**Supplementary information**

**Brain functional changes across mood states in bipolar disorder: from a large-scale network perspective**

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# Supplementary methods

## MRI data acquisition

Participants were scanned on a 3-Tesla Siemens Trio MR scanner in the 306th Hospital. The functional images scanning lasted seven minutes by using the T2-weighted gradient-echo echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; in-plane resolution of 3.3 × 3.3 mm2; matrix of 64 × 64; field of view (FOV) of 210 × 210 mm2; flip angle of 90°; 30 slices; 210 volumes; and a thickness/gap of 4.0 mm/0.8 mm. The structural images were obtained by using a T1-weighted, magnetization-prepared, rapidly acquired gradient-echo (MPRAGE) sequence with the following parameters: TR = 2300 ms; echo time (TE) = 3.01 ms; in-plane resolution of 1.0 × 1.0 mm2; matrix of 256 × 256; field of view (FOV) of 240 × 256 mm2; flip angle of 9°; 176 slices; and a thickness of 1.0 mm. During the resting-state scanning procedure, participants were instructed to relax with their eyes closed, to avoid head motion and to not fall asleep. A simple questionnaire was performed to confirm that the participants had followed the instructions. Only eligible participants were included in the study.

## MRI data preprocessing

The MRI data were preprocessed via the DPABISurf toolbox (DPABISurf\_V1.2\_190919, <http://rfmri.org/DPABISurf>) (Yan, Wang, & Lu, 2021), which is based on fMRIPrep (Esteban et al., 2019), FreeSurfer (Dale, Fischl, & Sereno, 1999), ANTs (Avants BB, 2009), FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki), AFNI (Cox, 1996), SPM (Ashburner, 2012), PALM (Winkler, Ridgway, Webster, Smith, & Nichols, 2014), dcm2niix (X. Li, Morgan, Ashburner, Smith, & Rorden, 2016), GNU Parallel (Tange, 2011), DPABI (Yan, Wang, Zuo, & Zang, 2016), MATLAB (The MathWorks Inc., Natick, MA, US) and Docker (http://docker.com). After removing the first 10 volumes of functional images, the functional and structural images were converted into BIDS format. The structural images were processed as follows: the T1-weighted image was corrected for intensity nonuniformity with N4BiasFieldCorrection (Tustison et al., 2010); the corrected T1-weighted image was then skull-stripped with ANTs (Avants BB, 2009); fast (FSL 5.0.9) (Zhang, Brady, & Smith, 2001) was used to segment brain tissue into cerebrospinal fluid (CSF), white-matter (WM) and gray matter (GM); recon -all (FreeSurfer 6.0.1) (Dale et al., 1999) was used to reconstruct brain surfaces; ANTs-derived brain masks and FreeSurfer-derived segmentations of the cortical GM were reconciled using a custom variation of the method of Mindboggle (Klein et al., 2017); nonlinear registration with antsRegistration (ANTs 2.3.3) was performed for the volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) (Fonov, Evans, McKinstry, Almli, & Collins, 2009), using brain-extracted versions of both T1w reference and the T1w template. The functional images were processed as follows: a reference volume and its skull-stripped version were generated with a custom methodology of fMRIPrep; the blood oxygen level-dependent (BOLD) reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve & Fischl, 2009); co-registration was configured with six degrees of freedom; head motion parameters with respect to BOLD reference (i.e., transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9); the BOLD time-series were slice-time corrected using 3dTshift from AFNI 20160207 (RRID:SCR\_005927) (Cox, 1996); the BOLD time-series were resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space; confounding time-series were calculated based on the preprocessed BOLD time-series that were in the original space: framewise displacement (FD, measured by Jenkinson method (Jenkinson, Bannister, Brady, & Smith, 2002)), derivative of root mean square variance (DVARS) and three region-wise timeseries (extracted from the CSF, the WM, and the whole-brain masks); then nuisance covariates were regressed out from the BOLD time-series, including the Friston-24 parameters of head motion (Friston, Williams, Howard, Frackowiak, & Turner, 1996), timeseries extracted from the CSF and WM, and linear trends. Finally, the functional images were bandpass temporally filtered (0.01-0.1 Hz) and spatially smoothed by using a 6 mm full width at half maximum. To minimize head motion effects on the data, we set a rigorous exclusion criterion for head motion (max translation > 3 mm in each direction, max rotation > 3°in each direction, mean FD > 0.3 mm). Participants with over-threshold head motion were excluded.

## Methodological validations on large-scale network connections

*Scrubbing*

In the above processing procedures, the 24 Friston head motion parameters were regressed out in nuisance regression. Nevertheless, considering that head motion has a vital impact on fMRI data, we processed the fMRI data with scrubbing method to minimize the head motion effect on network connections. Two strategies can be employed, i.e., volume removing and spike regression. In view of concern that volume removing may result in different numbers of volumes across subjects, thereby impacting the accuracy of FC, we used the overthreshold time points as separate regressors (Yan et al., 2013). The overthreshold time points were defined as over 0.3 mm mean frame-wise displacement measured by Jenkinson method (Jenkinson et al., 2002). Cross-sectional and longitudinal large-scale network functional connectivity comparison analyses were replicated as described above.

*Another brain atlas*

Considering that different brain parcellations impact measures of functional connectivity and brain-behavior association (Bryce et al., 2021), we replicated the large-scale network FC comparison analysis using the Dosenbach’s 160 brain atlas (Dosenbach et al., 2010) to confirm the robustness and generalizability of our findings on large-scale network FC. The brain atlas was generated based on a series of meta-analyses of task-based fMRI studies, consisting of 160 cortical regions, which were divided into similar brain networks. To reduce the effects of incomplete coverage of the cerebellum, 18 regions were specifically removed (L. Li et al., 2021). Because the limbic network defined by Yeo et al. is not covered by this brain atlas, we used the subcortical network (SCN) instead. Cross-sectional and longitudinal large-scale network functional connectivity comparison analyses were replicated as described above.

# Supplementary results

The confounding effects of medication should be concerned with caution. To investigate the eventual impact of medication status on functional network connections, we compared the 28 connections by using two-sample *t*-tests between the medicated patients and non-medicated patients in all BD patients in the cross-sectional sample at the time of scanning. We found no significant differences between medicated BD patients (n = 109) and non-medicated BD patients (n = 53) after FDR correction (Table S13).

To control for the potential impact of the number of current uses of different treatments, we repeated the analysis of covariance (ANCOVA) on the 28 connections, with sex, age, educational years, head motion, and number of current uses of mood stabilizers, antidepressants and antipsychotics as covariates. False Discovery Rate (FDR) was applied to correct for multiple comparisons. Post hoc two-sample *t*-tests were performed in significant network FCs with Bonferroni correction. All the findings were replicated except the VN-LN FC (Figure S2).

## Methodological validations of large-scale network connections

*Scrubbing*

For cross-sectional group analyses, the results of ANCOVA and post hoc analyses were all replicated using scrubbing during processing (Figure S3). Significant differences were observed in all between-network and within-network functional connectivities (FCs) among BDD, BDM, BDE patients and HCs. All between-network and within-network FCs were increased in BDM patients compared with BDD and BDE patients, but the number of increased FCs was less when comparing BDM patients with HCs. Compared with HCs, BDD patients showed decreased FC within LN. No significant differences were found between BDE patients and HCs.

For longitudinal group analyses replicated using scrubbing during processing, the main effect of episode was found in LN-VN, LN-SMN and LN-VAN FC (Figure S5).

*Another brain atlas*

For cross-sectional group analyses, the results of ANCOVA and post hoc analyses were mainly replicated using the Dosenbach’s 160 brain atlas to construct FC matrix except the LN-related FC (Figure S4). Significant network FC differences were observed among BDD, BDM, BDE patients and HCs in VN-DAN, VN-FPN, DMN-VN, DMN-SMN, DMN-DAN, DMN-VAN, DMN-SCN, DMN-FPN, within VN, within SMN and within DMN (Figure S4a). No significant differences were found in BDE patients and BDD patients compared with HCs (Figure S4b, c). Compared with BDD, BDE patients and HCs, BDM patients showed uniquely increased FCs in VN-DAN, DMN-related between-network pairs and within VN (Figure S4d, e, f). BDM patients showed increased VN-FPN FC compared with BDD and BDE patients, but not HCs. Increased within-SMN FC was found in BDM patients compared with BDD patients and HCs, but not BDD patients.

For longitudinal group analyses replicated using the Dosenbach’s 160 brain atlas, no significant main effect of episode was observed (Figure S5).

# Supplementary tables

Table S1. Demographic and clinical information.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| A. Subjects in cross-sectional cohort | | | | |  |  |  |
|  | BDD  (n = 65) | BDM  (n = 33) | BDE  (n = 64) | HC  (n = 80) | Statistic | *P* | Post hoc |
| Sex [female, N (%)] | 41 (63.1) | 15 (45.5) | 39 (60.9) | 58 (72.5) | *χ2* = 7.59 | 0.055 | – |
| Age [years, M (SD)] | 27.98 (7.63) | 30.64 (8.10) | 30.98 (9.68) | 28.99 (10.42) | *F* = 1.38 | 0.249 | – |
| Education [years, M (SD)] | 15.45 (3.24) | 14.73 (3.10) | 14.81 (3.12) | 15.55 (1.59) | *F* = 1.36 | 0.255 | – |
| Mean FD  [M (SD)] | 0.13 (0.06) | 0.12 (0.07) | 0.12 (0.07) | 0.11 (0.05) | *F* = 1.25 | 0.294 | – |
| Age at first episode  [years, M(SD)] | 21.66 (7.27) | 21.69 (6.40) | 23.15 (7.87) | – | *F* = 0.69 | 0.503 | – |
| Duration of current acute episode [days, M (SD)] | 121.34 (165.08) | 40.93 (42.88) | – | – | *T* = 3.59 | 0.001 | BDD>BDM |
| Number of subjects with no more than 3 prior episodes  [N (%)] \* | 32 (53.3) | 18 (66.7) | 31 (60.8) | – | *χ2* = 1.51 | 0.470 | – |
| Number of subjects with no more than 3 prior depressive episodes [N (%)] \* | 43 (72.9) | 23 (85.2) | 47 (92.2) | – | *χ2* = 7.20 | 0.027 | BDE>BDD |
| Number of subjects with no more than 3 prior (hypo)manic episodes [N (%)] \* | 49 (84.5) | 24 (82.8) | 48 (94.1) | – | *χ2* = 3.16 | 0.206 | – |
| YMRS score [M (SD)] | 0.82 (1.32) | 20.97 (7.31) | 0.50 (1.22) | – | *F* = 449.75 | <0.001 | BDM>BDD, BDE |
| HRSD score [M (SD)] | 22.95 (4.75) | 3.45 (3.31) | 1.59 (1.75) | – | *F* = 672.17 | <0.001 | BDD>BDM>BDE |
| PANAS-PA score [M (SD)] # | 18.25 (3.59) | 34.56 (9.63) | 26.53 (5.72) | – | *F* = 74.12 | <0.001 | BDM>BDE>BDD |
| PANAS-NA score [M (SD)] # | 31.32 (6.63) | 25.15 (9.47) | 18.98 (6.39) | – | *F* = 44.42 | <0.001 | BDD>BDM>BDE |
| Mood stabilizers [N (%)] # | 14 (40.0) | 9 (64.3) | 33 (70.2) | – | *χ2* = 7.77 | 0.021 | BDE>BDD |
| Antidepressants [N (%)] # | 21 (60.0) | 2 (14.3) | 17 (36.2) | – | *χ2* = 9.74 | 0.008 | BDD>BDM |
| Antipsychotics [N (%)] # | 16 (45.7) | 10 (71.4) | 29 (61.7) | – | *χ2* = 3.43 | 0.180 | – |
| Unmedicated [N (%)] | 28 (43.1) | 17 (51.5) | 8 (12.5) | – | *χ2* = 20.35 | <0.001 | BDD, BDM>BDE |
| B. Subjects in longitudinal sample | | | | | Statistic | | *P* |
| Sex [male/female, M (SD)] | 9/2 | | | | – | | – |
| Age at first scan (years, M (SD)) | 28.09 (11.58) | | | | – | | – |
| Education at first scan [years, M (SD)] | 14.36 (2.34) | | | | – | | – |
| Time between scans [months, M (SD)) | 3.71 (5.98) | | | | – | | – |
|  | Non-(hypo)manic state | | (Hypo)manic state | |  | |  |
| Mean FD [M (SD)] | 0.13 (0.07) | | 0.13 (0.05) | | *t* = 0.28 | | 0.785 |
| YMRS score [M (SD)] | 1.64 (2.69) | | 17.00 (6.74) | | *t* = -7.88 | | <0.001 |
| HRSD score [M (SD)] | 11.55 (9.87) | | 4.27 (4.69) | | *t* = 2.39 | | 0.038 |

\* Number of prior episodes were recorded as a categorical variable using three as threshold because multiple episodes suggested poor prognosis and smaller grey matter volume(Akiskal, 1996; Ekman, Lind, Ryden, Ingvar, & Landen, 2010; Suppes, Dennehy, & Gibbons, 2000). # Due to data collection error, the number of invalid values is as follows: PANAS-PA and PANAS-NA score (n = 17), medication information (2 for BDD, 2 for BDM, 9 for BDE; percentage was calculated as number of patients using corresponding medication divided by number of patients with valid medication information record). Abbreviations: M, mean; SD, standard deviation, YMRS, the Young Mania Rating Scale; HRSD, the 17-item Hamilton Rating Scale for Depression; FD, frame-wise displacement; PANAS, the Positive And Negative Affect Schedule.

Table S2. Episode and current medication information for the longitudinal sample.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | First scan | | Second scan | |
|  | episode | medication | episode | medication |
| P1 | manic | unmedicated | depressive | unmedicated |
| P2 | manic | unmedicated | euthymic | 1 mood stabilizer |
| P3 | hypomanic | 1 psychotic | euthymic | 1 psychotic, 2 mood stabilizers |
| P4 | hypomanic | 1 psychotic, 1 antidepressant | depressive | 2 mood stabilizers |
| P5 | hypomanic | 1 psychotic, 2 mood stabilizers | depressive | 1 psychotic, 1 antidepressant, 1 mood stabilizer |
| P6 | manic | 1 psychotic | euthymic | 1 psychotic |
| P7 | depressive | 1antidepressant, 1benzodiazepine | hypomanic | 1 antidepressant, 2 mood stabilizers |
| P8 | manic | 1 mood stabilizer | euthymic | 1 mood stabilizer |
| P9 | depressive | 2 antidepressants, 1 mood stabilizer | manic | unmedicated |
| P10 | manic | 1 psychotic, 1 mood stabilizer | euthymic | 1 psychotic, 1 mood stabilizer |
| P11 | manic | 1 psychotic, 1 mood stabilizer | depressive | 1 psychotic, 1 mood stabilizer |

P1-P11 indicate the 11 patients in the longitudinal sample.

Table S3. Large-scale network FC differences between BPM, BPD, BPE and HC.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | VN | SMN | DAN | VAN | LN | FPN | DMN |
| VN | 3.535\* |  |  |  |  |  |  |
| SMN | 2.418 | 2.962 |  |  |  |  |  |
| DAN | 4.507\* | 1.606 | 2.700 |  |  |  |  |
| VAN | 2.811 | 1.549 | 1.577 | 2.151 |  |  |  |
| LN | 3.649\* | 3.851\* | 2.204 | 5.570\* | 5.294\* |  |  |
| FPN | 4.884\* | 2.436 | 1.903 | 3.437\* | 4.941\* | 2.644 |  |
| DMN | 4.710\* | 4.836\* | 3.901\* | 5.128\* | 6.109\* | 6.284\* | 4.958\* |

The *F* values of ANCOVA are shown. Abbreviations: VN, visual network; SMN, somatosensory network; DAN, dorsal attention network; VAN, ventral attention network; FPN, frontoparietal network; DMN, default mode network. \*, significant after FDR correction to *P* < 0.05 among the 28 network connections.

Table S4. Increased large-scale network FCs in BDM patients compared to BDD patients.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | VN | SMN | DAN | VAN | LN | FPN | DMN |
| VN | 2.380\* |  |  |  |  |  |  |
| SMN | 2.267 | 2.918 |  |  |  |  |  |
| DAN | 3.216\* | 2.008 | 2.409 |  |  |  |  |
| VAN | 2.016 | 1.962 | 1.702 | 2.461 |  |  |  |
| LN | 2.103 | 3.043 | 2.146 | 3.576\* | 2.443\* |  |  |
| FPN | 3.201\* | 2.516 | 2.229 | 3.149\* | 3.528\* | 2.742 |  |
| DMN | 2.972\* | 3.261\* | 2.893\* | 3.118\* | 3.693\* | 3.785\* | 3.436\* |

The *t* values of two-sample *t*-tests on FC between BD-M and BD-D patients. \*, significant after Bonferroni correction.

Table S5. Increased large-scale network FCs in BDM patients compared to BDE patients.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | VN | SMN | DAN | VAN | LN | FPN | DMN |
| VN | 3.082\* |  |  |  |  |  |  |
| SMN | 1.770 | 1.719 |  |  |  |  |  |
| DAN | 3.073\* | 1.406 | 2.313 |  |  |  |  |
| VAN | 2.122 | 1.557 | 1.640 | 1.752 |  |  |  |
| LN | 2.073 | 2.231 | 1.913 | 3.388\* | 1.986 |  |  |
| FPN | 2.919\* | 2.033 | 1.718 | 2.393\* | 3.218\* | 1.872 |  |
| DMN | 2.955\* | 3.055\* | 2.764\* | 3.303\* | 3.394\* | 3.661\* | 3.111\* |

The *t* values of two-sample *t*-tests on FC between BDM and BDE patients. \*, significant after Bonferroni correction.

Table S6. Decreased large-scale network FCs in BDM patients compared to HCs.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | VN | SMN | DAN | VAN | LN | FPN | DMN |
| VN | 1.750 |  |  |  |  |  |  |
| SMN | 1.008 | 1.381 |  |  |  |  |  |
| DAN | 2.126\* | 1.309 | 1.212 |  |  |  |  |
| VAN | 0.624 | 0.897 | 1.317 | 1.303 |  |  |  |
| LN | -0.092 | 0.314 | 0.437 | 1.375 | -0.044 |  |  |
| FPN | 2.062\* | 1.499 | 0.967 | 1.765\* | 2.145 | 0.953 |  |
| DMN | 2.136\* | 2.318\* | 2.252\* | 2.151\* | 2.428\* | 2.521\* | 2.019 |

The *t* values of two-sample *t*-tests on FC between BDM patients and HCs. \*, significant after Bonferroni correction.

Table S7. Decreased large-scale network FCs in BDD patients compared to HCs.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | VN | SMN | DAN | VAN | LN | FPN | DMN |
| VN | -0.895 |  |  |  |  |  |  |
| SMN | -1.890 | -1.774 |  |  |  |  |  |
| DAN | -1.183 | -0.672 | -1.129 |  |  |  |  |
| VAN | -1.587 | -0.855 | -0.100 | -0.917 |  |  |  |
| LN | -2.605 | -2.615 | -1.681 | -1.952 | -3.610\* |  |  |
| FPN | -0.900 | -0.623 | -1.062 | -0.917 | -0.940 | -1.736 |  |
| DMN | -1.364 | -1.293 | -0.797 | -1.056 | -1.661 | -0.991 | -1.603 |

The *t* values of two-sample *t*-tests on FC between BDD patients and HCs. \*, significant after Bonferroni correction.

Table S8. Decreased large-scale network FCs in BDE patients compared to HCs.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | VN | SMN | DAN | VAN | LN | FPN | DMN |
| VN | -1.379 |  |  |  |  |  |  |
| SMN | -0.842 | -0.110 |  |  |  |  |  |
| DAN | -1.060 | 0.343 | -1.009 |  |  |  |  |
| VAN | -1.602 | -0.160 | -0.025 | -0.265 |  |  |  |
| LN | -2.227 | -1.570 | -1.268 | -1.806 | -2.341 |  |  |
| FPN | -1.194 | -0.074 | -0.566 | -0.449 | -0.811 | -0.717 |  |
| DMN | -0.953 | -0.436 | -0.209 | -0.956 | -0.856 | -0.695 | -0.726 |

The *t* values of two-sample *t*-tests on FC between BDE patients and HCs. No connections show significant differences after Bonferroni correction.

Table S9. Decreased large-scale network FCs in BDE patients compared to BDD patients.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | VN | SMN | DAN | VAN | LN | FPN | DMN |
| VN | -0.147 |  |  |  |  |  |  |
| SMN | 1.058 | 1.719 |  |  |  |  |  |
| DAN | 0.305 | 1.116 | 0.099 |  |  |  |  |
| VAN | -0.125 | 0.759 | 0.045 | 0.767 |  |  |  |
| LN | -0.027 | 0.860 | 0.144 | -0.055 | 0.415 |  |  |
| FPN | -0.445 | 0.603 | 0.509 | 0.703 | -0.128 | 1.111 |  |
| DMN | -0.054 | 0.820 | 0.537 | 0.121 | 0.288 | 0.194 | 0.538 |

The *t* values of two-sample *t*-tests on FC between BDE patients and BDD patients. No connections show significant differences after Bonferroni correction.

Table S10. The *F* values of the main effect of episode in the mixed effect model on network FCs.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | VN | SMN | DAN | VAN | LN | FPN | DMN |
| VN | 1.894 |  |  |  |  |  |  |
| SMN | 4.417 | 1.501 |  |  |  |  |  |
| DAN | 2.261 | 0.509 | 1.195 |  |  |  |  |
| VAN | 11.821 | 1.674 | 5.388 | 2.142 |  |  |  |
| LN | 13.104\* | 13.332\* | 8.701 | 25.425\* | 0.620 |  |  |
| FPN | 1.796 | 3.720 | 3.465 | 4.328 | 2.997 | 2.944 |  |
| DMN | 0.657 | 5.566 | 4.730 | 9.694\* | 2.786 | 5.704 | 4.752 |

\*, significant after FDR correction to *P* < 0.05 among the 16 significant network connections.

Table S11. Partial correlations between each FC and each clinical measurement score.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | DMN-LN FC | DMN-VAN FC | DMN-VN FC | DMN-SMN FC | DMN-DAN FC | DMN-FPN FC | Within DMN FC | Within VN FC | VN-DAN FC | VN-FPN FC |
| HRSD-17 score a | -0.103 | -0.065 | -0.053 | -0.090 | -0.080 | -0.101 | -0.117 | -0.068 | -0.091 | -0.034 |
| YMRS score a | 0.331\*\* | 0.320\*\* | 0.320\*\* | 0.338\*\* | 0.306\*\* | 0.370\*\* | 0.318\*\* | 0.246\* | 0.292\*\* | 0.303\*\* |
| PANAS-PA score b | 0.261\* | 0.269\* | 0.230\* | 0.245\* | 0.217\* | 0.235\* | 0.217\* | 0.265\* | 0.244\* | 0.197\* |
| PANAS-NA score b | -0.002 | 0.002 | 0.017 | -0.032 | 0.013 | 0.033 | -0.008 | -0.017 | -0.007 | 0.094 |

Significant correlation values (*r*) of each FC and each clinical measurement score. a *r*（156）, the partial correlation analyses were conducted among all BD patients. b *r*（139）, the partial correlation analyses were conducted among BD patients with valid data of the PANAS. \*, FDR-corrected *P* < 0.05. \*\*, FDR-corrected *P* < 0.001.

Table S12. Partial correlations between the area under the curve (AUC) parameter of nodal degree in each of the 14 brain regions and each clinical measurement score.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | HRSD-17 score a | YMRS score a | PANAS-PA score b | PANAS-NA score b |
| LH\_Vis\_7 | -0.044 | 0.352\*\* | 0.277\* | 0.038 |
| LH\_DorsAttn\_Post\_1 | -0.002 | 0.197\* | 0.149 | 0.036 |
| LH\_SalVentAttn\_ParOper\_2 | -0.108 | 0.285\*\* | 0.163 | -0.023 |
| LH\_Default\_Par\_5 | -0.115 | 0.287\*\* | 0.225 | -0.050 |
| LH\_Default\_pCunPCC\_1 | 0.063 | 0.253\* | 0.170 | -0.006 |
| LH\_Default\_pCunPCC\_2 | 0.111 | 0.306\*\* | 0.069 | -0.015 |
| LH\_Default\_pCunPCC\_5 | 0.054 | 0.344\*\* | 0.174 | 0.065 |
| RH\_SomMot\_2 | -0.147 | 0.394\*\* | 0.293\* | -0.076 |
| RH\_DorsAttn\_Post\_3 | -0.038 | 0.311\*\* | 0.180 | -0.024 |
| RH\_DorsAttn\_Post\_4 | 0.061 | 0.235\* | 0.101 | 0.046 |
| RH\_Cont\_pCun\_1 | 0.166 | 0.256\* | 0.012 | 0.157 |
| RH\_Default\_Par\_2 | -0.013 | 0.343\*\* | 0.138 | -0.019 |
| RH\_Default\_pCunPCC\_1 | 0.050 | 0.345\*\* | 0.150 | 0.056 |
| RH\_Default\_pCunPCC\_3 | 0.115 | 0.249\* | 0.027 | -0.056 |

Significant correlation values (*r*) between the AUC parameter of nodal degree in each of the 14 brain regions and each clinical measurement score. a *r(*156）, the partial correlation analyses were conducted among all BD patients. b *r*(139）, the partial correlation analyses were conducted among BD patients with valid data of the PANAS. \*, FDR-corrected *P* < 0.05. \*\*, FDR-corrected *P* < 0.001. The brain regions are reported according to Yeo et al.(Yeo et al., 2011). LH, left hemisphere; RH, right hemisphere; Default, default mode network; Vis, visual network; SomMot, somatosensory network; DorsAttn, dorsal attention network; SalVenAttn, ventral attention network; Cont, control network, i.e., frontoparietal network; Post, posterior; ParOper, parietal operculum; Par, parietal; pCunPCC, precuneus/posterior cingulate cortex.

Table S13. The *t* values of two-sample *t*-tests on FC between BD patients who were in treatment and those who were not.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | VN | SMN | DAN | VAN | lN | FPN | DMN |
| VN | -2.28 |  |  |  |  |  |  |
| SMN | -1.55 | -0.98 |  |  |  |  |  |
| DAN | -0.83 | -1.13 | -1.35 |  |  |  |  |
| VAN | -0.45 | -0.47 | -0.86 | -0.61 |  |  |  |
| LN | -1.49 | -1.31 | -1.48 | -1.06 | -0.37 |  |  |
| FPN | -0.51 | -0.92 | -0.76 | -0.63 | -1.42 | -0.72 |  |
| DMN | -1.83 | -1.61 | -1.39 | -0.67 | -1.38 | -1.36 | -1.43 |

No connections show significant differences after FDR-correction to *P <* 0.05.

# Supplementary figures

Figure S1. Between-group differences in the significant network functional connectivity (FC) among different mood states of patients with bipolar disorder and healthy controls. Post-hoc analyses in significant network FCs were conducted using two-sample *t*-tests with Bonferroni correction. **\***, Bonferroni-corrected *P* < 0.05.

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**Figure S2. Cross-sectional comparison for large-scale network functional connectivity (FC) in the main sample controlling for the number of different treatments currently in use.** (a) The *F* values of cross-sectional four group comparison on large-scale network FC. Other heatmaps show the *t* values of network FC for five contrasts: (b) BDM vs. BDD, (c) BDM vs. BDE, and (d) BDM vs. HC, (e) BDD vs. HC, (f) BDE vs. HC. For four-group comparison, the results were corrected for multiple comparison using FDR. For post hoc analyses, the results were corrected for multiple comparisons using Bonferroni correction. \*, *P*corrected < 0.05.

图片包含 游戏机, 画

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Figure S3. Cross-sectional comparison for large-scale network functional connectivity (FC) using scrubbing during processing. (**a)** The *F* values of cross-sectional four group comparison on large-scale network FC. Other heatmaps show the *t* values of network FC for five contrasts: (b) BDM vs. BDD, (c) BDM vs. BDE, and (d) BDM vs. HC, (e) BDD vs. HC, (f) BDE vs. HC. For four group comparison, the results were corrected for multiple comparison using FDR. For post hoc analyses, the results were corrected for multiple comparisons using Bonferroni correction. \*, *P*corrected < 0.05.



Figure S4. Cross-sectional comparison for large-scale network functional connectivity (FC) using the Dosenbach’s 160 brain atlas. (**a**) The *F* values of cross-sectional four group comparison on large-scale network FC. Other heatmaps show the *t* values of network FC for five contrasts: (**b**) BDM vs. BDD, (**c**) BDM vs. BDE, and (**d**) BDM vs. HC, (**e**) BDD vs. HC, (**f**) BDE vs. HC. For four group comparison, the results were corrected for multiple comparison using FDR. For post hoc analyses, the results were corrected for multiple comparisons using Bonferroni correction. \*, *P*corrected < 0.05. SCN, subcortical network.



Figure S5. The main effect of episode in the mixed effect model on FC for each pair of networks between (hypo)manic episode and non-(hypo)manic episode using the Dosenbach’s 160 brain atlas and using scrubbing during processing. The *F* and *P* values are showed. FDR correction was performed in the 16 significant network FCs. \*, significant after FDR correction to *P* < 0.05 among the 16 significant network connections.



Figure S6. Group differences in nodal degree among BDD, BDM, BDE patients and HCs. The violin plots show the area under the curve (AUC) parameters of nodal degree in the 14 brain regions with group differences in nodal degree. LH, left hemisphere; RH, right hemisphere; Default, default mode network; Vis, visual network; SomMot, somatosensory network; DorsAttn, dorsal attention network; SalVenAttn, ventral attention network; Cont, control network, i.e., frontoparietal network; Post, posterior; ParOper, parietal operculum; Par, parietal; pCunPCC, precuneus/posterior cingulate cortex.



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