

Aberrant connectivity of resting-state networks in borderline personality disorder

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Background: Several functional neuroimaging studies have reported regionally abnormal activation of the frontal cortex in individuals with borderline personality disorder (BPD) during cognitive and affective task performance. However, little is known about neural function in individuals with BPD during the resting state. Using functional magnetic resonance imaging (fMRI), this study investigated the functional connectivity of prefrontal and limbic networks in patients with BPD. **Methods:** Between January 2009 and March 2010, we investigated patients with BPD according to DSM-IV criteria and healthy controls by means of resting-state fMRI. The data were analyzed using a spatial group independent component analysis, and random effects *t* tests were used to compare spatial components between groups ($p < 0.005$, uncorrected). **Results:** There were 17 women with BPD and 17 female healthy controls enrolled in this study. Within a network comprising cortical midline regions (“default mode network”), patients with BPD showed an increase in functional connectivity in the left frontopolar cortex (FPC) and the left insula, whereas decreased connectivity was found in the left cuneus. Within a network comprising predominantly right lateral prefrontal and bilateral parietal regions, patients with BPD showed decreased connectivity of the left inferior parietal lobule and the right middle temporal cortex compared with healthy controls. Two networks comprising lateral prefrontal and cingulate regions did not exhibit significant between-group differences. We found correlations between functional connectivity of the FPC and measures of impulsivity as well as between connectivity of the insula/cuneus and dissociation tension. **Limitations:** Co-occurrent axis I disorders and medication use in this sample of patients with BPD have to be considered as potential limitations. **Conclusion:** These data suggest that abnormal functional connectivity of temporally coherent resting-state networks may underlie certain symptom clusters in patients with BPD.

Introduction

Borderline personality disorder (BPD) is a severe mental disorder characterized by dysfunctional affect regulation, impulse control, interpersonal relationships and self-image.¹ Research linking BPD to brain dysfunction dates as far back as 1980; however, along with the advent of more refined neuroimaging techniques, the past few years have seen a rapidly growing number of studies investigating the neurobiologic correlates of BPD.^{2,3} Investigations of resting-state cerebral blood flow (CBF) and metabolism in patients with BPD have suggested abnormal activation of cortical areas, including

prefrontal, cingulate, parietal and temporal regions,^{4,5} as well as perfusion and metabolic abnormalities of subcortical structures, such as the basal ganglia and the thalamus.^{5,6} Functional magnetic resonance imaging (fMRI) has been increasingly used to characterize the neural correlates of sensory, cognitive and affective processing, as well as the functional neuroanatomy of social cues⁷ in patients with BPD, suggesting several loci of neural dysfunction, most notably in prefrontal areas and limbic regions.^{8,9} Notwithstanding their heterogeneity, the extant data imply that a dysfunction of frontolimbic circuitry could underlie core symptom clusters in patients with BPD, such as affective dysregulation,¹⁰ poor

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inhibitory control,⁹ self-injurious behaviour¹¹ and dissociative symptoms.¹² Interestingly, however, although dynamic models of prefrontal control have been proposed,^{8,9} studies explicitly addressing functional interactions of neural networks in patients with BPD have been scarce.

In this study, we assessed functional connectivity characteristics of prefrontal networks in patients with BPD using resting-state functional connectivity.¹³ This approach essentially aims to identify temporally synchronous networks or “modes” characterized by ongoing spontaneous modulations of the blood oxygen level-dependence (BOLD) during resting-state conditions,¹³ thus providing insight into a dynamic neural architecture in the absence of specific task-related activity. In contrast to task-based fMRI, resting-state fMRI (rs-fMRI) does not require any explicit experimental input or stimulus variation, thus providing a way to remove confounds of task performance in psychiatric patient samples. One of the most extensively investigated resting-state networks (RSNs) is an organized, baseline set of brain regions that consistently exhibits activity decreases during cognitively demanding tasks; this neural assembly has been referred to as the “default mode network” (DMN), a mode of “baseline” brain function related to self-referential processing, inner speech, emotional control and episodic memory.^{14,15} Apart from the DMN, however, several other distinct neural networks have been identified during resting-state conditions, including lateral frontoparietal and medial-frontal networks.^{16,17} These RSNs have been suggested to reflect a dynamic functional organization of the brain,¹⁸ a notion supported by the finding of a close correspondence between RSNs and activation patterns underlying a wide range of cognitive processes, such as attention, memory, behavioural inhibition and executive control.¹⁷ Thus, the investigation of multiple RSNs may provide a rich source of information with regard to the functional architecture of altered brain states in patients with mental disorders, as previously shown in patients with schizophrenia¹⁹ and affective disorders.^{19,20}

In this study, we used a multivariate statistical method, independent component analysis (ICA), to identify multiple RSNs involving medial and lateral prefrontal regions. Independent component analysis is a technique that maximizes the independence between output components,²¹ thus identifying a set of spatially nonoverlapping and temporally coherent networks by measuring functional covariance patterns between different brain areas.²² With regard to the present study sample of patients with BPD, we predicted abnormal connectivity of the DMN, specifically in brain areas associated with self-referential processing, affective control and impulsive behaviour, such as the anterior frontal regions, cortical midline regions and cingulate areas. Apart from DMN dysfunction, we predicted that we would find connectivity differences in other prefrontal RSNs associated with executive control and behavioural inhibition, such as the ventro- and dorsolateral prefrontal cortex and the anterior cingulate. In addition, we explored the relation between regions exhibiting abnormal connectivity in patients with BPD and clinical core symptoms of the disorder, such as impulsivity and dissociation.

Methods

Participants

We studied female participants recruited among the in- and outpatients of the Department of Psychiatry and Psychotherapy III, University of Ulm, Germany, who met DSM-IV criteria for BPD. We chose to investigate female patients only since women account for about three-quarters of the documented cases of BPD,²³ and thus a female sample might be less biased by potential sex-related differences. Handedness was assessed using the Edinburgh Handedness Inventory.²⁴ Diagnostic assessments using the German versions of the Structured Clinical Interview for DSM-IV were performed by clinically trained and experienced raters (R.C.W. and N.D.W.) for patients with BPD and controls. All patients with BPD were on a stable drug regime for at least 2 weeks before scanning. Only patients with BPD with a currently sufficiently stable condition to undergo the MRI scanning process were included in this study. We excluded patients with an unstable physical condition for at least 1 month before scanning and patients who presented with acute suicidal ideation. Patients with a history of a neurologic disorder, head trauma or learning disabilities were also excluded from the study. Further exclusion criteria were lifetime diagnoses of schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD) and alcohol and illicit drug abuse within 6 months before study participation. Given reports of neural differences in patients with BPD with and without posttraumatic stress disorder (PTSD),³ we chose to include only patients who did not meet current criteria for PTSD. We assessed self-reported impulsivity in all participants using the German version of the Barratt Impulsiveness Scale (BIS).²⁵ Both patients with BPD and controls completed the Beck Depression Inventory (BDI)²⁶ and were rated by means of the Hamilton Rating Scale for Depression (HAM-D).²⁷ We assessed BPD symptoms in the patient group by means of the short version (23 items) of the Borderline Symptom List (BSL-23).²⁸ In patients with BPD, dissociative symptoms were assessed using the Dissociative Tension Scale (DTS).²⁹

The control group included unmedicated women matched for age, education and handedness. Participants with a neurologic or psychiatric disorder according to DSM-IV criteria or any substance abuse or dependence were excluded. Further exclusion criteria were a positive family history for psychiatric disorders and a history of seizures or major head trauma. The local Institutional Review Board (University of Ulm, Germany) approved our study protocol. We obtained written informed consent from all participants after providing them with a complete description of the study.

fMRI data acquisition

The functional data were acquired using a 3-T MAGNETOM Allegra (Siemens) head MRI system at the Department of Psychiatry and Psychotherapy III at the University of Ulm, Germany. Scanning was carried out in darkness, and the participants were explicitly instructed to relax without falling

asleep, to keep their eyes closed, not to think about something special and to move as little as possible. We obtained T_2 -weighted images using echo-planar imaging in an axial orientation (repetition time 2000 ms, echo time 30 ms, field of view 192 mm, flip angle 80°, voxel size $3 \times 3 \times 3$ mm, 33 slices, slice thickness 3 mm, gap 1 mm). Within a session, we acquired 180 whole-brain volumes. Prior to data processing, the first 8 volumes of the time series were discarded to account for MRI equilibration effects.

Data analysis

Data preprocessing was performed with SPM5 (Wellcome Trust Centre for Neuroimaging) and MATLAB 7.3 (MathWorks). The functional images were corrected for motion artifacts and then spatially normalized to the SPM5 EPI standard template. All images were spatially smoothed with a 9-mm full-width at half-maximum isotropic Gaussian kernel. We performed a spatial ICA using the Group ICA for fMRI Toolbox (GIFT; <http://icatb.sourceforge.net>).³⁰ The dimensionality of the functional data for each participant was reduced using 3 consecutive steps of principal component analysis alternated with data linked across participants, resulting in 1 aggregate mixing matrix for all participants. An ICA decomposition using the Infomax algorithm was used to extract 15 independent components, consisting of group spatial maps and related time courses. We used the "minimum description length"³¹ criteria to estimate the order selection (i.e., the number of independent components from the smoothed data sets after taking into account the spatial and temporal correlation of the fMRI data). A set of effectively independent and identically distributed data samples was first estimated for each participant through a subsampling algorithm, and we used the median of these values across the whole sample for order selection. The estimation of the number of the independent components performed directly on the data has been shown to effectively reduce the occurrence of over- or underfitting the data.³¹ We used the estimated independent components for a back reconstruction into individual independent components using the aggregate mixing matrix created during the dimensionality data reduction steps. The individual independent components consisting of individual spatial independent maps and time courses were eventually spatially sorted using a priori masks comprising medial and lateral prefrontal as well as cingulate regions, as defined by the Automatic Anatomic Labelling (AAL) Atlas.³² We used 2 masks for spatial sorting. First, as described by other groups,³³ we computed a DMN mask comprising the posterior parietal cortex (Brodmann area [BA] 7), the frontopolar cortex (FPC; BA 10), the posterior cingulate cortex, the precuneus and the occipitoparietal junction (BA 39). Second, we computed a prefrontal mask comprising the superior, middle and inferior frontal cortices and the anterior cingulate cortex. One component of interest that showed the highest spatial correlation with the DMN mask and 3 components of interest that showed the highest spatial correlation with the prefrontal mask were chosen for the second-level within- and between-group analyses. In addition, we analyzed 2 "control" components of interest

comprising a sensorimotor and an auditory network. These RSNs have been consistently replicated by rs-fMRI studies in both healthy controls and psychiatric patient samples.^{16,17,20} For the sensorimotor and auditory RSNs, we did not predict disease-related connectivity differences in contrast to the other networks of interest.

For each participant's spatial component of interest, we used the voxel weights as random-effects variables and analyzed them using SPM5. For within-group analyses, voxel-wise 1-sample t tests against the null hypothesis of zero magnitude were used to calculate within-group maps for each component of interest. The statistical threshold for these analyses was set at $p < 0.001$, uncorrected at the voxel level, and $p < 0.05$, corrected for spatial extent. On the second level, we compared spatial maps between controls and patients with BPD using 2-sample t tests. To fully include those brain regions that were recruited by at least 1 diagnostic group, we masked these between-group comparisons with a combined mask. This mask was created as follows: first, we computed 1-sample t tests per RSN and each diagnostic group. Second, thresholded t -maps ($p < 0.005$) were binarized using the "AND" Boolean operator, thus producing binary masks of the combined effect of each diagnostic group. These combined spatial maps were eventually used to explicitly mask the between-group comparisons computed for each RSN. A threshold of $p_{32} < 0.005$, uncorrected at the voxel level, and $p < 0.05$, corrected for spatial extent, was chosen for all second-level between-group comparisons. All anatomic regions and functional denominations are reported according to the atlases of Talairach and Tournoux³⁴ and Duvernoy.³⁵ Coordinates are maxima in a given cluster according to the Montreal Neurological Institute (MNI) template.

Correlations with psychometric measures

We calculated correlation analyses (uncorrected for multiple comparisons) between indices of functional connectivity and psychometric measures. Spearman correlations were computed using the appropriate psychometric variables (BSL-23 and BIS scores) and the extracted β parameters from the ICA (connectivity strength, corresponding to the mean voxel weights of the components of interest) from significant clusters emerging from the between-group comparisons. We extracted the β parameters from these clusters of interest using MarsBar 0.41³⁶ and then processed them off-line using the Statistica software package (Version 6.0, StatSoft Inc.).

Results

Participants

There were 17 women with BPD and 17 controls matched for age, education and sex enrolled in this study. Among the patients with BPD, 5 received psychotropic monotherapy, whereas 12 patients were treated with combinations of 2–3 drugs. Medication included antidepressants (escitalopram $n = 5$, fluoxetine $n = 2$, sertraline $n = 1$, venlafaxine $n = 4$ and agomelatin $n = 2$), mood stabilizers (lamotrigine $n = 10$,

topiramate $n = 1$) and antipsychotics (quetiapine $n = 8$, aripiprazole $n = 2$). Co-occurring axis I disorders in the BPD cohort included lifetime major depressive disorder ($n = 5$), past drug and alcohol abuse ($n = 6$), current major depression

($n = 9$), eating disorders ($n = 4$; 2 with bulimia nervosa, 2 with an eating disorder not otherwise specified) and current anxiety disorder not otherwise specified ($n = 1$). Demographic and psychometric data are shown in Table 1.

Table 1: Demographic and clinical characteristics of healthy controls and patients with borderline personality disorder enrolled in a resting-state functional magnetic resonance imaging study

Variable	Group; mean (SD)	
	Control, $n = 17$	Borderline personality disorder, $n = 17$
Age, yr	27.2 (8.0)	28.6 (7.3)
Education, yr	13.2 (1.8)	12.6 (1.8)
Test scores		
Edinburgh Handedness Inventory ²⁴	84.5 (14.3)	83.8 (14.5)
Beck Depression Inventory ²⁶	2.0 (2.7)	36.5 (9.6)*
Hamilton Rating Scale for Depression ²⁷	0.8 (1.6)	15.2 (5.7)†
Barratt Impulsiveness Scale ²⁵	52 (7.7)	71.3 (9.3)‡
Borderline Symptom List, short form ²⁸	NA	57.6 (19.8)
Dissociative Tension Scale ²⁹	NA	38.8 (28.5)

NA = not applicable; SD = standard deviation.
 * $t_{32} = -14.2, p < 0.001$.
 † $t_{32} = -10.0, p < 0.001$.
 ‡ $t_{32} = -6.6, p < 0.001$.

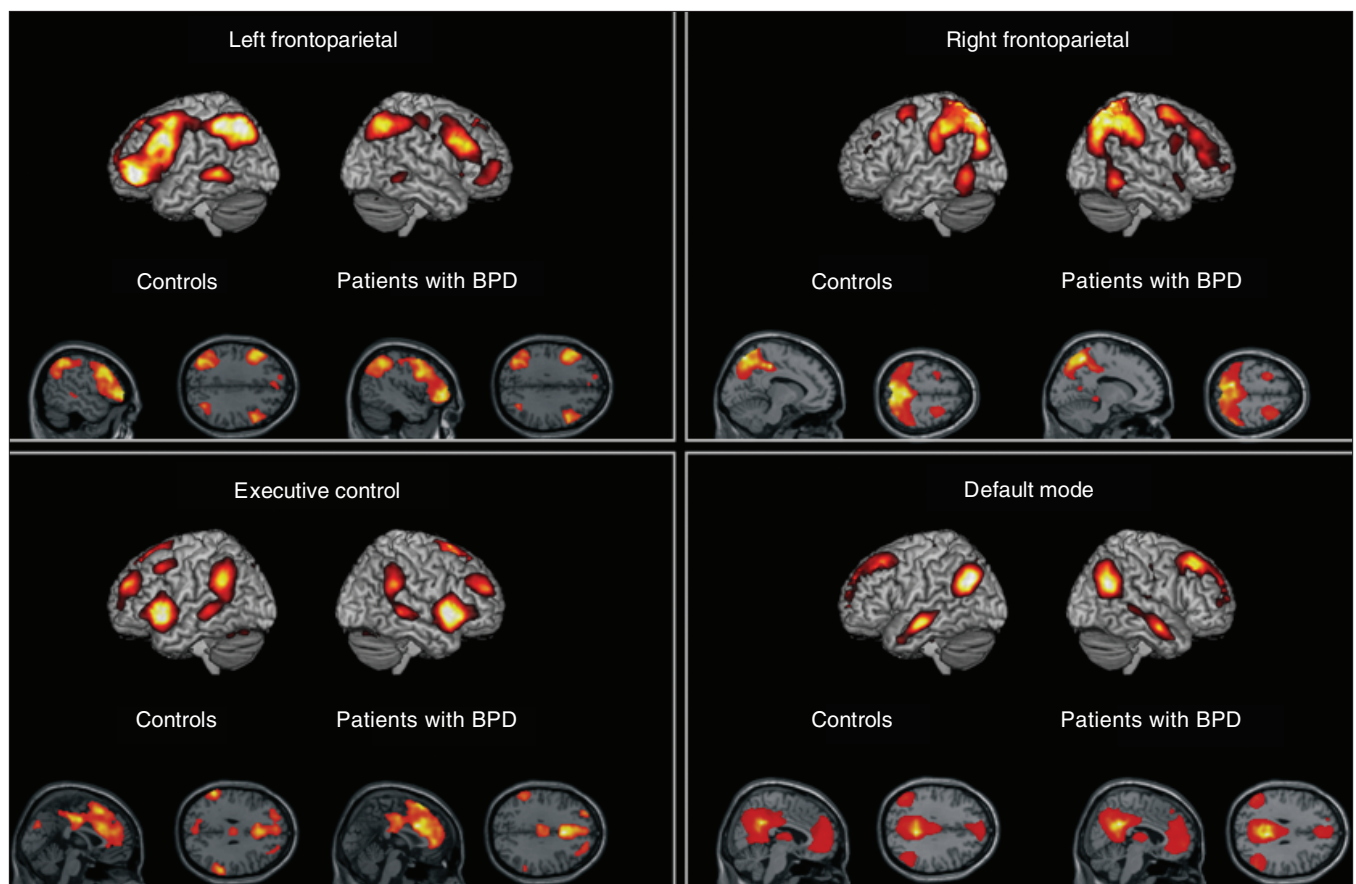


Fig. 1: Spatial pattern of prefrontal components of interest identified by the group independent component analysis. Results from the second-level within-group t tests, including controls and patients with borderline personality disorder (BPD); $p < 0.001$, uncorrected at the voxel level and $p < 0.05$, corrected for spatial extent (detailed stereotaxic coordinates and Z scores are available on request). The second-level maps are rendered on the anatomic templates implemented in (**top**) MRIcron (www.sph.sc.edu/comd/rorden/mricron/) and (**bottom**) SPM5.

Functional connectivity within-group analyses

Fifteen independent components were estimated, consisting of individual spatial independent maps and time courses. In healthy controls and patients with BPD, we identified 4 components of interest that showed the highest spatial correlation with the a priori prefrontal mask derived from the AAL atlas. Consistent with previous research,^{16,17,20} we identified the following network patterns:

- The first component of interest (left frontoparietal, Fig. 1, top left) revealed a spatial pattern comprising predominantly bilateral prefrontal parietal (left lateralized dorso- and ventrolateral prefrontal cortex, medial and superior prefrontal cortex) as well as temporoparietal regions.
- The second component of interest (right frontoparietal, Fig. 1, top right) revealed a network comprising right lateralized ventro- and dorsolateral prefrontal regions, superior and inferior parietal areas, the dorsal and posterior cingulate cortex and the precuneus.
- The third component of interest (executive control, Fig. 1, bottom left) comprised the bilateral ventrolateral prefrontal cortex, anterior prefrontal regions, the cingulate cortex and bilateral middle temporal and inferior parietal areas.
- The fourth component of interest showed a DMN pattern, as described in detail by previous RSN studies.¹⁴ The spatial pattern of this component of interest comprised predominantly cortical midline regions, including the medial prefrontal cortex, the anterior and posterior cingulate cortex, the cuneus and precuneus, as well as regions of the anterior prefrontal cortex, parietal cortex, middle temporal cortex, the thalamus and the insula (Fig. 1, bottom right).

We identified the control networks by visual inspection of the group components of interest and subsequently illustrated them using within-group 1-sample *t* tests. The sensorimotor network included the sensorimotor cortex, the supplementary motor area, the secondary somatosensory cortex, the striatum and the thalamus. The auditory network included predomi-

antly primary and association auditory cortices, Heschl gyrus and the superior and middle temporal cortex (Appendix 1, available at www.cma.ca/jpn).

Functional connectivity between-group analyses

Within the DMN, patients with BPD showed reduced connectivity in the left cuneus (MNI *x, y, z* = -6, -74, 6; *z* = 3.31) and increased functional connectivity in the left FPC (BA 10, MNI *x, y, z* = -22, 56, 18; *z* = 4.49) and the left insula (MNI *x, y, z* = -32, -18, 10; *z* = 4.01; Fig. 2). Within the right frontoparietal network, patients with BPD showed less functional connectivity in the left inferior parietal lobule (BA 40, MNI *x, y, z* = -32, -44, 48; *z* = 3.67) and the right middle temporal gyrus (BA 21, MNI *x, y, z* = 46, -56, 6; *z* = 4.66; Fig. 2).

We found no connectivity differences within the left frontoparietal and the executive control networks. Within the control networks (i.e., the sensorimotor and the auditory components of interest), no differences were observed between controls and patients with BPD.

To test for potential effects of comorbid depression, we re-analyzed the data after identifying those patients with and without current symptoms of major depression (9 v. 8 patients). Demographic and psychometric variables (i.e., age; education; and EHI, BDI, HAM-D, BSL-23 and DTS scores) did not significantly differ between the subgroups. We performed second-level comparisons between the patient subgroups for each RSN using the procedures and significance thresholds as described for the entire sample (see data analysis section). However, these comparisons did not reveal significant subgroup differences, regardless of the analyzed RSN.

Correlations between functional connectivity and psychometric measures

Connectivity of the left FPC showed a positive correlation with BIS scores ($\rho_{15} = 0.73$, $p = 0.001$) and BSL-23 scores

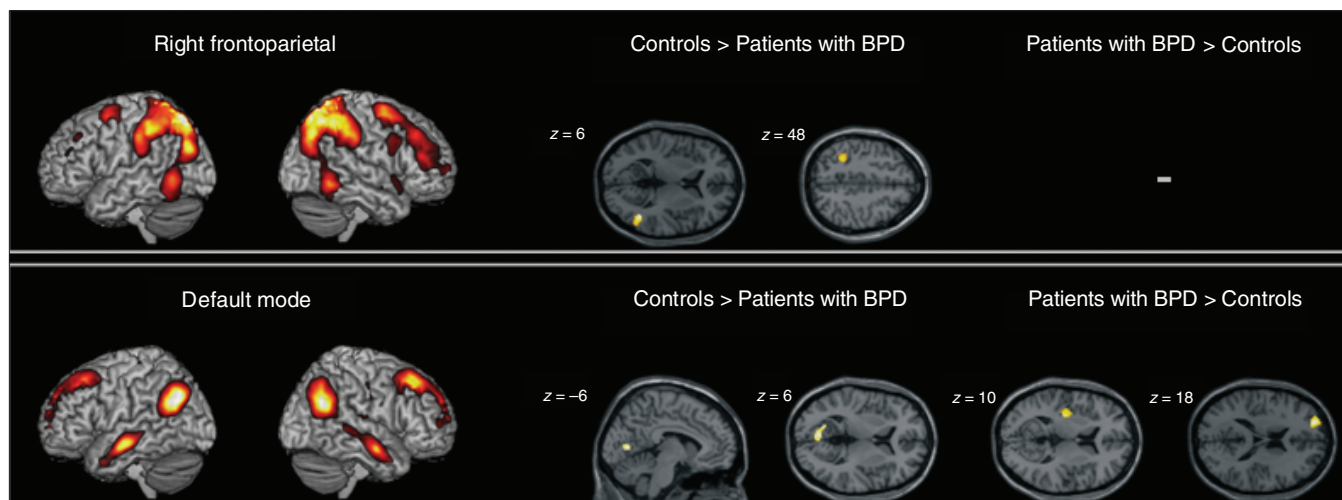


Fig. 2: Regions exhibiting differences in functional connectivity in patients with borderline personality disorder (BPD) compared with healthy controls. Results from the second-level between-group analysis ($p < 0.005$, uncorrected at the voxel-level, and $p < 0.05$, corrected for spatial extent). The second-level maps are rendered on anatomic templates implemented in (left) MRIcron (www.sph.sc.edu/comd/rorden/mricron/) and (right) SPM5.

($p_{15} = 0.57, p = 0.017$). Higher DTS scores were positively correlated with connectivity of the left insula ($p_{15} = 0.61, p = 0.009$) and negatively correlated with connectivity of the cuneus ($p_{15} = -0.58, p = 0.016$; Fig. 3). Measures of depression (BDI and HAM-D scores) were not significantly correlated with functional connectivity indices.

Discussion

This study aimed at characterizing functional connectivity of RSNs in patients with BPD. Two main findings emerged. First, functional connectivity differences were detected in the DMN and in a right frontoparietal network, whereas 2 other a priori RSNs and 2 "control" networks did not exhibit between-group differences. Second, regions of abnormal connectivity within the DMN (i.e., cuneus, insula and FPC) were related to BPD symptoms, as indicated by scores

of dissociation, impulsivity and measures of overall BPD psychopathology.

Converging functional imaging evidence supports the notion that the DMN is involved in a wide range of higher-order cognitive and affective functions, whereas the monitoring of self-referential activity has been suggested to be subserved by the DMN to a higher degree than processing of external stimuli.¹⁴ Possible functions of the DMN include internal mentalizing detached from external stimuli; processing of autobiographic memory traces; and monitoring of cognitive, affective and somatosensory states.^{14,15,37} Our data suggest that abnormal DMN connectivity in patients with BPD is restricted to a circumscribed set of brain regions, most notably the left FPC and the insula. Contributions of the FPC have been implicated in a variety of social-cognitive functions, most notably in the processing of intentional thoughts,³⁸ self-referential information and interpersonal

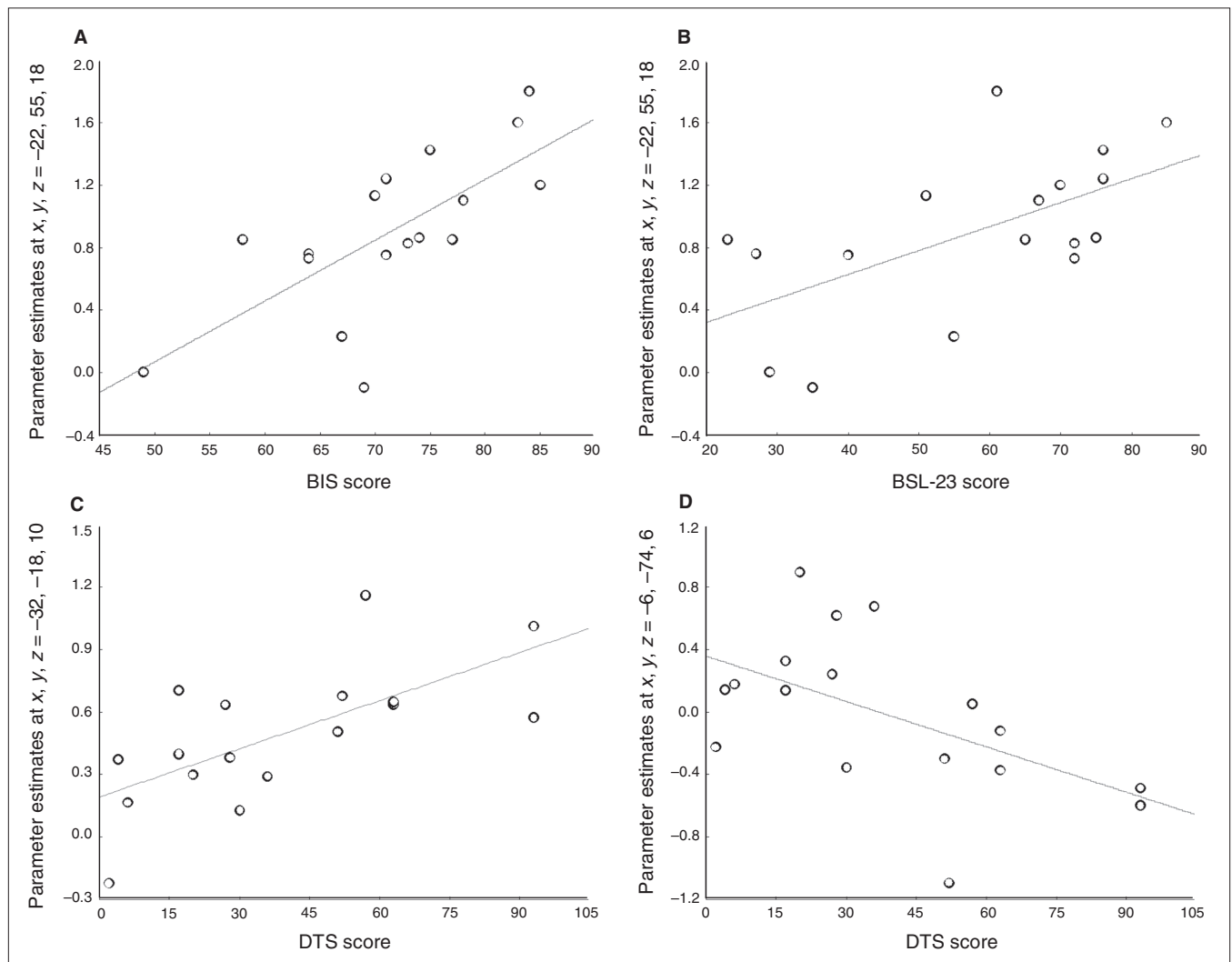


Fig. 3: Correlation plots ($p < 0.05$) between functional connectivity and psychometric measures. **(A)** Correlation between frontopolar cortex (Brodmann area [BA] 10) connectivity and Barratt Impulsiveness Scale (BIS)²⁵ score. **(B)** Correlation between frontopolar cortex (BA 10) connectivity and the 23-item Borderline Symptom List (BSL-23)²⁸ score. **(C)** Correlation between connectivity of the insula and the Dissociative Tension Scale (DTS)²⁹ score. **(D)** Correlation between connectivity of the cuneus and the DTS score.

interactions,³⁹ in good accordance with processes subserved by the DMN.¹⁵ In line with this notion, recent neuroimaging data indicate that the left FPC exhibits abnormal levels of activation in patients with BPD during the experience of social exclusion.⁴⁰ The finding of abnormally increased left FPC connectivity during resting-state conditions, however, is also suggestive of a task-independent neural signature of BPD. This view receives further support from the positive relation between left FPC connectivity and BPD symptoms, as assessed by the BSL-23. In addition, left FPC connectivity was also found to correlate with symptoms of impulsivity, supporting a role of the FPC in the expression of clinically relevant symptom clusters. This brain-behaviour relation is in line with previous findings of abnormal prefrontal physiology in patients with BPD and other personality disorders with core symptoms of impulsivity and aggression.^{5,6,8} Moreover, several neuroimaging studies have specifically implicated the FPC as a part of the neural network subserving inhibitory control, where the FPC substantially contributes to efficient cognitive inhibition⁴¹ and affective regulation.⁴² In addition, it is possible that the left FPC dysfunction might contribute to several symptom dimensions of BPD, such as poor inhibitory control and impaired social cognition, a hypothesis that could be further tested by combined investigations of resting-state and task-based fMRI.

Interestingly, patients with BPD also exhibited increased resting-state connectivity of the insula. Abnormal activation of the insula has been frequently reported in patients with BPD, suggesting an involvement of this region in emotional regulation, pain sensitivity and processing during dissociative states.^{11,12} Perhaps most relevant to BPD, many studies have found insular contributions to the processing of noxious somatosensory, cognitive and affective states, such as acute or chronic pain.^{37,43} The insula has been associated with sensory intensity encoding⁴⁴ and affective dimensions of noxious states,⁴⁵ thus subserving multiple associative processes related to salient intero- and exteroceptive stimuli. More generally, functions of the insula have been related to the perception and monitoring of internal states, including both the somatosensory and the affective domain.⁴⁵ The positive correlation between insula connectivity and measures of dissociation, as evidenced in our study, further supports the notion of insular involvement during dissociative states.^{12,46} Furthermore, increased activation of the insula has been previously linked to symptoms of dissociation along with reduced pain sensitivity in patients with BPD, suggesting a possible neural mechanism related to self-injurious behaviour.¹² It is noteworthy, however, that unlike other studies reporting insula activation in patients with BPD, we specifically found increased insular connectivity during resting-state conditions. Thus, this region might contribute to symptoms of dissociation, and possibly also pain insensitivity, even in the absence of external conditions, suggesting a possible trait marker of BPD. Apart from the insula, however, a relation between indices of functional connectivity and dissociative symptoms was also found in the cuneus. A previous neuroimaging study reported a pattern of increased covariation between the ventrolateral thalamus and the right cuneus associ-

ated with dissociative responses in patients with PTSD.⁴⁶ However, the precise contributions of the cuneus to dissociative symptoms or other symptom clusters of patients with BPD are unclear at present. Possible functions of the cuneus in the context of dissociation may include modulations of mental imagery⁴⁷ or reactions to affectively relevant events⁴⁸ that might be associated with an ongoing dissociative experience. However, the finding of lower cuneus connectivity argues against the occurrence of a vivid mental image or an increased vigilance response, thus discarding the possibility of spontaneous dissociation under scanning conditions. Alternatively, the finding of lower cuneus connectivity might suggest a decreased neural capacity for establishing and maintaining an attentional set,⁴⁹ possibly conveying proneness to dissociation. Nevertheless, whereas this speculation might appear plausible in the context of dissociative symptoms, the specific functions of the cuneus in patients with BPD cannot be fully elucidated by the present data set.

Apart from the DMN, connectivity differences in patients with BPD were also found in a right frontoparietal RSN, where patients with BPD showed less functional connectivity in left inferior parietal and right middle temporal regions. Abnormal function of temporoparietal regions in patients with BPD has been previously reported by several behavioural and functional imaging studies. For instance, some studies have shown decreased resting-state blood flow in right temporal regions⁹ and decreased activation of the temporal cortex during response inhibition.⁵⁰ In contrast, increased activation of middle and inferior temporal areas has been described during tasks requiring emotional processing.⁵¹ With regard to parietal regions, neuropsychologic studies have suggested visuospatial processing and learning deficits in patients with BPD,⁵² possibly linked to an impaired engagement of prefrontal and posterior parietal attentional systems. Moreover, abnormal posterior and right hemisphere γ synchrony has been discussed as suggestive of a lack of sensory integration and attentional control in patients with BPD.⁵³ Our data may lend some support to this hypothesis. For instance, a right lateralized ventral attentional system comprising middle and inferior prefrontal and posterior parietal regions has been described by numerous functional neuroimaging studies of attention, including studies of intrinsic and phasic alertness⁵⁴ and attentional control.⁵⁵ Moreover, several rs-fMRI studies have consistently reported a right frontoparietal network similar to the RSN identified in our study, possibly reflecting baseline properties of a network subserving attentional processes that persist in the absence of external events.^{17,37} In conjunction with findings of abnormal DMN connectivity, we speculate that decreased temporoparietal connectivity within an attention network in patients with BPD could indicate a decreased attentional capacity for relevant somatosensory stimuli or self-representational control. However, since the precise functions of the right frontoparietal network cannot be fully inferred by its resting-state characteristics, the preliminary conclusions drawn from the present resting-state findings clearly need further support from multimodal neuropsychologic, task-based and rs-fMRI studies. Moreover, unlike the regions within the DMN, the

temporoparietal loci of dysfunction were not related to BPD symptoms. Thus, a direct relation to circumscribed symptom clusters cannot be established by these findings.

Similarly, although we expected to find connectivity differences in networks associated with cognitive control, our study did not find evidence for altered resting-state connectivity within the executive control RSN or the left frontoparietal RSN. The executive control network, as identified by our study, has been previously referred to as corresponding to cognition paradigms of inhibitory control, affective processing and pain, whereas the left frontoparietal RSN has been implicated in language processes.¹⁷ The negative findings of our study do not necessarily imply intact executive, inhibitory or linguistic pathways in patients with BPD, or intact function of the anterior cingulate and ventro- and dorsolateral prefrontal cortices. The latter regions have been addressed by numerous neuroimaging studies in patients with BPD,^{2,3} although mostly within the context of cognitive, affective and somatosensory stimulation. Since a range of clinical features of BPD might especially occur in reaction to (mostly negative) experiences,⁵⁶ networks subserving cognitive control functions as a response to environmental demands might appear intact when studied under resting-state conditions. Thus, further research is needed to dissociate alterations of brain network connectivity during experimentally induced conditions and their interactions with baseline connectivity during the resting state.

From a clinical perspective, the question of whether the findings of the present study can be seen as specific for patients with BPD must remain open at this stage of research. Neuroimaging evidence from other clinical populations, such as patients with bipolar disorder, suggests left FPC (BA 10) dysfunction during tasks of response inhibition and working memory, regardless of the clinical status (i.e., in patients with acute mania,⁵⁷ euthymic individuals⁵⁸ and nonpsychotic first-degree relatives).⁵⁹ These studies at least suggest a more general link between deficient inhibitory control, abnormal left FPC activation and clinical populations characterized by mood instability. Similarly, aberrant neural responses of the insula and the cuneus have been shown in patients with PTSD and dissociative responses.⁴⁶ When considering these results, however, it is important to note that most of these findings have been derived from task-based protocols, where stimulus-related interactions with brain activation have to be taken into account. Moreover, when considering extant bipolar or PTSD samples with available resting-state data, baseline connectivity differences have been reported in DMN regions distinct from those found in our BPD sample.^{60,61} More recently, a study investigating multiple RSNs in medication-free patients with major depression²⁰ reported a pattern of dysfunction different from the pattern of dysconnectivity observed in our BPD sample. However, definite conclusions about the specificity of the present findings to BPD can only be drawn by rs-fMRI studies of 2 or more clinical groups.

Limitations

Several potential limitations of this study have to be considered.

First, our results should be cautiously interpreted given the potential influence of other comorbid axis I disorders on these findings. However, the question of whether patients with BPD with psychiatric comorbidities should be excluded to homogenize clinical sample characteristics remains controversial.² Most patients with BPD have an additional axis I disorder, such as depression, even in very early samples,⁶² and thus, fully excluding participants with other co-occurring axis I disorders may reduce the generalizability of findings to the larger BPD population. Although our patient subgroup analyses did not reveal differences between patients with and without symptoms of major depression, future studies using appropriate clinical comparison groups are necessary to determine the specificity of RSN abnormalities in patients with BPD with respect to additional psychiatric comorbidities. Second, given reports of neural differences between patients with BPD with and without comorbid symptoms of PTSD,³ we chose to investigate only those patients without PTSD as a first attempt to homogenize our patient sample. However, we acknowledge that this approach could also constrain our findings to this patient subgroup, whereas patients with BPD with symptoms of PTSD might exhibit differential patterns of RSN dysfunction. Third, we excluded patients with an unstable physical condition before scanning and patients who presented with acute suicidal ideation, which might restrict our findings to clinically more stable patients. Fourth, all of our patients were medicated, and it is unclear at present if and which RSNs are selectively modulated by specific psychotropic agents. Nevertheless, since at least antipsychotic drugs have been reported to modulate DMN function and low-frequency fluctuations of BOLD signals,^{33,63} we can neither rule out nor specify potential effects of psychotropic treatment in the present BPD sample.

Conclusion

The results of the present study suggest abnormal connectivity of distinct prefrontal RSNs in female patients with BPD without co-occurring PTSD. Differences in functional connectivity were restricted to the DMN and a right frontoparietal attention system, whereas RSNs associated with executive control and language did not exhibit changes during resting-state conditions. Within the DMN, connectivity of the left FPC and the insula were found to be associated with core symptom clusters of patients with BPD, such as impulsivity and dissociation. While confirming previous task-based findings of aberrant left FPC physiology in patients with BPD, this study also provided evidence for abnormal functional connectivity during resting-state conditions. Given the functional relevance of the left FPC within a wide spectrum of higher-order processes, future research involving patients with BPD could consider the dynamic interaction of baseline functional connectivity with processes elicited by more complex cognitive, affective and social stimuli.

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