum volume (post-hoc analysis)

To assess whether the observed reductions in interhemispheric connectivity were related to changes in white matter morphometry, the volume of the CC and five CC subdivisions was examined in a post-hoc analysis (Supporting Information). Compared to controls, patients showed reduced absolute (-6.1%, $P < 0.001$) and (age, gender, and total white matter volume) corrected (-4.1%, $P = 0.004$) total CC volume. Examining CC subdivisions revealed particularly central portions to be affected (Fig. 5). Moreover, affected CC portions showed significant associations with interhemispheric SD connectivity (Table II), suggesting these connectivity deficits to be related to reduced white matter volume of the CC.

Cognitive and Clinical Correlates of Affected Connectivity

Current IQ was significantly ($P < 0.001$) reduced in bipolar I disorder patients (mean [sd] = 99.0 [14.2]) as compared to controls (mean [sd] = 108.7 [15.2]), while premorbid IQ was not ($P = 0.28$). The majority of patient histories included at least one psychotic feature (54.4%), and most patients were on lithium treatment (69.0%).

As patients showed reduced interhemispheric connectivity, this impairment was examined for a link with clinical characteristics. Across subjects, there was a modest but significant association between interhemispheric SD connectivity and IQ ($\beta = 0.19$, $P = 0.001$) (Fig. 6a), also when "group" (i.e., patient or control) and overall average SD connectivity were included as covariates ($P = 0.012$ and 0.002, respectively). Separate analyses per subject group indicated that the associations were qualitatively similar between groups (Fig. 6b), but no longer statistically significant ($P = 0.067$ in patients; $P = 0.105$ in controls, respectively) in separate groups. There were no significant

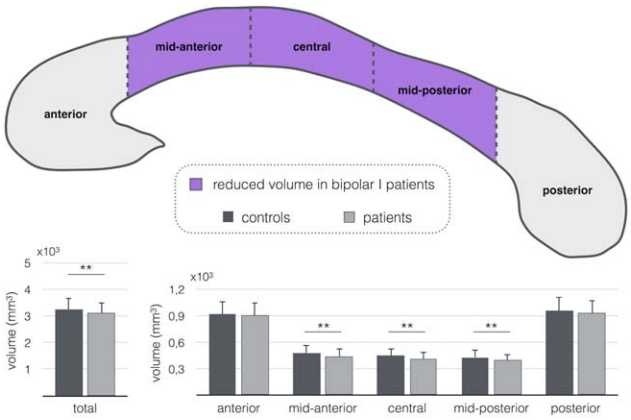

Figure 5.

Corpus callosum volumes. Total and mid-section subdivision corpus callosum volumes were significantly reduced in bipolar I disorder patients as compared to controls (all $P < 0.005$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

associations with premorbid IQ, or the number of manic or depressive episodes. Interhemispheric connectivity and CC volume were not different in patients on or off lithium or antipsychotic medication, or with a positive or negative history of psychotic features (all $P > 0.5$).

Validation Analyses

Node definition

To assess whether the main findings using the original 219-node definition were robust to variations in spatial resolution, two additional node definitions, comprising a total of 114 and 448 nodes, respectively, were employed. The results were highly comparable across scales: using both alternative node definitions—one at lower and one at higher spatial resolution (114 nodes | 448 nodes, respectively)—there were significant reductions in global efficiency (−4.1%, $P = 0.002$ | −3.8%, $P = 0.015$) and interhemispheric connectivity (−13.5%, $P = 0.002$ | −12.5%, $P < 0.001$), but not rich club connectivity ($P = 0.075$ | $P = 0.221$).

TABLE II. Corpus callosum volumes and correlations with interhemispheric connectivity

	Bipolar I disorder patients ($N = 216$)		Healthy controls ($N = 144$)		
	Volume	r	Volume	r	P
Total CC	3102.6 (407.5)	**0.34**	3236.0 (453.2)	**0.33**	0.004
Anterior CC	909.6 (142.3)	0.09	921.6 (142.7)	0.15	0.437
Mid anterior CC	447.4 (78.2)	**0.38**	473.9 (92.2)	**0.34**	0.004
Central CC	418.6 (68.9)	**0.46**	452.2 (85.9)	**0.32**	<0.001
Mid posterior CC	397.5 (75.1)	**0.46**	433.9 (90.1)	**0.52**	<0.001
Posterior CC	929.5 (151.2)	0.10	954.3 (156.6)	0.11	0.133

Mean (sd) volume (mm^3) of the corpus callosum (CC) and five CC subregions in patients and controls, and Pearson's correlations (r) of CC volumes with interhemispheric SD connectivity per subject group, with correlations below $P < 0.05$ in bold print. Volumes were corrected for the effects of age, gender and total WM volume using linear regression analysis. P-values indicate the statistical significance of group-differences in CC volumes.

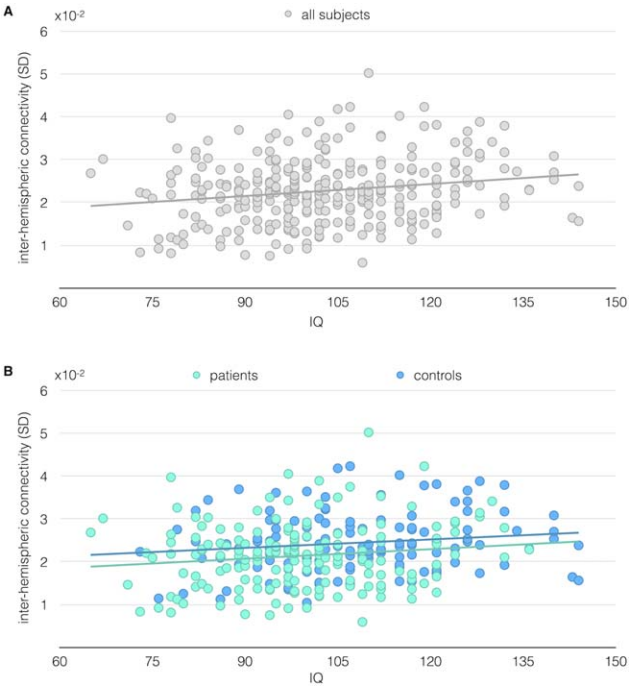

Figure 6.

Interhemispheric connectivity and IQ. A modest but significant association ($r = 0.19$, $P = 0.001$) was found between interhemispheric connectivity and IQ in all subjects (A). When subjects groups were examined separately, the associations were qualitatively similar between groups, but not statistically significant in the separate groups ($P = 0.067$ and 0.105) for patients and controls, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Mood status

Based on self-report, around half the patients were euthymic at inclusion and the majority (~70%) experienced mild symptoms at most (Table I). A minority reported moderate–severe depression (~17%), mania (~4%), or mixed symptoms (~10%). To assess the influence of mood status, connectivity measures were recomputed using only a- or mildly symptomatic patients ($N = 151$). This confirmed our main findings, showing reductions in global efficiency (−3.6%, $P = 0.017$) and interhemispheric connectivity (−10.8%, $P = 0.007$), but no significant effects of rich club connectivity ($P = 0.298$). Of note, moderate-severely symptomatic patients showed larger absolute differences with controls, but no significant

differences when compared to patients with no or mild symptoms (Supporting Information).

DISCUSSION

This study in 216 bipolar I disorder patients and 144 healthy comparison subjects shows that structural connectome organization is affected in bipolar I disorder. We find that global network efficiency is reduced in bipolar disorder patients, and that this deficit is associated with impaired interhemispheric connectivity. Notably, we found no indications that central brain hubs or the central "rich club" core are particularly affected in bipolar I disorder. In all, our findings are indicative of a reduced capacity for global communication in the brain because of disruptions in the structural connections linking the hemispheres in bipolar disorder.

The observed reductions in interhemispheric connectivity in bipolar I disorder patients are consistent with previous reports of reduced integrity of the CC in bipolar disorder [Barysheva et al., 2013; Emsell et al., 2013; Lagopoulos et al., 2013; Leow et al., 2013; Sarrazin et al., 2014; Torgerson et al., 2013; Wang et al., 2008] and may be reflective of a decrease in the number, density, caliber, and/or myelination of callosal axons, with recent findings pointing more towards myelination than axon abnormalities [Lewandowski et al., 2014]. Around 200–250 million axons pass through the CC [Nishikimi et al., 2013; Paul et al., 2007] to connect primary, secondary, and higher-order cortices [Aboitiz et al., 2003]. Interhemispheric axons have widespread arbors that terminate in many regions besides the topographically equivalent one [Houzel and Milleret, 1999] and it has been suggested that these heterotopic projections may be important to propagate activity to other areas, thereby contributing to the formation of large-scale neuronal ensembles promoting diverse aspects of cortical processing [Varela et al., 2001]. Indeed, the association between impaired interhemispheric connectivity and reduced efficiency observed here and in previous studies [Leow et al., 2012; Leow et al., 2013] indicates that damage to interhemispheric connections may impact the brain's capacity for global communication. We extend these findings by showing that interhemispheric connection density relates to estimated total IQ, suggesting commissural fibers to be relevant to cognitive performance [Poletti et al., 2015].

The etiology of affected interhemispheric connectivity in bipolar disorder remains to be determined. Studies in adolescents with overt bipolar disorder [Barnea-Goraly et al., 2009] or sub-threshold bipolar symptoms [Paillère Martinot et al., 2014] have reported similar connectivity changes in these individuals. Furthermore, healthy children with a parent with bipolar disorder have been shown to display a linear decrease in CC FA with age, contrasting an increase in CC FA with age in adolescent controls [Versace et al., 2010]. In addition, a recent study demonstrated volume and diffusion-weighted structural connectivity measures of the CC to be both heritable and associated with bipolar illness [Fears et al., 2014]. In all, impaired interhemispheric connectivity may reflect a deviant pattern of callosal development in association with high familial risk for bipolar disorder that may be mediated by genetic factors.

CC deficits in bipolar disorder patients have been suggested to be more pronounced in patients with a history of psychotic features [Sarrazin et al., 2014]. We currently did not identify differences in interhemispheric connectivity, or CC (subregion) volume, in patients with versus those without a history of one or more psychotic features. At inclusion, the majority of patients were either euthymic or experiencing mild symptoms at most, but a minority reported moderate–severe depression, mania, or mixed symptoms. When patients with current moderate–severe symptoms were excluded from the analyses, our main findings remained intact. Moreover, we did not find an association with the number of manic or depressive episodes, or whether patients were on or off lithium treatment.

Finding no clear changes in hub or rich club connectivity in bipolar I disorder patients is of interest in light of recent findings in schizophrenia indicating a disproportionate disturbance of brain hubs and their mutual connections in schizophrenia patients [Van den Heuvel et al., 2013] and their unaffected relatives [Collin et al., 2014a; Yan et al., 2015]. Moreover, it has been proposed that affected hub connectivity may be a general feature of brain disorders [Crossley et al., 2014]. Our current findings are suggestive of differential patterns of hub involvement across brain disorders. Putatively, the apparent sparing of central brain regions and their connections may relate to the relative preservation of psychosocial, scholastic, and vocational functioning in affective versus nonaffective psychotic disorders [Jarbin et al., 2003; Martínez-Arán et al., 2002; Tabarés-Seisdedos et al., 2008; Tohen et al., 2000; Vreeker et al., in press].

When interpreting the results of our study, it should be taken into consideration that the reported connectivity measures were derived from diffusion tractography, and are thus indirect estimations of true white matter connectivity. Despite limitations including issues with determining the exact termination of fibers, detecting collaterals and tracking fibers in areas with dense connectivity [Jbabdi and Johansen-Berg, 2011], diffusion tractography is the only currently available tool to reconstruct white matter pathways in vivo and noninvasively. In addition, in our study, node definition was based on the gyrification pattern of the cortex by means of the Desikan-Killiany atlas [Cammoun et al., 2012]. With no gold standard for regional parcellation in the reconstruction of imaging based connectome maps, we examined the potential impact of node definition [de Reus and van den Heuvel, 2013; Zalesky et al., 2010] on our findings, reanalyzing our data with two additional parcellation schemes of the Desikan-Killiany atlas, including, respectively, 114 and 448 regions. These post-hoc validation analyses revealed highly comparable effects across spatial scales.

Moreover, the majority of the patients in our investigation used psychotropic medication including lithium and antipsychotics, but we note that we observed no differences in connectivity measures between patients on or off these medications. Finally, although the group-difference in overall SD connectivity did not reach statistical significance after FDR-correction, effects in graph measures including global efficiency can be driven by differences in connectivity strength [Van den Heuvel et al., 2010]. As *GE* remained significantly reduced after correction for overall connectivity, it is likely reflective of network organizational differences, rather than "just" reduced connectivity.

In all, the findings of this study suggest that bipolar I disorder involves affected white matter connectivity and brain network topology, with marked connectivity deficits of interhemispheric connections, negatively impacting the brain's capacity for global communication. In addition, the finding that hub connections in general, and connections spanning brain hubs in particular (i.e., "rich club" connections) did not show predominant impairments in our large sample of bipolar I disorder patients is indicative of an etiology in which damage to central brain hubs and their mutual rich club connections does not seem to play a central role.

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