Trait-Related Cortical-Subcortical Dissociation in Bipolar Disorder: Analysis of Network Degree Centrality

Qian Zhou, MD[a,‡]; Fay Y. Womer, MD, PhD[b,‡]; Lingtao Kong, MD, PhD[a]; Feng Wu, MD, PhD[a]; Xiaowei Jiang, MD[c]; Yifang Zhou, MD[d]; Dahai Wang, MD[a]; Chuan Bai, MD[c]; Miao Chang, MD[c]; Guoguang Fan, MD, PhD[c]; Ke Xu, MD, PhD[c]; Yong He, PhD[e]; Yanqing Tang, MD, PhD[a,d,*]; and Fei Wang, MD, PhD[a,f,*]

ABSTRACT

Background: Bipolar disorder is a systemic brain disorder. Accumulated evidence suggested that cortical-subcortical imbalance could be a trait-related pathogenic factor of bipolar disorder. Degree centrality, a robust index of focal connectivity in which the number of direct connections from one node to all nodes is counted, has not previously been studied in bipolar disorder as a whole.

Methods: Resting state functional magnetic resonance imaging was performed on 52 patients with *DSM-IV* bipolar I disorder and 70 healthy controls recruited between September 2009 and July 2014. Degree centrality was calculated within cerebral gray matter for each subject and compared between patients with bipolar disorder and healthy controls. Hub distributions of both groups were explored. Effects of medication exposure and mood state on degree centrality, as well as cortical-subcortical degree centrality correlations, were explored.

Results: Compared to healthy controls, patients with bipolar disorder exhibited significant decrease in degree centrality in cortical regions, including the middle temporal pole, inferior temporal gyrus, and ventral prefrontal cortex, but showed significant increase in degree centrality mainly in subcortical regions, including caudate, thalamus, parahippocampal gyrus, hippocampi, anterior cingulate, insula, and amygdala, and a small portion of cortical regions, such as superior and middle frontal gyrus ($P < .05$, corrected). Spatial distributions of the 2 groups were very similar. No significant effects of medication exposure or mood state on degree centrality were found. Patients with bipolar disorder also showed significant decrease in cortical-subcortical degree centrality correlation ($P = .003$).

Conclusions: These findings further contribute to the mounting evidence of cortical-subcortical dissociation in bipolar disorder pathophysiology. In addition, this study supports the continued development and implementation of graph-based techniques to enhance our understanding of the underlying neural mechanisms in mental disorders such as bipolar disorder, which are increasingly viewed as systemic brain disorders rather than disorders arising from disruption within a single structure or a limited number of structures. Due to the heterogeneity of our sample, as well as the small sample size of each medication and mood state subgroups, further investigation is needed to support our findings.

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[a]Department of Psychiatry, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning, China
[b]Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri
[c]Department of Radiology, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning, China
[d]Department of Gerontology, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning, China
[e]State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, China
[f]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut
‡These two authors contributed equally to this work.
*Corresponding authors: Yanqing Tang, MD, PhD, and Fei Wang, MD, PhD, 155 Nanjing North St, Heping District, Shenyang, Liaoning, China (yanqingtang@163.com, fei.wang@mail.cmu.edu.cn).

Bipolar disorder is characterized by the episodic occurrence of abnormally elevated mood that is associated with changes in a wide range of behaviors, including sleep and goal-directed activity as well as cognitive and emotional processes.[1] Not surprisingly, neural abnormalities in bipolar disorder appear to be on a systemic level rather than within a single region,[2] adding to the challenges in studying the disorder. Convergent evidence suggests cortical-subcortical imbalance might be a key feature of bipolar disorder. For example, findings[3–7] of impaired association between cognitive and adaptive emotion regulation strategies implicate dissociation between cortical and subcortical function in bipolar disorder. Functional magnetic resonance imaging (fMRI) studies[8] have shown decreased activation in ventral prefrontal cortex and dorsolateral prefrontal cortex in bipolar depression during emotion processing tasks. Ventrolateral prefrontal cortex deactivation has been found in euthymic bipolar disorder during an affective faces task.[9] Hyperactivation of amygdala and hypoactivation of lateral orbitofrontal cortex have been found in the manic phase of bipolar disorder during an affective faces task.[10] These studies suggest that altered activations of cortical-subcortical areas might be influenced by mood states. However, a meta-analysis[11] concluded that decreased activity occurred in the right ventral prefrontal cortex in individuals with bipolar disorder compared to healthy controls regardless of current mood state and behavioral performance.

Cortical hypoactivation and subcortical hyperactivation in bipolar disorder are very likely mediated by the connections between cortical and subcortical regions. Decreased density of cortical γ-aminobutyric acid interneurons that mediate cortical inhibition has been found in the anterior cingulate cortex in individuals with bipolar disorder.[12] Decreased white matter integrity of uncinate fasciculus, which connects from ventral prefrontal cortex to amygdala, has been found in a diffusion tensor imaging study.[13] Decreased functional connectivity between dorsal

lateral prefrontal cortex and amygdala has been reported in individuals with euthymic bipolar disorder.[14] An excellent review[15] thoroughly explored the studies of connectivity between cortical and subcortical regions in bipolar disorder, concluding that reduced structural, functional, and effective connectivity between cortical and subcortical regions had been widely detected in bipolar disorder subjects across all mood states. These proofs support an imbalance of cortical and subcortical interaction in bipolar disorder.

The implementation of fMRI techniques has advanced our ability to study psychiatric disorders such as bipolar disorder. Resting state fMRI studies suggested that dysfunction of default mode network[16] is associated with neuropsychiatric disorders.[17] However, studies of default mode network in bipolar disorder did not reach consistent findings, but instead supported a cortical-limbic hypothesis.[18] Degree centrality is a particularly interesting graph metric of graph-based network analysis methods.[19] It is a robust index of focal connectivity ascertained by counting the number of direct connections from one node to all other nodes.[19,20] Fair to good test-retest reliability of this technique has been proved in previous studies.[21–23] Higher degree centrality values indicate nodes that are central within a network and that may have broad influence on the network and beyond through their connections. With regard to brain networks, this index may correlate with highly associative cortical areas reflecting the intrinsic cortical organization.[20,24,25] Degree centrality reveals the importance of a node inside a network, and distribution of degree centrality in the brain is substantially consistent and stable in healthy individuals, but will be altered in those with pathological processes.[24,26] Identification of areas with altered degree centrality may facilitate understanding of the neuropathophysiology of mental disorders and further provide potential targets for neuromodulation in the treatment of these disorders.

Degree centrality has been used to identify important differences in the functional architecture of mental disorders, including schizophrenia and clinical high risk individuals for psychosis.[24,27–29] Results of these studies have been supported by studies using other methods.[30–34] Degree centrality studies in bipolar disorder are relatively limited. Only one study[24] has examined degree centrality and cortical gyrification in bipolar disorder; that study focused on bipolar disorder with psychotic symptoms and schizophrenia, rather than on degree centrality in bipolar disorder as a whole. To our knowledge, this is the first degree centrality study of disease-associated features in bipolar disorder, regardless of mood states and medication status.

In this study, we aimed to compare degree centrality in patients with bipolar disorder and healthy controls with voxels as nodes and resting state functional connectivity as edges. We also explored the effects of medications and mood states on degree centrality in bipolar disorder as well as cortical-subcortical degree centrality relationship. Given the evidence suggesting impaired cortical regulation and subcortical overactivity in bipolar disorder, we hypothesized that degree centrality would be decreased in cortical regions and increased in subcortical regions.

Clinical Points

- Neuropathogenesis of bipolar disorder is unclear, and treatment targets are not fully determined.
- To terminate mood cycling of bipolar disorder, balancing cortical and subcortical functions may be a solution.

METHODS

Participants

Fifty-two subjects with bipolar I disorder and 70 age- and gender-matched healthy control subjects were included in this study. All subjects were right-handed and aged between 17 and 50 years. No subject had a history of neurologic illness, head trauma with loss of consciousness over 5 minutes, or major medical disorder. Subject recruitment started in September 2009 and ended in July 2014. Subjects with bipolar disorder were recruited from the outpatient clinic in the Department of Psychiatry of the First Affiliated Hospital of China Medical University, Shenyang, or the inpatient department at Shenyang Mental Health Center. Healthy control subjects were recruited via advertisement posted in this hospital and matched to patients according to gender and age. All individuals in the bipolar disorder group met the *DSM-IV* criteria for bipolar I diagnosis. The presence of *DSM-IV* diagnoses and current mood states (elevated mood, depression, or euthymia [absence of current manic, hypomanic, depression, or mixed episode]) were confirmed and determined by the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I)[35] translated into Chinese (http://www.scid4.org/trans.html). Healthy control subjects had no first-degree relatives with a history of Axis I disorder. All subjects provided signed informed consent that was approved by the ethics committee of China Medical University. The 17-item Hamilton Depression Rating Scale ($HDRS_{17}$),[75] Hamilton Anxiety Rating Scale (HARS),[76] and Young Mania Rating Scale (YMRS)[77] were administered to evaluate symptom severity. Data on age at onset, years of illness, and number of previous episodes were collected to evaluate patients' clinical characteristics.

In the bipolar disorder group, 24 subjects (46.1%) were euthymic, 16 (30.8%) were depressed, and 12 (23.1%) had elevated mood at the time of scan. With respect to medication status, 10 bipolar disorder subjects (19.2%) were naive to psychotropic medications, and the remaining 42 bipolar disorder subjects (80.8%) were treated with psychotropic medications at the time of scanning (28 subjects with anticonvulsants, 5 with lithium, 25 with antipsychotics, 14 with serotonin reuptake inhibitors, 4 with benzodiazepines, 1 with zopiclone, 1 with a β-blocker, 2 with herbal medications). Three patients (5.8%) had a history of psychotic symptoms, and 1 patient (1.9%) had a history of alcohol dependence.

Image Acquisition and Processing

All subjects underwent resting state fMRI scan using a GE Signa HDX 3.0T superconductive magnetic resonance imager (General Electric Company). Scan parameters were as follows: repetition time = 2,000 ms, echo time = 40 ms, matrix = 64 × 64, field of view = 24 × 24 cm^2, number of excitations = 5, slice thickness = 3 mm, slice interval = 0 mm, 35 slices, and scan time 6 min 40 seconds. Subjects were asked to remain awake with their eyes closed and without moving or thinking of any topic in particular during the scan. Preprocessing of images was managed by the Data Processing Assistant for Resting-State fMRI, advanced edition (DPARSFA)[36] package of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) software. The first 10 time points were removed, and then slice timing, realign, and normalize (using echo-planar imaging [EPI] templates) tasks were performed. This was then followed by detrending and further processing using a band-pass temporal filter (0.01–0.08 Hz).[37] Nuisance covariates, including the 6 head motion parameters, white matter signal, and cerebrospinal fluid signal, were regressed out.[36] If a head motion parameter exceeded 3 mm in displacement or 3° in rotation, then the subject was excluded from the final analysis. To access the head motion confounder, we compared the mean framewise displacement[38,39] between the bipolar disorder and healthy control groups and among bipolar disorder subgroups. Head motion comparison showed no significant differences between the bipolar disorder and healthy control groups ($P = .112$), between medicated and untreated bipolar disorder ($P = .756$), or among bipolar disorder states ($P = .860$).

Degree Centrality Calculation

Based on the built-in gray-matter probability template of SPM8, we set a threshold to 0.2, and voxels whose gray level was greater than 0.2 were considered gray matter. Using this set threshold, a whole brain gray matter mask was created. We utilized a weighted approach such that the weights of the connectivity matrix (ie, the correlation coefficients) determined the connectivity strengths of graph edges. We computed the weighted degree centrality of every voxel within the gray matter mask using graph theoretical network analysis (GRETNA).[40] Voxel by voxel within the gray matter mask, Pearson correlation coefficient (r) calculations were performed ($r > 0.2$ was a correlation threshold in order to eliminate weak correlations possibly arising from noise[41–43]). The correlation coefficient (r) was then transformed by Fisher Z to improve normality.[44] The correlations (Z values) of all voxel pairs were summarized indicating the total synchronism of the current voxel to all other voxels in gray matter of the whole brain; thus, maps of all gray matter voxels were obtained.[20] Overall, degree centrality takes into account a given region's relationship with all other brain areas, not just its relation to individual regions or to separate larger components. A Gaussian filter (6 × 6 × 6 mm full-width-at-half-maximum) was applied for spatial smoothing of the calculated degree centrality maps.

Table 1. Demographic and Clinical Information of the Bipolar Disorder and Healthy Control Groups

Variable	Bipolar Disorder	Healthy Control	t/χ^2	P
Sample size, N	52	70	…	…
Age, mean ± SD y	29.84 ± 8.97	29.37 ± 8.09	0.306	.76
Male/female, n	26/26	34/36	0.24	.876
$HDRS_{17}$ total, mean ± SD (n[a])	9.12 ± 8.73 (52)	0.74 ± 1.15 (65)	6.868	< .001
HARS total score, mean ± SD (n[a])	5.78 ± 7.40 (51)	0.39 ± 0.92 (64)	5.177	< .001
YMRS total score, mean ± SD (n[a])	7.76 ± 9.93 (51)	0.06 ± 0.30 (65)	5.536	< .001
Age at onset, mean ± SD y (n[a])	26.02 ± 8.45 (49)	…	…	…
Months of illness, mean ± SD (n[a])	51.67 ± 70.31 (49)	…	…	…
No. of previous episodes, mean ± SD (n[a])	3.31 ± 2.99 (39)	…	…	…

[a]Number of subjects for whom this information was available.
Abbreviations: HARS = Hamilton Anxiety Rating Scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, YMRS = Young Mania Rating Scale.
Symbol: … = not applicable.

Statistical Analyses

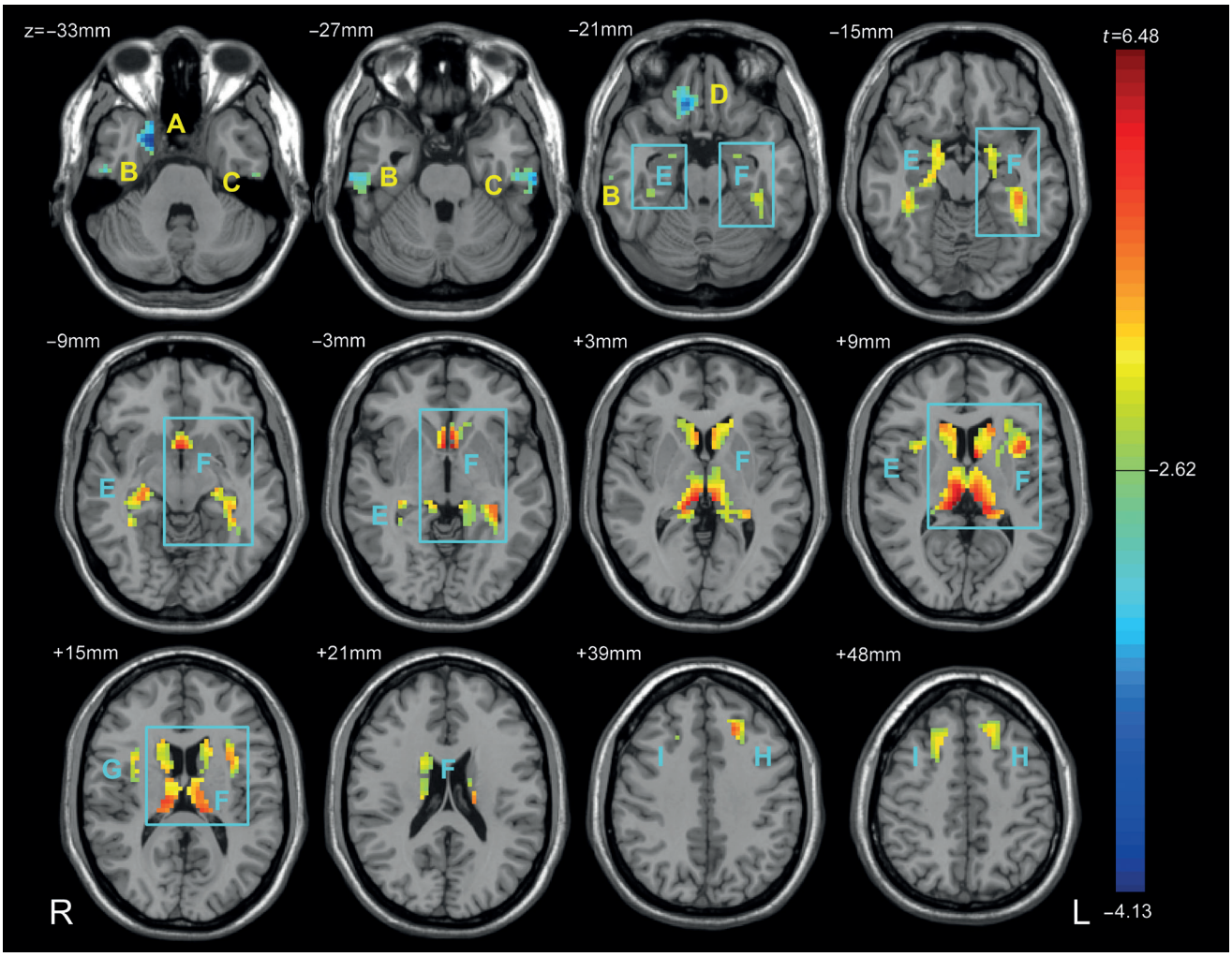
Demographic and clinical data were analyzed using a 1-way analysis of variance (ANOVA), 2-sample t test for continuous variables, or χ^2 test for categorical variables. The significance level was set at $P < .05$.

The primary analysis of degree centrality in the bipolar disorder and healthy control groups were performed using RESting-state fMRI data analysis Toolkit (REST) software.[45] Group differences in degree centrality were examined using voxel-based 2-sample t test. For multiple comparison correction (family-wise error), a Monte Carlo simulation (1,000 iterations) was employed to determine the minimum number of continuous clusters necessary for achieving a voxel-wise significance level of .01 (uncorrected) and cluster-wise significance of .05 (corrected). The cluster size was estimated to be 31 continuous clusters.

Hub distributions of the bipolar disorder and healthy control groups were completed by 1-sample t test within group (see eAppendix 1 at PSYCHIATRIST.COM). To enable this procedure, the degree centrality value of each voxel inside the maps (containing 42,185 voxels) of each individual was divided by the mean value of degree centrality inside the mask (mean-normalized degree centrality).[36] Then the test value of a 1-sample t test was set to 1 (mean value of the new map). Hub region was defined by higher mean degree centrality (> 1 SD beyond the global mean) within the mask.[43]

Exploratory analyses were performed using SPSS software. The P value was set at $P < .05$ uncorrected for all exploratory analyses to identify the most possible effects of clinical factors. For exploratory analyses of medication and mood state effects, the mean degree centrality value was extracted for clusters showing a significant difference between the bipolar disorder and healthy control groups. Analysis of covariance was performed to examine the effect of medications and mood states, including overall medication effect: medicated (yes/no); medication effects

Figure 1. Clusters Showing Significant Differences in Degree Centrality Between the Bipolar Disorder and Healthy Control Groups[a]



[a]Colors of clusters indicate *t* values, as shown in the color bar. Clusters A, B, C, and D show the regions where bipolar disorder patients have lower degree centrality than healthy controls, while clusters E, F, G, H, and I show the regions where bipolar disorder patients have higher degree centrality than healthy controls. Compared to the healthy control group, the bipolar disorder group showed decreased degree centrality in the right middle temporal pole (A), bilateral inferior temporal gyri (B, C), and right ventral prefrontal cortex (D) and increased degree centrality in bilateral caudate, bilateral thalami, bilateral parahippocampi, bilateral hippocampi, bilateral anterior cingulate, bilateral insula, and bilateral amygdalae (E, F, G) as well as part of the bilateral superior frontal gyri and bilateral middle frontal gyri (H, I).

of different drug types (taken by more than 5 subjects): anticonvulsants (yes/no), lithium (yes/no), antipsychotics (yes/no), serotonin reuptake inhibitors (yes/no); and mood states (elevated mood/depression/euthymia). We also did correlation analyses of degree centrality values in regions showing significant group differences and $HDRS_{17}$ score, HARS score, YMRS score, age at onset, years of illness, and number of previous episodes in bipolar disorder groups.

For exploratory analysis of the relationship between cortical and subcortical connectivity, we further detected the differences of the correlations between cortical and subcortical degree centrality values in healthy control and bipolar disorder groups. First, the mean degree centrality values were obtained in each participant within regions that showed significant degree centrality differences between the 2 groups; second, the correlation coefficients were calculated between mean cortical-subcortical values by Pearson correlation analyses; finally, the differences in cortical-subcortical correlations between healthy control and bipolar disorder groups were tested by the Fisher *Z* test.[46]

RESULTS

General demographics and symptom rating scores of the bipolar disorder and healthy control groups as well as age at onset, years of illness, and number of previous episodes are shown in Table 1. We also present clinical characteristics of bipolar disorder subjects on versus off medication and clinical characteristics of bipolar disorder subjects with different mood states in Supplementary eTables 1 and 2.

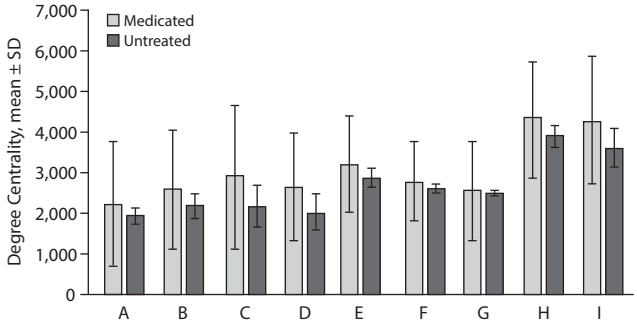
Compared to the healthy control group, the bipolar disorder group demonstrated significantly decreased degree

Table 2. Clusters That Showed a Significant Difference Between Bipolar Disorder and Healthy Control Groups

Cluster	No. of Voxels	PV_X	PV_Y	PV_Z	Hemisphere	Brain Regions	Brodmann Areas	*t*	*P* (corrected)
Bipolar disorder < healthy controls									
A	92	21	9	−36	R	Middle temporal pole	38/28/36/20/21	−4.129	< .05
B	59	57	−9	−39	R	Inferior temporal gyrus	20	−3.462	< .05
C	36	−63	−21	−27	L	Inferior temporal gyrus	20	−3.386	< .05
D	79	12	30	−21	R	Ventral prefrontal cortex	11/47/25	−3.466	< .05
Bipolar disorder > healthy controls									
E	172	24	−21	−12	R	Hippocampus, parahippocampal gyrus, amygdala	34/28/36/37/19/20	4.6961	< .05
F	1,196	9	−30	6	R/L	Caudate, thalamus, amygdala, anterior cingulate, insula, hippocampus, parahippocampal gyrus	13/25/37/30/36/20/ 19/24/27/44/34/28	6.4832	< .05
G	36	33	9	12	R	Insula	13	4.6119	< .05
H	120	−18	30	39	L	Superior frontal gyrus, middle frontal gyrus	8/9/6	4.8269	< .05
I	85	18	21	48	R	Superior frontal gyrus, middle frontal gyrus	8/6	3.8077	< .05

Abbreviations: PV = peak voxel; *t* = *t* values from a *t* test of the peak voxel (showing greatest statistical difference within a cluster); X, Y, Z = coordinates in the Montreal Neurological Institute space.

Figure 2. Comparison of Degree Centrality Value Between Medicated and Untreated Individuals



Abbreviations: A = right middle temporal pole; B = right inferior temporal gyrus; C = left inferior temporal gyrus; D = ventral prefrontal cortex; E = right hippocampus, parahippocampal gyrus, and amygdala; F = bilateral caudate, thalami, amygdalae, anterior cingulate, insula, hippocampi, and parahippocampal gyri; G = right insula; H = left superior frontal gyrus and middle frontal gyrus; I = right superior frontal gyrus and middle frontal gyrus.

centrality in the right middle temporal pole, bilateral inferior temporal gyri, and right ventral prefrontal cortex and significantly increased degree centrality in bilateral caudate, thalami, parahippocampal gyri, hippocampi, anterior cingulate, insula, and amygdalae as well as in small portions of the bilateral superior frontal gyri and middle frontal gyri ($P < .05$, corrected) (Figure 1, Table 2).

Degree centrality distributions of bipolar disorder and healthy control groups are showed in Supplementary eFigure 1. Visual inspection indicated that the spatial distributions were very similar to each other. Hub regions of the 2 groups defined by > 1 standard deviation beyond the global mean were mainly distributed in the default mode network,[16] including medial prefrontal cortex, anterior and posterior cingulate cortex, precuneus, and inferior parietal lobule. Additionally, insula, sensory-motor areas, and visual areas were present.

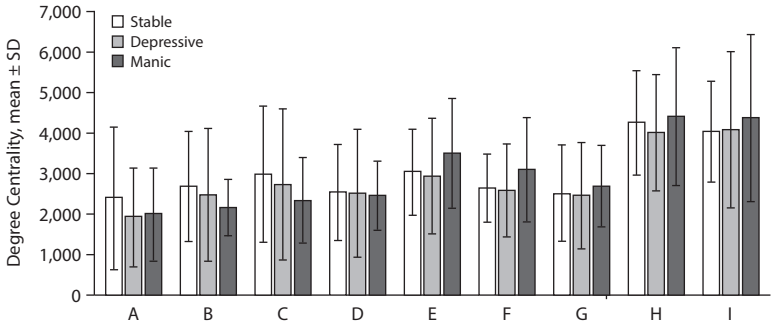
Significantly increased degree centrality was found only in the left inferior temporal gyrus in the medicated bipolar disorder subjects compared to the medication-naive bipolar disorder subjects for clusters showing significant difference in degree centrality between the bipolar disorder and healthy control groups ($P = .043$); for other clusters, there was no significant difference between medicated and medication-naive bipolar disorder subjects ($P = .058$–$.861$) (Figure 2). No significant medication effect of anticonvulsants, lithium, antipsychotics, or serotonin reuptake inhibitors was found ($P = .105$–$.944$). No significant difference was observed among the 3 mood states in the bipolar disorder group for clusters showing significant difference in degree centrality between the bipolar disorder and healthy control groups ($P = .382$–$.986$) (Figure 3). No significant correlation between degree centrality and $HDRS_{17}$ score, HARS score, YMRS score, age at onset, years of illness, and number of previous episodes in bipolar disorder groups ($P > .05$) was found.

Interestingly, both healthy control and bipolar disorder groups showed significant cortical-subcortical correlation ($r = 0.788$, $P < .001$ and $r = 0.446$, $P < .001$, respectively); however, significant group differences were identified in the correlations of cortical-subcortical degree centrality values ($P = .003$). The higher r values in healthy controls, compared to patients with bipolar disorder, indicate that bipolar disorder demonstrated reduced correlations between cortical and subcortical degree centrality.

DISCUSSION

In this study, we investigated global brain connectivity of participants with bipolar disorder using voxel-based weighted degree centrality. Results were consistent with our hypothesis in that (1) subjects with bipolar disorder showed significantly decreased degree centrality in cortical regions and increased degree centrality primarily in subcortical regions; (2) cortical-subcortical correlations were altered in bipolar disorder, further verified by a cortical-subcortical dissociation in bipolar disorder; and (3) these changes were not affected by medication exposure, mood state, symptom severity, or course of disease and thus might represent a trait-related feature of bipolar disorder. Taken together, the findings suggest that cortical-subcortical imbalance may be involved in the pathophysiology of bipolar disorder.

Figure 3. Comparison of Degree Centrality Value Among Different Mood States



Abbreviations: A = right middle temporal pole; B = right inferior temporal gyrus; C = left inferior temporal gyrus; D = ventral prefrontal cortex; E = right hippocampus, parahippocampal gyrus, and amygdala; F = bilateral caudate, thalami, amygdalae, anterior cingulate, insula, hippocampi, and parahippocampal gyri; G = right insula; H = left superior frontal gyrus and middle frontal gyrus; I = right superior frontal gyrus and middle frontal gyrus.

It has been widely reported that bipolar disorder subjects demonstrate decreased cortical function or increased subcortical function. Previous findings from brain injury and structural and functional MRI studies were consistent with decreased cortical degree centrality in bipolar disorder in this work. For example, researchers found that brain injury to the temporal pole resulted in rapid-cycling bipolar disorder.[47,48] Prior studies in bipolar disorder showed deactivation in the right temporal pole[49] and decreased cortical thickness in the right temporal pole.[50] Decreased gray matter volume in the right inferior temporal gyrus has been found in bipolar disorder with psychotic symptoms.[51] A meta-analysis[11] concluded that there was decreased cortical activation in ventral prefrontal cortex in bipolar disorder. Decreased volume and function of cortical structures have been strongly related to impaired cognitive control and executive dysfunction,[52] which are specific to bipolar disorder.

The increased subcortical degree centrality in our study was also consistent with previous findings. For instance, increased degree centrality in the hippocampus and parahippocampus has been seen in individuals with psychotic bipolar disorder compared to healthy controls.[24] Increased amygdala activity has been found in mania.[4] Increased regional homogeneity has been found in the caudate in pediatric bipolar disorder patients compared to healthy controls,[53] and increased amplitude of low-frequency fluctuation (ALFF) has been found in the right caudate in depressed bipolar disorder individuals compared to healthy controls.[54] An fMRI study[55] found increased activity in the left thalamus in bipolar disorder. Evidence showed increased ALFF in the left insula in bipolar disorder,[54] and another study[56] using fMRI under task conditions showed increased activation in the insula in bipolar disorder. The increased bottom-up subcortical overactivity of the insula has been surmised in many studies.[15,57] Prior research[58] has shown increased activity in the left dorsal anterior cingulate cortex during manic episodes of bipolar disorder. Increased function of amygdala-centered subcortical neural systems has been suggested to have a relationship with impaired emotion regulation in bipolar disorder, which is also one of the key features of the disorder.[59]

These previous studies have observed altered activation in the aforementioned brain regions, providing insight from a more localized perspective. Our findings using techniques based on degree centrality support these prior observations and enhance current understanding of bipolar disorder with further systemic details regarding the neural networks involved in the disorder. We noted that the spatial distribution of hub regions in bipolar disorder and healthy control groups was quite similar, and group comparison of our primary analysis showed no significant difference in most of the hub regions, suggesting preservation of hub functions in bipolar disorder. However, our findings indicate disruption in cortical-subcortical coordination, suggesting altered or impaired regulation of subcortical regions by cortical areas. Even though many previous studies found altered function in resting state hub regions (default mode network regions) in bipolar disorder, these findings did not reach consistency, but highly consistent results were shown in the corticolimbic system in bipolar disorder,[18] which were closer to our results.

The cortical-subcortical dissociation in bipolar disorder has been consistently reported by exploring functional connectivity and effective connectivity between cortical and subcortical areas.[5] Bipolar disorder participants showed decreased functional connectivity between the amygdala and the prefrontal cortex at resting state[60] as well as during emotional processing.[61] Reduced fronto-cingulate connectivity and frontal-basal ganglia connectivity were found during the Stroop task in individuals with bipolar disorder.[62] A recent study[63] continued to report a decreased resting state functional connectivity between inferior temporal gyrus and perigenual anterior cingulate cortex in subjects with bipolar disorder. Although the degree centrality technique could not directly explore the regulation of dynamic mechanical coupling between cortical and subcortical regions, reduced cortical-subcortical degree centrality correlation in patients with bipolar disorder, compared to healthy controls, suggested that imbalanced cortical-subcortical disassociation might be involved in the neuropathophysiology of bipolar disorder. Also, given that no differences were detected across the mood states in this study, we consider that cortical-subcortical imbalance might be a trait-related feature.

Our results of dissociated cortical-subcortical communications may explain observed regional changes in brain activation in many previous studies. Decreased cortical function and volume, increased subcortical function, and dissociation between these two areas were suggested to have a relationship with impaired cognitive control, executive dysfunction, and emotional dysregulation,[52,59] causing an elevated mood episode, which is a typical feature of bipolar disorder.

We generally did not find significant effects of medication exposure, mood state, symptom severity, or course of disease on degree centrality in clusters that were significantly different between the bipolar disorder and healthy control groups. Significant increase in degree centrality was noted between the medicated and medication-naive subgroups only in the inferior part of right temporal lobe; however, the magnitude of this difference was small. Many studies demonstrated that clinical factors, such as course of illness,[64–66] mood states,[67] medication status, and different medication type[68–73] would affect brain connectivity; however, other studies had inconsistent findings.[7,74] Although we did not detect significant effects of medication exposure, mood state, symptom severity, or course of disease, power may have been limited by small sample size. Further studies with a first-episode, unmedicated, and larger sample would be warranted to definitely determine the effects of medication exposure and other clinical factors on neural network integration.

There are additional limitations. We did not collect data on behavior or cognitive function in most participants; therefore, we are unable to explore the associations between degree centrality and cognitive function in bipolar disorder. Finally, the degree centrality technique could not directly explore how cortical areas regulate subcortical regions.

In conclusion, our study is the first to adopt degree centrality to investigate and provide new evidence of the dysfunction that accompanies the cortical-subcortical dissociation in bipolar disorder as a whole.. Future studies combining psychophysiologic interaction or dynamic causal modeling would be necessary to investigate the relationship within cortical-subcortical neural systems to ultimately deeply understand the neuropathophysiologic mechanism of imbalance in cortical-subcortical regions in bipolar disorder.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Trait-Related Cortical-Subcortical Dissociation in Bipolar Disorder:

Analysis of Network Degree Centrality

Author(s): Qian Zhou, MD[a,‡]; Fay Y. Womer, MD, PhD[b,‡]; Lingtao Kong, MD, PhD[a]; Feng Wu, MD, PhD[a]; Xiaowei Jiang, MD[c]; Yifang Zhou, MD[d]; Dahai Wang, MD[a]; Chuan Bai, MD[c]; Miao Chang, MD[c]; Guoguang Fan, MD, PhD[c], Ke Xu, MD, PhD[c]; Yong He, PhD[e]; Yanqing Tang, MD, PhD[a,d]*; and Fei Wang, MD, PhD[a,f]*

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eAppendix 1

Hub distributions in healthy control and bipolar disorder groups

Hub distributions of BD and HC group were completed by one-sample t-test within group. To enable this procedure, DC value of each voxel inside the maps (containing 42185 voxels) of each individuals was divided by mean value of DC inside the mask (mean-normalized DC, mDC) [1]. Then test value of one-sample t-test was set to 1 (mean value of the new map). Hub region was defined by higher mDC (>1 SD beyond the global mean) within the mask [2]. DC distributions of BD and HC groups were showed in Supplementary eFigure 1. Visual inspection indicated that the spatial distributions were very similar to each other. Hub regions of the two groups defined by >1 SD beyond global mean were mainly distributed in default mode network [3], including medial prefrontal cortex, anterior and posterior cingulate cortex, precuneus, inferior parietal lobule. Additionally, insula, sensory-motor areas and visual areas were present.

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Supplementary eTable 1. Clinical Characteristics of BD Subjects On/off Medication

	Medicated	Unmedicated	T/χ2	P
Age (mean±SD)	29.98±8.62	29.30±10.83	0.212	0.833
Gender (M/F)	23/19	3/7	1.981	0.159
HAMD-17 Total (mean±SD, n*)	7.33±7.31, 42	16.60±10.59, 10	-3.293	0.002
HAMA Total (mean±SD, n)	5.14±7.56, 42	8.78±6.06, 9	-1.349	0.184
YMRS Total (mean±SD, n)	7.50±9.41, 42	9.00±12.67, 9	-0.408	0.685
Age of Onset (mean±SD, n)	25.36±8.27, 41	29.41±9.08, 8	-1.246	0.219
Months of Illness (mean±SD, n)	55.38±73.48, 41	32.63±50.49, 8	0.835	0.408
Number of Previous Episodes (mean±SD, n)	3.59±3.03, 32	2.00±2.65, 7	1.287	0.206

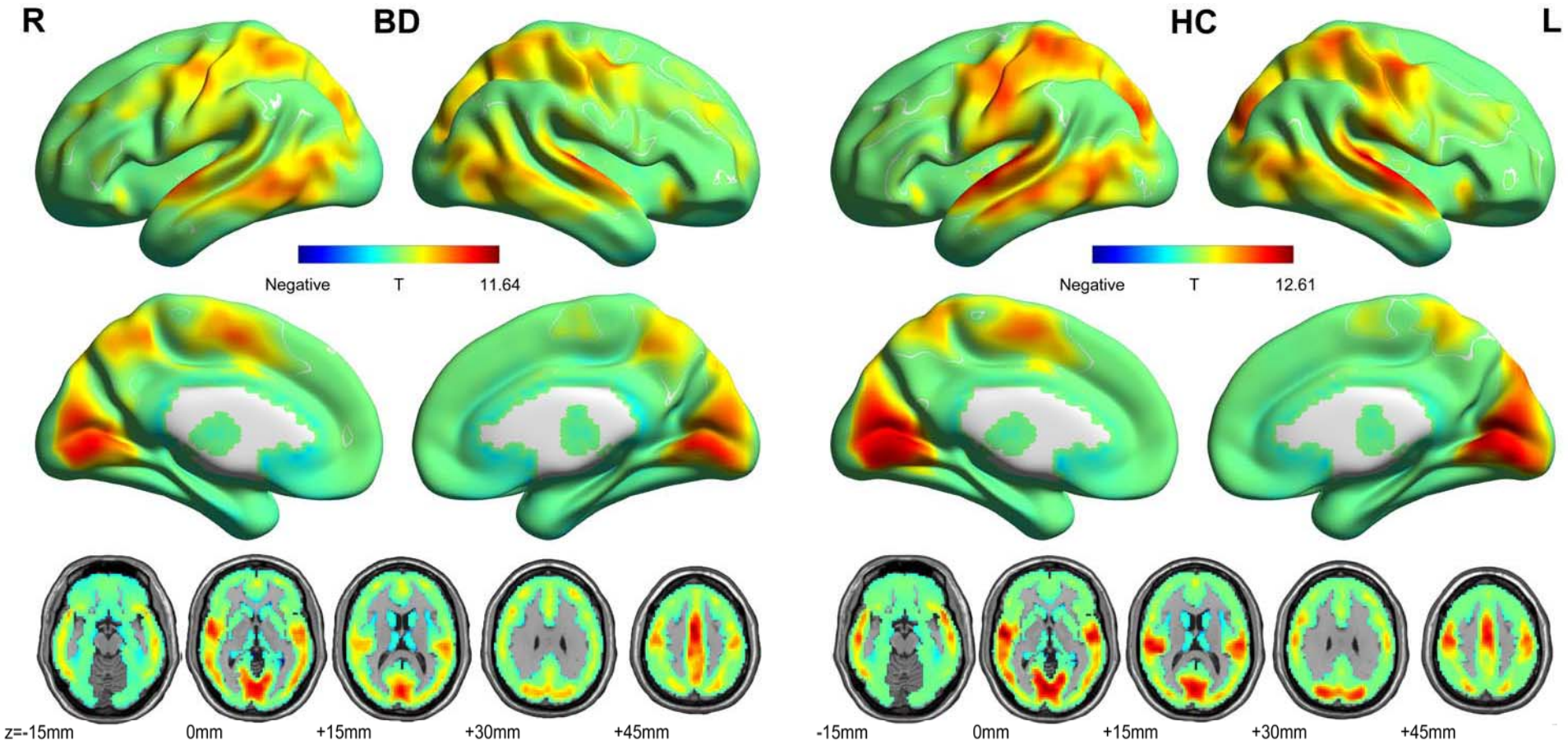
* Number of subjects that have this information

Supplementary eTable 2. Clinical Characteristics of BD Subjects of Different Mood States

Variable	Group, Mean (SD)			ANOVA		Post Hoc Test #, P		
	Euthymic	Depressed	Elevated	F/χ2	P	Euthymic-Depressed	Euthymic-Elevated	Depressed-Elevated
Age (mean±SD)	29.25±8.86	32.69±9.78	27.25±7.64	1.379	0.261	—	—	—
Gender (M/F)	13/11	8/8	5/7	0.500	0.779	—	—	—
HAMD-17 Total (mean±SD, n*)	3.00±3.11, 24	18.50±6.69, 16	8.83±7.92, 12	35.700	<0.001	0.000	0.085	0.008
HAMA Total (mean±SD, n)	1.13±1.98, 24	12.67±8.74, 15	6.50±5.54, 12	19.843	<0.001	0.000	0.019	0.102
YMRS Total (mean±SD, n)	3.29±4.21, 24	4.27±6.50, 15	21.08±10.19, 12	31.304	<0.001	0.941	0.000	0.000
Age of Onset (mean±SD, n)	25.46±8.05, 23	28.94±10.29, 15	23.22±5.45, 11	1.589	0.215	—	—	—
Months of Illness (mean±SD, n)	51.91±56.83, 23	55.93±70.14, 15	45.34±98.31, 11	0.070	0.933	—	—	—
Number of Previous Episodes (mean±SD, n)	3.40±2.72, 20	3.50±3.53, 12	2.71±3.15, 7	0.164	0.849	—	—	—

* Number of subjects that have this information

Least significant difference method (homogeneity of variance) for HAMD-17, HAMA and YMRS; Tamhane's T2 method (Heterogeneity of variance) for Age of Onset, Months of Illness and Number of Previous Episodes



Supplementary eFigure 1. One-sample T test of mDC, showing distribution of DC in BD and HC groups. T values were mapped on cortical suface by using BrainNet Viewer[1].

1. **Xia M, Wang J, He Y. BrainNet Viewer: a network visualization tool for human brain connectomics. PloS one 2013;8(7):e68910.**