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Distinct connectivity patterns in bipolar and unipolar depression: a functional connectivity multivariate pattern analysis study

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Abstract

Background Patients with bipolar disorder (BD) and major depressive disorder (MDD) exhibit depressive episodes with similar symptoms despite having different and poorly understood underlying neurobiology, often leading to misdiagnosis and improper treatment. This exploratory study examined whole-brain functional connectivity (FC) using FC multivariate pattern analysis (fc-MVPA) to identify the FC patterns with the greatest ability to distinguish between currently depressed patients with BD type I (BD I) and those with MDD.

Methodology In a cross-sectional design, 41 BD I, 40 MDD patients and 63 control participants completed resting state functional magnetic resonance imaging scans. Data-driven fc-MVPA, as implemented in the CONN toolbox, was used to identify clusters with differential FC patterns between BD patients and MDD patients. The identified cluster was used as a seed in a post hoc seed-based analysis (SBA) to reveal associated connectivity patterns, followed by a secondary ROI-to-ROI analysis to characterize differences in connectivity between these patterns among BD I patients, MDD patients and controls.

Results FC-MVPA identified one cluster located in the right frontal pole (RFP). The subsequent SBA revealed greater FC between the RFP and posterior cingulate cortex (PCC) and between the RFP and the left inferior/middle temporal gyrus (LI/MTG) and lower FC between the RFP and the left precentral gyrus (LPCG), left lingual gyrus/occipital cortex (LLG/OCC) and right occipital cortex (ROCC) in MDD patients than in BD patients. Compared with the controls, ROI-to-ROI analysis revealed lower FC between the RFP and the PCC and greater FC between the RFP and the LPCG, LLG/OCC and ROCC in BD patients; in MDD patients, the analysis revealed lower FC between the RFP and the LLG/OCC and ROCC and greater FC between the RFP and the LI/MTG.

Conclusions Differences in the RFP FC patterns between currently depressed patients with BD and those with MDD suggest potential neuroimaging markers that should be further examined. Specifically, BD patients exhibit increased FC between the RFP and the motor and visual networks, which is associated with psychomotor symptoms and

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heightened compensatory frontoparietal FC to counter distractibility. In contrast, MDD patients exhibit increased FC between the RFP and the default mode network, corresponding to sustained self-focus and rumination.

Keywords Bipolar disorder, Major depressive disorder, Multivariate pattern analysis, Functional connectivity, Resting state

Introduction

Depressive episodes (DEs) are clinical features shared by two closely related yet neurobiologically distinct mood disorders, major depressive disorder (MDD) and bipolar disorder (BD); the similarities in these episodes frequently result in diagnostic challenges (1). MDD is defined by one DE or recurring DEs characterized by sadness, anhedonia, decreased energy, social withdrawal, low self-esteem and sleep disturbances [2] and has a twelve-month prevalence in Europe between 3% and 10%[3]. BD, with a twelve-month prevalence of 1% [4], includes BD type I (BD I), defined by the presence of mania, and BD type II (BD II), defined by the presence of hypomania and DEs [2]. Although (hypo)mania defines BD, DEs are more frequent, last longer, and disproportionately account for morbidity and mortality in BD patients [5–11]. Moreover, since DEs are predominantly present at the onset of the illness, up to 40–60% of BD patients are misdiagnosed with MDD, and only 20% receive the correct diagnosis within the first year [12–14]. The repercussions of misdiagnosis include the risk of inappropriate drug prescription and switching to manic episodes, prolonged illness duration, risk of recurrence, suicide and overall poorer treatment response [15–19]. Thus, it is imperative to discern the differing neurobiological mechanisms underlying DEs in MDD patients and BD patients to refine diagnostic procedures and therapeutic interventions.

Manifestations of psychiatric disorders are associated with disturbances within and between networks of interacting regions in the brain [20]. One neuroimaging method used to assess these networks is resting-state functional magnetic resonance imaging (rs-fMRI), which examines low-frequency spontaneous fluctuations in blood oxygen level-dependent (BOLD) signals among voxels in the brain at rest [21, 22]. Temporally correlated voxels in brain regions are presumed to be functionally connected (i.e., communicating) and to form intrinsic functional networks [23]. Within this network perspective, three consistently identified networks and their subregions [24] have been related to symptoms of depression [25] and compared between BD and MDD patients [26, 27].

First, the task-free default mode network (DMN), anchored in the medial prefrontal and parietal cortices, is associated with internally focused, self-referential thought; "mind wandering"; and social cognition [24, 28]. Compared to BD patients, MDD patients have exhibited inconsistently increased, reduced or similar functional connectivity (FC) within the DMN across studies [29–36]. However, increased FC within the DMN was found to be associated with depression severity and rumination in MDD patients [36, 37]. The variability of these findings may be related to clinical heterogeneity, i.e., depression severity [36, 38], responsiveness to treatment [39], and length of the episode [40].

Second, the frontoparietal network (FPN), or central executive network, is associated with externally focused, goal-directed tasks and cognitive regulation; the core network regions include the lateral prefrontal and parietal cortices [24, 41]. Compared to MDD patients, increased within-network FC in the FPN was found in BD patients [42–44]. This was linked to compensatory attempts to navigate away from or to dampen distracting inner states and thoughts originating in the affective and salience networks [45, 46], increased depression severity [26], and disease progression in BD patients [47]. In contrast, reduced within-network FC in the FPN in MDD patients can be linked to cognitive symptoms.

Finally, the salience network (SN), which partially overlaps with the reward and affective networks, monitors and integrates internal and external sensory information while also eliciting FPN or DMN responses in association with internal experience and external environmental demands [24, 41, 48]. Compared to MDD patients, BD patients displayed increased connectivity among the key regions of the SN—the anterior cingulate, thalamus, striatum and insula [42, 49–55]. In addition, relative to MDD patients, BD patients exhibited reduced connectivity between the insula and the FPN and DMN [50, 56, 57], while other components of the SN displayed increased connectivity with the FPN and DMN [49, 54, 55]. These findings may be associated with emotional dysregulation and impaired emotional, reward and interoceptive input in regulating the FPN and DMN in BD patients [26].

The methods used to examine functional networks in rs-fMRI studies include seed-based analysis (SBA), region-of-interest (ROI)-to-ROI analysis and independent component analysis (ICA) [58, 59]. While SBA involves selecting specific seed regions and estimating their FC throughout the brain, ROI-to-ROI analysis investigates FC between predefined brain regions (ROIs), and ICA identifies spatially independent components reflecting distinct networks. However, each of these methods carries inherent limitations: SBA and ROI-to-ROI analysis overlook FC beyond the prespecified seeds

and ROIs, while ICA tends to converge on large-scale networks, potentially overlooking finer-scale functional organizations. FC multivariate pattern analysis (fc-MVPA) offers an alternative approach that can be used to estimate the entire FC pattern for each voxel in the brain [60, 61]. If used in a contrast setting, such as comparing two distinct groups, it can identify clusters of voxels with the most differential between-group FC patterns at the whole-brain level [61, 62]. This approach has not yet been used for the comparison of BD and MDD patients, it is data driven and exploratory and has the ability to find the most differential FC patterns that may not have been identified previously.

While comparisons of FC between currently depressed BD patients and MDD patients converge mainly on the three aforementioned networks [26, 27], there is marked heterogeneity in the rs-fMRI FC results. The reasons for this heterogeneity may include the patient's current clinical state, demographics, medication, and disorder subtype (BD I and II), all of which are likely related to the underlying neurobiological mechanism and result in heterogeneous FC findings.

The aim of this exploratory study was to identify the FC patterns with the greatest ability to differentiate between MDD patients and BD patients at the whole-brain level using the novel, data-driven fc-MVPA. To reduce commonly occurring clinical heterogeneity bias, we compared participants who were currently depressed; matched for age, sex, and depression severity; nonpsychotic; diagnosed with BD I and MDD; and, with the exception of participants who were treated with mood stabilizing agents, medication-free.

Methods

Participants

One hundred forty-six participants (42 BD I patients, 40 MDD patients, and 64 controls) were initially recruited for the study. Recruitment, inclusion and MRI scanning were performed at the National Institute of Mental Health, Klecany, between 2016 and 2020 by trained psychiatrists and radiologists. The included MDD and BD patients participated in two separate intervention studies with comparable inclusion criteria focused on the treatment of DEs with neurostimulation (EudraCT number 2015–001639-19 and ISRCTN77188420). MRI scans used in this study were baseline scans obtained after (1) a period of two weeks of medication washout (MDD, BD) excluding stabilizing agents (mood stabilizers or antipsychotics, BD) and (2) before therapeutic intervention. Control participants were recruited separately for this study via internet advertisement.

The inclusion criteria for the patients were age 18–70 years, met the DSM-IV (2) criteria for BD I or MDD, current DEs without psychosis as determined by the Mini-International Neuropsychiatric Interview (M.I.N.I.) [63], duration of current DE more than 1 month, Montgomery and Åsberg Depression Rating Scale (MADRS) score≥20 [64] and Young Mania Rating Scale (YMRS) score<12 in BD patients [65], the ability to provide informed written consent, and right handedness. The exclusion criteria were a history of any DSM-IV Axis I diagnosis other than BD I or MDD (excluding anxiety disorders) in the last year; personality disorders; a history of substance dependence in the last year except nicotine; pregnancy or breastfeeding; severe somatic disorders (cardiovascular disease, neoplasms, endocrine disorders, etc.) that could be associated with depression; contraindications for MRI (metal device in the head, applied pacemaker or other electronic stimulation devices, etc.); and treatment with electroconvulsive therapy less than 3 months before enrolment. The inclusion and exclusion criteria for the control subjects were identical, with the additional exclusion criterion of the presence of any psychiatric diagnosis, symptoms or medication use in their medical history.

The patients were age- and sex-matched. One BD patient and one control participant were excluded after rs-fMRI preprocessing and quality control assessment, resulting in a total of 144 (41 BD I patients, 40 MDD patients, and 63 controls) participants included in the analysis.

Data acquisition

All participants were scanned with the same protocols in a 3T Siemens Prisma MRI scanner. For anatomical reference, high-resolution 3D T1-weighted magnetization prepared by rapid acquisition gradient echo (MPRAGE) images of the whole brain were acquired with a 64-channel head/neck coil (repetition time (TR) 2400 ms, inversion time (TI) 1000 ms, echo time (TE) 2.34 ms, flip angle 8, slice thickness 0.7, acquisition matrix 320×320, voxel size 1×1×1 mm). Functional resting-state images covering the whole brain were obtained using a T2*-weighted 2D multiband echo planar imaging sequence with a multiband factor of 4 (MB4 EPI) with BOLD contrast (TE 30 ms, TR 700 ms, flip angle 52, slice thickness 3, acquisition matrix 74×74, voxel size 3×3×3 mm, 700 volumes per subject). The total resting scan duration per participant was 8.2 min.

Data preparation and statistical analysis

Preprocessing, denoising and data analysis of the neuroimaging data included in this manuscript were performed using CONN release 22.a [66, 67] and SPM release 12.7771 [68] using the default settings with author recommendations. Calculations of demographic and clinical variables were performed in IBM SPSS [69].

Data preprocessing

Default preprocessing was performed as recommended in the CONN toolbox [62]. Functional data were realigned using the SPM realign and unwarp procedure, where all scans were coregistered to a reference image (first scan of the first session) using a least squares approach and a 6-parameter (rigid body) transformation and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of the functional data was corrected following SPM slice-timing correction procedure, using sinc temporal interpolation to resample each slice BOLD time-series to a common mid-acquisition time. Potential outlier scans, defined as acquisitions with framewise displacement (FD) above 0.5 mm or global BOLD signal changes above 3 standard deviations, were identified using ART (https://www.nitrc.org/projects/artifact_detect/), and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. Functional and anatomical data were coregistered and normalized into standard MNI space; segmented into grey matter, white matter, and CSF tissue classes; and resampled to 2 mm isotropic voxels following an indirect normalization procedure using the SPM unified segmentation and normalization algorithm with the default IXI-549 tissue probability map template. Finally, functional data were smoothed using spatial convolution with a Gaussian kernel of 6 mm full width at half-maximum (FWHM).

Denoising

Functional data were denoised using a standard denoising pipeline [62], including the regression of potential confounding effects characterized by white matter time series (5 CompCor noise components), CSF time series (5 CompCor noise components), motion parameters and their first-order derivatives (12 factors), outlier scans, session effects and their first-order derivatives (2 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD time series between 0.008 Hz and 0.09 Hz. The CompCor noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to be satisfactory, ranging from 35.4 to 77.4 (average 73.7) across all subjects.

Quality control assessment

Quality control of the T1 and MB4 EPI data was performed according to previously described methods [70]. The structural data did not exhibit any artefacts. The coregistration of T1 images to the MNI template was performed with >80% accuracy. After visual inspection of the raw, preprocessed and denoised functional data, we excluded one BD participant after finding a systematic artefact in the right dorsal frontal area visible in all 700 scans and one HC participant due to the low number of obtained functional scans. After the ART excluded outlier scans with excessive motion and global signal changes, we evaluated the functional data using quality control measures to identify outlier participants to be excluded from the analysis (these measures are described in Supplement Fig. 1). No further participants were excluded. The quality control plots created in CONN confirmed satisfactory final preprocessing and denoising results (details in Supplement Figs. 2 and 3, and 4).

Data analysis

Primary analysis

Multivariate pattern analysis We performed fc-MVPA using CONN following the default procedure [61, 62]. Only BD and MDD participants were included in this part of the analysis, because including controls might shift the results towards the largest differences between the control group and the two possibly more similar clinical groups.

FC multivariate pattern analyses were performed to estimate the first 8 eigenpatterns (components) characterizing the principal axes of heterogeneity in FC across subjects. The number of components was determined by a convention ratio of 10:1 (number of BD and MDD participants: number of components), as recommended by the authors of the CONN toolbox [61, 66, 67]. From these eigenpatterns, 8 associated eigenpattern score images were derived for each individual subject, characterizing their brain-wide functional connectome state. Eigenpatterns and eigenpattern scores were computed separately for each individual seed voxel as left and right singular vectors, respectively, from a group-level singular value decomposition (SVD) of the matrix of FC values between this seed voxel and the rest of the brain (a matrix with one row per target voxel and one column per subject). Individual FC values were computed from the matrices of bivariate correlation coefficients between the BOLD time series from each pair of voxels, estimated using a singular value decomposition of the z score-normalized BOLD signal (subject-level SVD) with 64 components separately for each subject. The aforementioned 8 components were retained for group-level analysis.

Group-level analyses were performed for each individual voxel, with first-level connectivity measures at each

voxel as the dependent variables and groups as the independent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). We used the F test (ANCOVA) across all eight MVPA components to test for group differences (MDD > BD) in whole-brain connectivity, comparing the component scores between the two groups for each voxel. The results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold and a familywise corrected p-FWE < 0.05 cluster-size threshold and adjusted for age, sex and subject motion (FD) as covariates.

Seed-based analysis To characterize the FC patterns between the fc-MVPA clusters and the rest of the brain, post hoc SBA using the fc-MVPA clusters as seeds was performed [61]. FC strength was represented by Fisher-transformed bivariate correlation coefficients estimated for the seed region and each target voxel. Group-level analysis was performed using a GLM, in which a separate GLM was estimated for each voxel, with first-level connectivity at this voxel as the dependent variable, group (MDD, BD) as the independent variable, and age, sex and FD as covariates. Cluster-level inferences were based on parametric statistics from Gaussian random field theory, and the results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold and a familywise-corrected p-FWE < 0.05 cluster-size threshold. The regions identified in the fc-MVPA and subsequent SBA were assigned to specific networks using the atlases included in the CONN toolbox (Harvard-Oxford cortical atlas, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases; Yeo 7-network parcellation atlas [71]).

Secondary analysis

The secondary analysis explored how the differences between BD patients and MDD patients identified in the fc-MVPA and subsequent SBA represent abnormal neural functioning compared to the controls, representing the neurotypical population. In a series of ROI-to-ROI analyses compared with controls, the FC values of patients with MDD and BD were compared between clusters identified by fc-MVPA and clusters identified by the subsequent SBA. FC strength was represented by Fisher-transformed bivariate correlation coefficients estimated separately for each pair of ROIs. The groups were compared pairwise and controlled for age, sex, and FD. The results were considered significant if $p < 0.05$ and if they survived an FDR < 0.05 correction for multiple comparisons.

Results

Participants

Demographic and clinical characteristics are displayed in Table 1. MDD patients and BD I patients did not differ in age, sex, FD, current episode duration (weeks) or depression severity (MADRS score). BD I participants had a younger age of illness onset, longer illness duration, more DEs, more overall episodes, and greater illness severity (defined as episode/illness duration) than MDD participants. The control participants were significantly younger and had lower FD than did the MDD and BD I participants.

Table 1 Demographics and clinical characteristics

	BD ($n = 41$)	MDD ($n = 40$)	CON ($n = 63$)	*p* Value
Age (± SD)	44.09 (± 14)	47.03 (± 12.7)	33.55 (± 9.3)	BD vs. MDD < 0.32 BD vs. CON < 0.001* MDD vs. CON < 0.001*
Sex, no. of Females (%)	24 (57%)	25 (62%)	41 (64%)	BD vs. MDD vs. CON < 0.77
MADRS (Mean ± SD)	26.6 (± 4.58)	27.77 (± 2.97)	-	0.179
YMRS (Mean ± SD)	1.56 (± 2.58)	-	-	-
Age of onset (Mean ± SD)	27.92 (± 10.84)	38.1 (± 10.62)	-	0.001*
Illness duration (years) (Mean ± SD)	16.16(± 9.65)	8.49 (± 6.87)	-	0.001*
NO all episodes (Mean ± SD)	10.87 (± 7.47)	2.92 (± 1.74)	-	0.001*
NO depressive episodes (Mean ± SD)	7.73(± 5.59}	2.92(± 1.74)	-	0.001*
Current episode in weeks (Mean ± SD)	22.42 (± 16.93)	27.95 (± 24.1)	-	0.239
Illness severity (all episodes / illness duration) (Mean ± SD)	0.91 (± 0.84)	0.57(± 0.38)	-	0.024*
Framewise displacement (Mean ± SD)	0.21 (± 0.10)	0.17(± 0.09)	0.13 (± 0.05)	BD vs. MDD < 0.091 BD vs. CON < 0.001* MDD vs. CON < 0.104
MS (count)	35	1	-	-
AP (count)	30	1	-	-
AD (count)	25	39	-	-

Abbreviations: AD antidepressants, AP antipsychotics, BD bipolar disorder, CON controls, MADRS Montgomery–Åsberg Depression Rating Scale, MDD major depressive disorder, MS mood stabilizers, NO number of, SD standard deviation, YMRS Young Mania Rating Scale. * significant result (t-test, Mann- Whitney U test, ANOVA or the post hoc Tukey's HSD) Note: medication report is pre-washout.

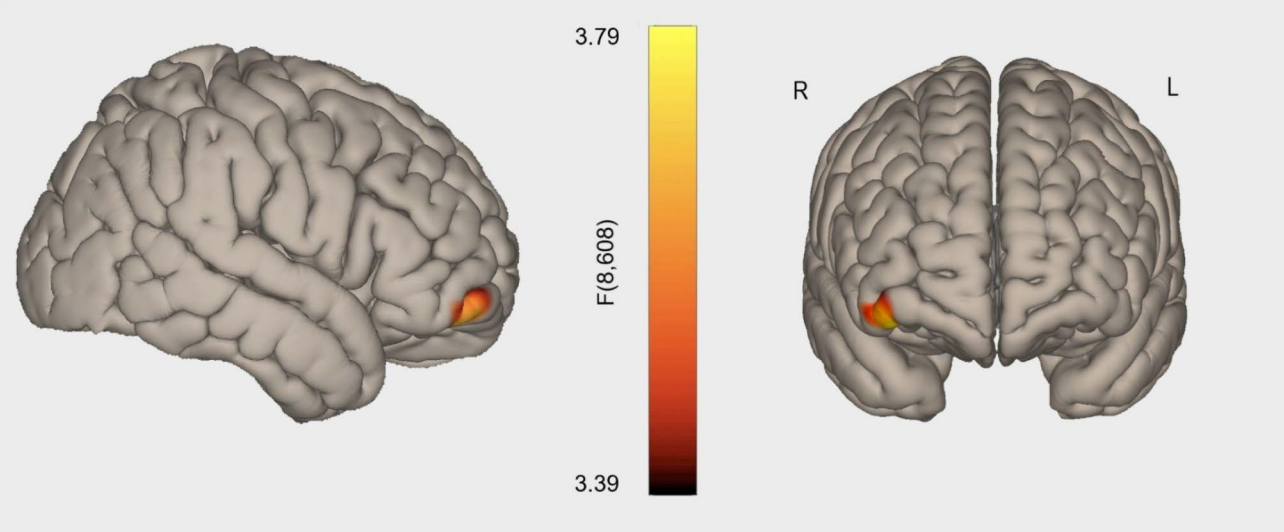

Fig. 1 Resulting cluster from fc-MVPA analysis - right frontal pole. Lateral and anterior view. Voxel level $p < 0.001$, cluster level p-FWE < 0.05

Table 2 Resulting cluster from fc-MVPA using MDD > BD contrast

Cluster (MNI x, y,z)	size	size *p*-FWE	size *p*-FDR	HO and AAL atlas	Brodmann	Network
40 52 – 12	31	0.01488	0.00486	Frontal pole right	Anterior prefrontal cortex - BA 47	FPN

Abbreviations: AAL automated anatomic labelling, BD bipolar disorder, FPN frontoparietal network, HO Harward-Oxford, MDD major depressive disorder

Table 3 Seed-based analysis results using right frontal Pole as seed

Contrast	Cluster (MNI x, y,z)	size	size *p*-FWE	size *p*-FDR	HO and AAL atlas	Brodmann area	Network
BD > MDD	**-4 -72 -8**	1174	0.0000	0.0000	L LG/OCC	L Primary/secondary/associative cortex - BA 17, 18, 19	FPN/DMN/ Visual
	+30–98+14	505	0.0000	0.0000	R OCC	R Primary/secondary/associative cortex - BA 17, 18, 19	Visual
	-54+02+48	92	0.0420	0.0135	L PCG	L Primary motor/premotor cortex - BA 4, 6	SMN/FPN
MDD > BD	**+04–38+34**	170	0.0013	0.0007	PCC	Dorsal Posterior Cingulate - BA 31	DMN
	-68 -42 -20	104	0.0238	0.0095	L ITG/MTG	L Inferior temporal gyrus/Fusiform gyrus - BA 20, 37,	FPN/DMN

Abbreviations: AAL automated anatomic labelling, BD bipolar disorder, DMN default mode network, FPN frontoparietal network, HO Harvard-Oxford, I/MTG inferior/middle temporal gyrus, L left, LG lingual gyrus, MDD major depressive disorder, OCC occipital cortex, PCG precentral gyrus, PCC posterior cingulate cortex, SMN somatosensory network, Visual visual network.

Primary analysis

The fc-MVPA revealed one cluster located in the right frontal pole (RFP) with significantly different connectivity patterns between BD patients and MDD patients (Fig. 1; Table 2). A post hoc analysis explored the associations of demographic and clinical variables with the fc-MVPA results. None of the correlations between any of the eight components extracted from the fc-MVPA and clinical or demographic variables were significant (details in Supplement Table 1).

SBA revealed significantly lower FC between the RFP and the left lingual gyrus/occipital cortex (LLG/OCC) (t(76)=-6.8, p-FWE<0.0001, d=1.51), right occipital cortex (ROCC)(t(76)=-5.7, p-FWE<0.0001, d=1.27), and left precentral gyrus (LPCG) (t(76)=-4.97, p-FWE=0.0421, d=1.11) and greater FC between the RFP and the left posterior inferior/middle temporal gyrus (LI/MTG) (t(76)=5.26, p-FWE=0.0238, d=1.17) and posterior cingulate cortex (PCC) (t(76)=5.17, p-FWE=0.0013, d=1.15) in MDD patients than in BD patients (Table 3; Fig. 2).

Secondary analysis

ROI-to-ROI analysis compared the FC between the RFP and the clusters found in the SBA among BD patients, MDD patients and controls. The MDD vs. BD comparison results were corresponding to the SBA results and are displayed for illustrative purposes (Figs. 3 and 4). Relative to BD patients, controls exhibited increased FC between the RFP and the PCC (t(99)=2.88, p-FDR=0.0081, d=0.58) and decreased FC between the RFP and the LLG/OCC (t(99)=-2.97, p-FDR=0.0093, d=0.60), ROCC (t(99)=-2.47, p-FDR=0.0189, d=0.50) and LPCG (t(99)=-3.21, p-FDR=0.009, d=0.65). Conversely, relative to MDD patients, controls exhibited increased FC between the RFP and the LLG/OCC (t(98)=2.67, p-FDR=0.0448,

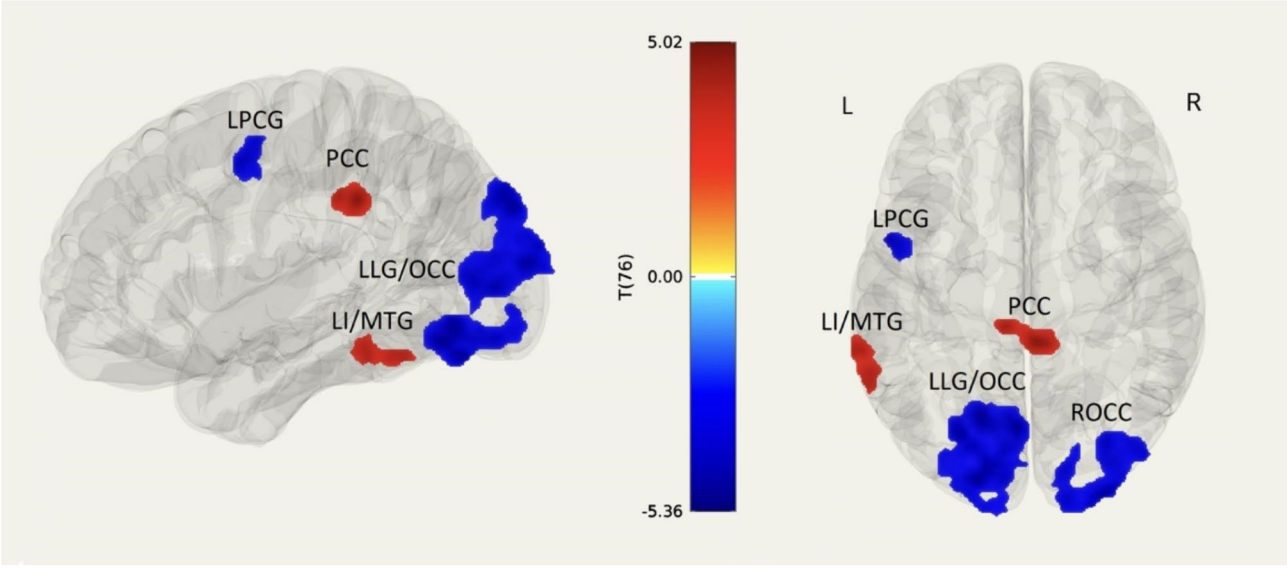

Fig. 2 Resulting clusters from seed-based analysis using the right frontal pole as seed. Red colour - higher connectivity between seed and cluster in MDD > BD. Blue colour - higher connectivity between seed and cluster in BD > MDD. Voxel level $p < 0.001$, cluster level p-FWE < 0.05. Abbreviations: L left, LI/MTG left inferior/middle temporal gyrus, LLG/OCC left lingual gyrus/occipital cortex, LPCG left precentral gyrus, PCC posterior cingulate cortex, R right, ROCC right occipital cortex

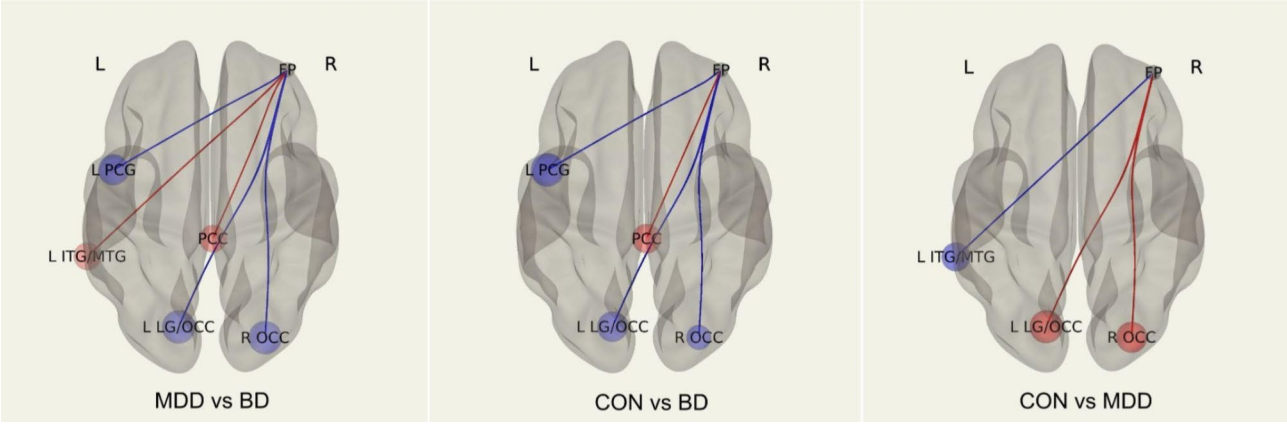

Fig. 3 ROI-to-ROI connectivity analyses results. MDD vs. BD comparisons of FC between FP and Left PCG, Left ITG/MTG, PCC, Left LG/OCC and Right OCC. CON vs. BD comparisons of FC between FP and Left PCG, PCC, Left LG/OCC and Right OCC. CON vs. MDD comparisons of FC between FP and Left ITG/MTG, Left LG/OCC and Right OCC. Results represent significant differences in correlation ($p < 0.05$, FDR < 0.05). Red colour - higher functional connectivity, blue colour - lower functional connectivity. Abbreviations: BD bipolar disorder, CON control participants, FP frontal pole, ITG/MTG inferior temporal gyrus/middle temporal gyrus, L left, LG lingual gyrus, MDD major depressive disorder, OCC occipital cortex, PCG precentral gyrus, PCC posterior cingulate cortex, R right, ROI region of interest

d=0.54) and ROCC (t(98)=2.53, p-FDR=0.0328, d=0.51) and decreased FC between the RFP and the LI/MTG (t(98)=-2.37, p-FDR=0.0325, d=0.48). The comparisons are displayed in Figs. 3 and 4, and the correlation matrices are shown in Supplement Table 2.

Discussion

The aim of this study was to explore resting-state FC differences between currently depressed BD patients and MDD patients using the data-driven fc-MVPA method. The main finding suggested that the connectivity patterns between the right frontal pole and associated brain regions were significantly different between the two groups, indicating that different FC patterns of the RFP in BD and MDD patients should be further investigated as potential neuroimaging markers.

The frontal pole is typically divided into three subparts, and the cluster found in our study in the right ventral/lateral frontal pole is associated with the processing of goals and action plans and the processing of information about stimuli, values and emotions [72]. A lesion study linked the frontal pole to the ability to disengage executive

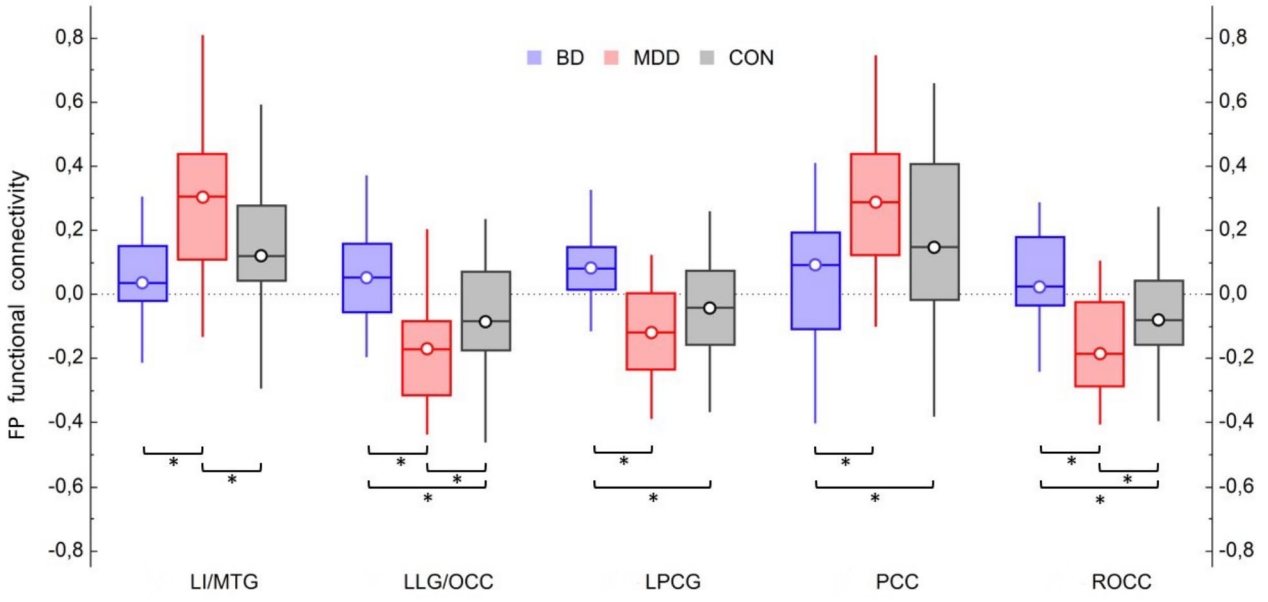

Fig. 4 Frontal pole connectivity differences between BD, MDD and CON in ROI-to-ROI analyses. Abbreviations: BD bipolar disorder, CON control participants, FP frontal pole, LI/MTG left inferior/middle temporal gyrus, LLG/OCC left lingual gyrus/occipital cortex, LPCG left precentral gyrus, MDD major depressive disorder. PCC posterior cingulate cortex, ROCC right occipital cortex. * p-FDR < 0.05

control from the current task and redistribute it to novel sources of rewards [73]. In addition, the lateral frontal pole integrates affective information into cognitive control representations originating in the anterior cingulate cortex [74] and is functionally connected with the FPN [75]. Some functional connectivity studies considered this region part of the DMN, while others considered it part of the FPN [75, 76]. The lateral frontal pole is a highly interconnected regulatory relay that acts between several neural networks and functions and likely plays a role in mood disorders. Specific differences in the FC patterns of the RFP among BD patients, MDD patients, and controls are discussed below.

We found decreased connectivity between the RFP and the PCC in BD patients compared to MDD patients and controls. The PCC, as a core hub of the DMN [77], is mostly associated with self-referential thoughts, mind wandering [78], and rumination during depression [79, 80]. It also has a lesser-known role in regulating the focus of attention (internal vs. external) [81, 82], its activity varies with arousal state [83], and its interactions with other brain networks may be important in conscious awareness [84]. The link between the PCC and the frontal pole is less evident, although its functional link has been established [83, 85]. Contrary to common understanding, the FPN, including the frontal pole, is also activated when attention is directed inwards [86]. Reduced connectivity between the RFP and PCC might indicate an impaired or decreased ability to balance attention between external stimuli and internal states in patients with BD. On the other hand, the difference between the MDD and controls was not significant, although there was a clear trend towards an increase in MDD patients (Fig. 4), suggesting increased self-focus and rumination.

Next, we found increased connectivity between the RFP and the LI/MTG in the MDD group compared to the BD and controls. The LI/MTG is connected to the frontal pole both anatomically via the arcuate fasciculus and functionally [87]. The inferior temporal gyrus is associated with visual object recognition, decision making, and impulsivity control and is also a component of the FPN and the ventral visual pathway [88–90]. The middle temporal gyrus is associated with memory, emotion regulation, and multimodal sensory integration and is considered a hub of the posterior DMN [91–93]. Increased connectivity between the RFP and the LI/MTG in RD MDD patients may correspond to complex and sustained rumination, i.e., the retrieval of memories and imagery with a corresponding, likely negative, affect. The significantly lower connectivity in BD patients compared to that in MDD patients and the trend compared to that in controls may be associated with impaired concentration, irritability, and impaired automatic emotion regulation.

The LPCG, the LLG/OCC, and the ROCC displayed negative, anticorrelated connectivity with the RFP in the MDD patients and controls and positive connectivity in the BD patients (Fig. 4). Anticorrelation in rs-fMRI is a debated concept, but it has been assumed to be

associated with inefficient synchronization in functionally connected brain regions [94]. Another study suggested that the anticorrelation between brain regions is a result of synchronized neuronal activity with heterogeneous (blood flow vs. blood volume) haemodynamic responses [95]. Therefore, we interpreted our findings as a decrease in FC coupling between functionally connected regions.

Increased connectivity between the RFP and LPCG in BD patients can be interpreted from more perspectives. The specific LPCG cluster found in our study is a part of the motor network (MN) and is associated with motor planning, i.e., the elaboration of information into a premovement plan, which can be suppressed and detached from action [29, 96]. The frontal pole mediates predictable event sequences and is involved in planning and controlling intentional motor acts [97, 98]. Increased FC between the RFP and LPCG may have a compensatory nature and account for psychomotor disturbances, most likely at the premovement planning phase [29]; soft neurological symptoms [99]; and typical BD symptoms such as psychomotor agitation, tension, and inability to relax. Consistent with this result, movement in the scanner, represented quantitatively as FD (Table 1), was significantly greater in the BD patients than in the controls and approached the significance threshold compared to that in the MDD patients. In addition, as the frontal pole and LPCG are parts of the FPN, increased FC corresponds to previous findings of overactivity in the FPN as a compensatory mechanism aimed at restoring the function of other disrupted networks [26, 45, 100]. On the other hand, lower connectivity/anticorrelation in MDD patients and controls might correspond to disengagement between the motor network (MV) and frontal pole and possibly to the ability to relax movements. Speculatively, the trend of significantly lower FC in MDD patients than in controls may suggest psychomotor slowness or delayed motor reactions.

Patients with BD had increased FC between the RFP and the left LLG/OCC and ROCC. Both regions are part of the visual network (VN) and fronto-occipital network and are connected to the prefrontal cortex anatomically and functionally [72, 75, 101]. While both regions are functionally associated with visual processing, the lingual gyrus is also associated with visual attention [89], facial emotion/empathy processing (102), visual memory and emotion [103], and even control of negative emotions associated with painful events [104]. As BD is characterized by overactivity within the SN resulting in increased input from visceral and sensory regions, causing emotional dysregulation and distractibility, increased FC between the RFP and the lingual gyrus and OCC in BD patients may have a compensatory function. This finding is also consistent with increased connectivity within the FPN in BD patients [26]. Another explanation may be the reported bias of BD patients towards external negative stimuli [35, 105]. On the other hand, lower connectivity in MDD patients than in both BD patients and controls may indicate visual attentional deficits, lower responsiveness to external stimuli, and an inability to disengage from internal focus.

Interestingly, two distinct patterns of RFP FC distributions among the three groups emerged, as shown in Fig. 4: between the RFP and the PCC and LI/MTG and between the RFP and the LPCG, LLG/OCC and ROCC. This broader view suggests a pattern in which MDD patients, compared to BD patients and controls, have increased FC between the RFP (FPN) and the DMN. This increased connectivity can be associated with increased self-focus, sustained depressive rumination, and difficulty detaching from internally focused processing. On the other hand, BD patients displayed increased connectivity between the RFP and the LPCG, LLG/OCC and ROCC, which indicates increased connectivity between the FPN and the MN and VN. This pattern can be associated with persisting psychomotor symptoms and compensatory attempts against distractibility, which are characteristic of BD.

This study did not replicate the most common findings in BD and MDD comparisons, namely, differences in SN FC [26]. One reason for this discrepancy may be the way in which the fc-MVPA calculates the differences in FC patterns, in which the differences in the SN may not be among the largest. Another possible reason, with a broader range of consequences, may lie in the clinical group, i.e., in the possible treatment resistance in MDD patients. All 40 MDD participants had at least one failed treatment attempt with an adequate dose and duration (first-stage treatment resistance according to Thase and Rush [106]); 20 patients had two failed attempts, and another 12 also had two failed attempts if neurostimulation was considered an adequate treatment [107]. Compared with BD, treatment-resistant MDD (TRD) is a poorly studied subtype of MDD, although differences in FC between TRD and MDD patients have been established mostly in the DMN [108] and may explain the heterogeneous findings in the DMN in previous studies. One branch of research suggests that TRD may fall between BD and MDD and may even be more similar to BD than to MDD from the bipolar diathesis perspective [109, 110]. Only one prior study compared currently depressed TRD patients with euthymic BD patients and euthymic MDD patients; surprisingly, this study also found differences in the FC of the frontal pole between BD patients and TRD patients [76]. If our MDD group is considered as having TRD, our findings may suggest similarities in the within- and between-network FC of the SN between patients with BD and patients with TRD. Increased FC within

the SN, which has typically been found in BD patients in previous studies, is associated with emotional dysregulation and impaired emotional, reward, somatosensory and interoceptive input for appropriate switching between the DMN and FPN. We propose that in this respect, BD and TRD are similar. This similarity may correspond with the variability of symptoms observed in both disorders, such as dysregulation of emotional control, inner tension and fearfulness, feelings of inhibition, heaviness, tiredness of the body, and slower thinking [111–113].

In addition, our findings correspond with the close to "normal" connectivity in the DMN in TRD patients compared to controls and lower connectivity in TRD patients compared to MDD patients. This finding is also consistent with studies indicating lower connectivity within the DMN and between the DMN and other brain regions in individuals with TRD than in those with MDD [108].

However, this study was not designed to assess TRD a priori, and this interpretation must be considered with caution. Moreover, there are several treatment resistance criteria, and a clear consensus is still being reached [114].

The study has several limitations related to the analysed samples. The sample sizes of the BD and MDD groups were too small to draw broader conclusions.

Next, the MDD and BD participants differed in several characteristics that might have affected the results, but these characteristics are difficult to control. While the clinical groups were well matched for sex, age, and depression severity, participants in the BD group had a younger age of onset, more episodes, longer illness duration, and greater illness severity and displayed a trend towards greater movement in the scanner. Additionally, participants in the control group, which was larger in size than the clinical groups, were younger and displayed significantly less in-scanner movement.

Another limitation is the selection process of the clinical groups. Since the rs-fMRI data were derived from subjects participating in two separate randomized controlled trials (RCTs), selection criteria were not defined prospectively. Both RCTs applied very similar inclusion and exclusion criteria, enhancing the comparability of participants and the robustness of the findings. However, while the good comparability of the clinical samples enhanced internal validity, it also introduced potential limitations in external validity. Specifically, the use of identical criteria may limit the generalizability of the results to a broader clinical population, as the selected participants might not fully represent the diversity seen in real-world settings. Additionally, the retrospective definition of the clinical groups could lead to selection bias, potentially impacting the applicability of the findings to wider clinical and community samples. These considerations are essential for interpreting the results and designing future studies to ensure a more inclusive and representative sample.

Another limitation to be considered is the effect of different medications on MDD and BD patients. While both groups underwent medication washout prior to scanning, participants from the BD group were still on mood-stabilizing agents (AP or MS) for medical reasons.

In conclusion, this exploratory study revealed that FC patterns of the right frontal pole differed between patients with BD and patients with MDD using fc-MVPA. The emerging patterns suggested that compared to MDD patients, BD patients had greater FC between the RFP and the MN and VN, which is likely associated with psychomotor symptoms and a compensatory function against increased distractibility from the inner states. Conversely, MDD patients displayed greater FC between the RFP and the DMN, which corresponds to sustained inner self-focus and depressive rumination. This study suggested that the RFP and its FC patterns should be further examined and possibly utilized as targets of treatment for depression. Given the exploratory nature of this study and considering its limitations, future studies are needed to confirm the findings in larger and more heterogeneous samples with prospectively defined study groups.

Supplementary Information

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Supplementary Material 1

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Author contributions

M.P. and T.N. conceived and designed the research. M.K., M.B. and T.N. recruited and assessed participants. M.P. and T.N. analyzed and interpreted the data, provided visualizations. M.P. wrote the first draft. All authors reviewed the manuscript.

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Data availability

The data that support the findings of this study are available on reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the National Institute of Mental Health, Klecany. The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All participants signed informed consent with participation. No monetary or other incentives were associated with study participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Declaration of generative AI in scientific writing
During the preparation of this work the authors did not use any AI methods.

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