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Opposing Changes in the Functional Architecture of Large-Scale Networks in Bipolar Mania and Depression

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Objective: **Manic and depressive phases of bipolar disorder (BD) show opposite symptoms in psychomotor, thought, and affective dimensions. Neuronally, these may depend on distinct patterns of alterations in the functional architecture of brain intrinsic activity. Therefore, the study aimed to characterize the spatial and temporal changes of resting-state activity in mania and depression, by investigating the regional homogeneity (ReHo) and degree of centrality (DC), in different frequency bands.** ***Methods:*** **Using resting-state functional magnetic resonance imaging (fMRI), voxel-wise ReHo and DC were calculated—in the standard frequency band (SFB: 0.01–0.10 Hz), as well as in Slow5 (0.01–0.027 Hz) and Slow4 (0.027–0.073 Hz)—and compared between manic (n = 36), depressed (n = 43), euthymic (n = 29) patients, and healthy controls (n = 112). Finally, clinical correlations were investigated.** ***Results:*** **Mania was mainly characterized by decreased ReHo and DC in Slow4 in the medial prefrontal cortex (as part of the default-mode network [DMN]), which in turn correlated with manic symptomatology. Conversely, depression was mainly characterized by decreased ReHo in SFB in the primary sensory-motor cortex (as part of the sensorimotor network [SMN]), which in turn correlated with depressive symptomatology.** ***Conclusions:*** **Our data show a functional reconfiguration of the spatiotemporal structure of intrinsic brain activity to occur in BD. Mania might be characterized by a predominance of sensorimotor over associative networks, possibly driven by a deficit of the DMN (reflecting in internal thought deficit). Conversely, depression might be characterized by a predominance of associative over sensorimotor networks, possibly driven by a deficit of the SMN (reflecting in psychomotor inhibition).**

Key words: bipolar disorder/regional homogeneity/degree of centrality/default-mode network/sensorimotor network

Introduction

Background

Episodes of mania and depression are distinctive disease states of bipolar disorder (BD). These phases show very different, often opposite, psychopathological features. Mania presents euphoric or irritable mood, externally focused thought, and excited psychomotor behavior.[1,2] By contrast, depression is typically characterized by depressed mood, internally focused thought, and inhibited psychomotor behavior.[1,2] Considering such opposite clinical symptomatology, mania and depression could be related to distinct patterns in neuronal activity, which remain to be established though.

Physiologically, intrinsic neuronal activity in the low frequencies (<0.1 Hz), as investigated by resting-state functional magnetic resonance imaging (fMRI), has shown to be organized in a specific functional architecture, so that temporally coherent fluctuations across distinct spatially distributed brain areas originate various large-scale

networks, and, in turn, such functional architecture is fundamental in the expression of different psychological and behavioral functions.[3–5] As recently demonstrated, these networks show a functional large-scale hierarchy.[6] At one end, sensorimotor systems—as organized in the sensorimotor network (SMN),[3,7,8] visual network (VN),[3] dorsal attention network (DAN),[9] and salience network (SN)—have strong recurrent connections and excitatory subcortical inputs, consistent with localized processing of external sensory inputs and motor outputs.[6] Thus, such networks are involved in externally or environmentally focused thought and behavior. At the opposing end, the default-mode network (DMN)[10–12] has weak recurrent connections and excitatory subcortical inputs, consistent with associative functions.[6] Thus, DMN is involved in internally focused thought and correspondent internally driven behavior. Between these 2 poles, the limbic network (LIM) and the central executive network (CEN) exhibit intermediate features.[6] Moreover, such sets of networks are frequently organized in balances, as shown, for instance, by the anticorrelated activity between the DMN and sensorimotor networks.[7,13]

The functional architecture of intrinsic brain activity was found to be disrupted in BD.[14,15] By investigating the different phases of illness, we previously detected distinct changes in such functional brain architecture underlying mania and depression. In particular, mania was characterized by a tilting of the balance between SMN and DMN toward the SMN at the expense of DMN (as measured by the temporal variability of BOLD signal),[16] along with a greater global signal representation in the SMN[17] and reduced functional connectivity (FC) within the DMN.[18,19] By contrast, depression was characterized by a tilting in SMN/DMN balance toward the DMN at the expense of SMN.[16] Following this line of evidence on a relationship between distinct functional brain alterations and psychopathological states, a further characterization of the spatiotemporal structure of resting-state activity during mania and depression may be highly relevant.

The spatial organization of intrinsic brain activity can be investigated both at a local and at a global level, by using specific and complementary measures such as the regional homogeneity (ReHo) and degree of centrality (DC), respectively.[20,21] ReHo measures intra-regional connectivity of resting-state signal. Specifically, a coefficient of concordance is calculated between the time-series for each voxel and those of its nearest neighbors.[22,23] Thus, high ReHo in a region might reflect high levels of local integration of resting-state activity (either by increased local activation in a functionally homogeneous region or by increased connectivity between functionally distinct local areas); as ReHo decreases, the activity becomes less integrated at a local level. DC quantifies instead the strength of resting-state connectivity of any voxel with all the other voxels of the brain, by using concepts from graph theory. Here, a complex system is modeled as a graph, which is defined as a set of nodes linked by edges. For a binary graph, DC is the number of edges connecting to a node.[24] Thus, high DC in a region might reflect its role as a central hub in the integration of global resting-state activity (involving both local and distant connections); as DC decreases, centrality becomes lower. Considering that sensorimotor networks show more local connectivity while associative networks display more global connectivity,[3] ReHo may be a relevant measure for networks like the SMN, while DC for networks like the DMN.

On the other hand, investigating the specific contribution of different frequencies of the resting-state signal can give information on the temporal organization of intrinsic brain activity. ReHo and DC are usually investigated within the standard frequency band (SFB) of low-frequency fluctuations (0.01–0.10 Hz), which are thought to reflect mainly neuronal oscillations.[4,25–28] Interestingly, SFB was recently subdivided into 2 sub-frequency bands that show differential contribution across brain areas and networks in the healthy brain, ie, Slow5 (0.01–0.027 Hz), which is stronger in the midline structures, and Slow4 (0.027–0.073 Hz), which is stronger throughout the sensorimotor regions.[4,26,27,29–31] Thus, such sub-frequencies could play distinct roles in functional changes at a network level.

ReHo has been previously investigated in BD during depression (in adults),[32–34] while DC has been explored in BD without considering the ongoing episode[35,36] or during the depressive phase only.[37] Therefore, a comprehensive characterization of these resting-state metrics, also considering the different sub-frequencies, during all the various phases of BD, needs still to be performed.

Aims of the Study

The aim of this study was to characterize the functional architecture of resting-state activity in the different phases of BD in terms of both local and global connectivity (spatial organization) along with the specific contribution of the different frequencies of slow signal fluctuations (temporal organization). For this purpose, ReHo and DC, in SFB and its sub-frequency bands Slow4 and Slow5, were compared between manic, depressed, and euthymic patients, and healthy subjects, by using a voxel-wise and data-driven approach.

Basing on our previous work, we expected distinct patterns in the spatiotemporal structure of resting-state activity with a predominance of SMN during mania and a predominance of DMN during depression. Considering the relationship of ReHo/DC and Slow4/Slow5 with such networks (see above), the predominance of SMN in mania could reflect in an increase of ReHo in the SMN and/or decrease of DC in the DMN, especially occurring in Slow4. By contrast, the predominance of DMN in depression could reflect in a decrease of ReHo in the SMN and/or increase of DC in the DMN, especially occurring in Slow5.

Methods

Sample, Data acquisition, and Preprocessing

The study was conducted on 108 patients with BD (36 in manic, 43 in depressive, and 29 in euthymic phases) and 112 healthy controls (HC) (supplementary table 1). For each subject, clinical data, resting-state fMRI, and structural images were collected. Imaging data underwent a standard preprocessing, resting-state data were then filtered with the SFB as well as Slow5 and Slow4, and, finally, DC and ReHo analyses were performed in the cerebral cortex.

See Supplementary Material for a detailed description of the sample and clinical assessment, as well as imaging data acquisition and preprocessing.

Regional Homogeneity

ReHo was calculated for each subject in the different frequency bands (ie, SFB, Slow5, and Slow4), using the AFNI program 3dReHo.[38] Specifically, for each voxel, Kendall's coefficient of concordance was calculated between the BOLD time-series for the specified voxel and those of its 26 nearest neighbors,[22,23] generating a voxel-wise ReHo map for each subject. The individual ReHo map was standardized into subject-level *z*-score maps by subtracting the mean voxel-wise ReHo obtained for the entire brain (global mean of ReHo) then dividing by the standard deviation across voxels.[23,27] After this, a spatial smoothing of 6 mm was performed on the ReHo map.[23]

Degree of Centrality

DC analysis was performed for each subject in the different frequency bands (ie, SFB, Slow5, and Slow4), using the AFNI program 3dTcorrMap. Specifically, voxel-based graphs were generated for each participant, where the correlation between the time-series of each voxel with every other voxel within the cortical mask was computed. A binary, undirected adjacency matrix was then obtained by thresholding each correlation at $r > 0.3$. Based on the graph, DC was calculated at the individual level.[24] DC was computed as the number of meaningful functional connections (positive correlations) between each voxel and all other voxels. In addition, normalized DC indices were calculated by transforming DC to *z*-scores based on the global mean of DC and standard deviation across voxels in the cortical mask.[24,39,40] After this, a spatial smoothing of 6 mm was performed on the DC map.[24,41]

Group Analyses on ReHo and DC

Each cortical map of ReHo and DC was entered into one-way ANOVA (3dANOVA) using the different groups as a factor, in SFB, and then explored in Slow4 and Slow5. The multiple-comparison error was corrected using the AFNI program 3dClustSim (AFNI version 19.2.26, the improved autocorrelation function was applied),[42] yielding a family-wise error (FWE) < 0.05 at $P < .01$ with a minimum cluster size of 91 voxels. After significant results in the ANOVA, *t*-tests between the different groups were performed for each measure in the various frequency bands. Only clusters overlapping with the results from the ANOVA were considered. The minimum cluster size (143 voxels) for the *t*-tests was recalculated with a Bonferroni correction to yield an FWE < 0.05, in order to account for the 6 *t*-tests performed. Finally, each significant cluster was mapped onto the different resting-state networks, as defined by Yeo and colleagues.[3]

Control and Additional Analyses

Firstly, control analyses were performed on ReHo and DC data, in order to test the robustness of the main results from the previous analysis. The estimated head motion was entered as a covariate in the comparison analyses of ReHo and DC. Then, a higher thresholding of $P < .001$ was set for the relevant comparisons of ReHo and DC. Moreover, contrast images with a thresholding of $P < .05$ were also reported, to show the general pattern of ReHo and DC changes in mania and depression.

Secondly, an additional analysis of FC was performed to further define the functional alterations at a spatial level in mania and depression.

Finally, an additional analysis of power-law exponent (PLE) was performed to further define the functional alterations at a temporal level in mania and depression.

See Supplementary Material for a detailed description of the methodology applied for the control and additional analyses.

Clinical Correlations

The potential relationship of ReHo and DC alterations with bipolar symptomatology was also investigated. Basing on results from the previous analyses, the total score of Young Mania Rating Scale (YMRS) and Hamilton Depression Scale (HAM-D) was entered into whole-brain voxel-wise regression analyses (using the AFNI program 3dtest++) with the relevant ReHo and DC data, within the BD group (regressions analyses with the other data were then performed for control of specificity). Moreover, voxel-wise regression analyses of specific relevant items from the clinical scales were also explored. A $P < .01$ was set.

Results

Results in ReHo Analysis and Sub-frequency Bands

ReHo showed significant differences between groups in SFB in the medial prefrontal cortex (part of the DMN), fusiform gyrus (part of the VN), and primary sensory-motor cortex (part of the SMN). In particular, manic

patients showed a significant decrease of ReHo in the medial prefrontal cortex (DMN) and an increase of ReHo in the fusiform gyrus (VN) when compared with HC. By contrast, depressed patients showed a significant decrease of ReHo in the primary sensory-motor cortex (SMN) when compared with HC.

Moreover, a significant difference between groups was found in ReHo in Slow4 in the medial prefrontal cortex (DMN), superior parietal lobule (DAN), fusiform gyrus (VN), and subcallosal cingulate cortex (LIM). In particular, manic patients showed a significant decrease of ReHo in the medial prefrontal cortex (DMN) and an increase of ReHo in the superior parietal lobule (DAN) when compared with both HC and euthymic patients, as well as an increase of ReHo in the fusiform gyrus (VN) when compared with HC. On the other hand, depressed patients showed a significant increase of ReHo in the subcallosal cingulate cortex (LIM) when compared with HC.

Finally, in Slow5, ReHo was significantly different between groups in the medial prefrontal cortex (DMN) and middle cingulate cortex (SMN), however, without showing any significant difference between the various phases of illness (see figure 1 and table 1).

Results in DC Analysis and Sub-frequency Bands

A significant difference between groups was found in DC in SFB in the medial prefrontal cortex (DMN), which was reduced in euthymic patients compared with HC, and in the fusiform gyrus (VN), which was increased in manic patients compared with HC.

Furthermore, a significant difference between groups was found in DC in Slow4 in the medial prefrontal cortex (DMN), showing significantly decreased values in manic patients when compared with HC.

No significant differences between groups were found in DC in Slow5 (see figure 2 and table 1).

Results of Control and Additional Analyses

Firstly, the control analyses on ReHo and DC confirmed our main results of reduced ReHo in SFB in the primary sensory-motor cortex in depression, as well as reduced ReHo and DC in Slow4 in the medial prefrontal cortex in mania, suggesting them as the most robust findings from our analyses (supplementary figures 1–3, supplementary tables 1–4). Moreover, an opposite trend of changes of both ReHo and DC between mania and depression was observed (ie, ReHo in SMN areas was decreased in

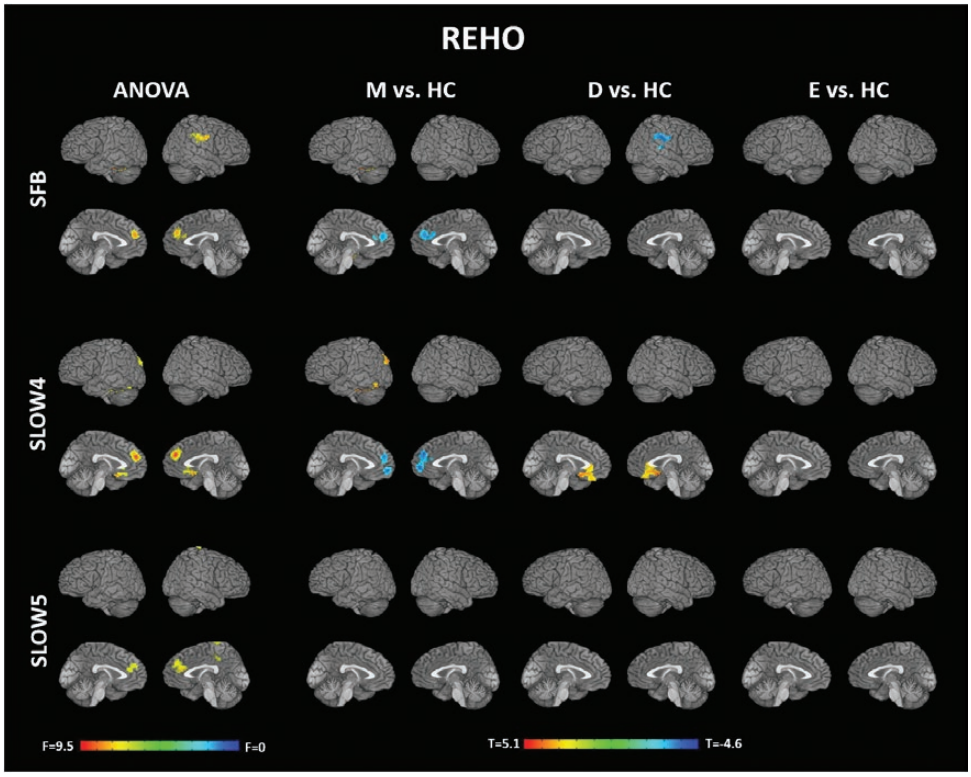

Fig. 1. ReHo results. Results from the between-groups comparison (ANOVA and *t*-tests) showing clusters with significant differences in ReHo values. The figure shows horizontally the results of comparisons of bipolar patients in the different phases of illness (ie, mania, depression, and euthymia) with HC; results for the different frequency bands are shown vertically. The f-maps of ReHo values (ANOVA) are thresholded at $P < .01$ (FWE < 0.05). The *t*-maps of ReHo values (*t*-tests) are thresholded at $P < .01$ (Bonferroni corrected FWE < 0.05). In the *t*-tests, only clusters overlapping with the results from the ANOVA are shown. *Note*: ReHo, Regional Homogeneity; M, Mania; D, Depression; E, Euthymia; HC, Healthy Controls; SFB, Standard Frequency Band.

Table 1. ReHo Results and DC Results

ReHo results															
SFB		**ANOVA**		**M vs HC**			**D vs HC**			**E vs HC**			**M vs E**		
Regions	**RSNs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**
L-FUG	VN	180	31.5; 31.5; −24.5	M > HC	339	31.5; 31.5; −24.5	—	—	—	—	—	—	—	—	—
L-MPFC	DMN	154	1.5; −46.5; 26.5	M < HC	221	−7.5; −31.5; 17.5	—	—	—	—	—	—	—	—	—
R-PSMC	SMN	104	−55.5; 7.5; 32.5	—	—	—	D < HC	214	−37.5; 22.5; 14.5	—	—	—	—	—	—
Slow4		**ANOVA**		**M vs HC**			**D vs HC**			**E vs HC**			**M vs E**		
Regions	**RSNs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**
R-MPFC	DMN	168	−1.5; −49.5; 23.5	M < HC	269	−4.5; −49.5; 20.5	—	—	—	—	—	—	M < E	187	−10.5; −55.5; 20.5
L-SPL	DAN	160	37.5; 52.5; 44.5	M > HC	216	22.5; 61.5; 29.5	—	—	—	—	—	—	M > E	237	22.5; 82.5; 29.5
L-FUG	VN	158	31.5; 31.5; −24.5	M > HC	201	31.5; 31.5; −24.5	—	—	—	—	—	—	—	—	—
L-SCCC	LIM	103	−4.5; −7.5; −9.5	—	—	—	D > HC	305	−4.5; −7.5; −9.5	—	—	—	—	—	—
Slow5		**ANOVA**		**M vs HC**			**D vs HC**			**E vs HC**			**M vs E**		
Regions	**RSNs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**
R-MPFC	DMN	144	−4.5; −34.5; 17.5	—	—	—	—	—	—	—	—	—	—	—	—
L-MCC	SMN	134	−7.5; 34.5; 38.5	—	—	—	—	—	—	—	—	—	—	—	—
DC results															
SFB		**ANOVA**		**M vs HC**			**D vs HC**			**E vs HC**			**M vs E**		
Regions	**RSNs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**
R-MPFC	DMN	150	−4.5; −49.5; −3.5	—	—	—	—	—	—	E < HC	295	−1.5; −49.5; −0.5	—	—	—
L-FUG	VN	133	43.5; 25.5; −21.5	M > HC	195	43.5; 25.5; −21.5	—	—	—	—	—	—	—	—	—
Slow4		**ANOVA**		**M vs HC**			**D vs HC**			**E vs HC**			**M vs E**		
Regions	**RSNs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**
R-MPFC	DMN	148	−10.5; 43.5; −3.5	M < HC	234	−10.5; −55.5; −12.5	—	—	—	—	—	—	—	—	—
Slow5		**ANOVA**		**M vs HC**			**D vs HC**			**E vs HC**			**M vs E**		
Regions	**RSNs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**	**vs**	**CS**	**x; y; z**
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Note: ReHo, regional homogeneity; DC, degree of centrality; RSNs, resting-state networks; CS, cluster size; SFB, standard frequency band; M, mania; D, depression; E, euthymia; HC, healthy controls; L-FUG, left fusiform gyrus; L-MPFC, left medial prefrontal cortex; R-PSMC, right primary sensory-motor cortex; R-MPFC, right medial prefrontal cortex; L-SPL, left superior parietal lobule; L-SCCC, left subcallosal cingulate cortex; L-MCC, left middle cingulate gyrus; VN, visual network; DMN, default-mode network; SMN, sensori-motor network; DAN, doral attention network; LIM, limbic network.
All the results are thresholded at a single-voxel $P < .01$; for the ANOVA, the minimum cluster size was set at 91 voxels (FWE < 0.05); a Bonferroni-correction was applied to the FWE in the post hoc *t*-tests, yielding a minimum cluster size of 143. The comparisons D vs E and M vs D are not shown as they yielded no significant results.

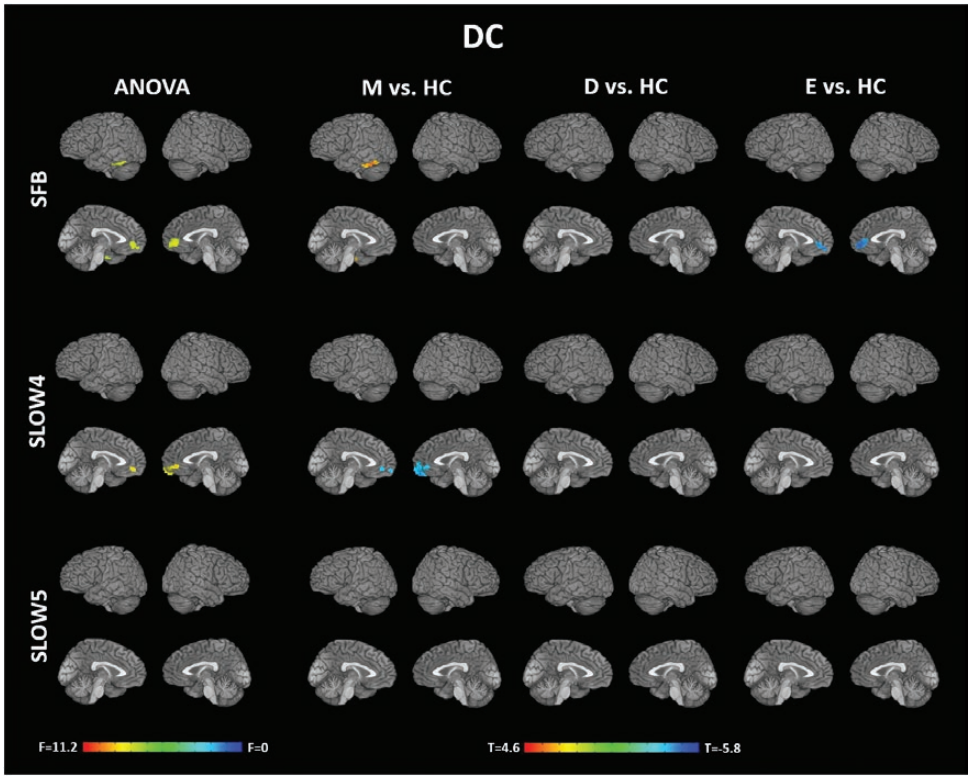

Fig. 2. DC results. Results from the between-groups comparison (ANOVA and *t*-tests) showing clusters with significant differences in DC values. The figure shows horizontally the results of comparisons of bipolar patients in the different phases of illness (ie, mania, depression, and euthymia) with HC; results for the different frequency bands are shown vertically. The f-maps of DC values (ANOVA) are thresholded at $P < .01$ (FWE < 0.05). The *t*-maps of DC values (*t*-tests) are thresholded at $P < .01$ (Bonferroni-corrected FWE < 0.05). In the *t*-tests, only clusters overlapping with the results from the ANOVA are shown. *Note*: DC, degree of centrality; M, mania; D, depression; E, euthymia; HC, healthy controls; SFB, standard frequency band.

depression and increased in mania, while DC in DMN areas was decreased in mania and increased in depression) (supplementary figure 4).

Secondly, the additional FC analysis showed that the ReHo alteration in the primary sensory-motor cortex is associated with disconnectivity of the SMN in depression, while the ReHo/DC alteration in the medial prefrontal cortex is associated with disconnectivity of the DMN in mania (supplementary figure 5). Moreover, changes of ReHo/DC in the SMN and DMN were found to be anticorrelated (supplementary figure 6).

Finally, the additional PLE analysis showed an abnormal contribution of higher frequencies over lower frequencies in resting-state alterations, especially throughout frontal and sensory-motor cortices, in mania (supplementary figure 7, supplementary table 5).

For a detailed description of the results from the control and additional analyses, see Supplementary Material.

Results of Clinical Correlations

Considering our main results, HAM-D total score was entered into voxel-wise regression analysis with ReHo in SFB, while YMRS total score with ReHo and DC in Slow4. HAM-D score showed a significant negative correlation with ReHo in SFB in the primary sensory-motor cortex (SMN), as well as a positive correlation with ReHo in SFB in the posterior cingulate cortex (DMN). By contrast, YMRS score showed a significant negative correlation with both ReHo and DC in Slow4 in the medial prefrontal cortex (DMN), as well as a positive correlation with ReHo in Slow4 in the primary sensory-motor cortex (SMN) and superior parietal lobule (DAN). The other contrasts yielded no significant results (with the exception of a positive correlation between HAM-D score and ReHo in Slow4 in the posterior cingulate cortex), confirming the specificity of our main results.

Moreover, considering our findings of ReHo in the SMN and DC in the DMN, as well as the well-known relationships of those networks with psychomotor activity and internal thought in healthy (see above), the score of psychomotor alteration (item 2 of YMRS) and thought disturbance (item 7 of YMRS) was entered into voxel-wise regression analyses with our ReHo and DC data, respectively. Thought disturbance (ie, distractibility and flight of ideas) showed a negative correlation with DC in Slow4 in the medial prefrontal cortex and middle temporal gyrus (DMN), while psychomotor alteration (ie,

increased motor activity and energy) showed a significant positive correlation with ReHo in Slow4 in the primary sensory-motor cortex (SMN). No significant results were detected in the regression analysis of mood alterations (both item 1 in YMRS and item 1 in HAM-D), confirming the specificity of these findings. See figure 3, supplementary figure 8, and supplementary table 6.

Discussion

Main Findings

The main findings were as follows. Mania was mainly characterized by decreased ReHo and DC in Slow4 in the medial prefrontal cortex (DMN), which in turn correlated with manic symptomatology. By contrast, depression was mainly characterized by decreased ReHo in SFB in the primary sensory-motor cortex (SMN), which in turn correlated with depressive symptomatology (see figure 4).

Altered Functional Architecture of Large-Scale Networks in Mania and Depression

The present work characterized the functional architecture of resting-state activity in the different phases of BD, by investigating ReHo and DC in SFB, Slow4, and Slow5.

Our findings suggest a topographical alteration of resting-state activity to occur in the manic and depressive phases of BD, with changes in both local and distant connectivity at a network level. In particular, significant changes in ReHo (a marker of local connectivity) were found in both primary sensory-motor cortex and medial prefrontal cortex, while significant changes in DC (a measure of both local and distant connectivity) were only found in the medial prefrontal cortex. The FC of the primary sensory-motor cortex clearly overlapped with the SMN, while the FC of the medial prefrontal cortex clearly overlapped with the DMN. Thus, our results may suggest a predominant disruption of local connectivity in the SMN in depression, while a disruption of both local and distant connectivity in the DMN in mania, coherently with the evidence that sensorimotor or associative networks show more local or global connectivity, respectively.[3] Moreover, such changes within sensorimotor and associative networks seem to balance, as ReHo in the SMN and ReHo/DC in the DMN were found to be anticorrelated and showed an opposite pattern of alterations in mania and depression. Thus, considering our results in the context of the recently described networks hierarchy,[6] our work may suggest a distortion of the functional architecture of intrinsic brain activity that favors the predominance of sensorimotor networks over associative networks (possibly driven by a DMN deficit) in mania, while the predominance of associative networks over sensorimotor networks (possibly driven by a SMN deficit) in depression. This may complement our previous findings of a network's disbalance in BD, as measured by neuronal variability, with a tilting toward the SMN in mania and toward the DMN in depression.[16] Within this framework, our present findings also coherently integrate into the other previous data of the altered intrinsic activity in BD. In particular, ReHo was previously investigated in BD during the depressive phase only, mainly detecting increased ReHo in regions belonging to the DMN and decreased ReHo in sensorimotor areas.[32–34] Few previous studies investigated DC in BD, detecting reduced values in temporal and ventral prefrontal cortices, while increased values in anterior cingulate, frontal, and parietal areas.[35,36] However, these data were obtained in BD samples regardless of the phase of illness, making it difficult to distinguish the relationship of such DC changes with manic or depressive states. When investigating bipolar depressed patients, DC was found to be increased in the precuneus.[37] Thus, our result of decreased ReHo in the SMN during depression is consistent with such previous

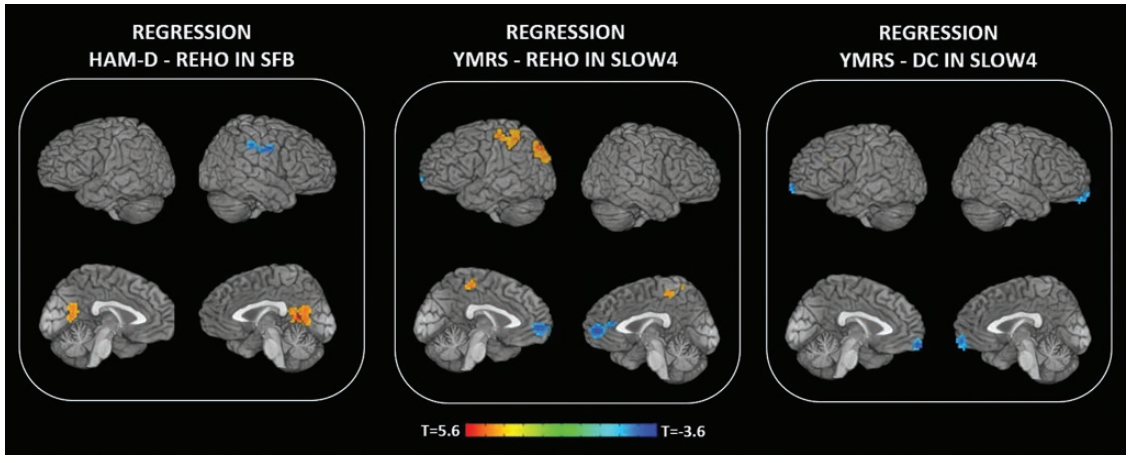

Fig. 3. Clinical correlations. Whole-brain voxel-wise regression analysis of ReHo in SFB with HAM-D total score, ReHo in Slow4 with YMRS total score, and DC in Slow4 with YMRS total score ($P < .01$, FWE < 0.05). *Note:*: ReHo, regional homogeneity; DC, degree of centrality; HAM-D, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; SFB, standard frequency band.

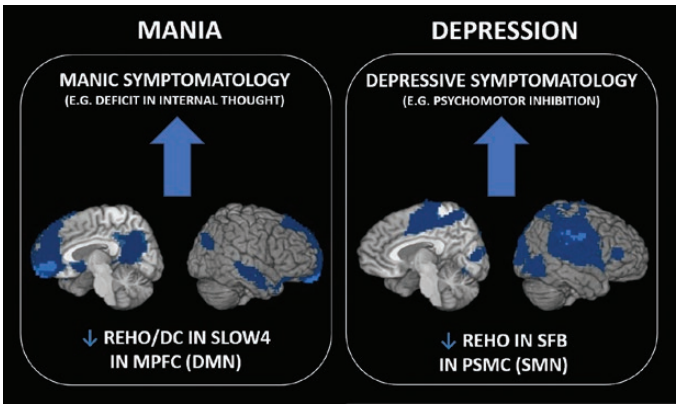

Fig. 4. Schema. Summary of the main alterations in the functional architecture of intrinsic brain activity, along with their psychopathological correlates, in manic and depressive phases of bipolar disorder. *Note*: ReHo, regional homogeneity; DC, degree of centrality; MPFC, medial prefrontal cortex; PSMC, primary sensory-motor cortex; DMN, default-mode network; SMN, sensorimotor network; SFB, standard frequency band.

findings, while our result of decreased ReHo and DC in the DMN during mania extends and complements them in a coherent way. Moreover, this also coherently complements our previous findings of disrupted FC within the DMN[18,19] and greater global signal representation in the SMN,[17] as well as other previous observations of increased connectivity of DAN,[43] during mania.

These alterations in the spatial organization of intrinsic activity were also related to changes in the temporal structure, as higher and lower frequency ranges of signal oscillations were found to be differently affected. In particular, the reduction of ReHo and DC in the DMN in mania mainly occurred in Slow4. Complementally, in mania again, a reduction of PLE (reflecting a relative increase in power of higher frequencies like Slow4 over the lower frequencies, within the low-frequency range investigated in resting-state fMRI) was detected throughout frontal and SMN areas. These data may suggest a deficit of faster frequencies like Slow4 within the DMN, along with their relative increase in frontal and sensory-motor areas, to occur in mania, potentially reflecting in increased contribution of sensorimotor processing within the global intrinsic activity (considering that Slow4 is stronger throughout the sensorimotor regions in healthy subjects).[4,26,27,29–31] Conversely, no specific contribution of Slow4 or Slow5 was detected during depression.

In turn, such alterations in the spatiotemporal organization of intrinsic activity may reflect in correspondent psychopathological symptomatology, as recently described in "Spatiotemporal psychopathology".[44–47] Decreased ReHo and DC in Slow4 in the DMN correlated with manic score, while decreased ReHo in SFB in the SMN correlated with the depressive score. Moreover, at symptom level, a reduction in centrality of the DMN (which is involved in internal thought) within the global intrinsic activity correlated with distractibility/flight of ideas, which may reflect a decrease in centrality of internal thought and correspondent predominance of externally focused thought. On the other hand, increased local integration of intrinsic activity within the SMN (which is involved in sensory awareness and motor functions) correlated with hyperactivity, reflecting an external/environmental-related sensorimotor processing and psychomotor excitation. Accordingly, we can suppose that a deficit of the DMN connectivity may account for a deficit of internal thought in mania, while a deficit of the SMN connectivity may account for psychomotor inhibition in depression.

Limitations

The main limitation of the present study was the possible confounding effects of medication. However, the clusters showing a significant correlation between medications and ReHo or DC values in whole-brain voxel-wise regression analysis did not overlap with any of our main results, suggesting that pharmacological therapy did not affect our ReHo and DC findings in mania and depression. See Supplementary Material, as well as supplementary figure 9 and supplementary table 7.

Another important issue is the reliability of the results, which is increasingly recognized as critical in neuroimaging and neuroscience in general. Intra-scan and inter-scan test-retest reliabilities have been investigated in different voxel-wise metrics and within different resting-state networks. Zuo and colleagues compared test-retest reliabilities of various resting-state metrics.[48] Notably, ReHo has shown robust test-retest reliability.[48] Conversely, a lower intra-class correlation has been shown for graph analysis-derived centrality metrics, like DC, compared with other resting-state metrics.[48] From a network perspective, DMN, CEN, and DAN displayed higher test-retest reliability than primary sensory and motor networks.[48] Accordingly, our results on ReHo alterations can be considered robust from this point of view. Moreover, our results on DC alterations in mania lie mainly in the DMN, partially mitigating the intrinsically lower reliability of this measure. However, this study did not provide multiple scans for a direct measure of test-retest reliability in the sample. Moreover, considering that large sample-size positively influences reliability,[49] it should be noted that patient groups in the present study were relatively small compared with the large brain imaging data samples available for healthy and other diseases.[50,51] However, to the best of our knowledge, our sample is one of the largest available samples including all the different phases of BD (mania, depression, euthymia). Furthermore, it is composed of real-world patients with severe disease (the vast majority of them were hospitalized at the time of study participation). Some clinical constraints should be also considered for BD. For instance, the intrinsic phasic

course of BD could make the reliability measurement relatively less valid when multiple scans are acquired distant in time.

Certainly, future studies are needed to confirm the present findings on a larger sample, with longer scan duration and better spatiotemporal resolution, importantly considering multiple scans within the same phase of illness (and ideally also acquiring measurements of physiological variables).[48,49,52]

Conclusion

The results of this study suggest a spatiotemporal reorganization of the functional architecture of intrinsic brain activity to occur in BD, with distinct changes in mania and depression. Mania is associated with a deficit in both local and distant connectivity of the DMN (ie, reduced ReHo and DC), mainly involving faster frequencies (ie, Slow4). The resulting functional architecture of intrinsic activity may thus favor a predominance of sensorimotor networks over the associative networks, reflecting in a behavioral pattern characterized by reduced internal thought and increased psychomotor activity. By contrast, depression is associated with a deficit in local connectivity of the SMN (ie, reduced ReHo). This functional architecture of resting-state activity may thus favor a predominance of the associative networks over the sensorimotor networks, reflecting in a behavioral pattern characterized by reduced psychomotor activity and increased internal thought.

This model may yield novel insight into the neurobiological background of BD, suggesting a link between distinct patterns of intrinsic brain activity and psychopathology, and, on the other hand, helping to elucidate the pathophysiology of the illness, a fundamental step in the developing of more specific and effective treatments.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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