Psychiatry Research: Neuroimaging 283 (2019) 118–124

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Abnormalities in functional connectivity in borderline personality disorder: Correlations with metacognition and emotion dysregulation

Giulia Quattrini[a,b], Lorenzo Pini[b,c], Michela Pievani[b], Laura R Magni[a], Mariangela Lanfredi[a], Clarissa Ferrari[g], Marina Boccardi[b,d], Stefano Bignotti[a], Silvia Magnaldi[e], Milena Cobelli[e], Luciana Rillosi[a], Rossella Beneduce[a], Giuseppe Rossi[a], Giovanni B Frisoni[b,f], Roberta Rossi[a,*]

[a] Unit of Psychiatry, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy
[b] Laboratory of Alzheimer's Neuroimaging and Epidemiology (LANE), IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy
[c] Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy
[d] Laboratoire de Neuroimagerie du Vieillissement, Department of Psychiatry, University of Geneva, Genève, Switzerland
[e] Department of Neuroradiology, Poliambulanza Hospital, Brescia, Italy
[f] Department of Psychiatry, LANVIE-Laboratory of Neuroimaging of Aging, University of Geneva, Genève, Switzerland
[g] Unit of Statistics, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

ARTICLE INFO

Keywords:
Borderline personality disorder
Resting-state Fmri
Functional connectivity
Metacognition
Emotion dysregulation

ABSTRACT

A few studies reported functional abnormalities at rest in borderline personality disorder (BPD), but their relationship with clinical aspect is unclear. We aimed to assess functional connectivity (FC) in BPD patients and its association with BPD clinical features. Twenty-one BPD patients and 14 healthy controls (HC) underwent a multidimensional assessment and resting-state fMRI. Independent component analysis was performed to identify three resting-state networks: default mode network (DMN), salience network (SN), and executive control network (ECN). FC differences between BPD and HC were assessed with voxel-wise two-sample *t*-tests. Additionally, we investigated the mean FC within each network and the relationship between connectivity measures and BPD clinical features. Patients showed significant lower mean FC in the DMN and SN, while, at the local level, a cluster of lower functional connectivity emerged in the posterior cingulate cortex of the DMN. The DMN connectivity was positively correlated with the anger-state intensity and expression, while the SN connectivity was positively correlated with metacognitive abilities and a negative correlation emerged with the interpersonal aggression. The dysfunctional connectivity within these networks might explain clinical features of BPD patients.

1. Introduction

Borderline personality disorder (BPD) is a psychiatric condition characterized by emotion and behavioral dysregulation, interpersonal hypersensitivity, self- disturbance and difficulties in mentalization functions (American Psychiatric Association, 2013). Two crucial domains have been largely investigated: mentalization/metacognitive deficits, and emotional dysregulation. Mentalizing (Bateman and Fonagy, 2004), or metacognition (Semerari et al., 2007), refers to the capacity to think about thinking. BPD patients experience difficulties in mentalization/metacognition, including deficits in monitoring and identifying emotions, inability to integrate different mental states, or failure to distinguish between one's inner world and external reality (Fonagy and Bateman, 2007; Semerari et al., 2015). The emotional dysregulation is described as the distinctive face of the disease, encompassing emotional awareness, understanding, and acceptance of one's emotions, in addition to the ability to manage emotional arousal (Vaskinn et al., 2015). Emotional dysregulation is a core feature in BPD and it is described both in terms of an increased emotional sensitivity and an inability to regulate emotional response that results in marked impulsive behavior and difficulties in anger control (Linehan et al, 2006). Metacognition and emotional dysregulation are strictly connected, since the ability to regulate and manage the emotion increases with the increasing of metacognitive abilities.

BPD is plausibly the result of a complex interaction between biological and psychosocial factors (Glenn, 2009), and increasing attention has been directed to the biological mechanisms. Neuroimaging studies revealed both structural and functional brain abnormalities particularly involving limbic structures. In BPD, structural MRI studies identified lower volumes in the hippocampus and amygdala (Nunes et al., 2009;

* Corresponding author at: Unit of Psychiatry, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Via Pilastroni 4, 25125 Brescia, Italy.
E-mail address: rrossi@fatebenefratelli.eu (R. Rossi).

https://doi.org/10.1016/j.pscychresns.2018.12.010
Received 10 April 2018; Received in revised form 17 December 2018; Accepted 19 December 2018
Available online 20 December 2018
0925-4927/

Rossi et al., 2012), prefrontal cortex (Sala et al., 2011; Soloff et al., 2012), and various regions of the temporal and parietal lobes (Soloff et al., 2008; Rossi et al., 2015), compared with healthy subjects. The most robust findings emerging from task fMRI studies were hyperactivity of the amygdala and hypo-activation of frontal areas in response to emotional stimuli (Mauchnik and Schmahl, 2010). These results were interpreted as the biological substrate of the core symptoms of BPD, in particular of the emotional dysregulation. Recent studies started focusing on brain networks emerging during rest (i.e. while the subject is not performing a task) and that are thought to contribute to functions impaired in BPD patients, such as self-, emotion-, and cognitive control processing (Mauchnik and Schmahl, 2010; Menon and Uddin, 2010). The default mode network (DMN), which includes the posterior cingulate cortex (PCC), inferior parietal lobule, lateral temporal lobes and bilateral hippocampi, medial prefrontal and dorsolateral prefrontal cortex, is thought to be involved in self-consciousness, self-processing and self-introspections, including emotional awareness and processing (Menon, 2011; Buckner et al., 2008). The salience network (SN), anchored to the bilateral insula and anterior cingulate cortex (ACC), contributes to a variety of functions, including social behavior and emotion regulation, and self-awareness (Menon, 2011; Craig and Craig, 2009). It has a central role in the detection of behaviorally relevant stimuli and the coordination of neural resources (Uddin, 2015). The executive control network (ECN), which includes the bilateral dorsolateral parietal and frontal cortices, is engaged when performing cognitively demanding tasks requiring attention (Gogolla et al., 2014), and it is associated with cognitive and executive control processes during goal-directed behavior (Dosenbach et al., 2008).

Few studies to date used resting-state fMRI (RS-fMRI) to assess dysfunctions of these networks in BPD, with mixed results. A recent meta-analysis of RS-fMRI in BPD concluded that patients exhibit an altered activity in DMN regions, and in particular in the midline core as well as in the dorsal subsystems (Visintin et al., 2016). Compared to controls, patients' neural activity at rest was greater in midline regions (medial prefrontal cortex/anterior cingulate and precuneus/ posterior cingulate) and decreased in middle/inferior temporal cortex and in orbitofrontal cortex (Visintin et al., 2016).

As reported in a recent review, altered RS-fMRI connectivity is observed in BPD within networks associated with processing of negative emotions, encoding of salient events, and self-referential processing (Krause-Utz et al., 2014b). However, the direction of these changes is not clear. In a study assessing the DMN and the ECN, Wolf et al. (2011) found both increased and reduced connectivity in the DMN, and reduced connectivity in the ECN. In line with this finding, Doll et al. (2013) reported altered (both increases and decreased) DMN functional connectivity (FC). However, differently from Wolf et al. (2011), this study found both increased and reduced connectivity in the ECN. Additionally, this study provided for the first time evidence of increased intrinsic connectivity in the SN (Doll et al., 2013). Krause-Utz et al. (2014a) found no difference in core DMN areas but increased anti-correlations between the DMN and the occipital cortex. The SN showed increased within-network connectivity and decreased anti-correlations with posterior DMN areas (Krause-Utz et al., 2014a). Finally, O'Neill and colleagues found increased FC between precuneus (DMN seed) and frontal regions during the rest, while Salvador and colleagues showed increased resting FC between temporolimbic and frontomedial structures (left hippocampus and amygdala with the anterior cingulate cortex) (O'Neill et al., 2015; Salvador et al., 2016).

In the present study, we assessed RS-fMRI changes in a group of unselected BPD patients compared with healthy controls (HC) to assess the pattern of FC at rest in BPD. Firstly, we focused the analysis on cortical networks that are known to be aberrant in BPD patients and that are involved in cognitive functions often described as impaired in BPD patients (i.e. the DMN for self-processing, the SN for top-down attention and cognitive control processes, and the ECN for executive control processes). Secondly, we explored the relationship between FC within these resting-state networks and the clinical symptoms. In particular, we expected that functional abnormalities would be correlated with the emotional dysregulation and metacognitive abilities.

2. Methods

2.1. . Subjects

Twenty-six BPD patients and 14 age- and sex-matched HC were included in the present study. BPD patients were recruited between June 2012 and March 2015 in the framework of a project aimed to study cerebral features associated with BPD carried out at the IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli (Brescia).

The clinical diagnosis was confirmed by the Structured Clinical Interview for DSM-IV (SCID I and II) (First et al., 1995; First et al., 1994) made by a clinically experienced interviewer. The assessment covered several clinical domains. The following self-report scales were administered: Symptoms Check List-90-R (SCL-90-R) (Derogatis et al., 1977), assessing general psychopathology; the Toronto Alexithymia Scale (TAS) (Bagby et al., 1994) to assess alexithymia; the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) to measure the level of impulsivity; the State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) and the State–Trait Anger Expression Inventory-2 (STAXI-2) (Spielberger, 1999) to assess anxiety and anger, respectively; the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004), a 36-items scale to assess emotion dysregulation; the Inventory of Interpersonal Problems (IIP) (Ubbiali et al., 2011) to check interpersonal difficulties. Furthermore, we assessed the global functioning with the Personal and Social Performance scale administered by the clinician (Gigantesco et al., 2008). Lastly, metacognitive abilities were assessed with the Metacognition Assessment Interview (MAI) (Semerari et al., 2012), a semistructured interview that evaluates two main functional skill domains of metacognition, 'the Self' and 'the Other', each one composed of two dimensions: monitoring and integrating for the Self, differentiating and decentring for the Other (Semerari et al., 2012). For each patient, we collected information about: history of psychiatric disease (years), history of alcohol and drug abuse, presence of suicidal attempts, self-injurious behaviors or aggression, and drug therapy. Exclusion criteria were: acute or lifetime major depressive disorder associated to psychotic trait, schizophrenia, schizoaffective disorder, and substance or alcohol abuse in the last three months, any cognitive impairment and neurological disease.

HC were volunteers free of any cognitive impairment or psychiatric/neurologic condition, including traumatic brain injury, alcohol/substance abuse, transient ischemic attack, and stroke. They underwent a clinical assessment including SCL-90-R, TAS, BIS, and STAI-Y.

All participants provided written informed consent. The study was approved by the local Ethics Committee (Comitato Etico delle Istituzioni Ospedaliere Cattoliche).

2.2. . MRI acquisition

BPD patients and HC underwent MRI exam including a gradient echo-planar imaging sequence for RS-fMRI on a 1.5 T GE scanner at Poliambulanza Foundation (Brescia), with the following parameters: TR = 3000 ms, TE = 30 ms, flip angle = 90°, matrix size = 64 × 64, FOV = 220 × 220 mm, 40 axial slices, slice thickness = 3 mm, number of volumes = 200. Subjects were instructed to lay down and relax during scanning, keeping their eyes closed, not to think of anything in particular, and not to fall asleep.

2.3. . MRI analysis

All RS-fMRI scans passed a first visual quality check, performed to ensure data did not present gross artifacts. RS-fMRI data were pre-

processed with Statistical Parametric Mapping 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The first five volumes of each session were discarded to allow for magnetic field stabilization. For each subject, the framewise displacement (FD) (Power et al., 2012) was calculated over the whole brain using the FMRIB Software Library v5.0 (FSL, http://fsl.fmrib.ox.ac.uk/) toolbox for motion outliers. RS-fMRI volumes were co-registered to the first scan to correct for head motion. Four patients were excluded due to excessive head movements (>3 mm for translation and >1.5° for rotation). Additionally, motion artefacts were corrected using the ArtRepair toolbox for SPM (Mazaika et al., 2009), and one patient was excluded (bad volumes more than 25%).

The definitive sample included 21 BPD patients and 14 HC. Individual RS-fMRI images were normalized to the Montreal Neurological Institute (MNI) template with the bounding box set to [−90 −126 −72; 90 90 108] and resliced to 3 × 3 × 3 mm to retain the original voxel size. Normalized images were spatially smoothed with a 6 × 6 × 6 mm Gaussian kernel.

An independent component analysis (ICA) was performed using the GIFT Toolbox (version 3.0a) to identify the 3 resting-state networks of interest: DMN, SN, and ECN. The latter was divided in its left (LECN) and right (RECN) components. Independent group components were estimated using the Infomax approach (Bell and Sejnowski, 1995). The estimated number of independent components was 20, a dimension determined using the minimum description length criteria. The resulting group maps were used to compute individual components, through a back reconstruction step. The estimated spatial maps were then converted into *Z* scores. Networks of interest were selected through a template matching spatial correlation procedure and standard template (Shirer et al., 2012).

2.4. . Statistical analysis

Sociodemographic and clinical differences between groups were assessed using chi-square test, two-sample *t*-test (two-tailed) or Mann–Whitney *U* test (based on data distribution).

For each network of interest, RS-fMRI differences between BPD and HC were assessed with voxel-wise two-sample *t*-tests and corrected for multiple comparisons with a permutation-based approach using *randomise* (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise) (family-wise error rate – FWE- correction at the cluster level using the threshold-free cluster enhancement –TFCE - method, 5000 permutations). Each contrast (BPD < HC, BPD > HC) was restricted to the network of interest according to the following procedure: a one-sample *t*-test ($p < 0.001$, FWE corrected) was conducted for each network (Fig. 1) and the resulting map was binarized; subsequently, a two-sample *t*-test ($p < 0.05$, FWE corrected) was performed by inclusively masking the contrast with the binary mask obtained at the previous step. Age (years), gender (binary), FD (mean), drug and/or alcohol abuse and pharmacological treatment (dichotomous variables) were included as covariates in all the analyses.

Additionally, we explored mean FC within each resting-state network. For each network and subject, spatial *Z* maps were thresholded at connectivity score >1.3 and averaged to compute the mean FC connectivity across all subjects for both groups (BPD or HC). Two-sample *t*-test or Mann–Whitney *U* test (based on data distribution) was used to assess differences in networks' mean FC ($p < 0.05$, multiple comparisons correction for the number of networks, $N = 4$).

To assess the clinical relevance of FC changes, measures of FC that emerged as statistically different from group comparisons (global: mean resting-state connectivity; local: voxel-wise derived clusters) were entered in a second level analysis to investigate their relationship with clinical features (STAXI-2, TAS, BIS-11, DERS, IIP and MAI scores and their subscales). This analysis was carried out only in the BPD sample using Pearson or Spearman correlations (based on the data distribution), and reported as a descriptive measure on pre-selected variables (Bender and Lange, 2001). Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 23.

3. Results

3.1. . Sociodemographical and clinical features of participants

BPD patients and HC differed for years of education (Table 1). The gender distribution between groups was not perfectly balanced, the percentage of females being slightly higher in BPD, although the difference was not statistically significant. Table 1 also shows that less than a half of BPD patients were inpatients with long disease duration, and between 50–60% had a history of alcohol and/or substance abuse although they were abstinent for at least three months. BPD patients and HC were significantly different for level of psychopathology, anxiety, and impulsiveness. Patients had a moderate level of impulsiveness, alexithymia, personal and social functioning, and more than 66% showed a high level of anxiety (Table 1). The majority of patients (86%) received pharmacotherapy. In line with the literature, in our BPD sample we observed the presence of comorbidities (lifetime): major depressive episode ($N = 7$), eating disorder ($N = 4$), and panic disorder ($N = 4$). Regarding comorbid personality disorders, one patient had also a diagnosis of dependent personality disorder and one a diagnosis of narcissistic personality disorder.

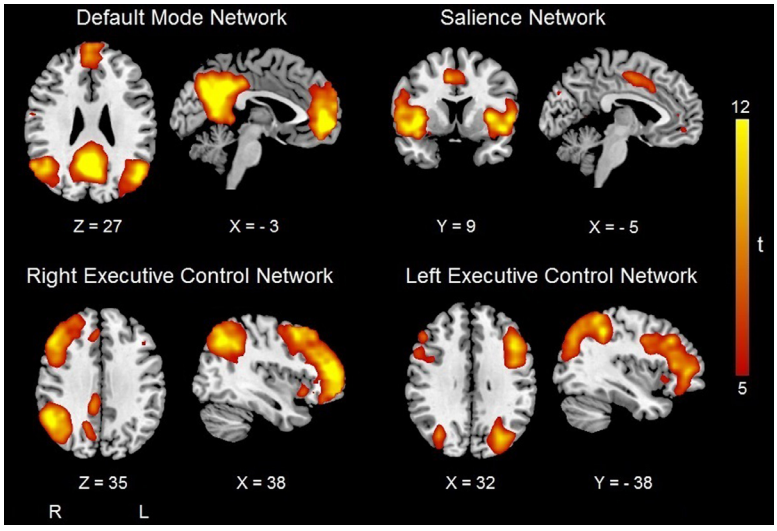

Fig. 1. Results of the one-sample *t*-tests from the entire sample (healthy controls and borderline personality disorder patients) for the resting-state networks of interest (default mode network, salience network, right and left executive control network). The color bar denotes the *t*-statistic range ($p < 0.001$, FWE corrected). Maps are overlaid onto the MNI standard template. MNI, Montreal Neurological Institute. R: right; L: left. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Sociodemographic and clinical features of borderline personality disorder (BPD) patients and healthy controls (HC).

	BPD $N = 21$	HC $N = 14$	Test value	p value
Age	35 ± 9	38 ± 7	$U = 144$	0.934
Sex (%female)	14 (67%)	5 (36%)	$X^2 = 3.243$	0.070
Education (years)	11 ± 3	16 ± 3	$U = 41$	<0.001
Years of Illness	13 ± 7	–		–
% inpatients	42.8%	–		–
Alcohol Abuse	52%	0%	$X^2 = 10.694$	<0.001
Substance Abuse	62%	0%	$X^2 = 13.788$	<0.001
Clinical Assessment				
Symptoms CheckList-90-R	150.6 ± 76.3	34.5 ± 30.6	$t = 8.441$	<0.001
State and Trait Anxiety Inventory - Y				
STATE	44.3 ± 7.9	35.9 ± 7.6	$t = 3.032$	0.005
High anxiety	66.6%	46%		
TRAIT	47.3 ± 8.2	37.7 ± 8.3	$t = 3.198$	0.003
High anxiety	80.9%	50%		
Toronto Alexithymia Scale	53.5 ± 17.3	43.46 ± 12.4	$t = 1.811$	0.080
Non alexithymic (<51)	52.4%	77%		
Borderline (52–60)	19%	8%		
Alexithymic (>61)	28.6%	15%		
Barratt Impulsiveness Scale-11	74.6 ± 10.2	59.69 ± 8.4	$t = 4.431$	<0.001
Low (<67)	28.6%	77%		
Moderate (68–89)	66.7%	23%		
High (>90)	4.7%	0%		
Personal and Social Functioning Scale	50.1 ± 13.1	–		–
Mild (>60)	23.8%			
Moderate (41–60)	42.8%			
Severe (<40)	28.6%			
Metacognitive Assessment Interview[a] (Range 16–80)	42 ± 2.1	–		–
Difficulties Emotional Regulation Scale[a] (Range 36–180)	120.6 ± 17.2	–		–
Inventory of Interpersonal Problems[a]	2.3 ± 0.5	–		–
Interpersonal Sensitivity	2.6 ± 0.7			
Interpersonal Ambivalence	2.1 ± 0.4			
Aggression	1.9 ± 0.8			
Need for Social Approval	2.4 ± 0.6			
Lack of Sociability	2.2 ± 0.8			
State and Trait Anger Expression Inventory-2[a]		–		–
State Anger	19.1 ± 9			
Trait Anger	2.8 ± 4.3			
Anger Expression-Out	18.9 ± 5.3			
Anger Expression-In	19.8 ± 6.2			
Anger Control-Out	12.8 ± 4.9			
Anger Control-In	16.7 ± 6.3			
Anger Expression Index	57.2 ± 18.9			
Pharmacotherapy:	18 (85.7%)	–		–
Typical Antipsychotic	3 (14.3%)			
Atypical Antipsychotic	7 (33.3%)			
Antidepressant SSRI	7 (33.3%)			
Benzodiazepine	12 (57.1%)			
Mood Stabilizers of whom with Lithium	9 (42.8%)			
	2 (9.5%)			

Values denote mean ± standard deviation, or percentage. Based on the data distribution, p denotes significance on two-sample t-test or Mann–Whitney U test (only for age, education and the State and Trait Anxiety Inventory – Y/ STATE) or on Chi-square test (categorical variables).
[a] Data available only for 11 BPD patients.

3.2. . Functional connectivity: Differences in mean and local connectivity

BPD patients showed lower mean FC than HC in the DMN, SN, and LECN, ($p < 0.05$), the first two surviving after multiple comparisons correction ($p < 0.0125$; Table 2).

In addition to alterations in the mean FC, lower DMN connectivity in BPD patients mapped to the right PCC ($p < 0.05$, FWE corrected; cluster size = 31 voxels, MNI coordinates = [+12 −57 +18], t score = 4.6; Fig. 2), while in the SN no significant differences emerged. Furthermore, only with an exploratory intent, we investigated the presence of local changes also in the ECN, but we did not find any difference between BPD patients and HC.

3.3. . Correlations between functional connectivity and psychometric measures

In the BPD group, we found significant correlations between FC, both at the global and local level, and core clinical features (Table 3). Specifically, in the DMN, mean FC was positively correlated with the anger-state intensity and expression, as assessed with the STAXI-2/State Anger subscale ($r = 0.778$, $p = 0.008$), and with the interpersonal aggression, assessed with IIP/Aggression subscale ($r = 0.617$, $p = 0.032$). At the local level, FC in the right PCC ($r = 0.734$, $p = 0.016$) was positively correlated with the expression of verbal physical anger (STAXI-2/ Anger Expression-Out).

Finally, mean FC of the SN strongly correlated with metacognitive abilities ($r = 0.826$, $p = 0.002$), while a negative correlation emerged

Table 2
Differences between borderline personality disorder patients (BPD) and healthy controls (HC) in mean functional connectivity.

Resting-state networks	BPD $N = 21$	HC $N = 14$	*Test value*	*p* value
Default mode network	2.121 ± 0.097	2.218 ± 0.084	$t = 3.016$	0.005
Salience network	2.098 ± 0.093	2.181 ± 0.089	$U = 64$	0.004
Left executive control network	2.091 ± 0.071	2.152 ± 0.092	$t = 2.200$	0.035
Right executive control network	2.173 ± 0.108	2.254 ± 0.130	$U = 90$	0.056

Values denote mean ± standard deviation. *p* denotes significance on two-sample *t*-test (default mode network and left executive control network) or Mann–Whitney test (salience network and right executive control network), based on data distribution.

Table 3
Correlations between functional connectivity (mean and local) and clinical features in borderline personality disorder patients.

Functional connectivity measure		Clinical feature	*r* value	*p* value
Default mode network	Mean FC	STAXI-2/State Anger	0.778	0.008
		IPP/Aggression	0.617	0.032
	Local FC: R PCC	STAXI-2/Anger Expression-Out	0.734	0.016
Salience network	Mean FC	IPP/Aggression	−0.707	0.010
		MAI	0.826	0.002

p denotes statistical significance on Pearson's correlation; *r* denotes the correlation coefficient for Pearson's test. Abbreviations: FC: functional connectivity; IIP: Inventory of Interpersonal Problems; MAI: Metacognition Assessment Interview; PCC: posterior cingulate cortex; STAXI-2: State–Trait Anger Expression Inventory-2; R: right hemisphere.

with the interpersonal aggression ($r = -0.707$, $p = 0.010$).

4. Discussion

In the present study, we investigated the FC of three resting-state networks (DMN, SN, and ECN) and the correlations between functional abnormalities and clinical symptoms. We considered both the mean connectivity, a global indicator of connectivity status and whose alteration suggests the temporal desynchronization of brain activity (Allen et al., 2011), and local clusters of alterations in the networks of interest. We found functional alterations in BPD compared with HC in all the networks considered, although only abnormalities in the DMN and the SN survived after multiple comparisons correction.

Our findings are only partially in line with previous studies, which reported altered connectivity in the form of both increased/decreased DMN connectivity and increased SN connectivity. Differently from these studies, we observed a coherent pattern of reduced networks connectivity rather than higher connectivity (Wolf et al., 2011; Krause-Utz et al., 2014a; Wolf et al., 2012). These differences might be due to differences in the clinical features of BPD patients and in the methodology. In particular, previous studies included almost exclusively female patients, while our sample was more balanced (67% females and 33% males). Indeed, sex-related differences in DMN, SN, and ECN connectivity have been described in healthy volunteers in fMRI studies (Filippi et al., 2013) and the inclusion of only female BPD patients could prevent the generalizability of the results. Furthermore, the diagnosis of BPD includes several different clinical patterns that are probably related to different neurobiological features. More importantly, our patients have a long history of disease and alcohol/drug abuse, all factors that might affect FC and reduce it (Wilcox et al., 2016). Unfortunately, in BPD patients no study has yet assessed the functional changes at different disease stages. Hence we can only speculate as to whether a longer disease course might have contributed to these changes. However, drug and/or alcohol abuse and pharmacological treatment were included as covariates in all the analyses. Future studies including patients at different disease stages or longitudinal evaluations might properly investigate the trajectory of connectivity changes over BPD course, to evaluate, for example, if connectivity changes are linear over time or characterized by distinct phases.

The dysfunctional connectivity within these networks might explain some of the behavioral and cognitive features observed in BPD patients. In particular, one of the core features of the BPD symptomatology are the mentalization deficits. BPD patients are as capable as controls of undertaking simple mentalization tasks, but mentalization deficits become evident when complexity increases and integration of multiple perspectives is required (Petersen et al., 2016). The inaccuracy in reading emotional states (in a hypersensitive way) and the difficulty in integrating facial and prosodic expressions of other people lead to difficulties in establishing and maintaining interpersonal relationships. In our sample, we found abnormalities in the SN, a circuit strictly involved in metacognitive processes, and these abnormalities were highly correlated with metacognitive performance. This result is in line with studies indicating that the SN, together with interconnected brain networks, contributes to a variety of complex brain functions, including communication, social behavior, and self-awareness through the integration of sensory, emotional, and cognitive information (Mauchnik and Schmahl, 2010; Buckner et al., 2008; Craig and Craig, 2009; Menon and Uddin, 2010). In the DMN, BPD patients showed abnormalities in the mean FC and in a local cluster localized in the right PCC. A diminished FC in BPD patients is in line with previous studies (Krause-Utz et al., 2014b). Interestingly, in our sample the connectivity in the DMN and in this local cluster were correlated with higher anger dimensions. In BPD, emotional dysregulation, and in particular the expression of anger, is one of the main clinical features and is often a focus of the clinical intervention (Linehan et al., 2006). Anger expression is strictly related to metacognitive abilities. Indeed, mentalized affectivity involves a reappraisal of affective experience that contributes to affect regulation. It could be not immediately intuitive that the direction of the association was positive, but this pattern could reflect an abnormal DMN regulation in more impaired patients. The PCC is a core node of the brain as it allows the functional integration between the medial frontal and the medial temporal subsystems. Furthermore, the PCC is a

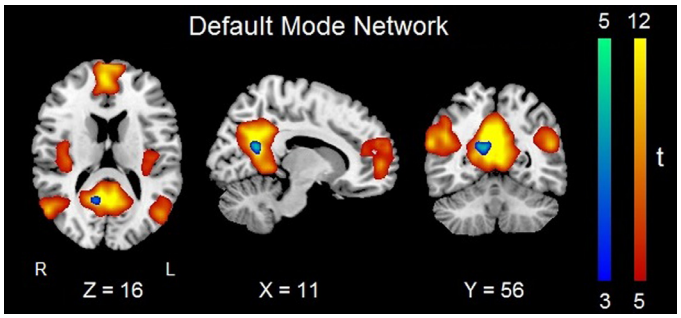

Fig. 2. Reduced connectivity in the default mode network in borderline personality disorder patients. Red voxels represent the one-sample *t*-tests from the entire sample (see Fig. 1); blue voxels show clusters of reduced connectivity in patients compared with controls ($p < 0.05$, FWE corrected). Results are corrected for age, gender, framewise displacement, drug and/or alcohol abuse and pharmacological treatment. The color bar denotes the *t*-statistic range. Maps are overlaid onto the MNI standard template. MNI, Montreal Neurological Institute. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

hub region contributing to several other networks, such as the SN, and the ECN (Leech and Sharp, 2014). It is a key region being part of the so-called "tripartite core-self system" related to thinking explicitly about the self (Davey et al., 2016). The PCC dysfunction might partially explain deficits in the reflexive function commonly present in BPD patients. The fact that local and global effects were coherent in the DMN (i.e., reduced connectivity without any increase), speaks for a consistent albeit weak reduction of connectivity within this network in this sample. Conversely, results in the SN survived multiple comparisons correction at the global but not voxel-wise analysis, suggesting that SN connectivity changes in BPD are subtle and broader rather than focal. An alternative explanation for the lack of voxel-based differences in the SN is that some factors might have contributed to reduce the sensitivity of this analysis, such as the scanner field strength. The blood oxygen level dependent (BOLD) signal is known to increase with field strength and 3 T scanners can provide a stronger signal than 1.5 T. Averaging the BOLD signal over broad areas can indeed reduce noise, while voxel-wise approaches might be more susceptible to this issue.

This study has several strengths. Firstly, it included both male and female BPD patients, and this may increase the generalizability of the results and overcome the limitation of previous studies that included only females. Secondly, our BPD sample was unselected and represents the clinical BPD population commonly admitted in rehabilitation psychiatric services, and might therefore be more representative of the real-practice.

Some caveats should be taken into account when interpreting our findings. Firstly, the sample size was very limited and the strength of the MRI field (1.5 T) was associated with a lower signal-to-noise-ratio. Secondly, there is the potential confounding effect of a history of alcohol and substance abuse. Although we adjusted the analyses for these variables, we did not systematically collect information about the length of the abuse and doses. It should be noted that there is a high degree of comorbidity between BPD and alcohol and substance use disorders (14–56%, median = 52%), and 23–84% of BPD patients (median = 65%) fulfill criteria for any substance use disorder (Rossi and de Girolamo, 2010). Furthermore, most of BPD patients (85%) were medicated, and the role of specific psychotropic drugs on FC is unclear. It is known that selective serotonin reuptake inhibitors (SSRIs) administration is associated with a reduction of the FC in the DMN (McCabe et al., 2011; McCabe and Mishor, 2011), the ECN, auditory and visual networks and limbic-frontal circuitry (van Wingen et al., 2014; Klaassens et al., 2017), while some antipsychotic drugs have been reported to modulate DMN function and low frequency fluctuations of BOLD signals (Sambataro et al., 2010; Wang et al., 2017). Therefore, despite the inclusion of these factors as covariates in the analysis, we cannot exclude the potential effects of psychotropic treatment in our sample, and the limited sample size did not allow any further stratification. However, it should be noted that pharmacotherapy is commonly prescribed (American Psychiatric Association, 2001) and drug-withdrawal in patients would pose ethical issues. In the future, a larger sample could give us the opportunity to stratify for these variables and better control for their impact. Furthermore, future studies will need to include the assessment of emotion dysregulation and metacognition in HC. This will be important to assess whether differences in functional activation in relation to these dimensions are present between BPD and HC in terms of intensity and/or cerebral regions involved.

5. Conclusions

The presence of dysfunctional connectivity within these networks might explain behavioral and cognitive features observed in BPD patients.

Funding

This work was supported by the Italian Ministry of Health ("ricerca corrente" and GR-2011-02351347) and 5× 1000 funds.

References

Allen, E.A., Erhardt, E.B., Damaraju, E., Gruner, W., Segall, J.M., Silva, R.F, Havlicek, M., Rachakonda, S., Fries, J., Kalyanam, R., Michael, A.M., Caprihan, A., Turner, J.A., Eichele, T., Adelsheim, S., Bryan, A.D., Bustillo, J., Clark, V.P., Feldstein Ewing, S.W., Filbey, F., Ford, C.C., Hutchison, K., Jung, R.E., Kiehl, K.A., Kodituwakku, P., Komesu, Y.M., Mayer, A.R., Pearlson, G.D., Phillips, J.P., Sadek, J.R., Stevens, M., Teuscher, U., Thoma, R.J., Calhoun, V.D., 2011. A baseline for the multivariate comparison of resting-state networks. Front. Syst. Neurosci. 5, 2.

American Psychiatric Association, 2001. Practice Guideline for the Treatment of Patients with Borderline Personality Disorder. American Psychiatric Pub.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders: DSM-5, fifth ed. American Psychiatric Association, Washington, D.C.

Bagby, R.M., Taylor, G.J., Parker, J.D., 1994. The twenty-item toronto alexithymia scale–II. Convergent, discriminant, and concurrent validity. J. Psychosom. Res. 38, 33–40.

Bateman, A.W., Fonagy, P., 2004. Mentalization-based treatment of BPD. J. Personal. Disord. 18, 36–51.

Bell, A.J., Sejnowski, T.J., 1995. An information-maximization approach to blind separation and blind deconvolution. Neural Comput. 7, 1129–1159.

Bender, R., Lange, S., 2001. Adjusting for multiple testing–when and how? J. Clin. Epidemiol. 54, 343–349.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N.Y. Acad. Sci. 1124, 1–38.

Craig, A.D., Craig, A., 2009. How do you feel–now? The anterior insula and human awareness. Nat. Rev. Neurosci. 10, 59–70.

Davey, C.G., Pujol, J., Harrison, B.J., 2016. Mapping the self in the brain's default mode network. Neuroimage 132, 390–397.

Derogatis, L.R., Lipman, R.S., Covi, L., 1977. Administration, Scoring and Procedures Manual-I for the R (revised) Version and Other Instruments of the Psychopathology Rating Scales Series. Johns Hopkins University School of Medicine, Chicago.

Doll, A., Sorg, C., Manoliu, A., Meng, C., Wöller, A., Förstl, H., Zimmer, C., Wohlschläger, A.M., Riedl, V., 2013. Shifted intrinsic connectivity of central executive and salience network in borderline personality disorder. Front. Hum. Neurosci. 7, 727.

Dosenbach, N.U., Fair, D.A., Cohen, A.L., Schlaggar, B.L., Petersen, S.E., 2008. A dual-networks architecture of top-down control. Trends Cognit. Sci. 12, 99–105.

Filippi, M., Valsasina, P., Misci, P., Falini, A., Comi, G., Rocca, M.A., 2013. The organization of intrinsic brain activity differs between genders: a resting-state fMRI study in a large cohort of young healthy subjects. Hum. Brain Mapp. 34, 1330–1343.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID-I/P). New York State Psychiatric Institute, Biometric Research Department, New York.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., Benjamin, L., 1994. Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II). New York State Psychiatric Institute, Biometric Research Department, New York.

Fonagy, P., Bateman, A.W., 2007. Mentalizing and borderline personality disorder. J. Ment. Health 16, 83–101.

Gigantesco, A., Morosini, P., Vittorielli, M., Pioli, R., 2008. The VADO approach in psychiatric rehabilitation: a randomized controlled trial. Eur. Psychiatry 23, S116–S117.

Glenn, C.R., 2009. Emotion dysregulation as a core feature of borderline personality disorder. J. Personal. Disord. 23, 20–28.

Gogolla, N., Takesian, A.E., Feng, G., Fagiolini, M., Hensch, T.K., 2014. Sensory integration in mouse insular cortex reflects GABA circuit maturation. Neuron 83, 894–905.

Gratz, K.L., Roemer, L., 2004. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J. Psychopathol. Behav. Assess. 26, 41–54.

Klaassens, B.L., Rombouts, S.A., Winkler, A.M., van Gorsel, H.C., van der Grond, J., van Gerven, J.M., 2017. Time related effects on functional brain connectivity after serotonergic and cholinergic neuromodulation. Hum. Brain Mapp. 38 (1), 308–325.

Krause-Utz, A., Veer, I.M., Rombouts, S.A., Bohus, M., Schmahl, C., Elzinga, B.M., 2014a. Amygdala and anterior cingulate resting-state functional connectivity in borderline personality disorder patients with a history of interpersonal trauma. Psychol. Med. 44, 2889–2901.

Krause-Utz, A., Winter, D., Niedtfeld, I., Schmahl, C., 2014b. The latest neuroimaging findings in borderline personality disorder. Curr. Psychiatry Rep. 16 (3), 438.

Leech, R., Sharp, D.J., 2014. The role of the posterior cingulate cortex in cognition and disease. Brain 137, 12–32.

Linehan, M.M., Comtois, K.A., Murray, A.M., Brown, M.Z., Gallop, R.J., Heard, H.L., Korslund, K.E., Tutek, D.A., Reynolds, S.K., Lindenboim, N., 2006. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. Arch. Gen. Psychiatry 63, 757–766.

Mauchnik, J., Schmahl, C., 2010. The latest neuroimaging findings in borderline personality disorder. Curr. Psychiatry Rep. 12, 46–55.

Mazaika, P., Hoeft, F., Glover, G., Reiss, A.L., 2009. Methods and software for fMRI analysis of clinical subjects. Neuroimage 47, S58.

McCabe, C., Mishor, Z., Filippini, N., Cowen, P.J., Taylor, M.J., Harmer, C.J., 2011. SSRI administration reduces resting state functional connectivity in dorso-medial

prefrontal cortex. Mol. Psychiatry 16 (6), 592–594.
McCabe, C., Mishor, Z., 2011. Antidepressant medications reduce subcortical–cortical resting-state functional connectivity in healthy volunteers. Neuroimage 57, 1317–1323.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cognit. Sci. 15, 483–506.
Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–667.
Nunes, P.M., Borges, K.T., Porto, C.R., 2009. Volumes of the hippocampus and amygdala in patients with borderline personality disorder: a meta-analysis. J. Personal. Disord. 23, 333–345.
O'Neill, A., D'Souza, A., Samson, A.C., Carballedo, A., Kerskens, C., Frodl, T., 2015. Dysregulation between emotion and theory of mind networks in borderline personality disorder. Psychiatry Res. 231, 25–32.
Patton, J.H., Stanford, M.S., Barratt, E.S., 1995. Factor structure of the Barratt impulsiveness scale. J. Clin. Psychol. 51, 768–774.
Petersen, R., Brakoulias, V., Langdon, R., 2016. An experimental investigation of mentalization ability in borderline personality disorder. Compr. Psychiatry 64, 12–21.
Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154.
Rossi, R., de Girolamo, G., 2010. Epidemiologia del disturbo borderline di personalità e delle comorbilità di Asse I, Disturbo borderline di personalità: continuià e discontinuità nel trattamento. Centro Scientifico Editore, Milan, Italy.
Rossi, R., Lanfredi, M., Pievani, M., Boccardi, M., Beneduce, R., Rillosi, L., Giannakopoulos, P., Thompson, P.M., Rossi, G., Frisoni, G.B., 2012. Volumetric and topographic differences in hippocampal subdivisions in borderline personality and bipolar disorders. Psychiatry Res. Neuroimaging 203, 132–138.
Rossi, R., Lanfredi, M., Pievani, M., Boccardi, M., Rasser, P.E., Thompson, P.M., Cavedo, E., Cotelli, M., Rosini, S., Beneduce, R., Bignotti, S., Magni, L.R., Rillosi, L., Magnaldi, S., Cobelli, M., Rossi, G., Frisoni, G.B., 2015. Abnormalities in cortical gray matter density in borderline personality disorder. Eur. Psychiatry 30, 221–227.
Sala, M., Caverzasi, E., Lazzaretti, M., Morandotti, N., De Vidovich, G., Marraffini, E., Gambini, F., Isola, M., De Bona, M., Rambaldelli, G., d'Allio, G., Barale, F., Zappoli, F., Brambilla, P., 2011. Dorsolateral prefrontal cortex and hippocampus sustain impulsivity and aggressiveness in borderline personality disorder. J. Affect. Disord. 131, 417–421.
Salvador, R., Vega, D., Pascual, J.C., Marco, J., Canales-Rodriguez, E.J., Aguilar, S., Anguera, M., Soto, A., Ribas, J., Soler, J., Maristany, T., Rodríguez-Fornells, A., Pomarol-Clotet, E., 2016. Converging medial frontal resting state and diffusion-based abnormalities in borderline personality disorder. Biol. Psychiatry 79, 107–116.
Sambataro, F., Blasi, G., Fazio, L., Caforio, G., Taurisano, P., Romano, R., Di Giorgio, A., Gelao, B., Lo Bianco, L., Papazacharias, A., Popolizio, T., Nardini, M., Bertolino, A., 2010. Treatment with olanzapine is associated with modulation of the default mode network in patients with Schizophrenia. Neuropsychopharmacology 35 (4), 904–912.
Semerari, A., Carcione, A., Dimaggio, G., Nicolò, G., Procacci, M., 2007. Understanding minds: different functions and different disorders? The contribution of psychotherapy research. Psychother. Res. 17, 106–119.
Semerari, A., Cucchi, M., Dimaggio, G., Cavadini, D., Carcione, A., Battelli, V., Nicolò, G., Pedone, R., Siccardi, T., D'Angerio, S., Ronchi, P., Maffei, C., Smeraldi, E., 2012. The development of the Metacognition Assessment Interview: instrument description, factor structure and reliability in a non-clinical sample. Psychiatry Res. 200, 890–895.
Semerari, A., Colle, L., Pellecchia, G., Carcione, A., Conti, L., Fiore, D., Moroni, F., Nicolò, G., Procacci, M., Pedone, R., 2015. Personality disorders and mindreading: specific impairments in patients with borderline personality disorder compared to other PDs. J. Nerv. Ment. Dis. 203, 626–631.
Shirer, W., Ryali, S., Rykhlevskaia, E., Menon, V., Greicius, M., 2012. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb. Cortex 22, 158–165.
Soloff, P., Nutche, J., Goradia, D., Diwadkar, V., 2008. Structural brain abnormalities in borderline personality disorder: a voxel-based morphometry study. Psychiatry Res. 164, 223–236.
Soloff, P.H., Pruitt, P., Sharma, M., Radwan, J., White, R., Diwadkar, V.A., 2012. Structural brain abnormalities and suicidal behavior in borderline personality disorder. J. Psychiatr. Res. 46, 516–525.
Spielberger, C.D., Gorsuch, R.L., Lushene, R., Vagg, P.R., Jacobs, G.A., 1983. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, CA.
Spielberger, C.D., 1999. State-Trait Anger Expression Inventory-2 (STAXI-2). Professional Manual. Psychological Assessment Resources, Tampa, FL.
Ubbiali, A., Chiorri, C., Donati, D., 2011. The Italian version of the Inventory of Interpersonal Problems Personality Disorders Scales (IIP-47): psychometric properties and clinical usefulness as a screening measure. J. Personal. Disord. 25, 528–541.
Uddin, L.Q., 2015. Salience processing and insular cortical function and dysfunction. Nat. Rev. Neurosci. 16, 55–61.
van Wingen, G.A., Tendolkar, I., Urner, M., van Marle, H.J., Denys, D., Verkes, R., Fernández, G., 2014. Short-term antidepressant administration reduces default mode and task-positive network connectivity in healthy individuals during rest. Neuroimage 88, 47–53.
Vaskinn, A., Antonsen, B.T., Fretland, R.A., Dziobek, I., Sundet, K., Wilberg, T., 2015. Theory of mind in women with borderline personality disorder or schizophrenia: differences in overall ability and error patterns. Front. Psychol. 6, 1239.
Visintin, E., De Panfilis, C., Amore, M., Balestrieri, M., Wolf, R.C., Sambataro, F., 2016. Mapping the brain correlates of borderline personality disorder: a functional neuroimaging meta-analysis of resting state studies. J. Affect. Disord. 204, 262–269.
Wang, Y., Tang, W., Fan, X., Zhang, J., Geng, D., Jiang, K., Zhu, D., Song, Z., Xiao, Z., Liu, D., 2017. Resting-state functional connectivity changes within the default mode network and the salience network after antipsychotic treatment in early-phase schizophrenia. Neuropsychiatr. Dis. Treat. 7 (13), 397–406.
Wilcox, C.E., Pommy, J.M., Adinoff, B., 2016. Neural circuitry of impaired emotion regulation in substance use disorders. Am. J. Psychiatry 173, 344–361.
Wolf, R.C., Thomann, P.A., Sambataro, F., Vasic, N., Schmid, M., Wolf, N.D., 2012. Orbitofrontal cortex and impulsivity in borderline personality disorder: an MRI study of baseline brain perfusion. Eur. Arch. Psychiatry Clin. Neurosci. 262, 677–685.
Wolf, R.C., Sambataro, F., Vasic, N., Schmid, M., Thomann, P.A., Bienentreu, S.D., Wolf, N.D., 2011. Aberrant connectivity of resting-state networks in borderline personality disorder. J. Psychiatry Neurosci. 36, 402–411.