Archival Report

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Affect Regulation–Related Emergent Brain Network Properties Differentiate Depressed Bipolar Disorder From Major Depression and Track Risk for Bipolar

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ABSTRACT

BACKGROUND: Individuals with or at risk for bipolar disorder (BD) often present initially for the treatment of depressive symptoms. Unfortunately, pharmacological treatments for major depressive disorder (MDD) can be iatrogenic, precipitating mania that may not have otherwise occurred. Current diagnostic procedures rely solely on self-reported/observable symptoms, and thus alternative data sources, such as brain network properties, are needed to supplement current self-report/observation–based indices of risk for mania.

METHODS: Brain connectivity during affect maintenance/regulation was examined in a large (N = 249), medication-free sample of currently depressed patients with BD (n = 50) and MDD (n = 116) and healthy control subjects (n = 83). BD risk was categorized in a subset of patients with MDD. We used graph theory to identify emergent network properties that differentiated between patients with BD and MDD and between patients with MDD at high and low risk for BD.

RESULTS: BD and MDD differed in the extent to which the rostral anterior cingulate cortex was embedded in the local network, amount of influence the hippocampus exerted over global network communication, and clarity of orbitofrontal cortex communication. Patients with MDD at high risk for BD showed a pattern of local network clustering around the right amygdala that was similar to the pattern observed in healthy control subjects, whereas patients with MDD at low risk for BD deviated from this pattern.

CONCLUSIONS: BD and MDD differed in emergent network mechanisms subserving affect regulation, and amygdala properties tracked BD risk in patients with MDD. If replicated, our findings may be combined with other markers to assess the presence of BD and/or BD risk in individuals presenting with depressive symptoms to prevent the use of iatrogenic treatments.

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Mood disorders are the most common and disabling forms of mental illness (1), affecting 1 in 5 individuals each year (2). At their core, mood disorders are characterized by disturbances in affect regulation, with euphoria/irritability and depression differentiating bipolar disorder (BD) and major depressive disorder (MDD), respectively. Although (hypo)manic episodes discriminate BD, individuals with BD 1) spend significantly more time in major depressive episodes than in manic/hypomanic episodes (3,4), 2) typically present with depressed symptoms in treatment settings, and 3) are often first misdiagnosed with MDD (5,6). Misdiagnosis is not simply academic because common psychotropic treatments for depression can precipitate the onset of mania if administered to individuals with or at risk for BD (6,7). Given that these individuals may never have gone on to develop mania otherwise, it is imperative to develop additional diagnostic indices that can identify BD risk while individuals are in a depressed state.

Neuroscience is a promising method for addressing the phenotypic overlap between currently depressed patients with BD and MDD, and several elegant neuroimaging studies have identified differences between BD and MDD. Meta-analyses indicate that both BD and MDD display amygdala hyperactivity to affective stimuli (8–10) but that this effect is stronger in BD than MDD (11). However, the majority of work in this area has not considered the inherent complexity of brain networks, the brain's chief organizational principle. Understanding the way mood-related pathology is instantiated in connections between brain regions and how those links are embedded in a larger network context could reveal differences between BD and MDD that are not apparent using traditional brain connectivity approaches. Furthermore, sophisticated network methods, such as graph theory, provide insight into emergent attributes of networks (i.e., properties only apparent when network complexity is considered) (12).

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To date, only two studies have examined currently depressed patients with MDD and BD using graph theory, both of which examined resting-state data from medication-free patients. The first study found more connectivity and local clustering (clustering coefficient) in BD (n = 13) than MDD (n = 40) in a largely prefrontal set of nodes (13). In the second study, MDD (n = 31) evidenced greater local clustering than BD (all BDII, n = 32) in a different set of regions (e.g., precuneus) (14). Although useful, these studies are limited by relatively small samples, reliance on resting state, and a failure to account for the presence of individuals at high risk for BD within the MDD sample.

To address these gaps, we examined network properties in a large sample of medication-free, young adults with depression (n = 50 BD [18 BDI, 32 BDII]; n = 116 MDD) and healthy control (HC) subjects (n = 83). We sought to identify graph properties that differentiated 1) BD from MDD, 2) patients with MDD at high risk for BD (hrMDD) and low risk for BD (lrMDD), and 3) patients from HC subjects. Although current self-report–based markers of BD risk are flawed, no other method of categorizing high-risk individuals is currently available without the use of large prospective imaging studies. Thus, BD risk was assessed in a subset of the MDD group (n = 80) using self-reported subthreshold mania symptoms to identify additional potential risk biomarkers. Specifically, brain differences underlying risk for mania should vary with self-report indices of risk because these indices are predictive (albeit imperfectly) of future BD. However, brain differences should index additional risk variance not captured by self-report markers because such brain mechanisms are likely closer to the causal mechanisms leading to BD. Thus, we chose to conceptually bootstrap the identification of brain biomarkers of BD risk using self-report indices, with the intention that such neuromarkers could be used in combination with other indices to provide more reliable methods for identifying BD risk.

To increase the likelihood of recruiting affect-relevant circuits, participants engaged in a continuous-performance emotion regulation task that involved viewing negatively valenced pictures while either maintaining or regulating (via cognitive reappraisal) affective responses (15). Continuous designs are more akin to real-world regulation, which occurs on a rolling basis (16,17), rather than in discrete segments (i.e., block/event-related design).

We examined four graph properties using a conservative correction procedure for multiple comparisons. Each property indexed complementary aspects of a node's ability to communicate with the larger network. Here, we briefly introduce the three properties for which we observed findings. Clustering coefficient measures the extent to which a node is part of a tightly interconnected local network (Figure 1A), and the existence of such subnetworks is necessary for different types of specialized processing within the global brain network (18). Lower levels of amygdala clustering, for example, could indicate disruption/inefficiency in the processes supported by the amygdala subnetwork (e.g., salience identification). Current flow betweenness centrality (Figure 1B) assays the level of influence a node has over information transmitted across the network. For example, decreases in amygdala betweenness could indicate that biologically salient aspects of the environment (e.g., threat) that the amygdala is central to identifying

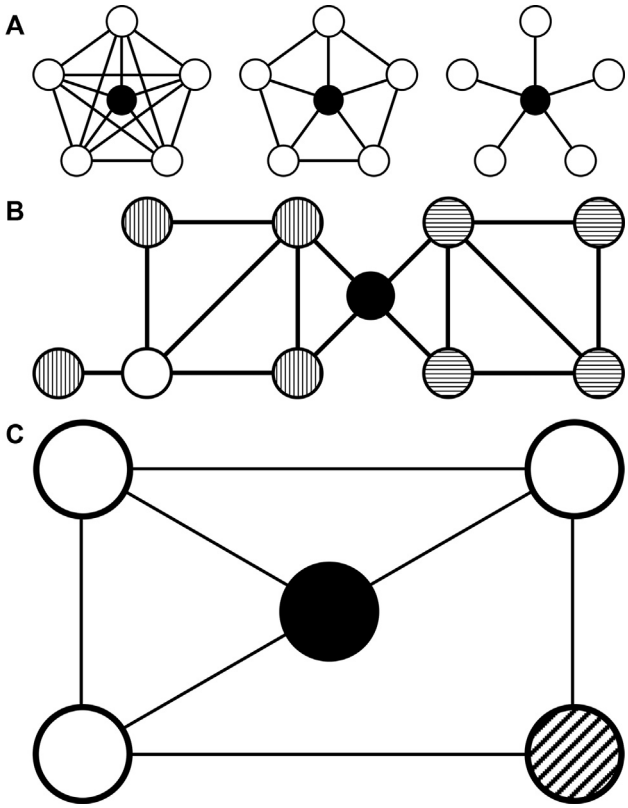

Figure 1. Example networks demonstrating graph properties. **(A)** Three different networks in which the center (solid black) node has increasing clustering coefficient moving right to left. Specifically, in the rightmost network, none of the neighbors of the center node are connected to each other, and thus there is no clustering around the black node. In contrast, all of the neighbors of the black node are connected to each other in the leftmost network, and thus the black node has the maximum level of clustering. **(B)** Current flow betweenness centrality. The solid black node has the highest level of betweenness, because all communication between the horizontally striped nodes and the vertically striped/empty nodes has to flow through the solid black node. In contrast, the empty node has approximately half the betweenness as the solid node, because it is not as central to the graph structure, despite the two nodes having an equal number of connections. **(C)** Communicability efficiency. This property reflects the balance between the number of parallel paths to the other nodes in the network and the number of self-loops. The greater the number of parallel paths, the more the noise along each path will be canceled out. The fewer the number of self-loops, the less of the information that is sent out will be wasted. The solid black node has the highest communicability efficiency because it has three parallel paths with which to reach other nodes but only five self-loops. The striped node has the lowest communicability efficiency because it has only two parallel paths and four self-loops.

(19) have less influence on ongoing processes. Communicability efficiency (Figure 1C) relates to the quality of the communication a node has with the rest of the network, with higher values reflecting higher quality communication (i.e., less information lost and/or clearer information flow). Thus, lower amygdala communicability efficiency could indicate that salience-related information is being degraded when sent from the amygdala to the rest of the brain.

Given evidence that amygdala hyperactivity to affective stimuli is evident in both BD and MDD (8–10) (vs. HC subjects)

and that this effect is stronger in BD than MDD (11), we hypothesized that patients (vs. HC subjects), BD (vs. MDD), and high-risk (vs. low-risk) MDD would display less adaptive reconfiguration of amygdala network communication in response to the demand for affect regulation. Specifically, given that 1) strengthening the impact of the amygdala on network processing would impede affect regulation and 2) higher levels of amygdala betweenness, clustering coefficient, and communicability efficiency would accomplish such strengthening, we predicted that patients with BD or hrMDD and patients overall would evidence relatively higher betweenness, clustering, and communicability during affect regulation.

METHODS AND MATERIALS

Participants

Participants (N = 298) were recruited from Indiana University Hospital/Cleveland Clinic outpatient psychiatry clinics and community advertisements. Procedures were approved by relevant institutional review boards, and informed consent was obtained. A psychiatrist administered the Mini-International Neuropsychiatric Interview, and patients satisfied DSM-IV-TR criteria for BD or MDD and had a current major depressive episode. After exclusion for low data quality, the following numbers of participants were included: total, N = 249; BD, n = 50 (18 BDI, 32 BDII); MDD, n = 116 (35 high-risk, 45 low-risk, 36 unspecified); and HC subjects, n = 83. See the Supplement for additional information (e.g., exclusion criteria).

Ascertainment of BD Risk in MDD

Three psychiatrists independently reviewed information for 80 patients with MDD (data for 36 were collected before review commenced) and classified them as hrMDD or lrMDD via consensus best-estimate agreement (20). Based on previous work (21–24), hrMDD (n = 35) was conservatively defined as having a past episode of 1) euphoric mood with at least two mania symptoms and/or 2) increased irritability with at least three mania symptoms. If full mania symptoms were present, then duration was <4 days (25). All other reviewed MDD cases were classified as lrMDD (n = 45). Family history of BD was also collected, and no patients with lrMDD had such a history (i.e., BD family history conformed to our classification).

Emotion Regulation Task

Separate runs were collected for affect maintenance and regulation conditions. During both, participants were continuously shown negatively valenced pictures from the International Affective Picture System (26). Each picture was shown for 15 seconds (21 pictures/scan), and conditions were matched for picture valence/arousal. Participants were instructed to maintain their emotional response to the pictures during the maintain scan and continuously regulate during the regulate scan using reappraisal techniques taught during a training session before the scan. Techniques included distancing oneself from what was occurring in the image and imagining it was not real. After each scan, participants rated the aversiveness of the entire picture set (for that condition). Ratings for 10 participants were not included in relevant analyses owing to missing data.

MRI Acquisition, Preprocessing, and Computation of Graph Properties

Figure 2 depicts the computation path. See the Supplement for details.

Statistical Analyses

Graph properties were entered into a 5000 permutation–based repeated-measures general linear model in the Graph Theory GLM toolbox v.46 (27) (repeated factor = maintain vs. regulate). One repeated-measures general linear model was computed per graph property (per node), with three between-subject categorical predictors of interest modeling the differences between 1) MDD versus BD, 2) hrMDD versus lrMDD, and 3) all patients (MDD and BD) versus HC subjects. Thus, we tested whether these moderated task effects (e.g., group × task interaction). See the Supplement for covariates. Orthogonal coding was used to reduce the impact of unbalanced sample sizes (28). Specifically, given that the MDD versus BD, hrMDD versus lrMDD, and BD subtype categorical predictors were each nested within one level of another predictor (e.g., hrMDD vs. lrMDD was nested within only the MDD level of the MDD vs. BD predictor), orthogonal coding ensures that there is no collinearity among these predictors.

To decrease the likelihood of type II errors, we only examined prefrontal and subcortical nodes, given that these regions consistently emerge across relevant meta-analyses (11,29), resulting in 111 nodes total. Given the large number of nodes, we took a two-pronged approach to ensure that the risk for false positives was minimized while simultaneously decreasing the risk of missing important effects. First, given the consistency with which amygdala disturbances have emerged for both BD and MDD individually, along with the comparison of BD and MDD (11,29), we examined amygdala properties without correcting for the other nodes in the network. Second,

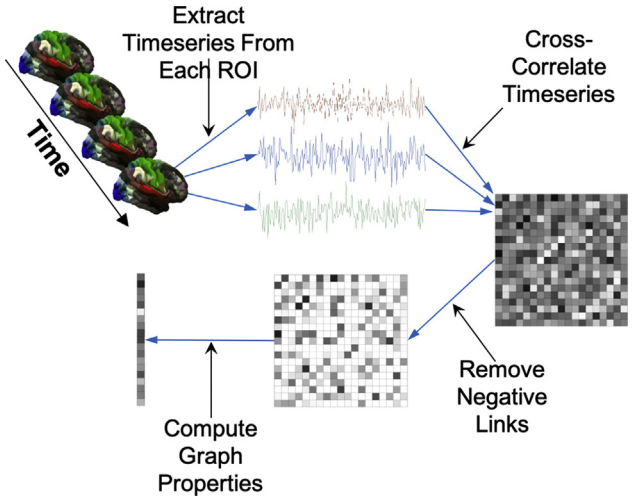

Figure 2. Data path. This figure illustrates the data processing path after preprocessing. This processing stream occurs separately for each condition (maintain, regulate). ROI, region of interest.

when examining properties for other nodes, we used the false discovery rate (FDR) (30) procedure to correct for multiple comparisons. Specifically, we corrected across both the number of nodes and the four properties examined to account for both sources of multiplicity. Critically, we included the amygdala in this correction, ensuring that (for nonamygdala nodes) we corrected across all nodes examined. Thus, we conducted (and FDR corrected across) 111 nodes × 4 properties = 444 analyses total.

To ensure that findings were not driven by characteristics that differed between groups, we repeated all analyses with the addition of eight covariates: illness duration, number of past mood episodes, medication history (i.e., treatment naïve vs. past medication use), gender, Young Mania Rating Scale, Hamilton Depression Rating Scale, and race (dummy coded). All findings remained significant, indicating that they were not driven by these variables (see the Supplement for further information).

To determine which condition drove significant findings, we examined the group effect within each condition. To gain insights into the impact of each property on affect, we correlated property values with participant ratings (within each condition). For both the group tests within condition and the correlations of property values with ratings, we corrected for multiple comparisons (i.e., the two conditions) by dividing the critical alpha by 2. For effects that emerged from the MDD versus BD and hrMDD versus lrMDD comparisons, we tested whether each group (individually) differed from HC subjects (within each condition) to identify groups exhibiting disturbances from this baseline. FDR correction (across conditions and groups) was used for the comparisons to HC subjects to correct for multiple comparisons.

RESULTS

Only significant analyses are reported. All findings below remained significant when confounds were accounted for in analyses.

BD Versus MDD

Patient group (BD vs. MDD) moderated the task effect for the right rostral anterior cingulate cortex (rACC) clustering coefficient (Table 1). As shown in Figure 3A, clustering was relatively higher for the regulate (vs. maintain) condition in BD, whereas the opposite pattern emerged for MDD. Follow-up analyses revealed that BD showed significantly greater rACC clustering than MDD for the regulate condition, whereas no significant difference was observed for the maintain condition. In addition, for the regulate condition, rACC clustering was higher in BD than HC subjects, whereas it was lower in MDD than HC subjects (Table 2). Finally, rACC clustering correlated positively (across groups) with valence ratings in the maintain condition.

Patient group also moderated the task effect in left hippocampus current flow betweenness centrality (Table 1). As illustrated in Figure 3B, betweenness was relatively higher for the maintain (vs. regulate) condition in BD, whereas the opposite pattern emerged for MDD. Follow-up analyses revealed that BD showed significantly lower betweenness than MDD for the regulate condition, but no significant differences emerged for the maintain condition. Furthermore, BD evidenced lower hippocampus betweenness than HC subjects for the regulate condition, whereas MDD evidenced lower values than HC subjects for the maintain condition (Table 2).

Finally, patient group moderated the task effect in left anterior-middle orbitofrontal cortex (OFC) (Brodmann area 11)

Table 1. Group × Task Interactions and Follow-up Analyses

Region	Metric	*p* Value, Uncorrected (FDR-Corrected)	η_p^2	Group		Correlation With Rating	
				Maintain	Regulate	Maintain	Regulate
MDD vs. BD							
Right rACC	Clustering coefficient	<.001 (<.030)	0.066	p = .262	BD>MDD; p < .001	0.15; p = .022	−0.03; p = .620
Left Hippocampus	Current flow betweenness centrality	<.001 (<.001)	0.055	p = .102	MDD>BD; p = .009	−0.10; p = .106	−0.03; p = .630
Left Orbitofrontal Cortex	Communicability efficiency	<.001 (<.001)	0.049	MDD>BD; p = .005	p = .145	0.09; p = .147	−0.03; p = .633
hrMDD vs. lrMDD							
Right Amygdala	Clustering coefficient	0.308 (NA)	0.022	p = .250	p = .126	0.20; p = .001	0.03; p = .653
Patients (D) vs. HC							
Left Amygdala	Clustering coefficient	0.32 (NA)	0.020	HC>D; p = .007	p = .895	0.23; p = <.001	0.05; p = .458

Entries in the uncorrected and FDR-corrected *p* values column are for the overall effect (see the Supplement for discussion of why amygdala *p* values were not corrected). Entries in the η_p^2 column are the partial eta squared for overall effect. Entries in the group column are direction of effects (if significant) and *p* values for the relevant group test within each condition. Entries in the correlation with rating column are the correlations between affect rating and the graph metrics (correlation and the associated *p* value). For the group and correlation with rating tests, the critical α was divided by 2 (i.e., number of conditions) to correct for multiple comparisons, and thus the *p* value for these tests must be <.025 to be significant.

BD, bipolar disorder; D, depressed (MDD+BD); FDR, false discovery rate; HC, healthy control; hrMDD, MDD at high risk for BD; lrMDD, MDD at low risk for BD; MDD, major depressive disorder; NA, not applicable; rACC, rostral anterior cingulate cortex.

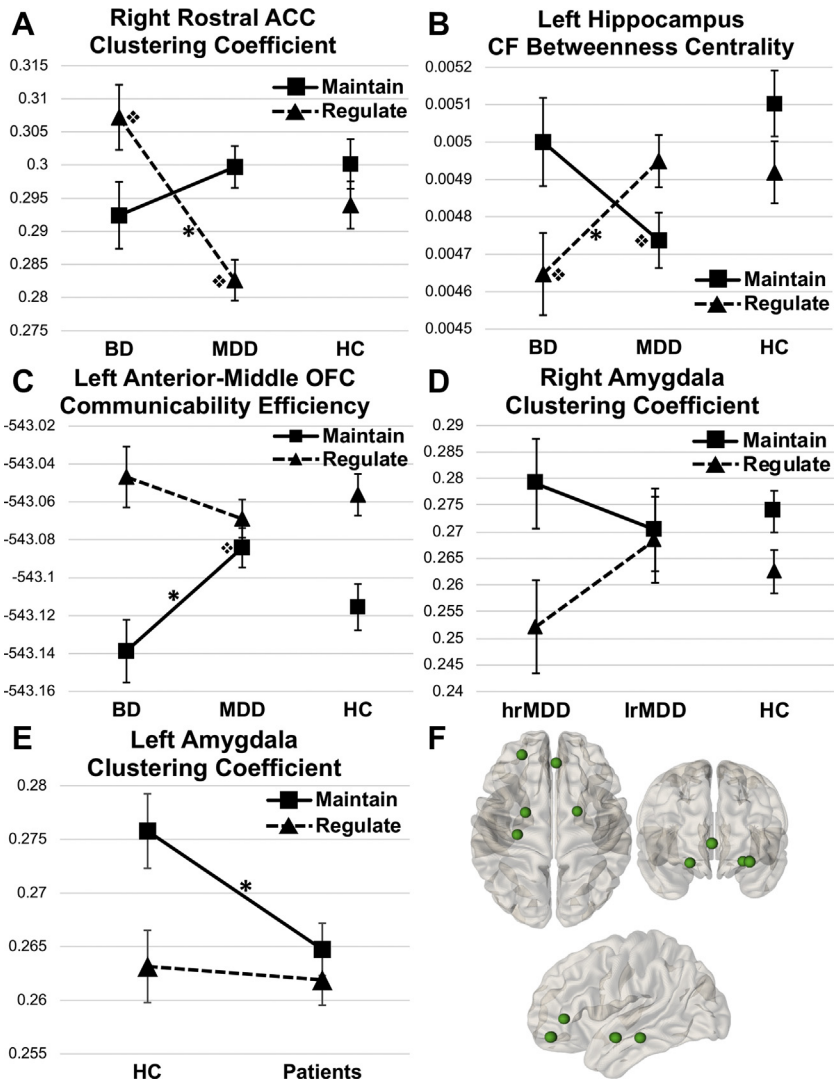

Figure 3. Graph properties differentiating patient groups. **(A–C)** Differences between the bipolar disorder (BD) and major depressive disorder (MDD) groups in the effect of condition (maintain vs. regulate). **(D)** Difference between patients with MDD at high risk for BD (hrMDD) and low risk for BD (lrMDD). **(E)** Difference between patients (MDD+BD) and healthy control (HC) subjects in the effect of condition. **(F)** Locations of the nodes identified. Means for HC subjects in panels **(A–D)** are provided for reference, even though this group was not part of the original effect tested (HC subjects were used in follow-up analyses). All graphs reflect the estimated marginal means (i.e., adjusted for the appropriate covariates). * indicates that groups are significantly different within task condition; ❖ indicates that the mean for that group in that condition is significantly different from the mean for HC subjects in the same condition. ACC, anterior cingulate cortex; CF, current flow; OFC, orbitofrontal cortex.

communicability efficiency (Table 1). As seen in Figure 3C, communicability efficiency was relatively higher for the regulate (vs. maintain) condition in BD, whereas MDD evidenced similar levels for both conditions. Follow-up analyses revealed that OFC communicability efficiency was significantly lower in BD than MDD for the maintain condition, but no significant differences emerged for the regulate condition. Furthermore, for the maintain condition, MDD evidenced higher OFC communicability efficiency values than HC subjects (Table 2).

High-Risk Versus Low-Risk MDD

Risk group (hrMDD vs. lrMDD) moderated the task effect in the right amygdala clustering coefficient (Table 1). As seen in Figure 3D, clustering was relatively higher for the maintain (vs. regulate) condition in BD, whereas MDD evidenced similar levels for both conditions. Follow-up analyses did not reveal any significant group differences when examined within each condition. Furthermore, right amygdala clustering coefficient positively correlated with valence ratings for the maintain condition.

All Patients With Depression Versus HC Subjects

Patients differed from HC subjects in the left amygdala clustering coefficient (Table 1). As seen in Figure 3E, clustering was relatively higher for the maintain (vs. regulate) condition in HC subjects, whereas patients evidenced similar levels for both conditions. Furthermore, left amygdala clustering positively correlated with valence ratings for the maintain condition.

DISCUSSION

This study leveraged new methods for indexing emergent properties of brain networks to identify biomarkers that differentiate BD from MDD in a large sample of currently depressed, medication-free patients. Specifically, we applied graph theory methods to fMRI data collected during a

Table 2. Comparisons to Healthy Control Subjects

Region	Metric	Uncorrected *p* (FDR-corrected *p*)		Uncorrected *p* (FDR-corrected *p*)	
		Maintain	Regulate	Maintain	Regulate
		BD		MDD	
Effects Emerging From Comparison of MDD to BD					
Right rACC	Clustering coefficient	.144 (.192)	BD>HC; .001 (.002)	.902 (.902)	HC>MDD; <.001 (.002)
Left Hippocampus	Current flow betweenness centrality	.455 (.445)	HC>BD; .012 (.024)	HC>MDD; .008 (.024)	.053 (.071)
Left Orbitofrontal Cortex	Communicability efficiency	.029 (.058)	.147 (.196)	MDD>HC; .003 (.012)	.326 (.326)
Effects Emerging From Comparison of hrMDD to lrMDD					
		hrMDD		lrMDD	
Right Amygdala	Clustering coefficient	.102 (.380)	.586 (.586)	.479 (.586)	.190 (.380)

Entries are the directions of effects (if significant) and the uncorrected and FDR-corrected (in parentheses) *p* values for the comparisons of the mean graph metric value for each group individually against the HC group, within each condition. Note that the HC group was not a part of the original effect tested. Thus, these tests were conducted to provide insight into which groups are demonstrating deviations from the typical pattern.

BD, bipolar disorder; FDR, false discovery rate; HC, healthy control; hrMDD, major depressive disorder at high risk for BD; lrMDD, major depressive disorder at low risk for BD; MDD, major depressive disorder; rACC, rostral anterior cingulate cortex.

continuous performance emotion regulation task and identified several potential biomarkers (see Table 3 for a summary). For example, clustering coefficient in the right rACC differentiated BD from MDD and tracked patients' self-report ratings of emotional aversiveness during the task. Furthermore, right amygdala clustering coefficient differentiated between patients with MDD at high and low risk for developing BD and also tracked self-reported aversiveness. These findings demonstrate the promise of using emergent brain network properties to identify novel metrics and improve early identification of patients with depression at high risk for developing BD.

Differentiating BD and MDD

Network clustering (clustering coefficient) around the right rACC differentiated BD from MDD in the regulate condition (Figure 3A). Moreover, BD patients exhibited higher levels of rACC network embeddedness than HC subjects when regulating affect, whereas rACC levels in MDD patients were lower than those in HC subjects. Thus, the local network surrounding the right rACC during emotion regulation appears to be most interconnected for BD, followed by HC subjects, then MDD. Because tightly interconnected local networks are crucial for engaging in specialized processing (18), this finding suggests that the processes supported by the rACC differ by group during emotion regulation. The rACC is crucial for affect-related top-down control [e.g., of amygdala (31)], suggesting that currently depressed patients with BD patients overengage top-down control of affect, whereas such control is weaker in MDD. This interpretation is supported by evidence that the rACC shows decreased resting-state connectivity with the amygdala in unipolar (32), but not bipolar (33), depression.

BD and MDD also differed in the level of influence the left hippocampus had over information transmitted in the network (current flow betweenness centrality) (Figure 3C). The hippocampus had less influence in MDD during maintenance of affect and in BD during regulation of affect compared with that in HC subjects. However, only MDD showed a flip in the condition effect relative to HC subjects, suggesting that this disturbance is more pronounced in MDD. Given the central role of the hippocampus in contextual binding (34), weaker hippocampal influence on network communication in MDD may lead

Table 3. Summary of Main Findings

Condition	Right rACC Clustering Coefficient	Left Hippocampus CF Betweenness Centrality	Left OFC Communicability Efficiency	Right Amygdala Clustering Coefficient	Left Amygdala Clustering Coefficient
Maintain	n.s.	n.s.	MDD>BD	Effect for hrMDD vs. lrMDD, but groups did not differ within condition	HC>patients
Regulate	BD>MDD	MDD>BD	n.s.		n.s.

BD, bipolar disorder; CF, current flow; HC, healthy control; hrMDD, MDD at high risk for BD; lrMDD, MDD at low risk for BD; MDD, major depressive disorder; n.s., nonsignificant difference; OFC, orbitofrontal cortex; rACC, rostral anterior cingulate cortex.

to weaker context-based modulation of ongoing processing. This is supported by the negative correlation between affect ratings and betweenness during the maintain condition. If true, processing of negative stimuli may not be limited to relevant contexts in individuals with MDD, potentially contributing to depressive rumination (i.e., repetitive negative thoughts, even when not contextually relevant) (35).

Finally, the quality (more information transmitted/less information wasted) of left anterior-middle OFC communication (communicability efficiency) (Figure 3C) was lower during the maintain condition for BD and HC subjects, whereas levels were higher in both conditions for MDD (i.e., similar to the regulate condition for BD and HC subjects). This suggests that BD and HC subjects are evidencing lower clarity of OFC communication during unregulated affective processing, whereas higher clarity communication was evident for MDD in both conditions. Given the role of the OFC in maintaining stimulus value in the current context (36), higher-quality OFC communication may reflect engagement in the trained reappraisal strategies, which involved reinterpreting stimuli by changing the context (e.g., telling oneself that individuals in a photograph depicting violence are actors and not in danger). If so, our finding that MDD shows higher-quality OFC communication during both conditions may reflect the fact that these individuals are continuously regulating affect, consistent with past findings of lower affect reactivity in MDD (37). Conversely, the fact that MDD is not differentiating between conditions could contribute to impairment.

Biomarkers of BD Risk in MDD

Right amygdala network embeddedness (clustering coefficient) differentiated between patients with hrMDD and lrMDD (Figure 3D). Contrary to our hypothesis, hrMDD evidenced a similar pattern as HC subjects, namely greater clustering during the maintain condition relative to the regulate condition. In contrast, lrMDD showed no difference between conditions, suggesting that patients with "true" MDD fail to modulate amygdala clustering appropriately based on context. Given that the lrMDD means for both conditions lie about midway between the means for both hrMDD and HC subjects, it is not the case that the disturbances observed in lrMDD are limited to one condition.

Interestingly, amygdala clustering during affect maintenance was positively related to self-reported aversiveness of task stimuli. Thus, such clustering may support processing of the aversive aspects of stimuli, consistent with the central role for the amygdala in determining motivational salience (19). As mentioned above, network clustering is crucial for supporting specialized processing within subcircuits. For example, higher clustering around the amygdala may reflect greater elaboration of amygdalar processing, because the regions that receive information from the amygdala also transmit to each other, and thus amygdalar information may be passed back and forth to a greater extent. Therefore, higher clustering during affect maintenance may drive increases in the detection of salient (i.e., aversive) stimulus features, consistent with the positive correlation between clustering and aversiveness ratings. When considered in this context, this suggests that individuals with "true" MDD (lrMDD) identify aversive salience similarly across contexts, which could impede emotion regulation. In contrast, those at high risk of BD (hrMDD) may identify salience similar to healthy individuals, at least when depressed.

Depression Across Disorders

Across mood disorders, patients with depression exhibited less differentiation (vs. HC subjects) in left amygdala clustering coefficient between task conditions (Figure 3E). Specifically, HC subjects evidenced increased amygdala clustering during the maintain (vs. regulate) condition, but patients with depression did not exhibit this increase. This may appear counterintuitive at first because depression is typically conceptualized as higher in negative affect. However, depressed individuals often exhibit lower state responsivity to negatively valenced stimuli, despite consistent negative mood (37). Thus, decreased amygdala clustering may reflect one mechanism by which reactivity to aversive stimuli is attenuated in depression.

Implications

One interpretation of these findings is that they lead to/maintain (hypo)mania because this is what differentiates BD from MDD. At the same time, because all patients were currently depressed, our findings may instead reflect differences in the way depressive symptoms are instantiated in BD versus MDD. Specifically, although they may experience the same surface symptomology, the mechanisms that cause/support such pathology may differ between disorders. Importantly, these findings are not due to differences in the severity of current depression or mania because all findings remained significant after controlling for Hamilton Depression Rating Scale and Young Mania Rating Scale.

One clue that may assist in differentiating between these explanations is comparisons between property levels/patterns of the patient groups to HC subjects. For example, BD and HC subjects showed a similar pattern (regulate $>$ maintain) of OFC communicability efficiency and there were no significant differences in property levels, whereas MDD showed a different pattern (regulate = maintain) and higher property levels during the maintain condition than both HC subjects and BD. Therefore, this neuromarker seems to be driven by disturbances in MDD, rather than BD, and thus may be a mechanism supporting depression uniquely in MDD. Similarly, right amygdala clustering coefficient in patients with MDD at high risk for BD showed a similar pattern (maintain $>$ regulate) to HC subjects, whereas patients with MDD at low risk for BD showed a different pattern (maintain = regulate). Thus, this may be a mechanism unique to "true" depression in MDD, and the absence of this pattern in current depression may indicate higher BD risk. No finding was particularly indicative of the first explanation mentioned above (i.e., that the neuromarker supports mania in some way). For example, the disturbances were evident in both groups' levels of right rACC clustering coefficient, and thus this neuromarker is likely to support pathology in both. Thus, future research integrating currently euthymic BD/MDD and/or (hypo)manic BD is needed to accurately parse these potential roles for the observed findings.

These findings may serve as useful neuromarkers for differentiating currently depressed individuals with BD or at

high versus low risk for BD, even without understanding how these findings support BD and/or MDD. For example, even if the observed differences are indicative of MDD proneness rather than BD, the absence of such markers in currently depressed individuals could still serve as a useful indicator of BD risk. The identified neuromarkers could be used in combination with other risk markers (e.g., subthreshold mania symptoms) to guide treatment decisions for those presenting with current depressive symptoms. Future research (e.g., using machine learning) is needed to determine the optimal contribution of each risk marker for making this determination.

Strengths, Limitations, and Future Directions

This study has a number of strengths, including a large sample size (n = 249), medication-free patients (quite uncommon in BD research), and a novel continuous-performance emotion regulation paradigm. We also used a cutting-edge analysis framework, investigating graph properties that were appropriate for use in brain networks and accounting analytically for the influence of lower-level network characteristics. Furthermore, to our knowledge, this is the first study to examine BD risk in MDD using graph properties.

Several limitations must be considered. First, we collapsed across BD subtypes (although subtype was covaried to account for this variance). Future studies, with larger samples, should test for subtype differences. Second, although participants were medication-free for at least 2 weeks, many had previously taken medication, which can have normalizing effects on network properties (38). Third, this study was cross-sectional, and thus longitudinal work will be key to understanding the predictive validity of findings. Fourth, the order of the task conditions was not counterbalanced, which could have had several effects (e.g., fatigue, carryover effects). Finally, although average age of the patients with MDD (26 years) was only slightly above the average age of onset of BD [23 years (39)], it is possible that sampling at this age reduced the likelihood of obtaining individuals who will actually go on to develop BD (e.g., these individuals would have already developed BD by this age, if they were going to develop it). In fact, these individuals might be somewhat resilient against developing BD.

Overall, this study provides some of the first insights into how depression is instantiated in emergent brain network properties and how such properties can differentiate BD from MDD, along with those at risk for BD. We found that BD and MDD evidenced differences in brain network mechanisms subserving depression-related disturbances in affect regulation, including in regions critical for both affect production and regulation (e.g., amygdala, OFC). Moreover, we identified neuromarkers that differentiated high and low risk for BD in currently depressed individuals who have not yet experienced (hypo)mania. Detecting risk markers for BD in depressed individuals is crucial given the lack of diagnostic tools for differentiating these patients and the life-changing consequences incorrect diagnoses can have for precipitating BD in currently unaffected individuals. Given that MDD appeared to differ from the typical pattern (i.e., in HC subjects) to a greater extent than BD in the majority of the observed findings, it is possible that these findings provide insight into mechanisms specific to depression in MDD. Thus, future research is needed to identify the mechanisms that lead to BD predisposition, in particular.

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ARTICLE INFORMATION

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REFERENCES

1. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T (2015): The global burden of mental, neurological and substance use disorders: An analysis from the Global Burden of Disease Study 2010. PLoS One 10: e0116820.
2. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen H-U (2012): Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res 21:169–184.
3. Perugi G, Micheli C, Akiskal HS, Madaro D, Socci C, Quilici C, Musetti L (2000): Polarity of the first episode, clinical characteristics, and course of manic depressive illness: A systematic retrospective investigation of 320 bipolar I patients. Compr Psychiatry 41:13–18.
4. Ghaemi SN, Boiman EE, Goodwin FK (2000): Diagnosing bipolar disorder and the effect of antidepressants: A naturalistic study. J Clin Psychiatry 61:804–808;quiz 809.
5. Hirschfeld RMA, Lewis L, Vornik LA (2003): Perceptions and impact of bipolar disorder: How far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 64:161–174.
6. Chun BJDH, Dunner DL (2004): A review of antidepressant-induced hypomania in major depression: Suggestions for DSM-V. Bipolar Disord 6:32–42.
7. Strawn JR, Adler CM, McNamara RK, Welge JA, Bitter SM, Mills NP, *et al.* (2014): Antidepressant tolerability in anxious and depressed youth at high risk for bipolar disorder: A prospective naturalistic treatment study. Bipolar Disord 16:523–530.
8. Chen CH, Suckling J, Lennox BR, Ooi C, Bullmore ET (2011): A quantitative meta-analysis of fMRI studies in bipolar disorder. Bipolar Disord 13:1–15.
9. Houenou J, Frommberger J, Carde S, Glasbrenner M, Diener C, Leboyer M, Wessa M (2011): Neuroimaging-based markers of bipolar disorder: Evidence from two meta-analyses. J Affect Disord 132:344–355.
10. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG (2013): Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies. Neurosci Biobehav Rev 37:152–163.
11. Delvecchio G, Fossati P, Boyer P, Brambilla P, Falkai P, Gruber O, *et al.* (2012): Common and distinct neural correlates of emotional processing in bipolar disorder and major depressive disorder: A voxel-based meta-analysis of functional magnetic resonance imaging studies. Eur Neuropsychopharmacol 22:100–113.

12. Bullmore E, Sporns O (2009): Complex brain networks: Graph theoretical analysis of structural and functional systems [published correction appears in Nat Rev Neurosci 2009; 10:312]. Nat Rev Neurosci 10:186–198.
13. He H, Yu Q, Du Y, Vergara V, Victor TA, Drevets WC, *et al.* (2016): Resting-state functional network connectivity in prefrontal regions differs between unmedicated patients with bipolar and major depressive disorders. J Affect Disord 190:483–493.
14. Wang Y, Wang J, Jia Y, Zhong S, Zhong M, Sun Y, *et al.* (2017): Topologically convergent and divergent functional connectivity patterns in unmedicated unipolar depression and bipolar disorder. Transl Psychiatry 7:e1165.
15. Anand A, Grandhi J, Karne H, Spielberg JM (2020): Intrinsic functional connectivity during continuous maintenance and suppression of emotion in bipolar disorder. Brain Imaging Behav 14:1747–1757.
16. Campos JJ, Walle EA, Dahl A, Main A (2011): Reconceptualizing emotion regulation. Emot Rev 3:26–35.
17. Hollenstein T (2015): This time, it's real: Affective flexibility, time scales, feedback loops, and the regulation of emotion. Emot Rev 7:308–315.
18. Saramäki J, Kivelä M, Onnela JP, Kaski K, Kertész J (2007): Generalizations of the clustering coefficient to weighted complex networks. Phys Rev E Stat Nonlin Soft Matter Phys 75:027105.
19. Cunningham WA, Brosch T (2012): Motivational salience: Amygdala tuning from traits, needs, values, and goals. Curr Dir Psychol Sci 21:54–59.
20. Nurnberger JI Jr, McInnis M, Reich W, Kastelic E, Wilcox HC, Glowinski A, *et al.* (2011): A high-risk study of bipolar disorder. Childhood clinical phenotypes as precursors of major mood disorders. Arch Gen Psychiatry 68:1012–1020.
21. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W (2003): Toward a re-definition of subthreshold bipolarity: Epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 73:133–146.
22. Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH (2011): Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. Am J Psychiatry 168:40–48.
23. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, *et al.* (2011): Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 68:241–251.
24. Zimmermann P, Brückl T, Nocon A, Pfister H, Lieb R, Wittchen HU, *et al.* (2009): Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. Arch Gen Psychiatry 66:1341–1352.
25. Koirala P, Hu B, Altinay M, Li M, DiVita AL, Bryant KA, *et al.* (2019): Sub-threshold bipolar disorder in medication-free young subjects with major depression: Clinical characteristics and antidepressant treatment response. J Psychiatr Res 110:1–8.
26. Lang PJ, Bradley MM, Cuthbert BN (1997): International Affective Picture System (IAPS): Technical Manual and Affective Ratings. NIMH Center for the Study of Emotion and Attention.
27. Spielberg JM, McGlinchey RE, Milberg WP, Salat DH (2015): Brain network disturbance related to posttraumatic stress and traumatic brain injury in veterans. Biol Psychiatry 78:210–216.
28. Blair RC, Higgins JJ (1978): Tests of hypotheses for unbalanced factorial designs under various regression/coding method combinations. Educ Psychol Meas 38:621–631.
29. Wise T, Radua J, Via E, Cardoner N, Abe O, Adams TM, *et al.* (2017): Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: Evidence from voxel-based meta-analysis. Mol Psychiatry 22:1455–1463.
30. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc B 57:289–300.
31. Di X, Huang J, Biswal BB (2017): Task modulated brain connectivity of the amygdala: A meta-analysis of psychophysiological interactions. Brain Struct Funct 222:619–634.
32. Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, *et al.* (2005): Activity and connectivity of brain mood regulating circuit in depression: A functional magnetic resonance study. Biol Psychiatry 57:1079–1088.
33. Anand A, Li Y, Wang Y, Lowe MJ, Dzemidzic M (2009): Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. Psychiatry Res 171:189–198.
34. Ranganath C (2010): Binding items and contexts: The cognitive neuroscience of episodic memory. Curr Dir Psychol Sci 19:131–137.
35. McLaughlin KA, Nolen-Hoeksema S (2011): Rumination as a transdiagnostic factor in depression and anxiety. Behav Res Ther 49:186–193.
36. Padoa-Schioppa C, Cai X (2011): The orbitofrontal cortex and the computation of subjective value: Consolidated concepts and new perspectives. Ann N Y Acad Sci 1239:130–137.
37. Bylsma LM, Morris BH, Rottenberg J (2008): A meta-analysis of emotional reactivity in major depressive disorder. Clin Psychol Rev 28:676–691.
38. Spielberg JM, Matyi MA, Karne H, Anand A (2019): Lithium monotherapy associated longitudinal effects on resting state brain networks in clinical treatment of bipolar disorder. Bipolar Disord 21:361–371.
39. Joslyn C, Hawes DJ, Hunt C, Mitchell PB (2016): Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review. Bipolar Disord 18:389–403.