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Differences in network properties of the structural connectome in bipolar and unipolar depression

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ABSTRACT

Background: Differentiation between Bipolar Disorder Depression (BDD) and Unipolar Major Depressive Disorder (MDD) is critical to clinical practice. This study investigated machine learning classification of BDD and MDD using graph properties of Diffusion-weighted Imaging (DWI)-based structural connectome.
Methods: This study included a large number of medication-free (N =229) subjects: 60 BDD, 95 MDD, and 74 Healthy Control (HC) subjects. DWI probabilistic tractography was performed to create Fractional Anisotropy (FA) and Total Streamline (TS)-based structural connectivity matrices. Global and nodal graph properties were computed from these matrices and tested for group differences. Next, using identified graph properties, machine learning classification (MLC) between BDD, MDD, MDD with risk factors for developing BD (MDD+), and MDD without risk factors for developing BD (MDD-) was conducted.
Results: Communicability Efficiency of the left superior frontal gyrus (SFG) was significantly higher in BDD vs. MDD. In particular, *Communicability Efficiency* using TS-based connectivity in the left SFG as well as FA-based connectivity in the right middle anterior cingulate area was higher in the BDD vs. MDD- group. There were no significant differences in graph properties between BDD and MDD+. Direct comparison between MDD+ and MDD- showed differences in *Eigenvector Centrality* (TS-based connectivity) of the left middle frontal sulcus. Acceptable Area Under Curve (AUC) for classification were seen between the BDD and MDD- groups, and between the MDD+ and MDD- groups, using the differing graph properties.
Conclusion: Graph properties of DWI-based connectivity can discriminate between BDD and MDD subjects without risk factors for BD.

1. Introduction

Bipolar disorder (BD) is a severe mood disorder characterized by recurring episodes of mania (or hypomania) and depression (Grande et al., 2016). Although manic/hypomanic episodes discriminate BD from other mood disorders, these individuals are often first misdiagnosed with Major Depressive Disorder (MDD) (Baldessarini et al., 2014; Ghaemi et al., 2000; Hirschfeld et al., 2003; Perugi et al., 2000). Thus, understanding the pathophysiology of bipolar depression (BDD), particularly how it differs from MDD, is crucially important (Harrison et al., 2018; Radaelli et al., 2015). Several studies to date, using both structural and functional MRI, have reported a fronto-limbic disconnection in both MDD and BDD (Chen et al., 2018; Fateh et al., 2019; Radaelli et al., 2015). Thus, it is crucial to determine whether fronto-limbic connectivity differs between BDD and MDD, given that this may serve as a useful biomarker if differences are observed.

A major difficulty in identifying the different pathophysiology of BDD and MDD is that individuals with MDD often evidence risk factors suggestive of underlying bipolar disorder (Han et al., 2019; Koirala et al., 2019). Thus, those with MDD may actually fall into 2 subgroups – 'pure' depression and latent BD. Known risk factors of BD include the presence of sub-threshold mania symptoms (found in around 30-50% of MDD) (Angst et al., 2010; Benazzi, 1997; Hoertel et al., 2013; Kukopulos et al., 1980; Zimmermann et al., 2009), family history of recurrent mood disorder (Coryell et al., 1995; Fiedorowicz et al., 2011; Leonpacher et al., 2015), and history of psychosis (Goldberg et al., 2001).

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Thus, individuals currently diagnosed with MDD who have one more of these risk factors may have an underlying BD pathology that will manifest itself in the future. Therefore, accounting for the presence (MDD+) or absence of these risk factors (MDD-) may provide a more nuanced understanding of the differences between BDD and MDD. This issue is particularly relevant in young adults, as it is known that in the early stages of BD, only depressive episodes may occur (Vieta et al., 2018).

Diffusion-Weighted Imaging (DWI) has emerged as one of the most powerful techniques for examining brain structural connectome. DWI assays white matter microstructure, including fiber density and myelin integrity (Beaulieu, 2002), by measuring the diffusion of water molecules along different axes in each voxel, thus indexing the directionality (or lack thereof) of white matter fibers in that voxel (Beaulieu, 2002). Several studies have reported less cohesive microstructure in BD patients (compared to healthy controls (HC)) in the corpus callosum (Barysheva et al., 2013; Benedetti et al., 2011; Chaddock et al., 2009; Haller et al., 2011; Lagopoulos et al., 2013; Macritchie et al., 2010), corona radiata (Benedetti et al., 2011; Lagopoulos et al., 2013; Sussmann et al., 2009), and longitudinal and uncinate fasciculus (Chaddock et al., 2009; Sussmann et al., 2009; Versace et al., 2008; Versace et al., 2010), whereas other studies show the opposite effect in these same tracts (Benedetti et al., 2011; Macritchie et al., 2010; Mahon et al., 2009; Versace et al., 2008; Yurgelun-Todd et al., 2007). Findings in MDD (vs. HC) have shown less cohesive microstructure in the corpus callosum (Chen et al., 2017; Chen et al., 2016), anterior limb of the internal capsule (Chen et al., 2017; Chen et al., 2016; Jia et al., 2010; Tha et al., 2013; Zhu et al., 2011; Zou et al., 2008), and longitudinal fasciculus (Zou et al., 2008). Only a few studies have investigated DWI differences between BD and MDD, which showed less cohesive microstructure in the cingulum (Wise et al., 2016) and longitudinal fasciculus (Repple et al., 2017; Versace et al., 2010) in BD, compared to MDD.

Region of interest based analysis provided information about connections between pairs of brain regions. However, it does not provide information regarding how networks are organized which may be crucial to emergent functional properties of networks. Graph theory analysis is an approach to investigate network properties that provides insight into the organization of networks (Sporns, 2012). A few studies have reported abnormal patterns in the graph properties of DWI-based connectivity in BD. For example, node-specific *Clustering Coefficient* in the BD group has been shown to be lower than the HC group in the left hippocampus (Leow et al., 2013), and another study reported that global *Clustering Coefficient* was higher in the BD group than the HC group (Roberts et al., 2018). However, few studies have focused on the graph property analysis using DWI-metrics for BD vs. MDD. The present study included 60 BDD and 95 MDD subjects to identify differences in BDD and MDD bipolar disorder using graph properties of DWI-based structural connectivity.

In this study, two different types of DWI networks were examined, each of which provides insight into different aspects of networks. First, we examined networks created by averaging the fractional Anisotropy (FA) along each connection. FA indexes the extent to which diffusion occurs most often in a single direction (vs. similarly in all directions) and thus reflects the microstructural integrity of the connection between regions. Second, we examined networks created based on the total streamline (TS) count between regions. Streamline count indexes the extent to which two regions connect via probabilistic propagation (Gong et al., 2009; Sporns et al., 2005), which reflects the likely strength of the connection between regions (Seguin et al., 2019).

Based on the literature reviewed above, we hypothesized that BDD patients would exhibit altered network organization in comparison to MDD subjects. We further hypothesized that the difference will be more evident between BDD and MDD- and no difference will be seen between BDD and MDD+.

2. Methods and materials

2.1. Participants

Participants were recruited by advertisement to outpatient psychiatry clinics at the Indiana University School of Medicine and Cleveland Clinic. All the participants in the BDD and MDD groups were medication-free for at least 2 weeks. All participants took part in the study after signing an informed consent document approved by the Institutional Review Board at the respective institutions. Subjects under the age of 18 signed an assent form and a parent signed the consent form. Each participant was paid $75 for screening and $75 for the magnetic resonance imaging (MRI) scan. All participants underwent a clinical interview with a psychiatrist, a detailed structured diagnostic interview (Mini Neuropsychiatric Interview (MINI)) (Sheehan et al., 1998), and administration of clinical scales for depression and mania.

2.2. Inclusion and exclusion criteria

Depressed participants satisfied DSM-IV-R criteria for BD or MDD in a current depressive episode, with Hamilton Depression Rating Scale (Hamilton, 1960) (HDRS) $\geq$ 15 and $\leq$ 28 at the time of screening. Exclusion criteria for all participants included Young Mania Rating Scale (Young et al., 1978) (YMRS) $>$ 10 at the time of screening; a lifetime diagnosis of schizophrenia or schizoaffective disorder; a current primary anxiety disorder; psychotropic medication use within the past 2 weeks; fluoxetine use within the past 4 weeks; acute suicidal or homicidal ideation or behavior; recent (<1 week) use of alcohol; current pregnancy or breastfeeding; positive urine toxicology test at baseline; and contraindications to MRI. Additional inclusion criteria for MDD subjects included having never met criteria for mania or hypomania.

Healthy participants had no personal or family history of psychiatric illness or alcohol or substance abuse/dependence; no current use of any centrally acting medications; no alcohol use in the past week; and no serious medical or neurological illness.

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-.

2.3. MRI acquisition and MRI preprocessing

Participants were scanned on a Siemens 3T Trio (at Indiana University Hospital and Cleveland Clinic) and a Siemens 3T Prisma at the Cleveland Clinic. DWI data were processed in the AFNI (Cox, 1996) pipeline that included routines in TORTOISE (Pierpaoli et al., 2010), FATCAT (Taylor & Saad, 2013) and FreeSurfer (Fischl, 2012). Details are presented in the online supplement.

2.4. Probabilistic tractography and total streamlines (TS) calculations

Whole-brain segmentation and parcellation were performed on the T1-weighted MPRAGE via the standard FreeSurfer pipeline, and the cortical Destrieux parcellation (Destrieux et al., 2010) and standard subcortical segmentation were used. Cerebellum and brainstem were excluded due to inconsistent spatial coverage and low signal-to-noise ratio. We also excluded the visual system ROIs since these regions are not involved in any specific function of mood regulation. Next, probabilistic tractography was performed on all pairs of ROIs. We chose to use probabilistic tractography (vs. deterministic), as probabilistic tractography integrates information regarding noise and the uncertainty of diffusion tensors into tract propagation, thus reducing both false negatives and positives (Taylor et al., 2015). Probabilistic tractography was performed using FATCAT (Taylor & Saad, 2013) in AFNI (Cox, 1996).

The total number of streamlines (TS) that connect each pair of ROIs were estimated. Since a larger size of ROI pair can have a higher number of TS, TS-based connectivity matrices were normalized by the average volume of the ROI pairs (Gong et al., 2009; Hagmann et al., 2008). Average FA along the obtained tractography connecting each pair of ROIs was calculated using 3dTrackID (Taylor et al., 2012).

2.5. Graph theory analysis

Graph properties were computed via the Graph Theory GLM (GTG) toolbox v.045 (Spielberg et al., 2015) using the FA- and TS-based connectivity matrices computed above. Since a larger size of ROI pair can have a higher number of TS, TS-based connectivity matrices were normalized by the average volume of the ROI pairs (Gong et al., 2009; Hagmann et al., 2008). In order to perform comprehensive assessments of network patterns in Graph Theory analysis, 10 graph properties were examined, including four global graph properties and six node-specific properties. Global network properties examined were: *Algebraic Connectivity, Assortativity, Transitivity, and Current-Flow Global Effciency*. Nodal graph properties examined were: *Clustering Coefficient, Communicability Efficiency, Eigenvector Centrality, Current-Flow Betweenness Centrality, Current-Flow Closeness Centrality*, and *Leverage Centrality*. Description of each graph-property is presented in Supplemental Material.

2.5.1. Group differences analysis

We tested several key comparisons (i) BDD vs. MDD and (ii) all patients (PA) vs, HC, and (iii) pair-wise differences among BDD, MDD+, and MDD-. Graph properties were entered into permutation-based (50,000 permutations) general linear models in the GTG toolbox. Two models were examined per graph property: the first model included all participants and two predictors of interest modeling the difference between BDD vs. MDD and PA vs. HC. Group was a between-subject factor. No demographic or symptom covariates were used, as the groups were closely matched for age, gender, race, scanner type, and HAM-D scores (Table 1). The second model did not include HC or those MDD participants for whom bipolar risk was not assessed. Group (BDD, MDD+, and MDD-) was used as a between-subject factor and as these groups were not closely matched - age, gender, race, scanner type, and HAM-D scores were used as covariates (Supplemental Table S-1). For both models, we covaried out two global (*Density, Total Strength*) and two node-specific (*Degree, Node Strength*) graph properties to remove confounds due to lower-level aspects of the network. FDR was used to correct for multiple comparisons across the number of ROIs examined and six node-specific graph properties.

Table 1
Demographics and illness characteristics

Demographics three group ANOVA		Bipolar depressed (N=60)	Major depressed (N=95)	Healthy control (N=74)	*p*-value
Age (years)(mean (SD))		30.0(10.3)	27.9(7.6)	27.8(8.1)	0.256
Female (n (%))		37(62%)	68(72%)	43(58%)	0.164
Race	Caucasian (n (%))	50(83%)	79(83%)	68(92%)	0.209
	African American (n (%))	10(17%)	16(17%)	6(8%)	
Scanner	Scanner 1 (n (%))	37(62%)	43(45%)	41(55%)	0.237
	Scanner 2 (n (%))	5(8%)	16(17%)	7(10%)	
	Scanner 3 (n (%))	18(30%)	36(38%)	26(35%)	
Illness characteristics two group ANOVA					
HAM-D 17 item (mean (SD))		19.4(4.0)	18.8(3.1)	-	0.354
Age at First Episode (years)(mean (SD))		15.0(7.2)	17.1(6.5)	-	0.053
Number of Depressive Episodes (mean (SD))¶		14.5(7.0)	12.2(8.2)	-	0.078
Medication Free Period (weeks)(mean (SD))		40.39(59.95)	69.24(90.9)	-	0.063
Classification Characteristics					
Bipolar I(n): Bipolar II(n)		23:37	-	-	-
Psychosis (n (%))		13(22%)	8(8%)	-	-

¶5 participants have missing information.
ANOVA test was performed on the continuous variables and chi-squared test was performed on the categorical variables.

2.5.2. Machine learning classification

We investigated whether machine learning classification could be used to differentiate between BDD and MDD subjects. We performed machine learning for the following classification models: 1) BDD vs. MDD groups, 2) BDD vs. MDD- groups, 3) BDD vs. MDD+ groups, and 4) MDD+ vs. MDD- groups, Logistic Regression classification approach was implemented using the properties identified in the analysis above. Graph properties were residualized for covariates of no interest. Logistic Regression classification is a supervised machine learning technique, which predicts the probability of a dependent variable using the sigmoid function (Hosmer et al., 2013).

In each classification model, participants were split into a training set (80%) which is used to train the model, and a test set (20%) which is used to evaluate the accuracy of the trained model. A ten-fold cross-validation (CV) was performed for each training set. In order to perform the ten-fold CV, the training set is split into ten subsets and then one subset is used to validate the model and the remaining subsets are used to train the model in each iteration. An imbalanced training data set may cause a classification problem which tends to classify with the majority observation. In order to oversample the minority class, Synthetic Majority Oversampling Technique (SMOTE) (Chawla et al., 2002) was also performed within each CV. The trained model was evaluated on the test set through the 100 permutations (Dhamala et al., 2020) using randomized splits for training set and test set (Dhamala et al., 2020), and then the classification performance metrics (accuracy and area under the receiver operating characteristics curve (AUC)), and finally the model was evaluated by averaged performance metrics across permutations.

3. Results

3.1. Demographics

Three-hundred and forty-two participants were enrolled in the study. Sixty-two participants were excluded for the following reasons: did not complete MRI scan (n=21), low MRI data quality (n=5), failed image acquisition (n=1), unreliable probabilistic tracking (n=25), unreliable information (n=10). In order to keep the sample homogenous and to match sample characteristics (i.e., age, gender, race, scanner type, HAM-D score) across groups, an additional fifty-one participants were removed (2 BDD, 36 MDD, 13 HC); One BDD, three MDD, and nine HC participants were excluded to match race across groups, twenty-seven MDD participants were excluded to match scanner across groups, two (1 BDD & 1 MDD-) participants were transgender on hormones, and nine participants were excluded because they only had a family history of BD (8 subjects) or psychosis (1 subject) only but no subthreshold symptoms. The final analyses included 229 medication-free participants: 60 BDD (23 BD I and 37 BD II), 95 MDD (48 MDD+, 37 MDD-), and 74 HC participants. In the final matched sample, age, gender, race, and scanner type did not differ significantly among groups.

There have been some suggestions from phenomenology, genetic epidemiology, and psychopharmacology studies that BDI and BDII may have different etiologies (Fletcher et al., 2018; Song et al., 2018). However, others have pointed out that there is considerable overlap in the biology of the two disorders and that no consistent replicated

differences between the two subtypes have emerged (Dunner, 2017; Song et al., 2018). Therefore, we did not divide the BD group into subtypes which would have also decreased the power for statistical analysis.

Demographic and Illness Characteristics are detailed in Table 1 and Supplemental Table S-1.

3.2. Graph theory properties

See Table 2 and 3 for the detailed results.

3.2.1. BDD vs. MDD

FA-Based Connectivity Matrices: No significant differences emerged.

TS-Based Connectivity Matrices: *Communicability Efficiency* of left superior frontal gyrus differed between BDD and MDD, with significantly higher values evident in BDD compared to MDD (Fig. 1).

3.2.2. PA vs. HC

No significant differences emerged.

3.2.3. BDD vs. MDD-

FA-Based Connectivity Matrices: *Communicability Efficiency* of the right middle anterior cingulate gyrus and sulcus differed between BDD and MDD-, with significantly higher values evident in BDD compared to MDD- group (Fig. 2(a)).

TS-Based Connectivity Matrices: *Communicability Efficiency* of the left superior frontal gyrus differed between BDD and MDD- with significantly higher values evident in BDD compared to MDD- group (Fig. 2 (b)).

3.2.4. BDD vs. MDD+

No significant differences emerged.

3.2.5. MDD+ vs. MDD-

FA-Based Connectivity Matrices: No significant differences emerged.

TS-Based Connectivity Matrices: *Eigenvector Centrality* of the left middle frontal sulcus differed between the two groups, with significantly lower values evident in MDD+ compared to MDD- (Supplemental Fig. S-1).

There were no significant differences between groups on global graph properties.

3.3. Machine learning classification

3.3.1. BDD vs MDD

The two groups were not adequately classified.

3.3.2. BDD vs. MDD-

For the classification model using both *Communicability Efficiency* of the right middle anterior cingulate gyrus and sulcus and *Communicability Efficiency* of the left superior frontal gyrus, a mean accuracy of 68% (SD = 14%) and a mean AUC of 0.70 (SD = 0.12) were achieved. ROC curve for classification was shown in Fig. 3.

3.3.3. BDD vs MDD+

The two groups were not adequately classified.

3.3.4. MDD+ vs. MDD-

For the classification model using *Eigenvector Centrality* for left middle frontal gyrus, a mean accuracy of 70% (SD = 14%) and a mean AUC of 0.71 (SD = 0.12) were achieved. ROC curves for classification are shown in Supplemental Fig. S-2.

4. Discussion

The present study shows that graph properties of brain networks using DWI-based structural connectivity matrices may serve as potential biomarkers of bipolar disorder in medication-free depressed patients. In particular, *Communicability Efficiency* using TS-based connectivity matrices in the left superior frontal gyrus differentiated BDD and MDD participants. The finding in the left superior frontal gyrus *Communicability Efficiency* consistently showed even for differentiating BDD and MDD-. Further, the right middle anterior cingulate area *Communicability Efficiency* from FA-based connectivity differentiated BDD and MDD-, and also the left middle frontal sulcus *Eigenvector Centrality* from TS-based connectivity differentiated MDD+ and MDD-. The present study demonstrates that graph properties of DWI-based structural connectivity may identify bipolar risk in depressed patients.

4.1. BDD vs. MDD

We found that *Communicability Efficiency* using TS-based connectivity in the left superior frontal gyrus was increased in BDD compared to MDD, which means that the efficiency of the superior frontal gyrus communication was greater in BDD than MDD as *Communicability Efficiency* is related to the quality of communication. The finding indicates that information in the network propagates from the superior frontal gyrus node to other brain area nodes with less degradation in BDD than in MDD. Previous studies reported abnormal frontal cortex connectivity including the connectivity of superior frontal gyrus in BD (Dvorak et al., 2019; Jeganathan et al., 2018), and also other studies for BD found the superior frontal gyrus has shown abnormal structural patterns such as cortical volume and cortical thickness compared to MDD or HC (Chen et al., 2018; Niu et al., 2017). Given the role of the superior frontal gyrus abnormalities in BDD, it is possible that the aberrant frontal gyrus communication with other brain regions may serve as biomarkers for bipolar risk in depressed subjects.

4.2. PA vs. HC

We found that there were no significant differences in graph properties between PA and HC. To investigate the level of the graph property in HC, we also represented the HC graph property level in the plot of the graph property difference between BD and MDD, even though the HC group was not included in the original effect tested. As shown in Figs. 1, the graph properties of HC showed values in between BDD and MDD, which may explain the difficulty in differentiating between PA (combined BDD and MDD) and HC.

4.3. BDD vs. MDD-

BDD and MDD- differed in TS-connectivity network property of *Communicability Efficiency* of the left superior frontal gyrus which was increased in BDD compared to MDD. In addition, we found that the BDD

Table 2
Significant results of group difference between the bipolar depressive disorder (BDD) and major depressive disorder (MDD) groups via GTG analysis.

Bipolar Depressive Disorder (BDD) vs. Major Depressive Disorder (MDD)					
DWI measure	Region	Graph property	Corrected *p*-value	Cohen'd	BDD vs. MDD
TS matrices	Left superior frontal gyrus	*Communicability efficiency*	0.016	0.822	BDD > MDD

Abbreviations: GTG=Graph Theory GLM; BDD=Bipolar Depressive Disorder group; MDD=Major Depressive Disorder group; FA=Fractional Anisotropy; TS= Total number of streamlines.

Table 3
Significant results of group difference (a) between the bipolar depressive disorder (BDD) and low risk major depressive disorder groups and (b) between the high risk major depressive disorder (MDD+) vs. low risk major depressive disorder (MDD-) groups via GTG analysis.

(a)
Bipolar depressive disorder (BDD) vs. low risk major depressive disorder (MDD-)

DWI measure	Region	Graph property	Corrected *p*-value	Cohen'd	BDD vs. MDD-
FA matrices	Right middle anterior cingulate gyrus and sulcus	*Communicability efficiency*	0.042	0.951	BDD > MDD-
TS matrices	Left superior frontal gyrus	*Communicability efficiency*	0.032	0.868	BDD > MDD-

(b)
High risk major depressive disorder (MDD+) vs. low risk major depressive disorder (MDD-)

DWI measure	Region	Graph property	Corrected *p*-value	Cohen'd	MDD+ vs. MDD-
TS matrices	Left Middle frontal sulcus	*Eigenvector centrality*	0.046	-0.920	MDD+ < MDD-

Abbreviations: GTG=Graph Theory GLM; BDD=Bipolar Depressive Disorder group; MDD+= High Risk Major Depressive Disorder; MDD-= Low Risk Major Depressive Disorder; FA=Fractional Anisotropy; TS= Total number of stream lines.

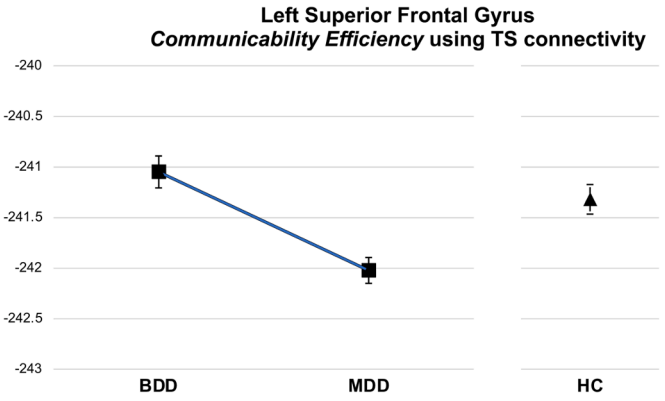

Fig. 1. *Communicability Efficiency* (inverse correlation with *Communicability Distance*) difference in the left superior frontal gyrus using TS (total number of streamlines) connectivity matrices between the Bipolar Depressive Disorder (BDD) group and the Major Depressive Disorder (MDD) group. Means for Healthy Controls (HC) are provided for reference with a dot line plot, even though HC group was not included in the original effect tested.

and MDD- were also different in terms of *Communicability Efficiency* using FA-based connectivity in the right middle anterior cingulate gyrus and sulcus (also called the dorsal Anterior Cingulate Cortex (ACC)) exhibiting a higher level of *Communicability Efficiency* in the brain network in BDD compared to MDD-. In other words, the influence of the dorsal ACC node in BDD is likely greater than in MDD-. The ACC is a part of limbic system in the brain, which plays an important role in the neuropathology of mood disorders (Strakowski et al., 2012). The dorsal part of ACC processed cognitive information, while the rostral-ventral part of ACC processed emotional information (Devinsky et al., 1995). Previous studies demonstrated greater dorsal anterior midcingulate cortex activity in MDD than BDD during emotional n-back task performance (Bertocci et al., 2012) and higher activation in MDD than BD in dorsal ACC from the global Activation Likelihood Estimation analyses of facial affect processing (Delvecchio et al., 2012). These findings indicate that *Communicability Efficiency* of the frontal cortical regions could serve as a biomarker of BD risk.

4.4. MDD+ vs. MDD-

MDD+ and MDD- also differed in *Eigenvector Centrality* using TS-based connectivity in the left middle frontal sulcus which decreased in MDD+ compared to MDD-. The middle frontal sulcus is part of the middle frontal gyrus. The middle frontal gyrus along with the inferior frontal gyrus has been implicated in cognitive reappraisal strategies for emotional stimuli and situations (Grecucci et al., 2013; Ochsner et al., 2012). The decreased connectivity of the middle frontal sulcus in MDD+ compared to MDD- indicates possible mechanism of impairment of mood regulation that may be present in individuals with subthreshold bipolar symptoms compared to depressed subjects which do not have subthreshold bipolarity. Though a distinction can be made between subjects with risk factors vs. subthreshold bipolarity for the most part the two terms are interchangeable as subthreshold bipolarity is usually defined by presence of risk factors of bipolarity.

In this study, there were no significant differences in graph properties between BDD vs MDD+ which suggests the similarity between two

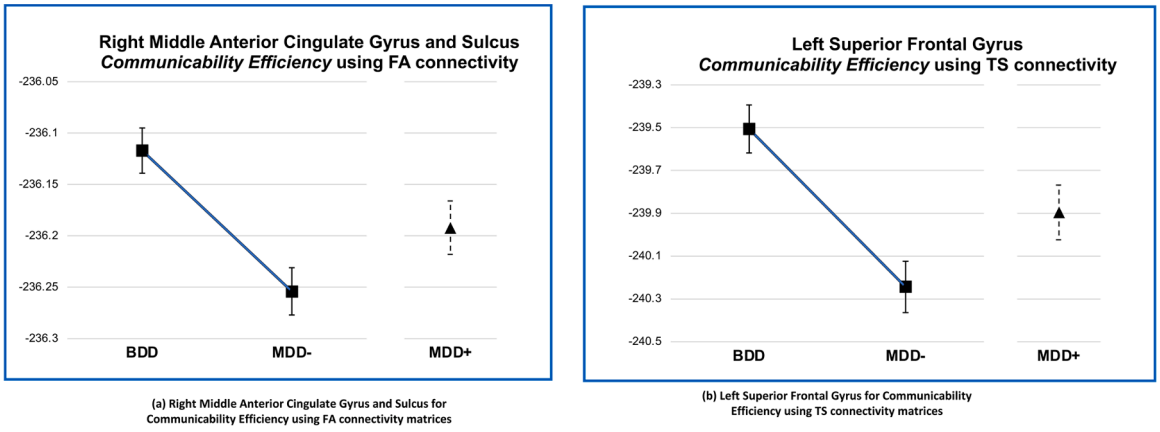

Fig. 2. *Communicability Efficiency* (inverse correlation with *Communicability Distance*) difference between the Bipolar Depressive Disorder (BDD) group and the Low Risk Major Depressive Disorder (MDD-) group (a) Right middle anterior cingulate gyrus and sulcus for *Communicability Efficiency* using FA connectivity matrices, and (b) Left superior frontal gyrus for *Communicability Efficiency* using TS (total number of streamlines) connectivity matrices. Means for and the High Risk Major Depressive Disorder (MDD+) group are provided for reference with a dot line plot, even though MDD+ group was not included in the original effect tested.

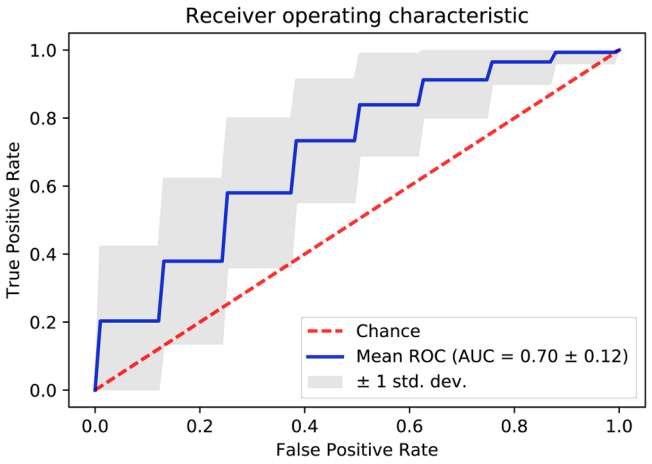

Fig. 3. *BDD vs. MDD- classification using both communicability efficiency for right middle anterior cingulate gyrus and communicability efficiency for left superior frontal gyrus.* Receiver operating characteristic (ROC) curve for gaussian process BDD vs. MDD- classification. Mean and SD of the area under the curve (AUC) values are indicated. Abbreviations: BDD=Bipolar Disorder Depression; MDD-= Low Risk Major Depressive Disorder.

groups.

To see group differences using machine learning classification, we identified that the Logistic Regression Classifier using the identified properties was able to reliably differentiate between BDD and MDD-, with moderate classification performance (AUC=.70) (Mandrekar, 2010; Shengping & Gilbert, 2017). Although this marker will certainly not be used in isolation, this finding further underscores the biomarker potential of this finding. 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 & Gilbert, 2017). This classification result suggests that graph properties could potentially serve as a biomarker for discriminating between BDD and MDD- subjects. For machine learning classification between MDD+ and MDD-, we identified that the Logistic Regression Classifier showed an acceptable discrimination in *Eigenvector Centrality* using TS-based connectivity in the left middle frontal sulcus (AUC: .71).

5. Strengths and limitations

The present study benefitted from a large sample size (n=229), particularly for neuroimaging studies in this area. Moreover, investigation of graph properties was a novel powerful approach to demonstrate the properties of brain networks. A limitation must be considered when evaluating the present study. The computation of DWI-based structural connectivity could be influenced by choices regarding analysis techniques (e.g., probabilistic vs. deterministic tractography) (Sotiropoulos & Zalesky, 2019).

6. Conclusions

In summary, the findings of the present study provide promising results that the BDD group was different from the MDD group. Specifically, we found that the *Communication Efficiency* for the superior frontal gyrus was increased in BDD compared to MDD or MDD-. Further, we identified that *Eigenvector Centrality* for the middle frontal sulcus was decreased in MDD+ compared to MDD. The findings of the present study have important implications for the understating of BD-related brain networks, mainly within the fronto-limbic network, and may provide useful biomarkers of bipolar risk across depressed participants.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2022.111442.

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