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Research paper

Resting-state functional connectivity graph-properties correlate with bipolar disorder-risk in young medication-free depressed subjects Bipolar-risk Resting State Functional Connectivity in Major Depression

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ABSTRACT

Background: Major Depressive Disorder (MDD) is frequently associated with risk factors for the development of Bipolar Disorder (BD). Using graph theory, we investigated brain network properties associated with BD risk factors in young MDD subjects.

Methods: Resting-state fMRI was acquired from a large cohort (N= 104) of medication-free currently depressed participants (25 BD depression (BDD), 79 MDD). Lifetime mania symptom count (LMSC), current Young Mania Rating Scale (YMRS) score, and family history of mood disorders (FHMD) were examined as BD risk factors. Functional connectivity matrices from 280 regions of interests (ROIs) were first entered into the Network Based Statistic (NBS) toolbox to identify connections that varied with each risk factor. Next, within the correlated network for each risk factor, global and nodal graph properties for the top five linked nodes were calculated. Last, using identified graph properties, machine learning classification (MLC) between BDD, MDD with BD risk factors (MDD+), and without BD risk factors (MDD-) was conducted.

Results: LMSC positively correlated with left lateral orbitofrontal cortex (LOFC) Communication Efficiency and with left middle temporal Eigenvector Centrality. Current YMRS score positively correlated with right amygdala Communication Efficiency and Closeness Centrality. FHMD positively correlated with right insula Eigenvector Centrality. Acceptable MLC accuracy was seen between BDD and MDD- using middle temporal Eigenvector Centrality, whereas moderate accuracy was seen between MDD+ and MDD- using OFC Communication Efficiency.

Limitation: Although participants were medication-free, they were not medication-naïve.

Conclusion: Functional connectome graph properties may serve as BD vulnerability biomarkers in young individuals with MDD.

1. Introduction

Major Depressive Disorder (MDD) is frequently accompanied by risk factors for the development of Bipolar Disorder (BD). This issue is of critical clinical relevance in young adults, as many individuals experience only depressive episodes in the early stages of BD, with mania emerging later (Vieta et al., 2018). Thus, reliable indicators of BD risk are needed to identify vulnerable individuals and intervene early (Koirala et al., 2019). Several such behavioral and historical indicators have been identified, including the presence of current or lifetime sub-threshold mania symptoms (occurring in around 30–50% of MDD participants (Angst et al., 2010; Benazzi, 1997; Zimmermann et al., 2009)), family history of recurrent mood disorder (Fiedorowicz et al., 2011; Leonpacher et al., 2015), and history of psychosis (Goldberg et al., 2001). However, neurobiological indicators are lacking, particularly indicators reflecting higher-level network processes, which may better capture the complexity of mood-related pathology (Bullmore and Sporns, 2009; Sporns, 2012). Such neurobiological metrics are thus needed to form a comprehensive risk profile. The present study attempts to fill this gap in the literature.

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Resting-State functional connectivity (RSFC) measures the temporal correlation of low-frequency blood-oxygen-level-dependent (BOLD) signal fluctuations between brain regions, which is thought to index connectivity between these areas (Anand et al., 2005; Biswal et al., 1995; Lowe et al., 2000). A growing number of RSFC studies have investigated connectivity differences in both BD and MDD (Anand et al., 2009; Anand et al., 2005). Several studies have reported disturbances in cortico-amygdala connectivity in BD, suggesting that the affective regulatory processes instantiated in these connections are disrupted. Compared to healthy controls (HC), BD show increased connectivity between amygdala and ventral or medial prefrontal cortex (Chepenik et al., 2010; Favre et al., 2014; Rey et al., 2016). Compared to MDD, BD also show increased hippocampal connectivity with lingual gyrus and inferior frontal gyrus (IFG) (Fateh et al., 2019). Several studies have also investigated cortico-cortical connectivity in BD. For example, compared to MDD, BD exhibited decreased coupling between right anterior insula and inferior parietal lobe (Ellard et al., 2018) and between left insula and left dorsolateral prefrontal cortex (dlPFC) (Ambrosi et al., 2017). In few study examining risk factors of BD, Kling and colleagues reported that striatal resting state connectivity correlated with sub-threshold mania symptoms in MDD participants (Kling et al., 2018), Fan et al. found that positive correlation between the Young Mania Rating Scale (YMRS) and the RSFC in the hate circuit (whose main components are insular, putamen, and superior frontal gyrus) across bipolar depression, bipolar mania, bipolar euthymia, and HC (Fan et al., 2020), and Shi et al. revealed that RSFC between orbitofrontal cortex (OFC) and right ventral striatum was positively correlated with YMRS across bipolar depression, bipolar mania, and HC (Shi et al., 2020).

Although existing research, as reviewed above, has provided an excellent insight into BD-related connectivity disturbances, this research has almost uniformly examined coupling between pairs of regions, which does not take into account the role of that link within the larger network. In other words, these studies looked at connections rather than networks. Understanding network disturbance over and above individual connections is crucial for several reasons. Changes in network properties can capture information not apparent using traditional connectivity approaches. Since network disturbance in a particular link may be compensated for other connections or itself in the network, giving consideration to the network context within which a particular link is embedded can greatly improve our ability to understand the impact of connectivity disturbances on function. Thus, graph properties correlates of BD risk factors are expected to provide a more comprehensive picture of functional brain abnormalities related to bipolarity (Cha and Anand, 2021). Graph theory involves the calculation of properties that provide insight into the organization of networks (e.g., communication efficiency) (Bullmore and Sporns, 2009). Thus, these properties reduce the vast search space of brain networks in a meaningful manner (Sporns, 2012). Using graph theory properties of RSFC in BD participants, we have previously reported disturbances in higher-level network properties related to mania and depressive symptoms in BD (Spielberg et al., 2016). Mania symptoms were associated with increased local network clustering around right amygdala (i.e., Clustering Coefficient), whereas depressive symptoms were associated with increased clustering around right OFC (Spielberg et al., 2016). In a second study, we found that clustering around right amygdala significantly decreased after lithium treatment in BD patients who were manic/hypomanic at baseline, whereas the opposite was observed in BD patients who were depressed at baseline (Spielberg et al., 2019).

Although our studies (Spielberg et al., 2016; Spielberg et al., 2019) included depressed patients, all patients had been diagnosed with BD, and thus it is unclear whether these indicators reflect risk for BD in depressed individuals from whom full BD pathology has not emerged. To fill this gap, we examined higher-level network properties in young, currently depressed individuals with either BD (BDD) or MDD. We included BD, in addition to those in whom BD pathology had not yet emerged (i.e., MDD), because the impact of these risk factors should also be present in BD, arguably more strongly than in MDD. We followed-up each significant result by testing the relationship in MDD only to ensure that BD was not driving the findings.

We examined network correlates of three BD risk factors: lifetime occurrence of mania symptoms, current mania symptoms, and family history of mood disorder. In addition, in order to quantify functional integration and segregation, centrality of brain regions, and resilience of networks, we expanded on previous work by examining several global and nodal graph properties in the brain network organization. Our hypothesis was that BD risk factors correlates of whole-brain connectivity will provide a network-property level understanding of BD pathophysiology as well as BD vulnerability in young MDD subjects. We further explored, using machine learning, the hypothesis that network properties correlated with BD risk factors will be able to classify between BDD, MDD without BD risk factors (MDD-) and MDD with BD risk factors (MDD+).

2. Materials and methods

2.1. Participants

Medication-free BDD and MDD participants (age range:15–30 years) were recruited from the outpatient psychiatry clinic at Cleveland Clinic for a study of neuroimaging correlates of bipolar risk factors in young depressed subjects (Koirala et al., 2019). All participants underwent a clinical interview with a psychiatrist, the Mini-International Neuropsychiatric Interview (MINI) for current and life-time assessment of psychiatric illness, and the administration of depression and mania scales for current mood state. Inclusion and Exclusion criteria are presented in the supplement.

Ascertainment of the presence of BD risk factors in MDD participants: Three psychiatrists reviewed the information of each participant independently before making the final ascertainment upon consensus (Nurnberger et al., 2011). Lifetime mania symptom count (LMSC) was derived from the number of life-time mania symptoms obtained in the MINI interview (Sheehan et al., 1998) using DSM-IV-TR (First, 2000) items, with at least one of the symptoms being euphoria or irritability. Current mania symptoms were assessed using YMRS (Young et al., 1978). Family history in first and second degree relatives for BD and MDD was obtained by participant report from the Family Instrument for Genetic Studies (FIGS) (Maxwell, 1992) as well as a clinical interview. Given that family history of both BD and MDD is associated with BD (Craddock and Jones, 1999), effect of family history was examined both as family history of BD or MDD separately as well as in combination as family history of mood disorders (FHMD) in first and/or second degree relatives. History of psychosis (HP) (Fiedorowicz et al., 2011), another known risk-factor for BD within a mood disorder was obtained from the MINI interview (First, 2000; Sheehan et al., 1998), although this was not examined, due to the small number of patients in our sample with this history (see Table 1).

Depression subgroup ascertainment using best practices: Based on review of previous studies (Angst et al., 2003; Fiedorowicz et al., 2011; Koirala et al., 2019; Merikangas et al., 2011; Zimmermann et al., 2009), subjects were grouped as MDD+ if they had any life-time mania symptoms, first degree family history of BD, or history of mood related psychosis. Rest of the MDD subjects were grouped as MDD-.

We did not include an HC group in our analysis the purpose of the study was to identify neural mechanisms associated with risk for BD among those who present with depression. Including an HC group would confound current depression with the risk factors of interest as the HC group subjects would not be currently depressed.

Table 1
Demographics and illness characteristics.

Demographics		Bipolar depressed ($N = 25$)	MDD+ high risk unipolar ($N = 46$)	MDD- low risk unipolar ($N = 33$)
Age (years) (mean (SD))		23.4(4.1)	22.6(3.4)	25.7(3.4)
Female (n (%))		18(72%)	36(78%)	21(64%)
Race	Caucasian (n (%))	21(84%)	35(76%)	31(94%)
	African American (n (%))	4(16%)	11(24%)	2(6%)
Scanner	Scanner 1	4(16%)	21(46%)	9(27%)
	Scanner 2	21(84%)	25(54%)	24(73%)
HAM-D 17 item (mean (SD))		18.1(5.2)	18.4(3.7)	16.2(3.2)
YMRS (mean (SD))		2.5(2.7)	1.9(2.5)	0.8(1.3)
Classification Characteristics				
First or Second degree family history (n (%))		17(68%)	40(87%)	24(73%)
History of psychosis (n (%))		2(8%)	4(9%)	0(0%)
Mania Symptoms (n (%))				
Euphoria or hyperactivity		24(96%)	25(54%)	0(0%)
Irritability		24(96%)	29(63%)	0(0%)
Grandiosity		18(72%)	15(33%)	0(0%)
Needing less sleep		21(84%)	19(41%)	0(0%)
Increased speech		23(92%)	21(46%)	0(0%)
Easily distracted		23(92%)	32(70%)	0(0%)
Active or physical restless		21(84%)	17(37%)	0(0%)
Risky behavior		22(98%)	22(48%)	0(0%)
Racing thoughts		25(100%)	25(54%)	0(0%)

Abbreviations: MDD = Major Depressive Disorder group; MDD+=MDD subjects with bipolar disorder risk factors; MDD-= MDD subjects without bipolar disorder risk factors; HAM-*D*= Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; SD = Standard Deviation.

2.2. Procedures

2.2.1. MRI acquisition and MRI preprocessing: details are presented in the online supplement

2.2.1.1. Computing functional connectivity matrices. We used the cortical atlas developed by the Human Connectome Project (HCP) (Glasser et al., 2016), along with the Harvard-Oxford subcortical (Frazier et al., 2005) atlas, which resulted in a total of 375 ROIs. Time series were extracted by calculating the average value across the ROI and a Pearson correlation matrix was computed for each participant using 3dNetCorr from AFNI (Cox, 1996).

2.3. NBS analysis

Connectivity matrices were entered as dependent variables into the Network Based Statistic (NBS) toolbox (Zalesky et al., 2010). Three models were examined, one each for LMSC, one for YMRS, and one for FHMD as the predictor of interest. Moreover, age, gender, race, and scanner type, and mean and maximum slice-wise motion parameters were used as covariates of no interest. Since the years of education was not associated with predictors in our preliminary analysis, it was not used as covariate. Resting state analysis also does not involve a task and it is usually with task-performance that years of education is correlated. NBS applies the regression model independently to each link, applies a cluster-defining t-threshold ($t = 3.4$ in the present analyses) to remove unassociated links, identifies clusters of suprathreshold connected links (i.e., a link is considered to be part of the cluster if it shares a node with at least one of the other links in the cluster), and performs permutation-based cluster correction for multiple comparison (5000 permutations; cluster-wise $p \leq 0.05$). In order to reduce the number of multiple comparisons, we excluded ROIs in the visual system from this analysis, leaving 280 ROIs. This was done due to the fact that participants viewed a fixation cross during the scan, and thus visual activity is likely to be due the visual stimulus.

2.4. Graph theory analysis

For the NBS network correlated with each of the BD risk factors global and nodal graph theory properties were computed. Computation was done for each participant's connectivity matrix via the Graph Theory GLM (GTG) toolbox v.045 (Spielberg et al., 2015). In order to perform comprehensive assessments of network patterns, 10 graph properties were computed which included four global graph properties and six node graph properties. Global network properties examined were: Algebraic Connectivity, Assortativity, Transitivity, and Current-Flow Global Efficiency. Nodal graph properties examined were: Clustering Coefficient, Communicability Efficiency (inversely related to Communicability Distance), Eigenvector Centrality, Current-Flow Betweenness Centrality, Current-Flow Closeness Centrality, and Leverage Centrality. Description of each graph-property is presented in Supplemental Material.

Graph properties were entered into permutation-based (5000 permutations) general linear models in the GTG toolbox. As in the NBS analyses, three models were computed, one each for LMSC, FHMD, or YMRS, with age, gender, race, scanner type, and mean and max slice-wise motion parameters as covariates of no interest. Moreover, to remove confounds due to lower-level aspects of the network, we included two global (Density and Total Strength) and two node-specific graph properties (Degree and Node Strength) as covariates of no interest.

In order to limit the number of comparisons, graph properties were examined only for the top five nodes in terms of the number of differential connections within each correlated network. False Discovery Rate (FDR) was used to correct for multiple comparisons across six nodal-specific graph properties. Moreover, we used Bonferroni correction to account for the top five nodes for each model.

2.5. Machine learning classification

Machine learning was performed for two classification models: 1) BDD vs. MDD- groups, and 2) MDD+ vs. MDD- groups. Gaussian process classification approach was implemented using graph properties, which showed significant correlations with risk factors for BD in the Graph Theory Analysis. Graph properties' residualized values corrected for covariates of no interest were used. Gaussian process classification is a supervised machine learning technique, which builds a model with (Gaussian) predictive probabilities of class membership, allowing us to estimate uncertainty in the prediction (Rasmussen, 2003).

In each classification model, participants were split into a training set (80%) and a test set (20%). Each training set was trained using a ten-fold cross-validation (CV). In order to perform the CV, 10% of subjects in

each group was selected and then allocated to the validation set. The imbalanced training data set may cause a classification problem which tends to classify with the majority observation. In order to compensate for imbalanced groups, the oversampling method was also performed within each CV using Synthetic Majority Oversampling Technique (SMOTE) (Chawla et al., 2002). This final trained model was examined on the test set, and then classification performance metrics (accuracy and area under the receiver operating characteristics curve (AUC)) were computed. This process was repeated through 100 permutations using randomized splits for training set and test set and finally the model was evaluated by averaged performance metrics across permutations.

3. Results

3.1. Demographics

One hundred thirty-six participants were enrolled in the study. Thirty participants were excluded for the following reasons: did not complete scan ($n = 9$), slept during scan ($n = 9$), problematic scan quality ($n = 6$), scan acquisition errors ($n = 2$), and unreliable clinical information ($n = 2$). In addition, two (1 BDD & 1 MDD) data for two participants were not used due to the fact that they were undergoing hormone therapy related to gender transition, which could have an unknown effect on the analysis. The final analyses included 104 participants: 25 BDD (10 Bipolar I, 15 Bipolar II), 79 MDD (46 MDD+, 33 MDD-). Demographic and Illness Characteristics are detailed in Table 1.

3.2. Network based statistics (NBS)

Lifetime Mania Symptom Count: LMSC was associated with higher connectivity in a 40-node, 40-link network (see Fig. 1). This network was largely comprised of right insula and adjacent regions (e.g., middle operculum), left temporal area, bilateral OFC, bilateral auditory cortex, bilateral somatosensory/motor cortex, and bilateral parietal areas. The top five nodes (HCP labels are in parenthesis) in terms of the number of differential links were in the right para-insular area (Right_PI), right middle operculum (Right_FOP1), left middle temporal area (Left_MT), left posterior lateral OFC (Left_47 s), and left lateral OFC (Left_47 m).

Current Young Mania Rating Scale Score: YMRS was associated with higher connectivity in a 43-node, 51-link network (see Fig. 2). This network was comprised of regions in PCC, insular and adjacent regions (e.g., posterior operculum), motor/premotor cortex, superior parietal regions, subcortical regions (e.g., amygdala), dlPFC, auditory cortex, anterior cingulate cortex (ACC), and sensory/somatosensory regions. The top five nodes in terms of the number of differential links were in the right hippocampus (Right_HIPP), right anterior dlPFC (Right_9_46d), right posterior insular area (Right_PoI2), right superior precuneous (Right_7Am), and right amygdala (Right_AMYG).

Family History of Mood Disorders: FHMD was associated with higher connectivity in a 26-node, 31-link mainly right hemisphere network (see Supplemental Figure S-1). This network was comprised of regions in inferior prefrontal cortex, insular and adjacent regions (e.g., anterior operculum), auditory cortex, posterior cingulate cortex (PCC), inferior parietal and adjacent somatosensory regions, and OFC. The top five nodes in terms of the number of differential links were in the right posterior ventrolateral prefrontal cortex (Right_IFJp), right premotor eye field (Right_PEF), right posterior para-insula (Right_52), right anterior operculum (Right_FOP4), and right medial belt complex (Right_MBelt). We also examined family history of BD alone, but no significant network was found.

3.3. Graph properties

Lifetime Mania Symptom Count: Communicability Efficiency for left lateral OFC (Left_47 m) was positively related to LMSC, indicating that a history of mania symptoms is related to more efficient communication for this region. Eigenvector Centrality for left middle temporal area (Left_MT) was greater in those with higher levels of lifetime mania symptoms. These relationships were significant when examined in the sample as a whole (Table 2), as well as in the MDD group alone, as

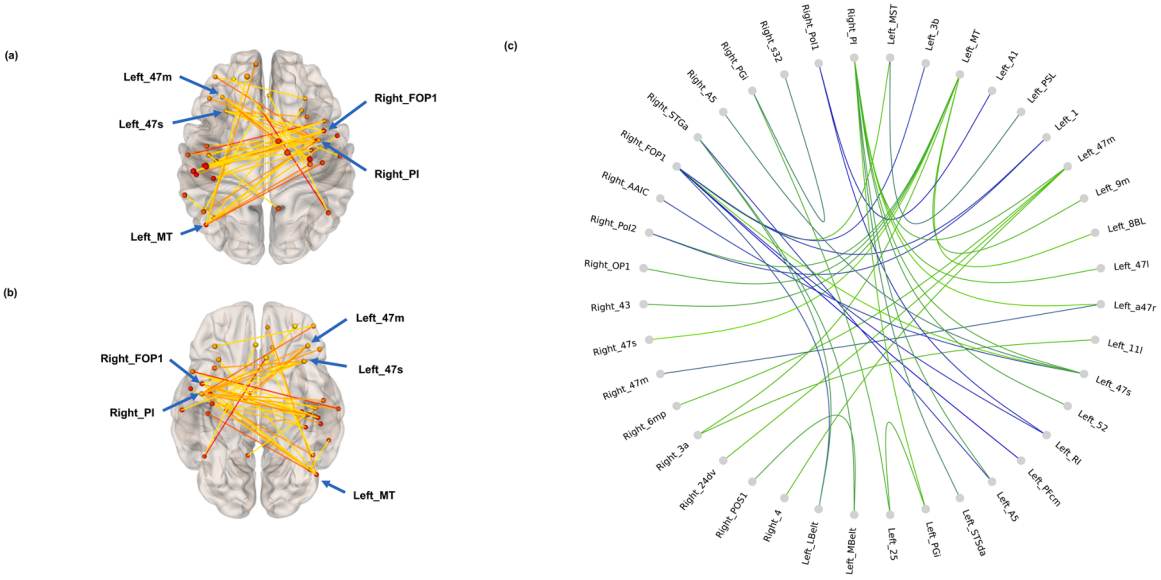

Fig. 1. Lifetime Mania Symptom Count Network.
Connectivity strength between nodes in this network correlated positively with the number of lifetime mania symptoms. Network Based Statistics (NBS) identifies clusters of connected links at cluster-wise corrected significance $p \leq 05$. Axial views from superior (a) and inferior (b) to brain. Sphere color reflects mean Node Strength across all participants, and link color reflects the effect size for the relevant test, with the color scales ranging from red (weakest) to yellow (strongest). The five nodes in terms of the number of differential connections (Right_PI = Right Para-insular area, Right_FOP1 = Right Middle Operculum, Left_MT = Left Middle Temporal Area, Left_47s = Left Posterior Lateral Orbitofrontal Cortex (OFC) and Left_47m = Left Lateral OFC) which showed Lifetime Mania Symptom Count correlation with graph properties are indicated. (c) Connectogram in which line color reflects connectivity strength (mean across all participants) ranging from green (weakest) to blue (strongest). Node names in figure correspond to the name HCP label for the atlas. ROI Abbreviations were detailed in the Supplemental Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

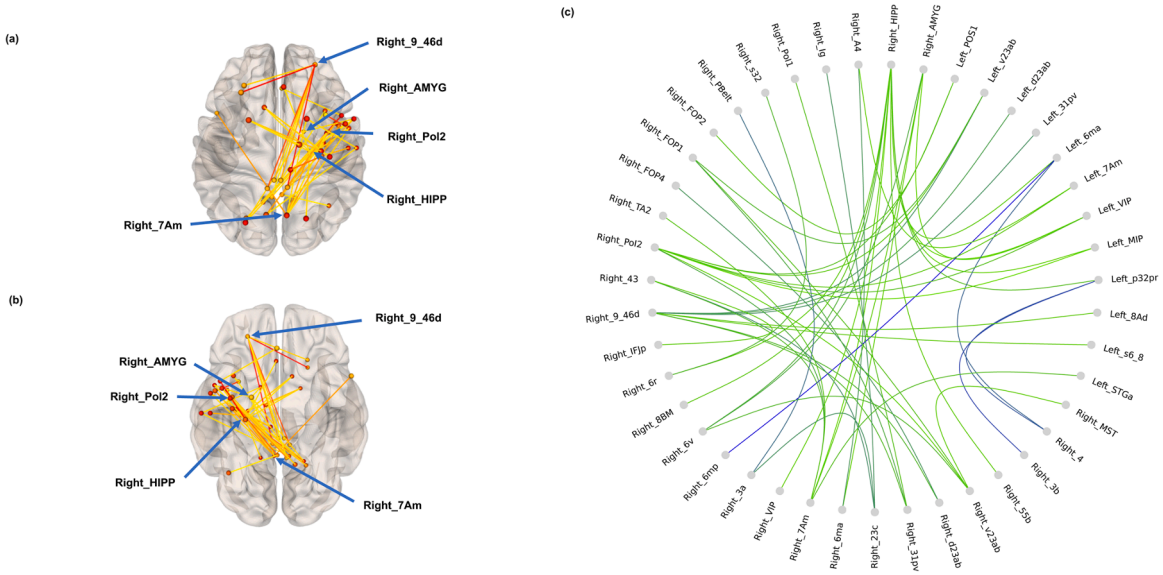

Fig. 2. Current Young Mania Rating Scale (YMRS) Score Network.
Connectivity strength between nodes in this network correlated positively with YMRS. Network Based Statistics (NBS) identifies clusters of connected links at cluster-wise corrected significance of $p \leq 05$. Axial views from superior (a) and inferior (b) to brain. Sphere color reflects mean Node Strength across all participants, and link color reflects the effect size for the relevant test, with the color scales ranging from red (weakest) to yellow (strongest). The five nodes in terms of the number of differential connections (Right_HIPP = Right Hippocampus, Right_9_46d = Right Anterior Dorsolateral Prefrontal Cortex (dlPFC), Right_PoI2 = Right Posterior Insular Area, Right_7Am = Right Superior Precuneous, and Right_AMYG = Right Amygdala) in which showed YMRS correlation with graph properties is indicated. (c) Connectogram in which line color reflects connectivity strength (mean across all participants) ranging from green (weakest) to blue (strongest). Node names in figure correspond to the name HCP label for the atlas. ROI Abbreviations were detailed in the Supplemental Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Graph property correlates of bipolar disorder (BD) risk factors in all depressed subjects (N= 104) (25 BD depression (BDD), 79 MDD).

BD risk factor	Graph property	HCP name	Region area	Corrected p-value
Mania symptom count	Communicability efficiency	Left_47m	Left lateral orbitofrontal cortex	.008
	Eigenvector centrality	Left_MT	Left middle temporal area	.014
Young mania rating scale	Communicability efficiency	Right_AMYG	Right Amygdala	.005
	Current-flow closeness centrality	Right_AMYG	Right Amygdala	.040
Family history of mood disorders	Eigenvector centrality	Right_52	Right posterior para insula	.010

Abbreviations: MDD = Major Depressive Disorder group.

shown in Supplemental Table 2.

Current Young Mania Rating Scale Score: Communicability Efficiency for right amygdala (Right_AMYG) was positively related to YMRS, indicating that YMRS is related to more efficient communication for this region. Current-Flow Closeness Centrality for right amygdala (Right_AMYG) was greater in those with higher levels of YMRS. This relationship was significant when examined in the sample as a whole (Table 2), as well as in the BD group alone (Supplemental Table 2).

Family History of Mood Disorders: Eigenvector Centrality for right posterior para insula (Right_52) was higher in those with FHMD (Table 2 and Supplemental Table 2).

There were no significant global graph properties related to BD risk factors.

3.4. Machine learning classification

BDD vs. MDD-. For the classification model using Eigenvector Centrality for left middle temporal area, a mean accuracy of 70% (SD = 13%) and a mean AUC of 0.75 (SD = 0.16) were achieved. Moreover, for the classification model using Current-Flow Closeness Centrality for right amygdala, a mean accuracy of 66% (SD = 14%) and a mean AUC of 0.66 (SD = 0.16) were achieved. ROC curve for classification were shown in Fig. 3 and in Supplemental Figure S-2 respectively.

MDD+ vs. MDD-. For the classification model using

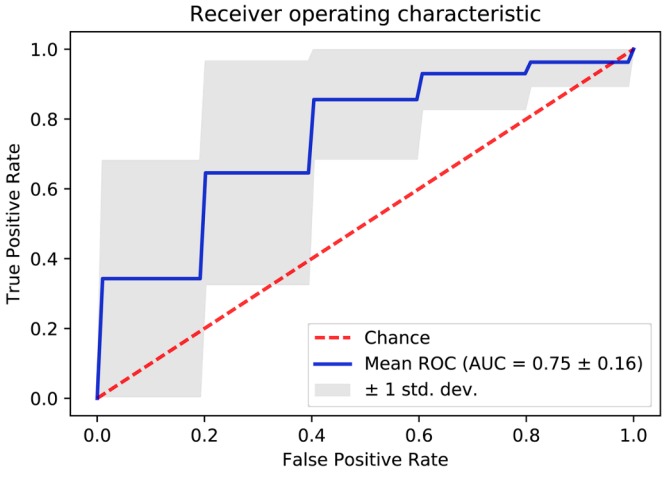

Fig. 3. BDD vs. MDD- classification using Eigenvector Centrality for left middle temporal area.
Receiver operating characteristic (ROC) curve for Gaussian Process BDD vs. MDD- classification. Mean and SD of the area under the curve (AUC) values are indicated. Abbreviations: BDD = Bipolar Disorder Depression; MDD+= MDD subjects with Bipolar Disorder (BD) risk factors; MDD-= MDD subjects without BD risk factors.

Communicability Efficiency for left lateral OFC, a mean accuracy of 65% (SD = 12%) and a mean AUC of 0.66 (SD = 0.14) were achieved. ROC curves for classification were shown in Supplemental Figure S-3.

Classification using other identified properties or combination of properties did not achieve higher accuracy.

4. Discussion

The present study identified several higher-level network correlates linked to known risk factors for BD in a sample of young medication-free, currently depressed BD and MDD patients. Specifically, we identified both clusters of differential connections and graph properties that varied with LMSC, YMRS and FHMD.

4.1. Lifetime mania symptom count (LMSC)

We identified a network in which higher connectivity strength was linked to higher LMSC (Fig. 1). Examination of the graph properties of the most connected nodes (Table 2) in this network revealed that LMSC was positively correlated with Communicability Efficiency within left lateral OFC. Given that Communicability Efficiency is inversely related to Communicability Distance (i.e., higher signal, less wasted information) with a node (Estrada, 2012), these findings suggest that the influence of these regions is likely greater at higher levels of lifetime mania symptoms. This finding is particularly interesting, given that all patients were currently depressed, suggesting that these differences in the efficiency of communication may serve as a risk factor for mania that is present even when symptoms are not i.e., it may serve as a trait-marker for BD. We also found that Eigenvector Centrality for the right middle temporal area was higher in those with a higher LMSC. Higher Eigenvector Centrality may indicate that the middle temporal area is more influential within the brain network. The middle temporal area is thought to be involved in social cognition and imitation (Grossman and Blake, 2002; Iacoboni, 2005). Middle temporal activation has been reported with explicit processing of facial emotion expression (Critchley et al., 2000). Social behavior involves processing of facial expression and social cognition such as picking up social cues. As BD is associated with changes in social behavior, which is either decreased in depression or increased in mania, it can be speculated that these behavioral changes may be related to increased influence of the temporal lobe regions. This hypothesis needs to be further tested in future studies.

4.2. Current mania symptoms (YMRS)

We identified a network in which higher connectivity strength was linked to higher YMRS (Fig. 2). Examination of the graph properties of the most connected nodes (Table 2) in this network revealed that YMRS was positively correlated with Communicability Efficiency for right amygdala and also was positively correlated with Current-Flow Closeness Centrality for right amygdala. The amygdala is an important component of the brain's mood circuit and we and other have reported abnormalities in its activation and connectivity in BD (Anand et al., 2009, 2005). We have previously reported that YMRS is related to increased amygdalar Clustering Coefficient in BD patients (Spielberg et al., 2016). The current finding of increase communicability efficiency (decreased Communicability Distance) with higher YMRS supports our previous finding that amygdala abnormalities are integral to symptoms of mania. As the YMRS captures current state of mania while the LMSC is used for the diagnosis of BD and is therefore a trait-related measure. The different networks related to lifetime and current mania symptoms may therefore be related to BD state-related and trait-related effects respectively.

4.3. Family history of mood disorders (FHMD)

We identified a right hemisphere network in which higher connectivity strength was observed in those with FHMD (BD or MDD) (Supplemental Figure S-1). Examination of the graph properties of the nodes (Table 2) in this network revealed that Eigenvector Centrality for posterior para insula was higher in those with a FHMD. The insula is generally involved in representing various internal states (e.g., affect, sensory), and meta-analytic evidence suggests that the regions we identified are involved in integrating information from other insular regions (e.g., anterior insula involved in attention and affect, posterior insula involved in interoception) (Kurth et al., 2010) and demonstrates white matter connection patterns similar to both anterior and posterior insula (Nomi et al., 2018). This finding is consistent with past work that evidenced abnormal insular functional connectivity in BD (Ambrosi et al., 2017; Fan et al., 2020; Yin et al., 2018). Eigenvector Centrality is a measure of the overall importance of a node and reflects the extent to which a node is connected to other highly connected nodes. Thus, our findings suggest that this integrative insular region is more influential in the brain networks of individuals with a history of mood disorders, which may lead to increases in the influence of integrated internal states over network processing.

4.4. Machine learning classification

Finally, we identified that the Gaussian Process Classifier between BDD and MDD- groups showed an acceptable discrimination using Eigenvector Centrality for left middle temporal area (AUC: 0.75). Generally, an AUC of 0.6 to 0.7 is considered a moderate classification performance, 0.7 to 0.8 is considered an acceptable classification performance, and 0.8 to 0.9 is considered excellent classification performance (Mandrekar, 2010; Shengping and Gilbert, 2017). This classification result suggests that Eigenvector Centrality in left middle temporal area could potentially serve as a biomarker for discriminating between BDD and MDD- subjects. Graph properties for different brain regions correlating with BD risk factors are detailed in Table 2. All significant results in the analysis were positively correlated to regional graph properties. There were no negative correlations.

Furthermore, the classifiers using other graph properties revealing significant correlations of BD risk factors to classify between BDD and MDD- groups, or MDD+ and MDD- groups only have shown a moderate or chance-level classification performance. It is possible that this is caused by large overlapping data distributions among different groups so that the characteristics boundaries of each group may not be clearly defined. Future studies may need to be conducted with a larger group of subjects.

4.5. Limitations

The present study benefitted from a number of strengths, including the inclusion of medication-free patients and a relatively large sample size for patient-based neuroimaging. A number of limitations must also be considered when making inferences about the present work. Although participants were medication-free, they were not medication-naïve. As such, present findings may be driven, in part, by long-term medication use. Furthermore, this work was cross-sectional and could not ascertain whether the observed neural differences actually predict the development of BD. An ideal study would longitudinally examine the same individuals over time to determine the predictive value of the findings. However, such work is extremely difficult, and it is unethical to keep patients medication-free if this is not clinically advised. Therefore, present findings should be regarded as complementary to studies with medicated participants. Finally, machine learning with a large training and test population samples needs to be conducted to further validate the classification between BDD, MDD- and MDD+ subjects using graph theoretic measures. Our results of classification were weaker than those seen with other studies for classification between BD and MDD groups (Gao et al., 2017; Rubin-Falcone et al., 2018). There could be many reasons for the weaker results including: the small sample size, that our

population samples were medication-free and thereby was not affected by medication effects which can increase differences between group, and that this study was conducted with younger subjects who are in the early stages of the illness.

5. Conclusions

In summary, we found network correlates of risk factors for BD across currently depressed BD and MDD patients. Specifically, we found that the communication efficiency metric for the lateral OFC and the amygdala is greater with higher levels of LMSC and YMRS respectively. Further, we identified that the influence of the insula regions is greater in the presence of FHMD. The findings of the present study have important implications for the understanding of BD-related neuropathology on brain networks and may provide useful biomarkers of risk for development of BD in depressed individuals.

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CRediT authorship contribution statement

Jungwon Cha: Formal analysis. **Jeffrey M. Spielberg:** Formal analysis. **Bo Hu:** Formal analysis. **Murat Altinay:** Investigation. **Amit Anand:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft.

Declaration of Competing Interest

Drs. Anand, Altinay, Cha, Spielberg, and Hu each report no financial interests or potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2022.01.033.

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