***Dataset and Participants***

In this study, PBD patients met DSM-IV criteria for bipolar disorder and were interviewed by pediatric psychiatrists. The exclusion criteria for PBD participants were: (1) physical illness causing mental disorders; (2) pregnancy; (3) illegal substance use within 60 days prior to admission; (4) other specified bipolar spectrum disorders or BD not otherwise specified; (5) history of physical therapies, including Transcranial Magnetic Stimulation (TMS) and electroconvulsive therapy (ECT); and (6) intellectual disability. Patients with episodes of mania or hypomania, as well as those diagnosed with euthymic PBD with at least one month of remission, were included.

Age- and sex-matched healthy controls (HCs) were recruited through public school advertisements. Exclusion criteria for HCs included: (1) current or past psychiatric diagnosis; (2) family history of psychiatric disorders in first-degree relatives; (3) sustained physical or neurological conditions; and (4) current pregnancy.

***Dynamic causal modeling***

We employed the Spectral DCM approach using DCM 12.5, as implemented in SPM12 v7771, to estimate effective connectivity within and between networks. Spectral DCM is a computationally efficient method for estimating effective connectivity from resting-state time series, summarizing them in terms of cross-spectral density.

Dynamic Causal Modeling is a well-established approach for estimating the causal architecture (effective connectivity) of distributed neuronal responses from observed BOLD (Blood-Oxygen-Level-Dependent) signals recorded in fMRI. It is based on two key equations. The first is the neuronal state equation, which models changes in a neuronal state vector over time depending on directed connectivity within a distributed set of regions. In the context of DCM for cross-spectral density, these regions are influenced by endogenous fluctuations, the spectrum of which is estimated. The second equation is an empirically validated hemodynamic model that describes the transformation of neuronal states into BOLD responses (Bouziane et al., 2022).

The underlying neural state equation is written as follows:

(1)

The function is the neural model (i.e., a description of neuronal dynamics), is the rate of change of the neural states x, is the unknown connectivity parameters (i.e., intrinsic effective connectivity) and represents a stochastic process that models the endogenous neural fluctuations, which drive the resting state.

The hemodynamic model equation is used to translate the transformation of neuronal state into a BOLD response:

(2)

Here, the function k specifies the biophysical processes that transform neural activity x into the BOLD response with parameters plus the observation noise .

Spectral DCM offers a computationally efficient inversion of the pursuing models of resting-state fMRI. Spectral DCM simplifies the estimation of a generative model by fitting data features into the frequency domain (i.e., using Fourier transforms) instead of the original BOLD time series as employed in the DCM of evoked induced responses. By switching to second-order statistics (i.e., complex cross-spectra), spectral DCM circumvents the problem of estimating time-varying fluctuations in neuronal states and estimates their spectra, which is time-invariant. In other words, the problem of estimating hidden neuronal states disappears and is replaced by the problem of estimating their correlation functions of time or spectral densities over frequencies (and observation noise) that are much easier to parameterize and estimate. For this purpose, a scale-free (power law) form for the endogenous and error fluctuations is used (Bullmore et al., 2001) and is written as follows:

(3)

(4)

Here, are the parameters controlling the amplitudes and exponents of the spectral density of these random effects. A standard Bayesian model inversion (i.e., Variational Laplace) is used to infer the parameters of the models from the observed signal i.e., the parameters of the fluctuations and the effective connectivity. A detailed mathematical description of spectral DCM can be found in (K. Friston & Kiebel, 2009).

***Parametric Empirical Bayes (PEB) for group DCM***

The combined cohort was used to compare causal connections between the PBD and HC groups within the PEB framework. The group-level design matrix (GLM) encoded covariates (subject-specific parameters) in each column, with one row per subject. By default, the group mean is the first regressor or covariate in the GLM. For this study, covariates such as age, sex, comorbidity, and medication were included.

PEB models were then run separately for the PBD cohort. The effects of clinical severity (depression and mania, respectively) on the causal connections were tested in the PBD group, with age, sex, comorbidity, and medication included as nuisance covariates.

We used Bayesian model reduction (BMR) to explore the space of potential models that could explain the resting-state data for all subjects. BMR examines candidate models by removing one or more connections from a full or parent model (Stephan et al., 2010). It prunes connection parameters from the full model by scoring each reduced model based on its log model-evidence. Bayesian model averaging (BMA) was then used to average the parameters of the selected models, weighted by the posterior probabilities of all models(K. J. Friston, 2007).

A 95% posterior probability threshold was used to denote "strong evidence" for the parameters calculated by BMA. Evidence was approximated by the (negative) variational free energy (see Appendix 3 of Zeidman, Jafarian, Seghier, et al., 2019).

To assess effective connectivity strength from a network perspective, Bayesian contrasts were used to compute averaged network ECs, accounting for the entire posterior parameter distribution of each EC rather than relying on the arithmetic mean of parameter expectations. Bayesian contrasts were also applied to determine whether the posterior probability of connections between networks differed from zero, with self-connections set to zero (Nicenboim et al., 2023, https://github.com/bnicenboim/bcogsci), as previously employed (Z. Zhang et al., 2022; Zhou et al., 2018).

***Results of Bayesian contrasts***

Table S1 results of Bayesian Contrasts

|  |  |  |
| --- | --- | --- |
|  | Connections | Correlation |
| Similarity across all participants | DMN→DMN | 0.0033 |
| DMN→CEN | − 0.0042 |
| DMN→SN | 0.0022 |
| DMN→LN | 0.0046 |
| CEN→DMN | − 0.0026 |
| CEN→SN | − 0.0045 |
| CEN→LN | 0.0019 |
| SN→DMN | 0.0040 |
| SN→CEN | 0.0091 |
| SN→SN | 0.0015 |
| SN→LN | 0.0032 |
| LN→DMN | 0.0049 |
| LN→CEN | 0.0120 |
| LN→SN | 0.0043 |
| LN→LN | 0.0064 |
| Group difference | DMN→SN | 0.0031 |
| CEN→DMN | 0.0006 |
| SN→DMN | 0.0031 |
| SN→LN | 0.0012 |
| SN→SN | 0.0013 |
| LN→DMN | 0.0008 |
| LN→SN | 0.0030 |
| LN→LN | 0.0014 |
| Mania with YARS/MDQ | DMN→DMN | − 0.0161 |
| DMN→CEN | 0.0086 |
| DMN→SN | 0.0001 |
| DMN→LN | − 0.0050 |
| CEN→DMN | 0.0158 |
| CEN→CEN | − 0.0127 |
| CEN→SN | − 0.0043 |
| CEN→LN | 0.0503 |
| SN→DMN | 0.0134 |
| SN→CEN | − 0.0002 |
| SN→SN | − 0.0195 |
| SN→LN | − 0.0147 |
| LN→DMN | − 0.0088 |
| LN→CEN | 0.0038 |
| LN→SN | − 0.0015 |
| LN→LN | − 0.1171 |

Table S1 continued

|  |  |  |
| --- | --- | --- |
|  | Connections | Correlation |
| Depression with HAMD/MFQ | DMN→DMN | 0.014 |
| DMN→CEN | − 0.011 |
| DMN→SN | − 0.007 |
| DMN→LN | 0.006 |
| CEN→DMN | − 0.008 |
| CEN→CEN | 0.010 |
| CEN→SN | − 0.006 |
| CEN→LN | 0.036 |
| SN→DMN | − 0.006 |
| SN→CEN | − 0.011 |
| SN→SN | − 0.015 |
| SN→LN | 0.005 |
| LN→DMN | − 0.002 |
| LN→CEN | 0.016 |
| LN→SN | − 0.004 |
| LN→LN | 0.004 |

***Results of Cross validation***

Table S2 results of LOOCV

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Connections | Correlation | *p* value |
| Group differences | 1 | sgACC→Amyg\_R | 0.26 | 0.0012 |
| 2 | PCC-Precun→dACC\_L | 0.19 | 0.015 |
| 3 | dACC\_R→Angular\_R | 0.23 | 0.0045 |
| 4 | dACC\_R→Amyg\_R | 0.22 | 0.0062 |
| 5 | dACC\_L→Amyg\_R | 0.21 | 0.0083 |
| 6 | AI\_L→dACC\_R | 0.19 | 0.013 |
| 7 | AI\_L→dACC\_L | 0.29 | 0.0004 |
| 8 | Hippo\_R→dACC\_L | 0.28 | 0.0006 |
| 9 | Amyg\_R→dACC\_R | 0.21 | 0.0074 |
| 10 | Amyg\_L→sgACC | 0.18 | 0.018 |
| 11 | Amyg\_L→dACC\_R | 0.36 | < 0.0001 |
| 12 | Amyg\_L→dACC\_L | 0.28 | 0.0006 |
| 13 | Caudate\_L→Amyg\_R | 0.28 | 0.0006 |
| 14 | Caudate\_L→Amyg\_L | 0.24 | 0.0028 |
| 15 | Caudate\_R→IPL\_L | 0.15 | 0.044 |
| 16 | Caudate\_R→AI\_R | 0.20 | 0.010 |
| Mania with YARS/MDQ | 1 | Angular\_L→Caudate\_R | 0.11 | 0.015 |
| 2 | IPL\_R→Amyg\_R | 0.12 | 0.013 |
| 3 | Hippo\_R→Caudate\_L | 0.12 | 0.014 |
| 4 | Caudate\_L→Angular\_R | 0.13 | 0.012 |
| 5 | Caudate\_L→Hippo\_R | 0.13 | 0.012 |
| 6 | Caudate\_R→Angular\_R | 0.26 | 0.006 |
| Depression with HAMD/MFQ | 1 | sgACC→Angular\_R | 0.21 | 0.023 |
| 2 | sgACC→Angular\_L | 0.20 | 0.028 |
| 3 | Angular\_L→Hippo\_R | 0.20 | 0.035 |
| 4 | MFG\_R→dACC\_R | 0.33 | 0.001 |
| 5 | IPL\_L→IPL\_L | 0.31 | 0.002 |
| 6 | dACC\_R→MFG\_R | 0.33 | 0.001 |
| 7 | dACC\_R→Caudate\_R | 0.31 | 0.001 |
| 8 | AI\_L→PCC-Precun | 0.27 | 0.005 |
| 9 | AI\_L→Hippo\_R | 0.19 | 0.035 |
| 10 | AI\_R→Hippo\_R | 0.20 | 0.031 |
| 11 | Hippo\_R→Angular\_L | 0.23 | 0.013 |
| 12 | Hippo\_R→AI\_L | 0.20 | 0.031 |
| 13 | Hippo\_L→MFG\_R | 0.46 | < 0.0001 |

figure S1 The mania and depression severity relevant results of LOOCV. The left panel: mania severity of PBDs was relevant to the inhibitory connections about caudate. The right panel: depression severity of PBDs in hippocampus as three forms of models. The red panel represents the dorsal emotional circuitry, the purple panel represents the cortical insular-limbic network, and the green panel represents hippocampal-parietal network. The red circle, purple circles, green circles, and blue circle are the representative regions of CEN, SN, DMN and LN, respectively.

***Meta-Analysis Cognitive Terms Relevant to Caudate and Hippocampus***



figure S2 The specific posterior probability values of top terms relevant to the caudate and hippocampus.

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