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Dynamic functional network connectivity impairment in bipolar disorder and its relationship with global functioning

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ABSTRACT

Abnormal functional connectivity (FC) has been consistently associated with bipolar disorders (BD). Classical FC analyses assume stationarity of brain interactions, although connectivity actually varies over time. Here, we examined alterations in dynamic functional network connectivity (dFNC) in BD, their associations with symptom severity and global functioning, and potential differences between bipolar disorder type I (BD1) and type II (BD2).

In this case-control study, we investigated dFNC in 57 patients with BD (29 BD1, 28 BD2) and 43 healthy controls (HCs). Most patients were euthymic at scanning (~86 %), with only a minority showing residual depressive or hypomanic/mixed symptoms. Resting-state fMRI data were decomposed with spatially constrained independent component analysis and analyzed using a sliding-window approach. Meta-state metrics—number of meta-states, transitions, total distance, and span—were derived and compared across groups. Correlations with clinical measures and Global Assessment of Functioning (GAF) scores were tested. Dynamic metrics (number of meta-states, state transitions, and total distance) were reduced in BD relative to HCs, with the greatest reduction in BD1, followed by BD2. State span did not differ between groups. Across the BD sample, higher GAF scores were positively associated with greater dynamic fluidity, whereas no significant associations emerged with standard symptom scales.

In conclusion, BD is characterized by a graded disruption of the spatio-temporal dynamics of large-scale brain networks, most pronounced in BD1. Reduced neural flexibility is linked to poorer global functioning, suggesting that dFNC meta-state metrics may provide clinically relevant markers of illness burden in bipolar disorder.

1. Introduction

Bipolar disorder (BD) is a chronic mental health condition characterized by episodic alterations in energy, mood, cognitive, and psychomotor functions (Benazzi, 2007; Grande et al., 2016; Skjelstad et al., 2010; Solomon et al., 2010). BD is frequently unrecognized due to its heterogeneous clinical features resulting in delayed diagnosis, inadequate treatment, substantial medical costs, and high rates of comorbidity (Keramatian et al., 2025; Keck et al., 2008). Affecting approximately 1 % of the general population, it is a leading cause of disability (Oliva et al., 2025). Importantly, disability in BD is not confined to acute mood episodes and functional impairments often persist during clinical remission (Murru et al., 2018; Samalin et al., 2016).

Recent evidence highlights that many individuals with BD continue to experience significant difficulties in occupational, social, and cognitive domains, despite symptomatic recovery (Arvilommi et al., 2022; Huxley and Baldessarini, 2007). These enduring deficits, often referred to as "residual disability", are linked to factors such as cognitive dysfunction, subthreshold mood symptoms, low self-efficacy and poor illness insight, reinforcing the notion that remission in BD should not be defined solely by symptom reduction, but also by functional recovery (Baş et al., 2015; Burdick et al., 2022).

Increasing efforts have been made to understand the brain

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mechanisms associated with BD, and recent advances in the analysis of functional neuroimaging data have highlighted an important role of "functional connectivity" (FC) as a possible biomarker of psychiatric disorders, including BD (Claeys et al., 2022). FC is defined as the statistical dependence between fMRI blood oxygen level dependent (BOLD) signal of neuronal activation of two or more remote brain regions or networks and is usually estimated from the entire scan with an underlying assumption of the stationarity of the BOLD signal, the so-called static FC. Indeed, the BOLD signal undergoes several temporal-dependent reconfigurations, and the reciprocal interplay between regions or networks changes over time, thus proposing dynamic functional network connectivity (dFNC) "chronnectome" as being a more adequate framework of the brain physiology and pathophysiology (Allen et al., 2014; Calhoun et al., 2014; Hutchison et al., 2013; Miller et al., 2014; Preti et al., 2017).

Recent studies have shown dFNC changes in BD as reported in (Cattarinussi et al., 2023), even during euthymia, patients with BD exhibit persistent network-level instability, as shown by increased transitions between high-level cognitive and low-level sensory states (Du et al., 2021), suggesting an intrinsic alteration in the brain's ability to flexibly reconfigure over time. In the depressive phase, alterations in global and interhemispheric dFNC emerge prominently (Y. Yang et al., 2020). Previous dFNC studies in BD have reported alterations across multiple large-scale systems, including cortico-striatal, fronto-thalamic, salience, and emotion-related circuits, suggesting that BD is characterized by widespread dysregulation of functional integration rather than focal network abnormalities (Chen et al., 2022; Fateh et al., 2020; Liu et al., 2021; Pang et al., 2018; Tang et al., 2022). These findings collectively point to reduced flexibility and impaired coordination across distributed brain networks, consistent with a system-level dysfunction underlying affective and cognitive disturbances in BD.

Furthermore, dFNC changes can differ between diagnoses. Rashid et al. compared dFNC properties between schizophrenia, mixed psychotic and non-psychotic patients with BD, and HC, identifying different patterns of connectivity involving the fronto–parietal regions in diagnostic groups. Specifically, patients with BD tend to remain longer in "rigid" connectivity states characterized by reduced temporal variability, indicating decreased flexibility in the DMN, the SN, and the sensorimotor network, with a reduced frequency of transitions between distinct functional states (Rashid et al., 2014).

Furthermore, studies have demonstrated a continuum of symptoms in BD. This conceptualization is grounded in findings from genetic, neurocognitive, and neuroimaging studies, which suggest a gradual progression of dysfunction across these groups (Li et al., 2025; Thomas et al., 2019; Zheng, 2025). At the neuroimaging level, BD1 showed more abnormal functional connectivity of large-scale network — such as the DMN, fronto-parietal network (FPN), SN, and limbic system — compared with BD2 (Xiao et al., 2024).

Based on this framework, we hypothesized that several dynamic functional connectivity measures would exhibit monotonic changes from BD2 to BD1, reflecting increasing levels of neural dysregulation.

Global functioning is a multidimensional construct that reflects an individual's capacity to fulfill occupational, social, and educational roles. In BD, global functioning is often significantly impaired and this impairment is closely associated with neurocognitive deficits that are considered core, primary features of the disorder, rather than being secondary to mood states or medication effects (Fountoulakis, 2020).

Recent research has highlighted impairments not only in traditional domains of cold cognition but also in more complex areas of social cognition (Gillissie et al., 2022) including theory of mind (Bora et al., 2016; Mitchell and Young, 2016), facial affect recognition (Işık Ulusoy et al., 2020; Miola et al., 2024, 2022) and other aspects of social cognition (Bora and Pantelis, 2015; Samamé et al., 2015). These cognitive deficits are significantly correlated with patient functioning (Vlad et al., 2018) and are notably stable, remaining present even during long periods of euthymia, which suggests that they reflect trait-like features rather than transient mood states (Clark and Goodwin, 2004; Srivastava et al., 2019). Crucially, impaired global functioning has clear clinical implications: (1) it is a robust predictor of long-term outcome, often more than symptom severity alone (Watson et al., 2023); (2) it captures the burden of illness, even in the absence of overt mood symptoms (Bonnín et al., 2012); (3) it is a central treatment and rehabilitation goal, alongside clinical remission (Vieta and Torrent, 2016); (4) it underscores the need for personalized therapeutic interventions targeting not only mood stabilization but also cognitive and functional recovery (McIntyre et al., 2022).

Functioning has been associated with brain anatomy (Ferro et al., 2017) and functional connectivity indexes in psychosis (Collin et al., 2020), however, this relationship remains underexplored in BD.

In this study, we employed resting-state fMRI to investigate dFNC in BD. First, we calculated dFNC to identify a set of distinct dFNC states and meta-state metrics and compared BD with healthy controls (HCs). We hypothesized that patients would show greater dFNC impairments, with the greatest change in BD1. Finally, we wanted to associate aberrant dFNC patterns with clinical and functional outcome variables.

2. Experimental procedures

The current case-control study was approved by the Ethics Committee of Padua University Hospital and conducted in accordance with the Helsinki Declaration of 1975 guidelines. All participants gave their written informed consent to participate in the study after they received a complete explanation of the procedures.

2.1. Participants

A total of 57 caucasian patients with BD (29 with BD1 and 28 with BD2) and 43 caucasian HCs, matched for age, sex, and handedness, participated in this study. Patients were recruited from the inpatient and outpatient Mood Disorder Units of the Padua University Hospital, and diagnoses were confirmed by trained psychiatrists using the Structured Clinical Interview for DSM-5 (SCID-5). Inclusion criteria for patients were: a diagnosis of BD, (1) age between 18 and 65 years, (2) at least 1 month of stable pharmacotherapy for BD. Healthy controls were recruited through word-of-mouth, and were screened via telephone interview followed by a clinical assessment to exclude any current or past psychiatric or neurological disorder. All participants underwent identical exclusion criteria: history of alcohol or drug abuse in the six months before the assessment, lifetime drug dependence, traumatic head injury with loss of consciousness, past or present major medical illness or neurological disorders, mental retardation, minor or major neurocognitive disorder according to DSM-5 criteria, and Mini Mental State Examination (MMSE) (Folstein et al., 1975) score <25; MRI identified brain abnormality or microvascular lesion on T1-weighted, T2-weighted images, or fluid attenuated inversion recovery (FLAIR) sequences; contraindications to MRI scan. Additionally, patients were excluded if they had an additional psychiatric disorder other than BD. Normal controls with a history or current diagnosis of psychiatric disorders were also excluded.

2.2. Clinical assessment

Clinical and demographic data were collected, including age at onset of affective symptoms, duration of untreated illness, and history of childhood onset. Psychiatric history encompassed the number and type of previous affective episodes (depressive, manic, mixed, and hypomanic), current mood state, presence of psychotic features, and family history of psychiatric disorders. Information was also gathered on past and current pharmacological treatment, including the use of antidepressants, antipsychotics, antiepileptics, benzodiazepines, and lithium, along with lithium plasma levels (see Table 1 and Supplementary).

The overall severity of affective symptoms on the day of the scan was

Table 1
Demographic, clinical and functional outcomes characteristics in patients with bipolar disorders and healthy controls. The statistics refer to the comparison between patients with BD1 and BD2. MADRS: Montgomery and Asberg Depression Rating Scale; HAM-D: Hamilton Rating Scale for Depression; HAM-A: Hamilton Rating Scale for Anxiety; YMRS: Young Mania Rating; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning.

Characteristics	BD-1 (N = 29)	BD-2 (N = 28)	HC (N = 43)	p
Age (years), mean ± SD	43.7 ± 12.8	39.1 ± 12.8	40.8 ± 13.0	0.409
Males, n (%)	20 (68.96)	17 (60.71)	24 (55.81)	0.532
Duration of illness (years), mean ± SD	18.2 ± 10.7	11.1 ± 8.25	—	0.011*
Current mood state:				
Euthymia, n (%)	20 (68.96)	24 (85.71)	—	0.132
Depression, n (%)	2 (6.89)	2 (7.14)	—	0.970
Hypomania, n (%)	2 (6.89)	0	—	0.157
Mania/mixed n (%)	2 (6.89)	0	—	0.157
HAMD, mean ± SD	3.71 ± 8.43	1.65 ± 2.27	—	0.259
HAMA, mean ± SD	3.71 ± 7.55	1.39 ± 1.92	—	0.279
MADRS, mean ± SD	4.83 ± 11.2	2.13 ± 4.26	—	0.171
YMRS, mean ± SD	4.80 ± 11.5	1.09 ± 2.45	—	0.158
PANSS, mean ± SD	3.11 ± 8.56	0	—	0.131
GAF, mean ± SD	60.8 ± 26.9	78.1 ± 9.7	—	0.012*
Childhood onset, n (%)	7 (24.1)	10 (35.7)	—	0.339
Previous psychotic symptoms, n (%)	18 (62.1)	1 (3.6)	—	<0.001
Familiarity, n (%)	20 (69.0)	18 (64.3)	—	0.707
No. of previous hospitalizations, mean ± SD	2.7 ± 2.5	0.8 ± 1.4	—	0.027
Depressive episodes (0/1/2+)	7/0/13	1/2/19	—	—
Manic episodes (0/1/2+)	1/8/11	20/0/0	—	—
Mixed episodes (0/1/2+)	13/5/2	20/1/0	—	—
Hypomanic episodes (0/1/2+)	15/2/3	3/6/11	—	—
Euthymia n (%)	23 (79.3)	26 (92.9)	—	0.132
Depression n (%)	2 (6.9)	2 (7.1)	—	0.970
Hypomania n (%)	2 (6.9)	0	—	0.157
Mania/mixed n (%)	2 (6.9)	0	—	0.157
Antidepressants, n (%)	6 (20.7)	20 (71.4)	—	<0.001*
Antipsychotics, n (%)	14 (48.3)	10 (35.7)	—	0.337
Antiepileptics, n (%)	6 (20.7)	3 (10.7)	—	0.302
Benzodiazepines, n (%)	10 (34.5)	2 (7.1)	—	0.011*
Lithium, n (%)	21 (72.4)	27 (96.4)	—	—
Lithium exposure (months)	63.3 ± 89.2	28.2 ± 41.5	—	0.124

assessed using the Montgomery and Asberg Depression Rating Scale (MADRS)(Quilty et al., 2013) and the 17-item Hamilton Rating Scale for Depression (HAM-D)(Hamilton, 1960) for depressive symptoms, the Hamilton Rating Scale for Anxiety (HAM-A)(Maier et al., 1988) to assess anxiety symptoms, and the Young Mania Rating Scale (YMRS)(Young et al., 1978) to evaluate (hypo)manic symptoms. Psychotic symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS)(Kay et al., 1987). The assessment of lithium exposure was made by a review of clinical data provided by each participant's treating psychiatrist(s), and the lithium treatment duration (LiTD) was reported in months. Specifically, lithium serum levels were collected from the patient's physician charts to ensure good compliance and stability of lithium blood levels. Global functioning was assessed by the Global Assessment of Functioning (GAF) Scale (Pedersen et al., 2018).

2.3. Image acquisition

All MRI images were acquired on a 3 T MR scanner (Philips Ingenia, Best, The Netherlands) with a 32-channel quadrature head-coil. T1-weighted images were acquired using 3D-MPRAGE sequence with the following parameters: TR = 6580 ms; TE = 3 ms; FOV = 240 × 240 mm^2; flip-angle = 8°, resolution = 1.0 × 1.0 × 1.0 mm^3; number of slices = 181.

For rs-fMRI, 360 whole-brain echo planar imaging (EPI) volumes were recorded with the following imaging parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 240 × 240 mm^2, voxel size = 2.875 × 2.875 × 3.5 mm^3, 38 slices, and slice thickness = 3.5 mm. For the acquisition of resting-state data, participants were instructed to remain as still as possible, to keep their eyes closed, not to think about anything, and not to fall asleep. Data were collected on a single scanner.

2.4. Imaging pre-processing

The preprocessing pipeline was run in DPABI (http://rfmri.org/dpabi)(Yan et al., 2016) on SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). All scans were visually inspected by an expert neuroradiologist (RM) to exclude brain abnormalities, artifacts, or lesions. Functional and anatomical images were reoriented by setting the origin at the anterior commissure and aligning the horizontal axis with the AC-PC line. Then, the functional images were realigned using a least-squares approach with a six-parameter spatial transformation to correct for head motion and subsequently co-registered to each subject's structural scan. The anatomical images were segmented and normalized into the Montreal Neurological Institute standard space using the MNI152 template. The estimated normalization parameters were applied to all functional images, which were resampled to a 3 × 3 × 3 mm^3 voxel size. Finally, images were smoothed using a 6 mm full-width at half-maximum Gaussian kernel to increase the signal-to-noise ratio and account for residual anatomical variability across subjects.

2.5. Independent component analysis

One group of spatial ICA using ICASSO was performed on pre-processed data using the Group ICA of fMRI Toolbox [GIFT; https://trendscenter.org/software/, (Calhoun et al., 2001)] entering the data of all subjects. An ICA decomposition using the GIG-ICA algorithm was used and the number of independent components was set to the number of spatial references selected. Neuromark53 (Du et al., 2020) was used as a reference for constrained ICA resulting in 53 intrinsic networks (INs) independent components (ICs) which included the following features per each subject: 53 spatial maps (SM), 53 spectra, and one between-functional network connectivity (FNC) matrix.

2.6. Dynamic functional network connectivity

The dFNC was performed with a sliding windows approach using the dFNC toolbox in GIFT (Damaraju et al., 2014). This approach allows the study of a fixed segment of the data ("window") that moves over the whole time-courses of the scan with a minimum overlap between the windows. Each segment was modelled had a size of 30 TR (60 s) and a sigma of 3 TR (6 s) to taper along the window edges advancing 1 TR at each step, resulting in 329 windows.

These configuration parameters, which apply a Gaussian weighting function to smooth window edges, are widely used in dFNC studies and provide an optimal trade-off between temporal sensitivity and reliability of correlation estimates (You et al., 2022; Savva et al., 2019; Wang et al., 2024). Pre-processing included removing the mean, the slope, and period π and 2 π sines and cosines over the full timecourse, despiking, filtering using a 5th order Butterworth filter (0.01–0.15 Hz), and regressing orthogonalized with respect to 12-motion parameters.

To improve the estimation of pairwise correlations between TCs, a

Least Absolute Shrinkage and Selection Operator approach with L1 regularization (10 repetitions) was used to compute the covariance between the time-courses, thus resulting in a total of 32,900 windowed functional network connectivity matrices (wFNC). Then, the wFNC values were Fisher's Z-transformed and residualized with respect to significant nuisance covariates, including age, sex, and education.

2.6.1. Meta-states dFNC

In this approach, the dFNCs were modelled as a weighted sum of maximally statistically independent connectivity patterns. Each wFNC was decomposed into maximally independent prototype connectivity patterns (CPs) using principal component analysis (PCA) with a model order of 5, that has been proven to be sufficient to include complex additive effects and keep a richly featured basis pattern in literature (Miller et al., 2016). CP time-courses underwent a transformation in the correspondent discretized quartile, so that the weight of each pattern could have a positive or negative value, defining whether the contribution is given by the pro-state, or in the case of a negative sign, by the anti-state form. Thus, a time-indexed vector of 5 dimensions was obtained, which represents the 5-timepoints in which the time-course varies from one level to another. In this framework, a subject could be in more than one meta-state at a specific time point, and the probability of being in one meta-state changes dynamically (Meta-states dFNC). The dynamic changes during the whole scan were quantified using the following parameters: (i) *meta-state number*, which is the number of meta-states the subjects occupied, (ii) *meta-state changes*, which is the number of switch between meta-states (an estimation of the speed of switches), (iii) *meta-state span*, which is the largest L1 distance between two meta-states (an estimation of divergency between states) and (iv) *meta-state total distance*, which is the overall distance traveled through the space state (sum of L1 distances between successive meta-states).

2.7. Statistical analysis

Demographics, clinical, and functional features were compared across diagnostic groups using one-way ANOVA and two-sample *t*-test for continuous variables and $\chi 2$ test for categorical variables, respectively. When a variable's distribution was skewed, log transformation was applied to achieve a normal distribution (West, 2022). This case included GAF scores, which were log-transformed in all analyses. ANOVAs followed by post-hoc *t*-tests were conducted for each measure across all meta-states to test for pairwise differences in dFNC between BD1, BD2, and HC. Furthermore, to test the hypothesis of an ordered trend in the impairment of the meta-state variable (with BD2 expected to be less impaired than BD1 relative to HC), the Jonckheere-Terpstra test was applied. This non-parametric test is specifically designed to detect monotonic trends across a priori ordered groups. Diagnostic categories were coded as an ordinal variable (HC < BD2 < BD1), and each of the metrics derived from the PCA analysis was assessed along this direction. To explore the relationship between the dynamic connectivity parameters, clinical, and functional outcomes we performed a Pearson's correlation analyses.

To account for potential confounding effects of psychotropic medications, current pharmacological treatments were converted into defined daily doses (DDD) following the WHO ATC/DDD system. DDD values were computed for antidepressants (AD), antipsychotics (AP), and mood stabilizers. For lithium, dosage was standardized by considering 83 mg lithium sulfate ≈ 450 mg lithium carbonate = 1 equivalent unit. We run partial correlation with psychotropic drugs dosages as confounding (see Supplementary materials).

All the analyses are two-tailed and the level of significance was set to $p < 0.05$. Because the four dFNC meta-state metrics (number of meta-states, number of changes, total distance, and state span) are conceptually related and strongly intercorrelated, multiple comparisons were controlled using the effective number of independent tests (M_{eff}) method (Li and Ji, 2005). M_{eff} was derived from the eigenvalues of the inter-metric correlation matrix, capturing the actual number of independent dimensions among the four measures. For each family of analyses (group comparisons, ordered trend tests, and correlations with LN (GAF)), p-values were adjusted using a Bonferroni-M_{eff} correction, which divides the significance threshold by M_{eff} rather than by the raw number of tests. This provides a more appropriate control of Type I error while accounting for shared variance among dFNC metrics.

Data analysis was performed with Jamovi ("The jamovi project 2024). jamovi (Version 2.5) [Computer Software]. Retrieved from https://www.jamovi.org," n.d.).

Before performing parametric tests, the distributional assumptions were verified through visual inspection of Q–Q plots and by testing model residuals for normality using the Shapiro–Wilk test. We also inspected residual skewness and kurtosis (acceptable range ±2). Although some raw clinical variables displayed right-skewed distributions, residuals from ANOVA and Pearson correlation models were approximately normal and homoscedastic, supporting the use of parametric inference in the present sample (see Supplementary materials).

3. Results

3.1. Demographic, clinical, and functional outcomes characteristics

Demographics were comparable between the three groups, with no significant differences in age or sex distribution (F_{Age}=0.90, $p = 0.409$; Chi-squared$_{Gender}$= 1.26, $p = 0.532$). Compared to BD-2, individuals with BD-1 showed a significantly longer illness duration ($p = 0.011$) and lower GAF scores ($p = 0.012$). Most BD participants were euthymic at the time of scanning (BD1: 79.3 %; BD2: 92.9 %) and no significant group differences were observed in current mood state or symptom severity as assessed by standard clinical scales (HAMD, HAMA, MADRS, YMRS, PANSS). Detailed demographic and clinical data are shown in Table 1. Across the groups, a Kruskal–Wallis test revealed a significant difference in mean FD ($H = 8.27, p = 0.016$), with BD1 patients showing greater motion compared to healthy controls ($p = 0.014$, Dunn's post-hoc, Bonferroni corrected), while BD2 patients did not differ significantly from either group. Importantly, individual FD parameters were included as nuisance regressors during denoising in dFNC preprocessing.

3.2. Meta-states dFNC

5 PCA connectivity patterns were estimated (see Fig. 1). The number meta-states [F(2, 96)= 4.993, $p = 0.009$, p_adj=0.015], the number of meta-state changes [F(2, 96)= 4.086, $p = 0.019$, p_adj=0.032] and the total distance between metastates [F(2, 96)=3.978, $p = 0.022$, p_adj=0.037] but not the state span [F(2, 96)= 0.040, $p = 0.9607$, p_adj> 0.99] was significantly different across samples (see Fig. 2). Fig. 3

In particular, BD1 showed a significantly lower number of meta-states ($p = 0.009$, p_adj=0.0152) number of meta-state changes ($p = 0.016$, p_adj=0.0271) and a smaller total distance ($p = 0.016$, p_adj=0.0271) relative to HC. BD2 show a trend with HC for number of meta-state ($p = 0.039$, p_adj=0.0660) and Total distance ($p = 0.052$, p_adj=0.087) but no difference with the other two metrics (Change state, $p = 0.073$, p_adj=0.1235; State-span, $p = 0.781$, p_adj>0.9).

The Jonckheere-Terpstra test provided evidence of a statistically significant ordered trend (HC>BD2>BD1) for three out of the four examined metrics, including the number of meta-states (JT = 1208.5, $p = 0.0069$, p_adj= 0.012), the change states (JT = 1225, $p = 0.0095$, p_adj=0.016), the total distance (JT = 1256, $p = 0.016$, p_adj=0.027). No significant trend was observed for the state span (JT = 1569, $p = 0.6923$, p_adj>0.8).

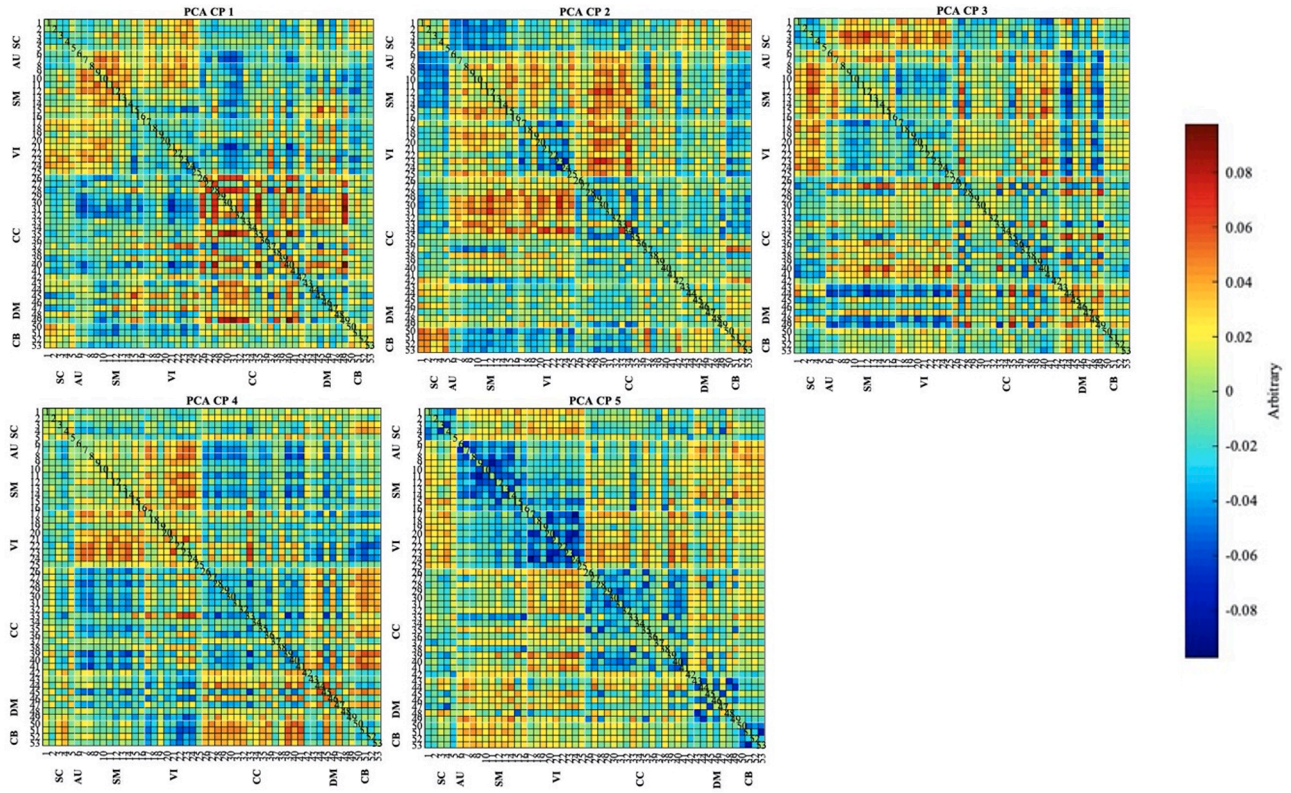

Fig. 1. Principal connectivity patterns identified using dynamic functional network connectivity. Each matrix represents the mean functional connectivity for each pattern for 53 networks extracted from the neuromark53 template calculated using the correlation between pairs of networks. The colorbar indicates the magnitude of the correlation in a.u. with red color indicating stronger positive and blue colors indicating anti-correlations. Brain networks are arranged by domains: SC: subcortical networks [1–5]; AU: auditory networks [6–7]; SM: somatomotor networks [8–16]; VI: visual networks [17–25]; CC: cognitive control networks [26–42]; DM: default mode networks [43–49]; CB: cerebellar networks [50–53]. Colors close to red indicate a positive correlation; colors close to blue indicate a negative correlation.

3.3. Relationship between brain dynamics, clinical, and functioning domains in patients with BD

The number of meta-states, the number of change states, and the total distance between meta-states showed a significant positive correlation with LN(GAF) scores in the overall BD sample ($r = 0.487$ with p_adj= 0.0010, $r = 0.465$ with p_adj=0.0019, $r = 0.458$ with p_adj=0.0023, respectively), as well as within the BD1 ($r = 0.459$ with p_adj=0.0442, $r = 0.475$ with p_adj=0.0574, $r = 0.492$ with p_adj=0.0457) and BD2 ($r = 0.589$ with p_adj=0.003, $r = 0.582$ with p_adj=0.003, $r = 0.610$ with p_adj=0.002) subgroups. The correlation with state span was not significant ($r = 0.068$, p_adj > 0.8). Associations between dynamic metrics and LN(GAF) remained significant and virtually unchanged after including medication dosage covariates, indicating that results were not driven by pharmacological treatment (see Supplementary materials). No association was found between clinical scales and dynamic metrics.

4. Discussion

In the present study, we investigated intrinsic neural network dynamics in BD. The metrics that express dynamic fluidity were reduced in BD, with a greater impairment observed in patients with BD1 relative to patient with BD2, and this impairment was positively associated with general functioning.

In line with previous findings suggesting reduced neural flexibility in BD (Damaraju et al., 2014; Rashid et al., 2014), our results show a significant reduction in dFNC-derived metrics reflecting dynamic fluidity—namely, the number of metastates, state transitions, and total distance—in BD compared to HCs. This supports the hypothesis that BD is characterized by a diminished ability to explore a diverse functional network repertoire over time. Notably, while prior studies mainly investigated BD as part of broader transdiagnostic samples or compared BD with schizophrenia, our study provides focused evidence specifically on BD subtypes, thereby advancing the characterization of aberrant dynamic connectivity profiles in affective disorders. BD1 and BD2 subjects seem to move occupying fewer meta-states, but they also seem to be characterized by fewer transitions between one meta-state and the next, and a decrease in the total distance traveled within the connectivity space. However, no significant differences were identified between state span, a metric indicative of the greater interval traveled between one meta-state and another: both groups move within a hypercube of the same radial size.

The observed pattern—characterized by progressively lower values from HCs to BD2 and then BD1 patients—suggests a graded disruption of dynamic functional properties in relation to clinical severity. This gradient aligns with the conceptualization of BD as a spectrum and highlights the potential of these metrics to capture subtle variations in disease burden that may not emerge from traditional group comparisons alone as also suggested by recent unpublished findings (Miola et al., personal communication, July 2025).

Second, we found a significant association between global functioning, measured by the GAF scale, and dynamic fluidity indices within the BD group. This relationship remained statistically significant when examined separately in BD1 and BD2 subgroups.

These findings indicate that the observed links between greater dynamic neural flexibility and better functioning are not attributable to current medication dosage. While cumulative exposure could not be modeled due to lack of detailed longitudinal dosing data, the stability of results after controlling for current treatment supports the robustness of

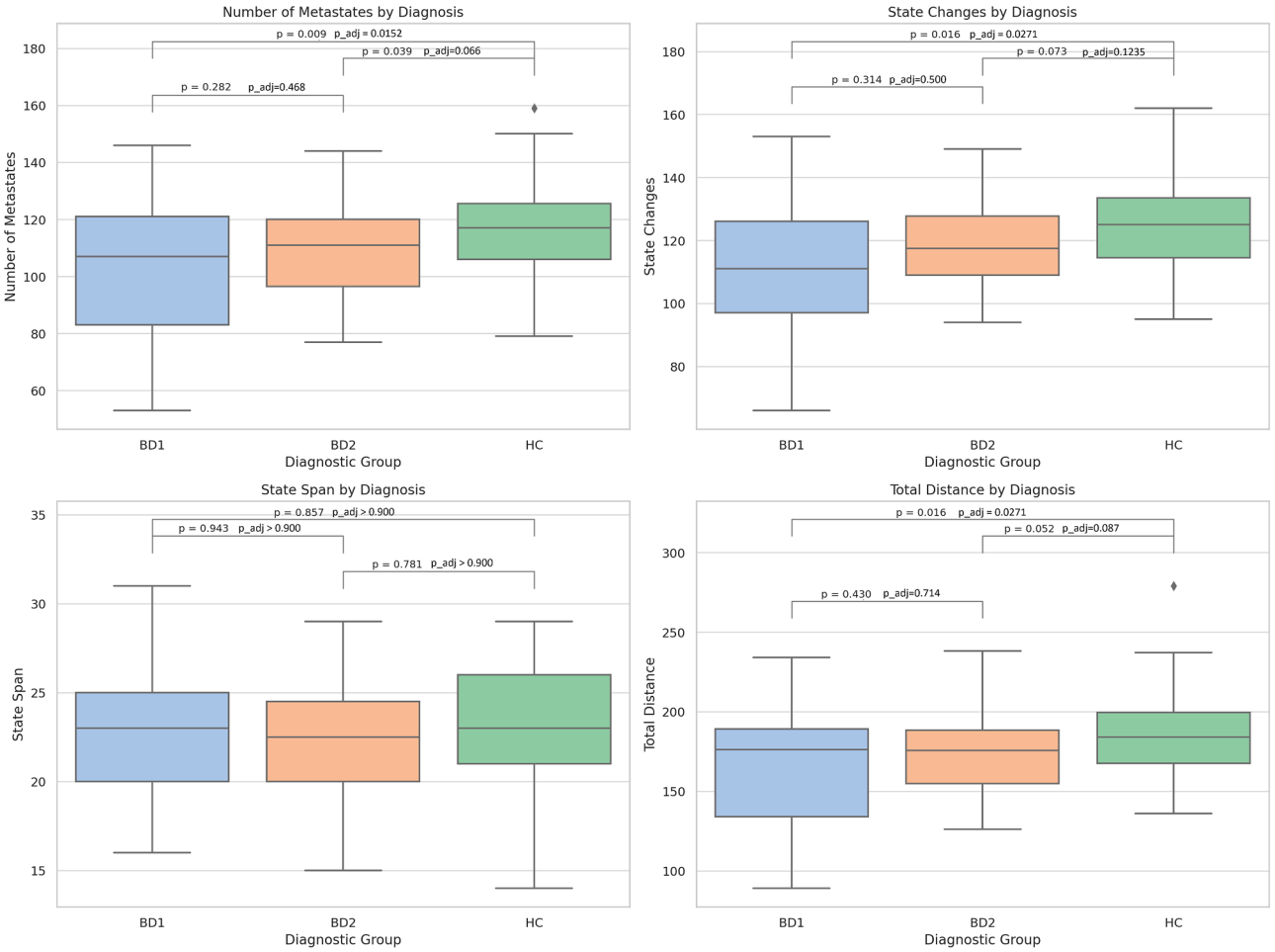

Fig. 2. Meta-state metrics estimated using dynamic functional connectivity across diagnostic groups. Boxplots report the number of metastates (upper left), state changes (upper right), state span (lower left) and total distance (lower right) that were estimated for each individual and compared between BD1 (blue), BD2 (orange), and HC (green). Boxes indicate the interquartile range (IQR), the horizontal line within each box represents the median, and whiskers represent the 95 % confidence intervals. Individual comparisons between groups are annotated with exact p-values derived from unpaired two-sample *t*-tests with Welch's correction.

the main conclusions.

These results support the hypothesis that reduced neural dynamism—reflected by fewer state transitions, lower number of metastates, and reduced total distance—may constrain the brain's capacity to flexibly reconfigure into functionally advantageous network states, ultimately contributing to functional impairment in BD.

Our findings converge with previous meta-state studies reporting reduced dynamical flexibility of functional connectivity in clinical populations. Fu et al. demonstrated diminished global metastate dynamism in patients with depressive episodes that normalized after ECT, supporting the link between reduced neural fluidity and impaired adaptability (Fu et al., 2022). Similarly, Lahti et al. observed a reduced meta-state range and transitions in very-preterm adolescents, suggesting that the constrained dynamic repertoire represents a transdiagnostic marker of altered brain maturation and functional capacity (Lahti et al., 2022).

Extending this pattern to affective disorders, work in major depression indicates that dynamic, rather than static, connectivity abnormalities—particularly within the default-mode and cognitive-control networks—relate more closely to individual differences in neurocognitive and functional outcomes (Kaiser et al., 2016), reinforcing the clinical relevance of reduced neural flexibility observed here.

Notably, Demirtaş et al. demonstrated that patients with MDD exhibit increased global synchronization and reduced variability of dynamic functional connectivity, particularly between the DMN and the fronto-parietal network—a pattern interpreted as reduced network flexibility and greater temporal rigidity (Demirtaş et al., 2016)

Our results extend this literature by demonstrating that in BD—across diagnostic subtypes—diminished temporal flexibility in large-scale brain networks is likewise associated with poorer global functioning, underscoring the transdiagnostic relevance of dynamic neural biomarkers in affective psychopathology.

At the level of brain circuits, the metrics dynamics changes may arise from reconfiguration in local cortical states, which can then interact with each other's across large-scale networks (Hutchison et al., 2013). The reconfiguration of these brain networks can either be sustained or lead to variations in neurotransmitter signaling systems. Dopamine has been associated with brain network dynamics due to its role in the fine-tuning process of cortical responses by modulating pyramidal neurons and GABA-inhibitory interneurons (Sambataro et al., 2009; Seamans and Yang, 2004). Additionally, GABA can influence the frequency of membrane oscillations and increase synchronization within large-scale networks. Presynaptic dopamine hyperactivity has been implicated in psychotic symptoms and increased D2/D3 expression and striatal dopamine transporter levels have been reported in BD (Ashok et al., 2017).

From a pathophysiological perspective, these findings may also be interpreted in the light of glutamatergic dysregulation. Glutamate signaling, especially via NMDA receptors, has been shown to influence large-scale brain dynamics by modulating synaptic plasticity, excitability, and the coordination of network activity over time. Notably, receptor density studies suggest a relative decrease of NMDA receptor

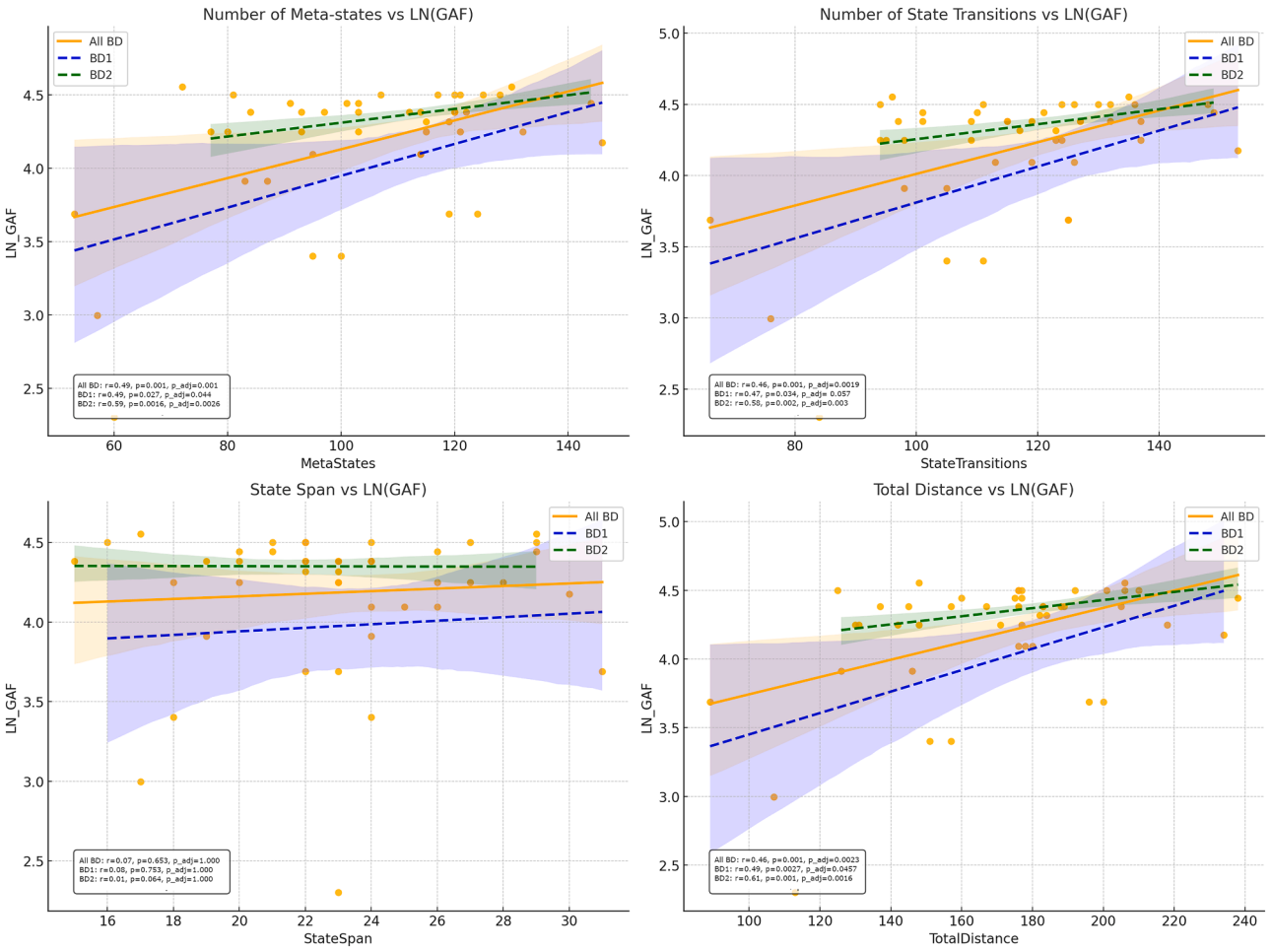

Fig. 3. Scatterplots with linear regression and 95 % confidence intervals showing associations between PCA metrics and LN(GAF) in individuals with bipolar disorder. The overall BD sample is indicated in yellow, B1 are in blue and BD2 are in green, respectively. The graphs illustrate the relationships between LN(GAF) and each of the four PCA-derived metrics (Number of Meta-states, Number of State Transitions, State Span, Total Distance).

availability in BD and MDD, contrasting with increased density in schizophrenia (Konstantinos N. Fountoulakis, 2012; Nudmamud-Thanoi and Reynolds, 2004), thus supporting a differential excitation/inhibition (E/I) balance across diagnostic groups. Such glutamatergic alterations may contribute to impaired dynamic flexibility via multiple, converging mechanisms: (1) *E/I imbalance*: reduced NMDA receptor function may disrupt cortical E/I balance, impairing the brain's ability to transiently engage and disengage from different functional network configurations. This aligns with both glutamatergic hypofunction and evidence of GABAergic deficits in BD, which together may reduce the capacity for coordinated network switching (Zarate et al., 2003); (2) *Mitochondrial dysfunction and oxidative stress*: glutamate excitotoxicity and associated mitochondrial impairment—frequently reported in BD—may lead to metabolic inefficiency, impacting the energy-dependent processes that support rapid reconfiguration of networks. This hypothesis is consistent with reduced dynamic range and metastability observed in dFNC studies of BD (Scaini et al., 2016); (3) *Neurotoxicity and plasticity failure*: chronic glutamatergic dysregulation may impair synaptic plasticity, limiting the functional repertoire available to large-scale networks (Sanacora et al., 2008). Altogether, these considerations suggest that alterations in glutamate-mediated neurotransmission may play a central role in shaping aberrant functional brain dynamics in BD, and may serve as a neurochemical substrate for the reduced flexibility and increased rigidity of intrinsic brain activity observed in our cohort.

Some methodological aspects limit the generalizability of our results: first, to improve adherence to the scan and obtain analyzable images, most of the data obtained from patients were collected in the euthymic phase so that we cannot ascertain whether these changes are modulated by affective episodes. Second, group-independent component analysis, which can identify resting-state networks in a subject's sample may emphasize the characteristics of the chosen sample, limiting the replicability of the results. A more detailed discussion of spatial and temporal ICA and other possible models for decomposing intrinsic activity can be found elsewhere (Calhoun and Adali, 2012). Third, subjects with alcohol or drug abuse were excluded. As discussed by Li et al., univariate brain–clinical correlations may overestimate effect sizes and show limited generalizability (Li et al., 2023). Given these considerations, the present findings should be interpreted with caution and as hypothesis-generating rather than conclusive. Future studies employing larger samples and multivariate approaches (e.g., canonical correlation analysis or machine-learning–based models) will be essential to validate and extend these results.

4.1. Clinical and research implications

Our findings indicate that reduced dynamics of large-scale brain networks may represent key feature of bipolar disorders, contributing to impaired functional outcomes even during euthymia. Clinically, this may underlie the persistent cognitive and psychosocial inflexibility present in BD (Nguyen et al., 2017), suggesting potential targets for interventions aimed at enhancing network adaptability. In particular,

neuromodulation techniques, including neurofeedback and brain stimulation (Bernabei et al., 2024), targeting network rigidity, could provide complementary benefits to pharmacological treatments. From a research perspective, the results highlight the added value of dynamic over static functional connectivity measures for capturing state-dependent alterations in brain organization (Ramos-Nuñez et al., 2017). The pattern across BD subtypes supports a dimensional view of network dysregulation rather than discrete diagnostic categories. These results encourage future investigations to validate dFNC metrics as potential biomarkers of illness burden and recovery. The present findings warrant replication in larger and medication-stratified samples before firm conclusions can be drawn.

Ultimately, the most recent theoretical models suggest that structural and functional alterations of the chronnectome are shared by a broad spectrum of neurological and psychiatric disorders, and that there are several dimensions along which the connectome is organized, including modularity and integration of brain networks. These dimensions could be used in the future as a "coordinate system" to describe and categorize different affective disorders and, ideally, other psychiatric conditions within more innovative frameworks. Some might argue that it is necessary to study brain connectivity in terms of alteration of brain plasticity expressed at the molecular level as an alteration of cellular communication (cell adhesion, neuroglia integrity, neurotransmitter systems etc.) (Kato, 2017; Mullins et al., 2020; Scaini et al., 2020; Smith et al., 2019; The International Schizophrenia Consortium, 2009).

Beyond functional dynamics, the integration of structural and functional imaging features represents a promising direction to better characterize the architecture of BD. Combining complementary modalities, such as morphometric and dFNC measures, could provide a more comprehensive view to understand the interplay between brain structure and dynamic function (Wang et al., 2025). This work represents an invitation to adopt new technologies and innovative computational techniques that allow to uncover "functional fingerprints", proxies of the aforementioned molecular alterations but useful in vivo and capable of refining diagnosis, better targeting treatment, and providing new pathogenetic models for psychiatric diseases.

5. Conclusion

In this study, we investigated a novel dynamic connectivity analysis applied to a sample composed of patients with BD and HCs. Decreased dFNC indexes of neural dynamism found in BD group may reflect compromised information processing, which is associated with a poorer general individual functioning.

Even though the analysis of dynamic connectivity is a new approach that has not yet been widely applied, it offers an opportunity, allowing a more detailed exploration of underlying neural behavior. Therefore, dynamic functional connectivity analysis could be a proper method to obtain the temporal information of the connections between brain regions, enabling the identification of biomarkers strongly linked to cognitive, clinical, or functional outcomes. This approach may support more precise assessments of vulnerability, enhance diagnostic accuracy, and improve predictions of disease trajectories and treatment response, ultimately facilitating the development of targeted therapies. However, further studies with larger samples and longitudinal designs are needed to rigorously validate these hypotheses and assess their clinical utility over time.

Credit authorship contribution statement

Olivo: Conceptualization, Investigation, Data curation, Formal analysis, Methodology, Visualization, Writing– original draft, Writing – review & editing. **Miola**: Investigation, Data curation, Methodology, Writing – review & editing. **Folena**: Data curation, Methodology, Writing – review & editing**. Trevisan**: Data curation, Formal analysis, Methodology, Writing – review & editing. **Librizzi**: Data curation, Methodology, Writing – review & editing. **Toffanin**: Data curation, Supervision, Writing – review & editing. **Manara**: Data curation, Supervision, Writing – review & editing. **Sambataro**: Conceptualization, Methodology, Supervision, Writing original draft, Writing – review & editing.

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Declaration of competing interest

All the authors declare that they have no conflicts of interest.

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Supplementary materials

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References

Allen, E.A., Damaraju, E., Plis, S.M., Erhardt, E.B., Eichele, T., Calhoun, V.D., 2014. Tracking whole-brain connectivity dynamics in the resting State. Cereb. Cortex. 24, 663–676. https://doi.org/10.1093/cercor/bhs352.

Arvilommi, P., Pallaskorpi, S., Linnaranta, O., Suominen, K., Leppämäki, S., Valtonen, H., Isometsä, E., 2022. Long-term work disability due to type I and II bipolar disorder: findings of a six-year prospective study. Int. J. Bipolar Disord. 10, 19. https://doi.org/10.1186/s40345-022-00264-6.

Ashok, A.H., Marques, T.R., Jauhar, S., Nour, M.M., Goodwin, G.M., Young, A.H., Howes, O.D., 2017. The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. Mol. Psychiatry 22, 666–679. https://doi.org/10.1038/mp.2017.16.

Baş, T.Ö., Poyraz, C.A., Baş, A., Poyraz, B.Ç., Tosun, M., 2015. The impact of cognitive impairment, neurological soft signs and subdepressive symptoms on functional outcome in bipolar disorder. J. Affect. Disord. 174, 336–341. https://doi.org/10.1016/j.jad.2014.12.026.

Benazzi, F., 2007. Bipolar disorder—Focus on bipolar II disorder and mixed depression. The Lancet 369, 935–945. https://doi.org/10.1016/S0140-6736(07)60453-X.

Bernabei, L., Leone, B., Hirsch, D., Mentuccia, V., Panzera, A., Riggio, F., Sangiovanni, L., Piserchia, V., Nicolò, G., Pompili, E., 2024. Neuromodulation strategies in Lifelong Bipolar disorder: a narrative review. Behav. Sci. 14, 1176. https://doi.org/10.3390/bs14121176.

Bonnín, C.M., Sánchez-Moreno, J., Martínez-Arán, A., Solé, B., Reinares, M., Rosa, A.R., Goikolea, J.M., Benabarre, A., Ayuso-Mateos, J.L., Ferrer, M., Vieta, E., Torrent, C., 2012. Subthreshold symptoms in bipolar disorder: impact on neurocognition, quality of life and disability. J. Affect. Disord. 136, 650–659. https://doi.org/10.1016/j.jad.2011.10.012.

Bora, E., Bartholomeusz, C., Pantelis, C., 2016. Meta-analysis of Theory of Mind (ToM) impairment in bipolar disorder. Psychol. Med. 46, 253–264. https://doi.org/10.1017/S0033291715001993.

Bora, E., Pantelis, C., 2015. Meta-analysis of cognitive impairment in first-episode bipolar disorder: comparison with first-episode schizophrenia and healthy controls. Schizophr. Bull. 41, 1095–1104. https://doi.org/10.1093/schbul/sbu198.

Burdick, K.E., Millett, C.E., Yocum, A.K., Altimus, C.M., Andreassen, O.A., Aubin, V., Belzeaux, R., Berk, M., Biernacka, J.M., Blumberg, H.P., Cleare, A.J., Diaz-Byrd, C., Dubertret, C., Etain, B., Eyler, L.T., Forester, B.P., Fullerton, J.M., Frye, M.A., Gard, S., Godin, O., Haffen, E., Klaus, F., Lagerberg, T.V., Leboyer, M., Martinez-Aran, A., McElroy, S., Mitchell, P.B., Olie, E., Olorunfemi, P., Passerieux, C., Peters, A.T., Pham, D.L., Polosan, M., Potter, J.R., Sajatovic, M., Samalin, L., Schwan, R., Shanahan, M., Solé, B., Strawbridge, R., Stuart, A.L., Torres, I., Ueland, T., Vieta, E., Williams, L.J., Wrobel, A.L., Yatham, L.N., Young, A.H., Nierenberg, A.A., McInnis, M.G., 2022. Predictors of functional impairment in bipolar disorder: results from 13 cohorts from seven countries by the global bipolar cohort collaborative. Bipolar Disord 24, 709–719. https://doi.org/10.1111/bdi.13208.

Calhoun, V.D., Adali, T., 2012. Multisubject independent component analysis of fMRI: a decade of intrinsic networks, default mode, and neurodiagnostic discovery. IEEE Rev. Biomed. Eng. 5, 60–73. https://doi.org/10.1109/RBME.2012.2211076.

Calhoun, V.D., Miller, R., Pearlson, G., Adalı, T., 2014. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron 84, 262–274. https://doi.org/10.1016/j.neuron.2014.10.015.

Cattarinussi, G., Di Giorgio, A., Moretti, F., Bondi, E., Sambataro, F., 2023. Dynamic functional connectivity in schizophrenia and bipolar disorder: a review of the evidence and associations with psychopathological features. Prog. Neuropsychopharmacol. Biol. Psychiatry 127, 110827. https://doi.org/10.1016/j.pnpbp.2023.110827.

Chen, G., Chen, P., Gong, J., Jia, Y., Zhong, S., Chen, F., Wang, J., Luo, Z., Qi, Z., Huang, L., Wang, Y., 2022. Shared and specific patterns of dynamic functional connectivity variability of striato-cortical circuitry in unmedicated bipolar and major depressive disorders. Psychol. Med. 52, 747–756. https://doi.org/10.1017/S0033291720002378.

Claeys, E.H.I., Mantingh, T., Morrens, M., Yalin, N., Stokes, P.R.A., 2022. Resting-state fMRI in depressive and (hypo)manic mood states in bipolar disorders: a systematic review. Prog. Neuropsychopharmacol. Biol. Psychiatry 113, 110465. https://doi.org/10.1016/j.pnpbp.2021.110465.

Clark, L., Goodwin, G.M., 2004. State- and trait-related deficits in sustained attention in bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 254, 61–68. https://doi.org/10.1007/s00406-004-0460-y.

Collin, G., Nieto-Castanon, A., Shenton, M.E., Pasternak, O., Kelly, S., Keshavan, M.S., Seidman, L.J., McCarley, R.W., Niznikiewicz, M.A., Li, H., Zhang, T., Tang, Y., Stone, W.S., Wang, J., Whitfield-Gabrieli, S., 2020. Brain functional connectivity data enhance prediction of clinical outcome in youth at risk for psychosis. NeuroImage Clin 26, 102108. https://doi.org/10.1016/j.nicl.2019.102108.

Damaraju, E., Allen, E.A., Belger, A., Ford, J.M., McEwen, S., Mathalon, D.H., Mueller, B. A., Pearlson, G.D., Potkin, S.G., Preda, A., Turner, J.A., Vaidya, J.G., van Erp, T.G., Calhoun, V.D., 2014. Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. NeuroImage Clin 5, 298–308. https://doi.org/10.1016/j.nicl.2014.07.003.

Demirtaş, M., Tornador, C., Falcón, C., López-Solà, M., Hernández-Ribas, R., Pujol, J., Menchón, J.M., Ritter, P., Cardoner, N., Soriano-Mas, C., Deco, G., 2016. Dynamic functional connectivity reveals altered variability in functional connectivity among patients with major depressive disorder. Hum. Brain Mapp. 37, 2918–2930. https://doi.org/10.1002/hbm.23215.

Du, Y., Fu, Z., Sui, J., Gao, S., Xing, Y., Lin, D., Salman, M., Abrol, A., Rahaman, M.A., Chen, J., Hong, L.E., Kochunov, P., Osuch, E.A., Calhoun, V.D., 2020. NeuroMark: an automated and adaptive ICA based pipeline to identify reproducible fMRI markers of brain disorders. NeuroImage Clin 28, 102375. https://doi.org/10.1016/j.nicl.2020.102375.

Du, Y., He, X., Calhoun, V.D., 2021. A new semi-supervised non-negative matrix factorization method for brain dynamic functional connectivity analysis. In: 2021 IEEE 18th International Symposium on Biomedical Imaging (ISBI). Presented at the 2021 IEEE 18th International Symposium on Biomedical Imaging (ISBI), IEEE, Nice, France, pp. 1591–1594. https://doi.org/10.1109/ISBI48211.2021.9433988.

Fateh, A.A., Cui, Q., Duan, X., Yang, Y., Chen, Y., Li, D., He, Z., Chen, H., 2020. Disrupted dynamic functional connectivity in right amygdalar subregions differentiates bipolar disorder from major depressive disorder. Psychiatry Res. Neuroimaging 304, 111149. https://doi.org/10.1016/j.pscychresns.2020.111149.

Ferro, A., Bonivento, C., Delvecchio, G., Bellani, M., Perlini, C., Dusi, N., Marinelli, V., Ruggeri, M., Altamura, A.C., Crespo-Facorro, B., Brambilla, P., 2017. Longitudinal investigation of the parietal lobe anatomy in bipolar disorder and its association with general functioning. Psychiatry Res. Neuroimaging 267, 22–31. https://doi.org/10.1016/j.pscychresns.2017.06.010.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state. J. Psychiatr. Res. 12, 189–198. https://doi.org/10.1016/0022-3956(75)90026-6.

Fountoulakis, K.N., 2020. Neurocognitive impairment and evidence-based treatment options in bipolar disorder. Ann. Gen. Psychiatry 19, 54. https://doi.org/10.1186/s12991-020-00304-4.

Fu, Z., Sui, J., Espinoza, R., Narr, K., Qi, S., Sendi, M.S.E., Abbott, C.C., Calhoun, V.D., 2022. Whole-brain functional connectivity dynamics associated with electroconvulsive therapy treatment response. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 7, 312–322. https://doi.org/10.1016/j.bpsc.2021.07.004.

Gillissie, E.S., Lui, L.M.W., Ceban, F., Miskowiak, K., Gok, S., Cao, B., Teopiz, K.M., Ho, R., Lee, Y., Rosenblat, J.D., McIntyre, R.S., 2022. Deficits of social cognition in bipolar disorder: systematic review and meta-analysis. Bipolar Disord 24, 137–148. https://doi.org/10.1111/bdi.13163.

Grande, I., Berk, M., Birmaher, B., Vieta, E., 2016. Bipolar disorder. Lancet. 387, 1561–1572. https://doi.org/10.1016/S0140-6736(15)00241-X.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 7.

Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., Della Penna, S., Duyn, J.H., Glover, G.H., Gonzalez-Castillo, J., Handwerker, D.A., Keilholz, S., Kiviniemi, V., Leopold, D.A., de Pasquale, F., Sporns, O., Walter, M., Chang, C., 2013. Dynamic functional connectivity: promise, issues, and interpretations. NeuroImage 80, 360–378. https://doi.org/10.1016/j.neuroimage.2013.05.079.

Huxley, N., Baldessarini, R.J., 2007. Disability and its treatment in bipolar disorder patients. Bipolar Disord 9, 183–196. https://doi.org/10.1111/j.1399-5618.2007.00430.x.

Işık Ulusoy, S., Gülseren, Ş.A., Özkan, N., Bilen, C., 2020. Facial emotion recognition deficits in patients with bipolar disorder and their healthy parents. Gen. Hosp. Psychiatry 65, 9–14. https://doi.org/10.1016/j.genhosppsych.2020.04.008.

Kaiser, R.H., Whitfield-Gabrieli, S., Dillon, D.G., Goer, F., Beltzer, M., Minkel, J., Smoski, M., Dichter, G., Pizzagalli, D.A., 2016. Dynamic resting-State functional connectivity in major depression. Neuropsychopharmacology 41, 1822–1830. https://doi.org/10.1038/npp.2015.352.

Kato, T., 2017. Neurobiological basis of bipolar disorder: mitochondrial dysfunction hypothesis and beyond. Schizophr. Res. 187, 62–66. https://doi.org/10.1016/j.schres.2016.10.037.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.

Keck, P.E., Kessler, R.C., Ross, R., 2008. Clinical and economic effects of unrecognized or inadequately treated bipolar disorder. J. Psychiatr. Pract. 14, 31–38. https://doi.org/10.1097/01.pra.0000320124.91799.2a.

Keramatian, K., Pinto, J.V., Tsang, V.W.L., Chakrabarty, T., Yatham, L.N., 2025. Duration of untreated or undiagnosed bipolar disorder and clinical characteristics and outcomes: systematic review and meta-analysis. Br. J. Psychiatry 1–11. https://doi.org/10.1192/bjp.2025.63.

Fountoulakis, Konstantinos N., 2012. The possible involvement of NMDA glutamate receptor in the etiopathogenesis of bipolar disorder. Curr. Pharm. Des. 18, 1605–1608. https://doi.org/10.2174/138161212799958585.

Lahti, K., Setänen, S., Vorobyev, V., Nyman, A., Haataja, L., Parkkola, R., 2022. Altered temporal connectivity and reduced meta-state dynamism in adolescents born very preterm. Brain Commun 5, fcad009. https://doi.org/10.1093/braincomms/fcad009.

Li, J., Ji, L., 2005. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. Heredity (Edinb). 95, 221–227. https://doi.org/10.1038/sj.hdy.6800717.

Li, J., Long, Z., Ji, G.-J., Han, S., Chen, Y., Yao, G., Xu, Y., Zhang, K., Zhang, Y., Cheng, J., Wang, K., Chen, H., Liao, W., 2025. Major depressive disorder on a neuromorphic continuum. Nat. Commun. 16. https://doi.org/10.1038/s41467-025-57682-0.

Li, Q., Yao, L., You, W., Liu, J., Deng, S., Li, B., Luo, L., Zhao, Y., Wang, Yuxia, Wang, Yaxuan, Zhang, Q., Long, F., Sweeney, J.A., Gu, S., Li, F., Gong, Q., 2023. Controllability of functional brain networks and its clinical significance in first-episode schizophrenia. Schizophr. Bull. 49, 659–668. https://doi.org/10.1093/schbul/sbac177.

Liu, M., Yuchen, Wang, Zhang, A., Yang, C., Liu, P., Wang, J., Zhang, K., Yanfang, Wang, Sun, N., 2021. Altered dynamic functional connectivity across mood states in bipolar disorder. Brain Res 1750, 147143. https://doi.org/10.1016/j.brainres.2020.147143.

Maier, W., Buller, R., Philipp, M., Heuser, I., 1988. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J. Affect. Disord. 14, 61–68. https://doi.org/10.1016/0165-0327(88)90072-9.

McIntyre, R.S., Alda, M., Baldessarini, R.J., Bauer, M., Berk, M., Correll, C.U., Fagiolini, A., Fountoulakis, K., Frye, M.A., Grunze, H., Kessing, L.V., Miklowitz, D.J., Parker, G., Post, R.M., Swann, A.C., Suppes, T., Vieta, E., Young, A., Maj, M., 2022. The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management. World Psychiatry 21, 364–387. https://doi.org/10.1002/wps.20997.

Miller, R.L., Yaesoubi, M., Calhoun, V.D., 2014. Higher dimensional analysis shows reduced dynamism of time-varying network connectivity in schizophrenia patients. In: 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Presented at the 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), IEEE, Chicago, IL, pp. 3837–3840. https://doi.org/10.1109/EMBC.2014.6944460.

Miola, A., Cattarinussi, G., Loré, M.L., Ghiotto, N., Collantoni, E., Sambataro, F., 2022. Brain gyrification in bipolar disorder: a systematic review of neuroimaging studies. Brain Imaging Behav. https://doi.org/10.1007/s11682-022-00713-x.

Miola, A., Trevisan, N., Salvucci, M., Minerva, M., Valeggia, S., Manara, R., Sambataro, F., 2024. Network dysfunction of sadness facial expression processing and morphometry in euthymic bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 274, 525–536. https://doi.org/10.1007/s00406-023-01649-z.

Mitchell, R.L.C., Young, A.H., 2016. Theory of mind in bipolar disorder, with comparison to the impairments observed in schizophrenia. Front. Psychiatry 6. https://doi.org/10.3389/fpsyt.2015.00188.

Mullins, N., Forstner, A.J., O'Connell, K.S., Coombes, B., Coleman, J.R.I., Qiao, Z., Als, T. D., Bigdeli, T.B., Børte, S., Bryois, J., Charney, A.W., Drange, O.K., Gandal, M.J., Hagenaars, S.P., Ikeda, M., Kamitaki, N., Kim, M., Krebs, K., Panagiotaropoulou, G., Schilder, B.M., Sloofman, L.G., Steinberg, S., Trubetskoy, V., Winsvold, B.S., Won, H.-H., Abramova, L., Adorjan, K., Agerbo, E., Al Eissa, M., Albani, D., Alliey-Rodriguez, N., Anjorin, A., Antilla, V., Antoniou, A., Awasthi, S., Baek, J.H., Bækvad-Hansen, M., Bass, N., Bauer, M., Beins, E.C., Bergen, S.E., Birner, A., Bøcker Pedersen, C., Bøen, E., Boks, M.P., Bosch, R., Brum, M., Brumpton, B.M., Brunkhorst-Kanaan, N., Budde, M., Bybjerg-Grauholm, J., Byerley, W., Cairns, M., Casas, M., Cervantes, P., Clarke, T.-K., Cruceanu, C., Cuellar-Barboza, A., Cunningham, J., Curtis, D., Czerski, P.M., Dale, A.M., Dalkner, N., David, F.S., Degenhardt, F., Djurovic, S., Dobbyn, A.L., Douzenis, A., Elvsåshagen, T., Escott-Price, V., Ferrier, I. N., Fiorentino, A., Foroud, T.M., Forty, L., Frank, J., Frei, O., Freimer, N.B., Frisén, L., Gade, K., Garnham, J., Gelernter, J., Giørtz Pedersen, M., Gizer, I.R., Gordon, S.D., Gordon-Smith, K., Greenwood, T.A., Grove, J., Guzman-Parra, J., Ha, K., Haraldsson, M., Hautzinger, M., Heilbronner, U., Hellgren, D., Herms, S., Hoffmann, P., Holmans, P.A., Huckins, L., Jamain, S., Johnson, J.S., Kalman, J.L., Kamatani, Y., Kennedy, J.L., Kittel-Schneider, S., Knowles, J.A., Kogevinas, M., Koromina, M., Kranz, T.M., Kranzler, H.R., Kubo, M., Kupka, R., Kushner, S.A., Lavebratt, C., Lawrence, J., Leber, M., Lee, H.-J., Lee, P.H., Levy, S.E., Lewis, C., Liao, C., Lucae, S., Lundberg, M., MacIntyre, D.J., Magnusson, S.H., Maier, W., Maihofer, A., Malaspina, D., Maratou, E., Martinsson, L., Mattheisen, M., McCarroll, S.A., McGregor, N.W., McGuffin, P., McKay, J.D., Medeiros, H., Medland, S.E., Millischer, V., Montgomery, G.W., Moran, J.L., Morris, D.W.,

Mühleisen, T.W., O'Brien, N., O'Donovan, C., Loohuis, L.M.O., Oruc, L., Papiol, S., Pardiñas, A.F., Perry, A., Pfennig, A., Porichi, E., Potash, J.B., Quested, D., Raj, T., Rapaport, M.H., DePaulo, J.R., Regeer, E.J., Rice, J.P., Rivas, F., Rivera, M., Roth, J., Roussos, P., Ruderfer, D.M., Sánchez-Mora, C., Schulte, E.C., Senner, F., Sharp, S., Shilling, P.D., Sigurdsson, E., Sirignano, L., Slaney, C., Smeland, O.B., Smith, D.J., Sobell, J.L., Søholm Hansen, C., Artigas, M.S., Spijker, A.T., Stein, D.J., Strauss, J.S., Świątkowska, B., Terao, C., Thorgeirsson, T.E., Toma, C., Tooney, P., Tsermpini, E.-E., Vawter, M.P., Vedder, H., Walters, J.T.R., Witt, S.H., Xi, S., Xu, W., Yang, J.M.K., Young, A.H., Young, H., Zandi, P.P., Zhou, H., Zillich, L., Psychiatry, H.A.-I., Adolfsson, R., Agartz, I., Alda, M., Alfredsson, L., Babadjanova, G., Backlund, L., Baune, B.T., Bellivier, F., Bengesser, S., Berrettini, W.H., Blackwood, D.H.R., Boehnke, M., Børglum, A.D., Breen, G., Carr, V.J., Catts, S., Corvin, A., Craddock, N., Dannlowski, U., Dikeos, D., Esko, T., Etain, B., Ferentinos, P., Frye, M., Fullerton, J. M., Gawlik, M., Gershon, E.S., Goes, F.S., Green, M.J., Grigoroiu-Serbanescu, M., Hauser, J., Henskens, F., Hillert, J., Hong, K.S., Hougaard, D.M., Hultman, C.M., Hveem, K., Iwata, N., Jablensky, A.V., Jones, I., Jones, L.A., Kahn, S., Kelsoe, R., Kirov, J.R., Landén, G., Leboyer, M., M., Lewis, C.M., Li, Q.S., Lissowska, J., Lochner, C., Loughland, C., Martin, N.G., Mathews, C.A., Mayoral, F., McElroy, S.L., McIntosh, A.M., McMahon, F.J., Melle, I., Michie, P., Milani, L., Mitchell, P.B., Morken, G., Mors, O., Mortensen, P.B., Mowry, B., Müller-Myhsok, B., Myers, R.M., Neale, B.M., Nievergelt, C.M., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Oedegaard, K.J., Olsson, T., Owen, M.J., Paciga, S.A., Pantelis, C., Pato, C., Pato, M. T., Patrinos, G.P., Perlis, R.H., Posthuma, D., Ramos-Quiroga, J.A., Reif, A., Reininghaus, E.Z., Ribasés, M., Rietschel, M., Ripke, S., Rouleau, G.A., Saito, T., Schall, U., Schalling, M., Schofield, P.R., Schulze, T.G., Scott, L.J., Scott, R.J., Serretti, A., Weickert, C.S., Smoller, J.W., Stefansson, H., Stefansson, K., Stordal, E., Streit, F., Sullivan, P.F., Turecki, G., Vaaler, A.E., Vieta, E., Vincent, J.B., Waldman, . I..D.., Weickert, T.W., Werge, T., Wray, N.R., Zwart, J.-A., Biernacka, J.M., Nurnberger, J.I., Cichon, S., Edenberg, H.J., Stahl, E.A., McQuillin, A., Di Florio, A., Ophoff, R.A., Andreassen, O.A., 2020. Genome-wide association study of over 40,000 bipolar disorder cases provides new insights into the underlying biology (preprint). Genetic Genomic Med. https://doi.org/10.1101/2020.09.17.20187054.

Murru, A., Pacchiarotti, I., Verdolini, N., Reinares, M., Torrent, C., Geoffroy, P.-A., Bellivier, F., Llorca, P.-M., Vieta, E., Samalin, L., 2018. Modifiable and non-modifiable factors associated with functional impairment during the inter-episodic periods of bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 268, 749–755. https://doi.org/10.1007/s00406-017-0811-0.

Nguyen, T.T., Kovacevic, S., Dev, S.I., Lu, K., Liu, T.T., Eyler, L.T., 2017. Dynamic functional connectivity in bipolar disorder is associated with executive function and processing speed: a preliminary study. Neuropsychology 31, 73–83. https://doi.org/10.1037/neu0000317.

Nudmamud-Thanoi, S., Reynolds, G.P., 2004. The NR1 subunit of the glutamate/NMDA receptor in the superior temporal cortex in schizophrenia and affective disorders. Neurosci. Lett. 372, 173–177. https://doi.org/10.1016/j.neulet.2004.09.035.

Oliva, V., Fico, G., De Prisco, M., Gonda, X., Rosa, A.R., Vieta, E., 2025. Bipolar disorders: an update on critical aspects. Lancet Reg. Health - Eur. 48, 101135. https://doi.org/10.1016/j.lanepe.2024.101135.

Pang, Y., Chen, Heng, Wang, Y., Long, Z., He, Z., Zhang, H., Liao, W., Cui, Q., Chen, Huafu, 2018. Transdiagnostic and diagnosis-specific dynamic functional connectivity anchored in the right anterior insula in major depressive disorder and bipolar depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 85, 7–15. https://doi.org/10.1016/j.pnpbp.2018.03.020.

Pedersen, G., Urnes, Ø., Hummelen, B., Wilberg, T., Kvarstein, E.H., 2018. Revised manual for the Global Assessment of Functioning scale. Eur. Psychiatry 51, 16–19. https://doi.org/10.1016/j.eurpsy.2017.12.028.

Preti, M.G., Bolton, T.A., Van De Ville, D., 2017. The dynamic functional connectome: state-of-the-art and perspectives. NeuroImage 160, 41–54. https://doi.org/10.1016/j.neuroimage.2016.12.061.

Quilty, L.C., Robinson, J.J., Rolland, J.-P., Fruyt, F.D., Rouillon, F., Bagby, R.M., 2013. The structure of the Montgomery-Åsberg depression rating scale over the course of treatment for depression: structure of the MADRS over treatment. Int. J. Methods Psychiatr. Res. 22, 175–184. https://doi.org/10.1002/mpr.1388.

Ramos-Nuñez, A.I., Fischer-Baum, S., Martin, R.C., Yue, Q., Ye, F., Deem, M.W., 2017. Static and dynamic measures of Human brain connectivity predict complementary aspects of Human cognitive performance. Front. Hum. Neurosci. 11, 420. https://doi.org/10.3389/fnhum.2017.00420.

Rashid, B., Damaraju, E., Pearlson, G.D., Calhoun, V.D., 2014. Dynamic connectivity states estimated from resting fMRI identify differences among Schizophrenia, bipolar disorder, and healthy control subjects. Front. Hum. Neurosci. 8. https://doi.org/10.3389/fnhum.2014.00897.

Samalin, L., De Chazeron, I., Vieta, E., Bellivier, F., Llorca, P., 2016. Residual symptoms and specific functional impairments in euthymic patients with bipolar disorder. Bipolar Disord 18, 164–173. https://doi.org/10.1111/bdi.12376.

Samamé, C., Martino, D.J., Strejilevich, S.A., 2015. An individual task meta-analysis of social cognition in euthymic bipolar disorders. J. Affect. Disord. 173, 146–153. https://doi.org/10.1016/j.jad.2014.10.055.

Sambataro, F., Reed, J.D., Murty, V.P., Das, S., Tan, H.Y., Callicott, J.H., Weinberger, D. R., Mattay, V.S., 2009. Catechol-O-methyltransferase Valine158Methionine polymorphism modulates brain networks underlying working memory across adulthood. Biol. Psychiatry 66, 540–548. https://doi.org/10.1016/j.biopsych.2009.04.014.

Sanacora, G., Zarate, C.A., Krystal, J.H., Manji, H.K., 2008. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat. Rev. Drug Discov. 7, 426–437. https://doi.org/10.1038/nrd2462.

Savva, A.D., Mitsis, G.D., Matsopoulos, G.K., 2019. Assessment of dynamic functional connectivity in resting-state fMRI using the sliding window technique. Brain Behav 9, e01255. https://doi.org/10.1002/brb3.1255.

Scaini, G., Rezin, G.T., Carvalho, A.F., Streck, E.L., Berk, M., Quevedo, J., 2016. Mitochondrial dysfunction in bipolar disorder: evidence, pathophysiology and translational implications. Neurosci. Biobehav. Rev. 68, 694–713. https://doi.org/10.1016/j.neubiorev.2016.06.040.

Scaini, G., Valvassori, S.S., Diaz, A.P., Lima, C.N., Benevenuto, D., Fries, G.R., Quevedo, J., 2020. Neurobiology of bipolar disorders: a review of genetic components, signaling pathways, biochemical changes, and neuroimaging findings. Braz. J. Psychiatry 42, 536–551. https://doi.org/10.1590/1516-4446-2019-0732.

Seamans, J.K., Yang, C.R., 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog. Neurobiol. 74, 1–58. https://doi.org/10.1016/j.pneurobio.2004.05.006.

Skjelstad, D.V., Malt, U.F., Holte, A., 2010. Symptoms and signs of the initial prodrome of bipolar disorderA systematic review. J. Affect. Disord. 126, 1–13. https://doi.org/10.1016/j.jad.2009.10.003.

Smith, M.R., Readhead, B., Dudley, J.T., Morishita, H., 2019. Critical period plasticity-related transcriptional aberrations in schizophrenia and bipolar disorder. Schizophr. Res. 207, 12–21. https://doi.org/10.1016/j.schres.2018.10.021.

Solomon, D.A., Leon, A.C., Coryell, W.H., Endicott, J., Li, C., Fiedorowicz, J.G., Boyken, L., Keller, M.B., 2010. Longitudinal course of Bipolar I disorder: duration of mood episodes. Arch. Gen. Psychiatry 67, 339. https://doi.org/10.1001/archgenpsychiatry.2010.15.

Srivastava, C., Bhardwaj, A., Sharma, M., Kumar, S., 2019. Cognitive deficits in euthymic patients with bipolar disorder: state or trait marker? J. Nerv. Ment. Dis. 207, 100–105. https://doi.org/10.1097/NMD.0000000000000920.

Tang, Q., Cui, Q., Chen, Y., Deng, J., Sheng, W., Yang, Y., Lu, F., Zeng, Y., Jiang, K., Chen, H., 2022. Shared and distinct changes in local dynamic functional connectivity patterns in major depressive and bipolar depressive disorders. J. Affect. Disord. 298, 43–50. https://doi.org/10.1016/j.jad.2021.10.109.

The International Schizophrenia Consortium, 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460, 748–752. https://doi.org/10.1038/nature08185.

The jamovi project (2024). jamovi (Version 2.5) [Computer Software]. Retrieved from https://www.jamovi.org, n.d.

Thomas, S.A., Christensen, R.E., Schettini, E., Saletin, J.M., Ruggieri, A.L., MacPherson, H.A., Kim, K.L., Dickstein, D.P., 2019. Preliminary analysis of resting state functional connectivity in young adults with subtypes of bipolar disorder. J. Affect. Disord. 246, 716–726. https://doi.org/10.1016/j.jad.2018.12.068.

Vieta, E., Torrent, C., 2016. Functional remediation: the pathway from remission to recovery in bipolar disorder. World Psychiatry 15, 288–289. https://doi.org/10.1002/wps.20351.

Vlad, M., Raucher-Chéné, D., Henry, A., Kaladjian, A., 2018. Functional outcome and social cognition in bipolar disorder: is there a connection? Eur. Psychiatry 52, 116–125. https://doi.org/10.1016/j.eurpsy.2018.05.002.

Wang, Y., Huang, G., Wu, Y., Xiong, L., Chen, Y., Li, H., Long, F., Li, Q., Sun, H., Kemp, G. J., Liu, L., Gong, Q., Li, F., 2025. Brain structural and functional magnetic resonance imaging alterations in individuals with convergence insufficiency. Ophthalmic Physiol. Opt. 45, 656–665. https://doi.org/10.1111/opo.13459.

Wang, Y., Shu, Y., Cai, G., Guo, Y., Gao, J., Chen, Y., Lv, L., Zeng, X., 2024. Altered static and dynamic functional network connectivity in primary angle-closure glaucoma patients. Sci. Rep. 14, 11682. https://doi.org/10.1038/s41598-024-62635-6.

Watson, M., Filia, K., Stevens, A., Cotton, S., Nelson, B., Ratheesh, A., 2023. A systematic review and meta-analysis of global and social functioning among people at risk of bipolar disorder. J. Affect. Disord. 321, 290–303. https://doi.org/10.1016/j.jad.2022.10.019.

West, R.M., 2022. Best practice in statistics: the use of log transformation. Ann. Clin. Biochem. Int. J. Lab. Med. 59, 162–165. https://doi.org/10.1177/00045632211050531.

Xiao, Q., Zhang, G., Zhong, Y., 2024. Abnormal functional connectivity of the intrinsic networks in adolescent bipolar I versus bipolar II disorder. Psychiatry Res. Neuroimaging 340, 111802. https://doi.org/10.1016/j.pscychresns.2024.111802.

Yang, Y., Qian, C., Huafu, C., 2020. Altered inter-hemispheric functional connectivity dynamics in bipolar disorder. In: 2020 17th International Computer Conference on Wavelet Active Media Technology and Information Processing (ICCWAMTIP). Presented at the 2020 17th International Computer Conference on Wavelet Active Media Technology and Information Processing (ICCWAMTIP), pp. 334–337. https://doi.org/10.1109/ICCWAMTIP51612.2020.9317369.

Yan, C.-G., Wang, X.-D., Zuo, X.-N., Zang, Y.-F., 2016. DPABI: data processing & analysis for (Resting-State) Brain imaging. Neuroinformatics 14, 339–351. https://doi.org/10.1007/s12021-016-9299-4.

You, W., Luo, L., Yao, L., Zhao, Y., Li, Q., Wang, Yuxia, Wang, Yaxuan, Zhang, Q., Long, F., Sweeney, J.A., Gong, Q., Li, F., 2022. Impaired dynamic functional brain properties and their relationship to symptoms in never treated first-episode patients with schizophrenia. Schizophrenia 8, 90. https://doi.org/10.1038/s41537-022-00299-9.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435. https://doi.org/10.1192/bjp.133.5.429.

Zarate, C.A., Du, J., Quiroz, J., Gray, N.A., Denicoff, K.D., Singh, J., Charney, D.S., Manji, H.K., 2003. Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: role of the glutamatergic system. Ann. N. Y. Acad. Sci. 1003, 273–291. https://doi.org/10.1196/annals.1300.017.

Zheng, M., 2025. Thinking bipolar disorder as a symptom rather than a disease. Asian J. Psychiatry 109, 104540. https://doi.org/10.1016/j.ajp.2025.104540.