INTRODUCTION

Borderline personality disorder (BPD) is characterized by “stable instability” (Schmideberg, 1959) of emotions, impulsivity, social relationships, and self-image. Additionally most patients suffer from chronic feelings of emptiness, complex dissociations, self-injury, and suicidal tendencies with a suicide rate of 10% (Koelsch, 2006). BPD, which often co-occurs with other psychiatric disorders (about 85% of patients with BPD fulfill criteria for having at least one Axis I disorder; Lenzenweger et al., 2007), is common with a prevalence of more than 20% for psychiatric inpatients (Torgersen, 2005). Behavioral and emotional dysregulation is suggested as critical factors underlying this variety of symptoms (Lichter et al., 2011). We suggest that the stability of fluctuating symptoms across time and different situations might be related to consistent and profound functional alterations in the patient’s brain intrinsic functional architecture, particularly in brain regions involved in behavior/ emotion regulation.

Previous functional neuroimaging studies revealed context-specific patterns of altered brain activity in BPD patients during emotion- or self-related tasks. For example, negative emotional pictures or fearful/angry faces evoke stronger activity in the extra- striate, posterior cingulate, and frontal cortices, as well as weaker activity in the amygdala (Minzenberg et al., 2007; Koenigsberg et al., 2009b). Patients with BPD, however, fail to activate the DMN but show increased activity in the amygdala. On the contrary, memories of unresolved life events activate regions of the DMN in addition to amygdala, insula, and occipital cortices in patients (Beblo et al., 2006). Overall, emotional and self-related context increasingly activates an aberrant distributed pattern of brain regions including the DMN, insula, amygdala, and occipital cortices in BPD patients.

The measure of intrinsic functional connectivity (iFC), i.e., coherence of ongoing blood-oxygenation-level-dependent (BOLD) signal fluctuations in resting-state functional magnetic
resonance imaging (rs-fMRI) data, is a surrogate for organized intrinsic brain activity (Fox and Raichle, 2007). At a large-scale level, coherent BOLD activity across remote brain areas forms consistent intrinsic connectivity networks (ICNs) in humans (Damoiseaux et al., 2006). Importantly, ICNs show strong spatial correspondence in independent analyses of resting-state and task-related activity patterns (Smith et al., 2009; Laird et al., 2011), suggesting that certain intrinsically coupled functional networks are also systematically engaged during cognition and behavior. Moreover, direct evidence exists that ongoing activity in ICNs serves as a scaffold for patterns of evoked neuronal activity (Keller et al., 2011), supporting the idea that the intrinsic architecture maintains and updates the brain’s repertoire of functional responses.

A recently proposed neurocognitive framework identified ICNs related to self-, emotion-, and cognitive control processing as neurocognitive “core” networks to study higher cognitive functions (Menon and Uddin, 2010). Important networks include the default mode network (DMN), salience network (SN), central executive network (CEN), and to a lesser extent the dorsal attention network (DAN). These core networks consist of intrinsically coupled functional networks (ICNs) that show coherent ongoing activity across remote brain areas (Raichle et al., 2001), which may be reflective of the neural substrate for coordinated neural processing (Buckner et al., 2008).

We recently examined the relationship, i.e., iFC, within the so far only previous study focusing on iFC in BPD, Wölfer et al., 2013). Due to both the persistent nature of BPD and its “stability” in emotion-, self-, and control-related functions, we suggest altered iFC among DMN, SN, and CEN in BPD. In this regard, we recently found aberrant iFC within the DMN and CEN of patients with BPD; but this did not yield information about the SN and the intrinsic connectivity across networks. To test our hypotheses about aberrant iFC within and across SN, DMN, and CEN in BPD, we acquired rs-fMRI data from patients with BPD and matched healthy controls (HC). We applied data-driven, high-model order independent component analysis (ICA) to the rs-fMRI data to extract ICNs of coherent ongoing BOLD activity (Calhoun et al., 2001; Allen et al., 2011). We then examined the relationship, i.e., iFC, within (intra-iFC) and between (inter-iFC) ICNs of interest and provide a new measure capturing the balance across these neurocognitive networks.

**MATERIALS AND METHODS**

**SUBJECTS**

Fourteen right-handed patients and 16 age-, sex-, and handedness-matched HC participated in the study after signing the informed consent form in accordance with the Human Research Committee guidelines of the Klinikum Rechts der Isar, Technische Universität München (Table 1). Patients were recruited from the Department of Psychiatry, Klinikum rechts der Isar, Technische Universität München. Controls were recruited by word-of-mouth advertising from the larger Munich area. Participants’ examination included medical history, psychometric assessments (e.g., Beck Depression Inventory (BDI; Beck et al., 1961), Hamilton Depression Scale (HDS; Hamilton, 1960), short version of the Borderline Symptom List (BSL; Bohus et al., 2001), and Global Assessment of Functioning (GAF) Scale (Endicott et al., 1976)) and a structured psychiatric interview for patients only (Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1996b) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II, First et al., 1996a), German version). All participants were examined by their psychiatrists (Andreas Wöller, Christian Sorg), professionally trained for SCID-based interviews with an inter-rater reliability of more than 95%. Psychiatric diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders-IV (DSM IV).

Patients with BPD constitute a heterogeneous group of patients, who vary in diagnostic subcategories (e.g., with/without feeling of emptiness or stress-related paranoid ideation), comorbidity (e.g., with/without MD or post-traumatic stress disorder, PTSD), and degree of medication (e.g., with/without neuroleptica; Skodol et al., 2002). We adopted selection criteria for a representative group of patients recommended by Skodol et al. (1999) based on a longitudinal examination of 248 patients with BPD. BPD was the primary diagnosis for all patients. We excluded patients with current psychosis, intoxication, or confusional states, with a

| Parameter | Patients with BPD | HC |
|-----------|-------------------|----|
| n         | 14                | 16 |
| Age (year)| 30.4              | 34.0 |
| Sex, male/female | 1/13 | 1/15 |
| GAF       | 43.7 ± 9.1*       | 100 ± 0 |
| HDS       | 171 ± 74*         | 0.5 ± 0.8 |
| BDI       | 18.1 ± 15.4*      | 18 ± 2.7 |
| BSL       | 510 ± 174*        | 109 ± 3.9 |

Data are presented as mean ± SD. HC, healthy controls; BPD, borderline personality disorder; GAF, Global Assessment of Functioning; HDS, Hamilton Depression Scale; BDI, Beck Depression Inventory; BSL, Borderline Symptom List; *p < 0.05 (two-sample t-test).
history of schizophrenia, schizoaffective disorder or bipolar disorder but we allowed co-occurrence of Axis I disorders MD or PTSD and psychotropic medication (Skodol et al., 1999). Additional exclusion criteria were an age below 18 or above 60 years, pregnancy, neurological or internal systemic diseases, and general contraindications for MRI assessment. A detailed description of each patient’s current comorbidity and medication can be found in Table 2. All control subjects were free of any current or past neurological or psychiatric disorder or psychotropic medication.

All participants in this study underwent 10 min of rs-fMRI with the instruction to keep their eyes closed and not to fall asleep. We verified that subjects stayed awake by interrogating via intercom immediately after the rs-fMRI scan. Before and after scanning, a medical examination of patients validated their stable condition and investigated whether they had feelings of odd situations during the scanning. No patient dropped out during the scanning session.

**MRI DATA ACQUISITION**

Magnetic resonance imaging was performed on a 3-T whole body MR scanner (Achieva, Philips, Netherlands) using an eight-channel phased-array head coil. For co-registration of functional data, T1-weighted anatomical data were obtained from each subject by using a magnetization-prepared rapid acquisition gradient echo sequence (TE = 4 ms, TR = 9 ms, TI = 100 ms, flip angle = 5°, FoV = 240 mm × 240 mm, matrix = 240 × 240, 170 slices, voxel size = 1 mm × 1 mm × 1 mm). fMRI data were collected using a gradient echo planar imaging (EPI) sequence (TE = 35 ms, TR = 2000 ms, flip angle = 82°, FoV = 220 mm × 220 mm, matrix = 80 × 80, 32 slices, slice thickness = 4 mm, and 0 mm interslice gap, an fMRI run of 10 min results in 300 volumes).

**fMRI DATA ANALYSIS**

**Preprocessing**

For each participant the first three functional scans of each fMRI session were discarded due to magnetization effects. SPM51 (Wellcome Department of Cognitive Neurology, London) was used for motion correction, spatial normalization into the stereotactic space of the Montreal Neurological Institute (MNI) with resampling of voxel size to 3 mm × 3 mm × 3 mm, and spatial smoothing by applying an 8 mm × 8 mm × 8 mm Gaussian kernel. None of the participants had to be excluded due to excessive head motion (linear shift < 3 mm across run and on a frame-to-frame basis, rotation < 1.5°). Two-sample t-tests between groups yielded no significant results regarding translational and rotational movements of any direction as well as voxel-wise signal-to-noise ratio of fMRI data calculated with DPARSFA toolbox2 (p < 0.05).

**Independent component analysis of fMRI data**

Following a recent approach (Manoliu et al., 2013b), we applied high-model-order ICA to the preprocessed data by using the

http://www.fil.ion.ucl.ac.uk/spm/

http://www.restfmri.net

| Table 2 | Detailed clinical characteristics of patients with BPD. |
|---------|--------------------------------------------------------|
| Patients | Medication | Current comorbidity | History of comorbidity |
| 1 | Quetiapine 50 mg, Fluoxetine 20 mg | PTSD | Substance abuse |
| 2 | Olanzapine 5 mg, Quetiapine 600 mg (prolong), Escitalopram 20 mg | Alcohol abuse | MDD |
| 3 | Escitalopram 20 mg, Zopiclone 75 mg | Bulimia nervosa | Recurrent MDD |
| 4 | Quetiapine 100 mg, Lamotrigine 12.5 mg | Substance abuse, Cannabis dependence | Recurrent MDD |
| 5 | Quetiapine 300 mg (prolong), Sertaline 150 mg, Antipiprazole 10 mg | Multiple personality disorders | None |
| 6 | None | None | None |
| 7 | Atomoxetine 50 mg, Fluoxetine 20 mg, Paliperidone 3 mg | MDD, ADHD, alcohol abuse | Anorexia nervosa, recurrent MDD |
| 8 | Fluoxetine 40 mg | MDD | Substance abuse |
| 9 | Fluoxetine 30 mg, Quetiapine 12.5 mg, Pregabalin 225 mg | Undifferentiated somatoform disorder, alcohol abuse | Alcohol abuse |
| 10 | Antipiprazole 20 mg, Venlafaxine 150 mg | Alcohol abuse | None |
| 11 | Pregabalin 300 mg, Quetiapine 60 mg, Venlafaxine 225 mg | PTSD, undifferentiated somatoform disorder, alcohol dependence | Recurrent MDD |
| 12 | None | None | None |
| 13 | Sertaline 75 mg | PTSD, substance abuse | Recurrent MDD |
| 14 | Sertaline 50 mg | Cannabis abuse | Recurrent MDD |

BPD, borderline personality disorder; PTSD, post-traumatic stress disorder; MDD, major depressive disorder.
As previously described (Manoliu et al., 2013b), we ran a multiple rected for false discovery rate, FDR). W e then examined group components, which are then back reconstructed into sin-
sequently ran 40 ICAs (ICASSO) to ensure stability of the estimated connectivit, was thereby rendered independent of the original BOLD signal magnitude across subjects. Data were concatenated and reduced by two-step principal component analysis (PCA), followed by IC estimation with the infomax algorithm. We subse-
quently ran 40 ICAs (ICASSO) to ensure stability of the estimated components (Himberg et al., 2004). This results in a set of average components (Himberg et al., 2004). Each thus reconstructed IC results in a spatial map of signal fluctuations representative for this IC. We then reintegrated the initially calculated scaling factor $q_k$ into the data by voxel-
wise multiplication in order to preserve each individual’s profile of variance magnitude while leaving the normalized time course component unchanged.

Network selection
As previously described (Manoliu et al., 2013b), we ran a multiple spatial regression with a previously established baseline set of func-
tionally relevant ICNs as regressors of interest (Allen et al., 2011) to automatically identify DMN, SN, and CEN in our dataset. From this publication, we selected the posterior (IC 53) and anterior (IC 25) DMN, left and right lateralized fronto-parietal net-
works (IC 34 and 60) reflecting left and right CEN, and an insular network (IC 55) reflecting the SN. The template for the insular network revealed a second component covering P1 and bilateral amygdala and hippocampus (which we called posterior SN (pSN) in contrast to the anterior SN (aSN); see also Seeley et al., 2007; Taylor et al., 2009; Leighton et al., 2011). Due to the importance of insular structures in BPD we also selected this component for further analyses.

Statistical analysis
To evaluate the spatial consistency of ICNs (intra-iFC), we calculated voxel-wise one-sample t-tests on participants’ reconstructed spatial maps using SPM8 for each ICN and group ($p < 0.05$, cor-
corrected for false discovery rate, FDR). We then examined group differences of intra-iFC. The individual z-maps were entered into voxel-wise two-sample t-tests and a conjunction map of the one-sample t-test image ($p < 0.001$ uncorrected) was applied as a mask to the analysis. In order to control for antipsychotic medication we added chlorpromazine (CPZ)-equivalent doses (Woods, 2003) as covariate-of-no-interest in all imaging analyses. The resulting SPMs were thresholded at $p < 0.001$ (voxel level) and $p < 0.05$ [corrected for family wise error (FWE) at cluster level].

In order to investigate group effects of inter-iFC between ICNs, we extracted each subject’s IC-timecourse of a/pDMN, l/r CEN, and a/pSN, calculated pairwise Pearson’s correlation coeffi-
cients between the time course of all ICNs for each subject, transformed the correlation matrix into z-values via Fisher’s r-to-

results, we selected the posterior (IC 53) and anterior (IC 25) DMN, left and right lateralized fronto-parietal net-
works (IC 34 and 60) reflecting left and right CEN, and an insular network (IC 55) reflecting the SN. The template for the insular network revealed a second component covering P1 and bilateral amygdala and hippocampus (which we called posterior SN (pSN) in contrast to the anterior SN (aSN); see also Seeley et al., 2007; Taylor et al., 2009; Leighton et al., 2011). Due to the importance of insular structures in BPD we also selected this component for further analyses.

Statistical analysis
To evaluate the spatial consistency of ICNs (intra-iFC), we calculated voxel-wise one-sample t-tests on participants’ reconstructed spatial maps using SPM8 for each ICN and group ($p < 0.05$, cor-
corrected for false discovery rate, FDR). We then examined group differences of intra-iFC. The individual z-maps were entered into voxel-wise two-sample t-tests and a conjunction map of the one-sample t-test image ($p < 0.001$ uncorrected) was applied as a mask to the analysis. In order to control for antipsychotic medication we added chlorpromazine (CPZ)-equivalent doses (Woods, 2003) as covariate-of-no-interest in all imaging analyses. The resulting SPMs were thresholded at $p < 0.001$ (voxel level) and $p < 0.05$ [corrected for family wise error (FWE) at cluster level].

In order to investigate group effects of inter-iFC between ICNs, we extracted each subject’s IC-timecourse of a/pDMN, l/r CEN, and a/pSN, calculated pairwise Pearson’s correlation coeffi-
cients between the time course of all ICNs for each subject, transformed the correlation matrix into z-values via Fisher’s r-to-
-z-transformation and tested differences between the two groups (two-sample t-tests with CPZ as covariate-of-no-interest, $p < 0.05$, Bonferroni-corrected for 15 pairwise correlations).

RESULTS
Psychometric assessment revealed significant differences between patients and controls for GAF (two-sample t-test, $t = 17.3$, $p < 0.05$), HDS ($t = −7.1$, $p < 0.05$), BDI ($t = −3.1$, $p < 0.05$), and BSL ($t = −5.8$, $p < 0.05$) between the two groups (Table 1).

INTRA-iFC
Automated component selection, which was based on spatial tem-
plates representing subsystems of the DMN, SN, and CEN (see Figure 4 in Allen et al., 2011 for spatial templates), revealed six IC of interest from high-model-order analysis of fMRI data for each individual. The SN was represented in an anterior and posterior insular network (a/pSN), the DMN in an a/pDMN, and the CEN in left and right (L/R) CEN. Selected components were spa-
tially consistent across groups and matched previous results of SN, DMN, and CEN (Allen et al., 2011; see Figure 1 and Table 3 for detailed description of intra-iFC within selected ICNs, $p < 0.05$, FDR-corrected).

Group comparisons of networks’ intra-iFC revealed regionally increased intra-iFC in each ICN of patients and decreased intra-
iFC in only two ICNs (i.e., pSN, ICEN, $p < 0.05$ FWE-corrected cluster level and Bonferroni-corrected for six ICNs. Figure 2;
FIGURE 1 | Spatial maps and time courses of default mode, salience, and central executive network (DMN, SN, CEN) in healthy controls and patients. Spatial statistical parametric maps (SPM, one-sample t-tests controlled for medication) and associated time courses of intrinsic networks in healthy controls (HC) and patients with borderline personality disorder (BPD). Maps and time courses are derived from independent component analysis of resting-state fMRI of subjects. SPMs are thresholded at \( p < 0.05 \) FDR-corrected and superimposed on a single subject high resolution T1 image. Color coding (red > yellow) represents \( t \)-values ranging from 3 to 25. The x-axis of signal time courses reflects number of fMRI scans; the y-axis represents normalized signal amplitude. First to third row: anterior and posterior (a/p) DMN, anterior and posterior SN, left and right (l/r) CEN.

Table 4. Increased intra-iFC in the BPD group covered various brain regions (midline structures: ACC, PCC, medial frontal gyrus; parietal lobe: bilateral SPL, insula: posterior part), decreased intra-iFC occurred in right hippocampus and left superior frontal gyrus.

**INTER-iFC**

To explore inter-iFC across DMN, SN, and CEN, we calculated the pairwise correlation between network time courses and tested significance of correlations and their potential group differences by using one- and two-sample \( t \)-tests controlling for effects of medication (CPZ covariate-of-no-interest). In HC, we found significant inter-iFC for 9 of 15 network pairs, while only four significant correlations occurred in BPD (\( p < 0.05 \). Bonferroni-corrected, black lines in Figure 3A; Table 5). The analysis of group differences revealed specific changes in the intrinsic functional architecture of patients (\( p < 0.05 \), Bonferroni-corrected for 15 connections; Table 5). More specifically, absent inter-network connectivity was found mainly for interactions concerning the CEN where four of six connections significantly decreased. Contrary to this overall decrease of iFC in patients, two additional intrinsic inter-network connections occurred in the patients group for the SN (red lines in Figure 3A).

Interestingly, in our correlation analysis of ICA-derived network time courses we found increased connectivity between the rICEN and a/pDMN in HC. This finding might be...
Table 3 | Spatial intra-iFC maps of DMN, SN, and CEN in controls and patients.

| Networks and brain regions | HC Cluster size | HC t_{max} | HC MNI | BPD Cluster size | BPD t_{max} | BPD MNI |
|----------------------------|-----------------|------------|--------|------------------|-------------|--------|
| aDMN                       |                 |            |        |                  |             |        |
| Superior frontal gyrus      | 2506            | 18.39      | 15     | 63               | 21          | 1460   | 14.39  | –6 | 54 | 15 |
| Anterior cingulate cortex   | 1768            | 6          | 48     | 21               |             |        |        |    |
| Inferior frontal gyrus      | 63              | 6.24       | –45    | 33               | –13         |        |        |    |
| Middle cingulate cortex     | 76              | 4.8        | 0      | –3               | 30          |        |        |    |
| Posterior cingulate cortex, precuneus | 195        | 6.78       | 0      | –60              | 27          |        |        |    |
| Angular gyrus               | 266             | 10.91      | –51    | –66              | 30          |        |        |    |
| Precentral sulcus           | 54              | 6.5        | –6     | –36              | 66          |        |        |    |
| Cerebellum                  | 155             | 10.11      | 12     | –54              | –42         |        |        |    |
| Putamen                     | 25              | 5.41       | –21    | 6                | 12          |        |        |    |
| Middle occipital gyrus      | 21              | 5.08       | 57     | –63              | 24          |        |        |    |
| pDMN                       |                 |            |        |                  |             |        |
| Posterior cingulate cortex  | 2749            | 1713       | 3      | –48              | 21          | 4122   | 26.56  | 12 | –48 | 30 |
| Precuneus                   | 247             | 15.48      | 45     | –51              | 27          |        |        |    |
| Angular gyrus               | 39              | 3.87       | 6      | 39               | 21          |        |        |    |
| Middle temporal gyrus       | 34              | 5.69       | 60     | 0                | –21         | 79     | 4.67   | –57 | 3  | –24 |
| Hippocampus                 | 40              | 6.71       | 24     | –36              | –3          |        |        |    |
| Cerebellum                  | 47              | 4.12       | –3     | –24              | –21         |        |        |    |
| Fusiform gyrus              | 42              | 3.62       | 36     | –75              | –3          |        |        |    |
| aSN                        |                 |            |        |                  |             |        |
| Right anterior insula       | 882             | 18.58      | 39     | 18               | –3          | 723    | 19.88  | 48 | 24 | –3 |
| Left anterior insula        | 606             | 12.94      | –33    | 9                | –6          | 631    | 12.78  | –30 | 27 | –6 |
| Olfactory gyri              | 275             | 6.41       | 9      | 39               | 15          | 868    | 8.19   | –9  | 48 | 18 |
| Anterior cingulate cortex   | 81              | 6.39       | –6     | –36              | 45          | 9.32   | 9      | 24  | 33 |
| Middle cingulate cortex     | 138             | 7.46       | –9     | –21              | 6           | 14     | 4.86   | –9  | –9  | 9  |
| Superior medial gyrus       | 53              | 6.33       | 9      | –57              | –30         |        |        |    |
| Middle frontal gyrus        | 37              | 5.02       | 33     | 51               | 12          | 12.78  | –39    | 27  | –6 |
| Angular gyrus               | 150             | 6.31       | 48     | –45              | 30          |        |        |    |
| pSN                        |                 |            |        |                  |             |        |
| Right posterior insula      | 1239            | 11.6       | 48     | 9                | 0           | 679    | 14.82  | 51  | –3 | –12 |
| Left posterior insula       | 802             | 11.03      | –45    | –12              | 3           | 467    | 11.96  | –51 | 0  | –6 |
| Hippocampus                 | 969             | 13.07      | –15    | –30              | –6          |        |        |    |
| Anterior cingulate cortex   | 298             | 7.03       | 0      | 36               | 9           | 111    | 8.32   | 0    | 36 | 9  |
| Inferior frontal gyrus      | 85              | 5.37       | –48    | 30               | 15          | 50     | 5.91   | –54 | 33 | 3  |
| Right Amygdala              | 31              | 4.02       | 24     | –3               | –15         |        |        |    |
| lCEN                       |                 |            |        |                  |             |        |
| Middle frontal gyrus        | 1229            | 13.95      | –24    | 23               | 59          | 2580   | 14.51  | –45 | 36 | 18 |
| Superior frontal gyrus      | 10.09           | –15        | 36     | 51               |             |        |        |    |

(Continued)
counterintuitive, since CEN and DMN are usually found anti-correlated (e.g., Fox et al., 2005). However, our findings for CEN and DMN sub-networks are perfectly in line with those of Allen et al. (2011), suggesting that such sub-networks are positively related among each other. This result might be explained by recent findings of Smith et al. (2012) based on a combination of high-model order spatial and temporal ICA; these authors demonstrated that the DMN can be subdivided into several functionally distinct sub-networks, each with its own characteristic patterns of correlations and anticorrelations with other intrinsic networks.

Finally, the observed global “shift” of inter-iFC among SN and CEN in patients was reflected by an altered CEN/SN-inter-iFC index ($r$) (Figure 3B). This ratio reflects the relative intrinsic impact of the CEN in comparison to the SN within the global intrinsic functional architecture of SN, CEN, and DMN. We found a significant difference between $r$ (controls) = 1.64 ± 0.80 and $r$ (BPD) = 0.99 ± 0.52 with $p = 0.015$ (two-sample t-test), potentially indicating a relative shift from cognitive control to emotion processing in patients with BPD (Figure 3B).

**DISCUSSION**

The aim of this study was to investigate iFC among SN, DMN, and CEN in patients with BPD. This aim was motivated by previous findings demonstrating that interactions within and between these three networks contribute critically to behavior and emotion regulation; impaired emotion/behavior regulation, in turn, is suggested as an essential property of BPD. In a sample of 14 patients, we found aberrant intra-iFC in all three networks. While patients’ inter-iFC of the CEN was generally decreased, only inter-iFC of the SN was increased. In particular, a “balance” index reflecting the relationship of CEN- and SN-inter-iFC across networks was strongly shifted from CEN to SN connectivity in patients. This result provides first preliminary evidence for aberrant intrinsic connectivity among the DMN, SN, and CEN in BPD. Data suggest that patients’ impaired emotion/behavior regulation may rely on

Table 3 | Continued

| Networks and brain regions | HC | BPD |
|----------------------------|----|-----|
|                            | Cluster size | $t_{max}$ | MNI | Cluster size | $t_{max}$ | MNI |
|                            | $x$ | $y$ | $z$ | $x$ | $y$ | $z$ |
| Inferior frontal gyrus     | 277 | 10.05 | 48 | 36 | 21 |
| Superior medial gyrus      | 181 | 7.25 | 0 | 63 | 0 |
| Middle orbital gyrus       | 47  | 5.44 | -42 | 48 | -3 |
| Middle cingulate cortex    | 388 | 8.86 | 0 | -36 | 36 |
| Thalamus                   | 128 | 6.52 | 48 | -60 | 27 |
| Inferior parietal lobe     | 62  | 5.95 | -6 | -15 | 12 |
| Superior temporal gyrus    | 2071| 14.46| -27 | -66 | 39 |
| Insula                     | 45  | 4.86 | 66 | -15 | 6 |
| Hippocampus                | 66  | 4.27 | 62 | 0 | 6 |
| Cerebellum                 | 298 | 7.78 | 39 | -75 | 30 |
| Superior occipital gyrus   | 255 | 8.13 | 33 | -72 | 45 |
| Middle frontal gyrus       | 1271| 11.93| 39 | 18 | 54 |
| Middle orbital gyrus       | 54  | 4.92 | -39 | 48 | -9 |
| Middle cingulate cortex    | 85  | 7.88 | 3 | -39 | 39 |
| Middle temporal gyrus      | 46  | 5.81 | 69 | -42 | 0 |
| Inferior parietal lobe     | 641 | 19.16| -51 | -54 | 45 |
| Angular gyrus              | 1047| 19.2 | 42 | -60 | 39 |
| Precuneus                  | 133 | 7.65 | 6 | -78 | 42 |
| Cerebellum                 | 210 | 9.39 | -36 | -66 | -42 |
| Fusiform gyrus             | 83  | 4.57 | 30 | -66 | -9 |

One-sample t-test (corrected for medication), $p < 0.05$ corrected for false discovery rate. HC, healthy controls; BPD, borderline personality disorder; aDMN, pDMN, anterior and posterior default mode network; aSN, pSN, anterior and posterior salience network; lCEN, rCEN, left and right central executive network. Coordinates are presented in MNI standard space.
anomalous iFC among intrinsic networks that is centered on the SN.

**ABERRANT INTRA-iFC IN SALIENCE, DEFAULT MODE, AND CENTRAL EXECUTIVE NETWORK IN BPD**

In patients, we found increased intra-iFC in the DMN, SN, and CEN with increases covering midline structures such as frontal and parietal cingulate cortices, prefrontal cortices (PFC), parietal lobes, and insular regions (Figure 2; Table 4). Decreased intra-iFC was found in right hippocampi and in the left dorsolateral frontal cortex (Figure 2; Table 4). Identified group differences were not due to a disintegration of investigated networks in patients, since basic spatial maps of networks were both largely consistent across groups (Figure 1; Table 3) and in line with previous findings (Damoiseaux et al., 2006; Allen et al., 2011). Patients’ counter-intuitively increased and decreased intra-iFC in intrinsic networks particularly in one and the same network (such as CEN) has been observed also in other neuropsychiatric disorders such as schizophrenia (Manoliu et al., 2013b) or Alzheimer’s disease (Zhou et al., 2010) and – in line with our findings – in BPD (Wolff et al., 2011); however, the functional significance of the direction of intra-iFC changes in brain disorders is still unclear (e.g., iFC decreases are suggested to reflect connectivity disruptions while iFC-increases might reflect compensatory processes; but also a loss of desynchronization and therefore system complexity may play a role; Zhou et al., 2010).

Previous imaging studies, which explored the neural correlates of impaired self- or emotion-processing in BPD, revealed aberrant task-related activity in areas similar to those of aberrant intra-iFC we found (Minzenberg et al., 2007; King-Casas et al., 2008; Smoski et al., 2011; Holtmann et al., 2013). For example, patients with BPD, who had to engage with emotional stimuli, had aberrant levels of activity in ACC, dorsolateral PFC, and amygdala (Minzenberg et al., 2007; Koenigberg et al., 2009a; Holtmann et al., 2013); the insula was found to be the key region distinguishing BPD patients from HC in a more complex setting of a gambling task (King-Casas et al., 2008); in healthy subjects, self-distancing of negative pictures activates parietal regions overlapping with DMN (Koenigberg et al., 2009a), while patients with BPD fail to activate the DMN. Furthermore, so far limited literature of resting-state imaging data in BPD supports the spatially widespread pattern of functional changes in BPD: A study using 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) found aberrant brain metabolism in prefrontal and cuneal regions (Jengling et al., 2003). Importantly, the only rs-fMRI study in BPD reported altered intra-iFC of prefrontal, cuneal, and insular regions within the DMN and CEN (Wolff et al., 2011), in line with our results. Taken together, our result demonstrates regionally specific iFC changes within DMN, SN, and CEN, which fit spatially previous findings of aberrant activity during tasks involved in emotion- and self-related processing.

**ABERRANT INTER-iFC AMONG DMN, SN, AND CEN IN PATIENTS**

In addition, we found altered inter-iFC among DMN, SN, and CEN in patients (Figure 3; Table 5). More specifically, we observed an overall decrease of inter-iFC (with only two significant exceptions); this decrease of inter-iFC concerned mainly the CEN while increases were only found in the SN (Figure 3A; Table 5). The “shift” from a rather evenly spread inter-iFC pattern among the three networks in HC (Figure 3A) to a SN-centered pattern in patients (Figure 3A) was further indicated...
Table 4 | Group differences of intra-iFC maps for DMN, SN, and CEN.

| Network with brain region     | HC Cluster size | tmax MNI | BDP Cluster size | tmax MNI |
|-------------------------------|-----------------|---------|------------------|---------|
| aDMN                          |                 |         |                  |         |
| Left superior medial frontal gyrus | 108              | 7.35    | 57               | 24      |
| Left superior frontal gyrus   | 3.92            | 12      | 51               | 33      |
| Interaural junction           | 55              | 3.42    | −51              | −63     | 33     |
| pDMN                          |                 |         |                  |         |
| Left precuneus                | 207             | 6.67    | −3               | −63     | 24     |
| aSN                           |                 |         |                  |         |
| Left superior medial gyrus    | 111             | 5.13    | 48               | 18      |
| Left anterior cingulate gyrus | 4.15            | −3      | 45               | 9       |
| Right anterior cingulate gyrus| 4.07            | 6       | 45               | 12      |
| pSN                           |                 |         |                  |         |
| Right insular lobe            | 186             | 5.64    | 48               | 6       | −6     |
| Right hippocampus             | 38              | 4.45    | 21               | −30     | 12     |
| ICEN                          |                 |         |                  |         |
| Left precuneus                | 639             | 8.12    | −45              | 12      | 30     |
| Left inferior frontal gyrus   | 777             | −42     | 3921             |        |
| Left inferior parietal lobule | 396             | 9.06    | −45              | −45     | 51     |
| Left middle temporal gyrus    | 47              | 5.51    | −57              | −54     | 0      |
| Left superior frontal gyrus   | 85              | 5.21    | −15              | 36      | 51     |
| rCEN                          |                 |         |                  |         |
| Right angular gyrus           | 168             | 5.49    | 54               | −48     | 30     |
| Right inferior parietal lobule| 5.54            | 45      | −51              | −39     | 0      |

Two-sample t-test (corrected for medication), p < 0.05 corrected for family wise error at cluster level and Benferroni-corrected for six comparisons; green indicates increased intra-iFC in patients, red reduced intra-iFC. HC, healthy controls; BPD, borderline personality disorder; aDMN, pDMN, anterior and posterior default mode network; aSN, pSN, anterior and posterior salience network; ICEN, rCEN, left and right central executive network. Coordinates are presented in MNI standard space.

by a strongly reduced CEN-/SN-inter-iFC index (Figure 3B).

The strong impairment of coordinated activity among these networks appears to be in line with a previous EEG study that found strongly impaired gamma-band synchrony in the parietal lobes of BPD patients during a cognitive control task (Williams et al., 2006). The most prominent cognitive model of BPD suggests that patients have deficits in emotion regulation due to impeded interactions between (pre-)frontal and limbic areas (Skodol et al., 2002; Mauchnik and Schmahl, 2010; Malhi et al., 2013). This is supported by several above-mentioned task-fMRI studies of either emotion processing (Minzenberg et al., 2007; Koenigsberg et al., 2009a) or cognitive control (Driessen et al., 2009; Koenigsberg et al., 2009b; Lang et al., 2012). Since these prefrontal–limbic areas largely overlap with the DMN, CEN, and SN, our results suggest an integrative model of altered intrinsic connectivity between emotion- and cognitive control-relevant intrinsic networks in BPD, which may be related to prefrontal–limbic regulatory deficits. This model implicates that neither system nor brain region alone is responsible for the various and stable behavioral symptoms in BPD. Future studies combining rs-fMRI and task-fMRI are necessary to test explicitly the relationship between aberrant iFC and emotion-evoked activity in BPD.

PARALLELS WITH OTHER NEUROPSYCHIATRIC DISORDERS

Our result of aberrant iFC among DMN, SN, and CEN is largely consistent with the more general triple network hypothesis of psychopathology (Menon, 2011). This hypothesis states that psychopathological symptoms are associated with specifically altered coordinated activity across SN, DMN, and CEN; particularly, aberrant SN control function of DMN and CEN might underlie specific mental dysfunctions (Palaniyappan and Liddle, 2012). For example patients with schizophrenia with and without psychotic symptoms demonstrate distinctive changes of intra- and inter-iFC in the insular SN that are associated with impaired DMN/CEN interactions and positive and negative symptoms of patients (Manoliu et al., 2013a,b); in depressive patients, rumination is associated with aberrant coordination of intrinsic SN, DMN, and CEN activity (Hamilton et al., 2011). Concerning BPD, our data suggest that impaired behavior/emotion...
Doll et al. Shifted connectivity in borderline disorder

**FIGURE 3** | Aberrant intrinsic functional connectivity between DMN, SN, and CEN (inter-iFC) of patients. (A) Int iFC between two networks is based on Pearson’s correlation between network time courses. In healthy controls (HC), black lines indicate significant inter-iFC (one-sample t-tests, p < 0.05, Bonferroni-corrected for 15 correlations). Thickness of lines reflects absolute values of Fisher–z-normalized correlation coefficients. In patients with BPD, red lines indicate increased inter-iFC compared to healthy controls, while missing lines indicate significantly reduced and absent connections in BPD (two-sample t-tests, p < 0.05, Bonferroni-corrected). See also Table 5 for correlation coefficients of significant inter-iFC. Results are controlled for antipsychotic medication. (B) For each subject, the ratio (r) of overall inter-iFC for CEN and SN within the intrinsic functional architecture of DMN, SN, and CEN was calculated by r = inter-iFCsum(CEN)/inter-iFCsum(SN), with inter-iFCsum for CEN and SN, respectively, reflecting summarized absolute z-values of inter-iFC. We found significantly reduced r in patients (two-sample t-test, **p = 0.007).
Table 5 | Inter-iFC between DMN, SN, and CEN.

| ICNs | Healthy controls | BPD patients | Two-sample t-test (p) |
|------|------------------|--------------|---------------------|
| SEM  | Mean             | One-sample t-test (p) | SEM  | Mean               | One-sample t-test (p) |
| aDMN–aSN | 0.083 | –0.089 | 0.300 | 0.112 | 0.144 | 0.220 | 0.177 |
| aDMN–aCEN | 0.059 | 0.472 | 0.000** | 0.059 | –0.036 | 0.550 | 0.000** |
| aDMN–pDMN | 0.077 | 0.391 | 0.000** | 0.086 | 0.417 | 0.000** | 0.867 |
| aDMN–aSN | 0.067 | 0.361 | 0.000** | 0.073 | –0.063 | 0.406 | 0.000** |
| aDMN–aCEN | 0.075 | 0.348 | 0.000** | 0.086 | 0.262 | 0.010** | 0.574 |
| aSN–ICEN | 0.089 | –0.392 | 0.001** | 0.079 | 0.014 | 0.860 | 0.003** |
| aSN–pSN | 0.056 | 0.041 | 0.472 | 0.075 | 0.372 | 0.000** | 0.009** |
| aSN–aCEN | 0.084 | –0.150 | 0.095 | 0.118 | –0.017 | 0.889 | 0.323 |
| pDMN–aSN | 0.064 | 0.563 | 0.000** | 0.062 | –0.112 | 0.095 | 0.000** |
| pDMN–pSN | 0.112 | 0.236 | 0.053 | 0.097 | 0.056 | 0.574 | 0.220 |
| pDMN–aCEN | 0.083 | –0.347 | 0.000** | 0.081 | –0.236 | 0.012** | 0.461 |
| pDMN–ICEN | 0.082 | –0.019 | 0.824 | 0.076 | –0.446 | 0.000** | 0.003** |
| pDMN–SN | 0.083 | 0.356 | 0.001** | 0.093 | 0.437 | 0.000** | 0.672 |
| pDMN–ICEN | 0.077 | 0.354 | 0.000** | 0.089 | –0.252 | 0.014** | 0.600** |

One-sample and two-sample t-tests (*p < 0.05 uncorrected, **p < 0.025, Bonferroni-corrected for 10 tests) including CPZ-equivalent doses as covariate-of-no-interest for inter-iFC between intrinsic networks in healthy controls and patients with BPD (mean and standard error of Fisher r-to-z-transformed Pearson’s correlation coefficient among network time courses). aDMN, pDMN, anterior and posterior default mode network; aSN, pSN, anterior and posterior salience network; ICN, rCEN, left and right central executive network.

(Table 2). While we did control for antidepressive medication, we did not control for antidepressive medication because no appropriate numerical procedure (comparable to CPZ conversion) is available for antidepressants. Previously, antidepressant effects on brain activity and functional connectivity have been discussed for the BOLD signal (Miller et al., 2001; Phillips et al., 2008; Heller et al., 2013). Although recent studies suggest that antidepressants normalize brain function (Anand et al., 2005; Fu et al., 2007; Heller et al., 2013), we cannot exclude antidepressant medication effects on our results. Future studies of non-medicated patients are necessary. Forth, some limitations concerning the use of ICA to identify ICNs have to be considered. Our selection of a model order 70 was empirical; although a model order of about 75 components seems to be an optimal choice (Abou Elseoud et al., 2010), no clear computational or objective criterion for that number is available. Furthermore, the selection of ICNs of interest from ICA-derived components is intricate, particularly due to subjective bias; to account for this problem, we performed maximally controlled spatial regression analysis of all ICs on ICN templates as previously described (Manoliu et al., 2013b), which stem from a previous study using a very similar approach (Allen et al., 2011).

CONCLUSION

The current study provides evidence for aberrant iFC within and across DMN, SN, and CEN in patients with BPD. Data suggest a “shift” of inter-network iFC from networks of cognitive control to those of emotion-related activity, potentially reflecting the persistent instability of emotion regulation in patients.

ACKNOWLEDGMENTS

This work was supported by the Bayerisches Elitförderungsgesetz (BayEFG, Anselm Doll), the German Federal Ministry of Education and Research (BMBF 01EV0710 to Afra M. Wohlschläger, BMBF 01ER0803 to Christian Sorg) and the Kommission für Klinische Forschung, Technische Universität München (KKF-8765162 to Christian Sorg). We are grateful to the participants of the study and the staff of the Department of Psychiatry and Neurorehabilitation for their help in recruitment and data collection.

REFERENCES

Abou Elseoud, A., Littow, H., Remes, J., Starck, T., Nikkinen, J., Niiniluoto, J., et al. (2011). Group-ICA model order highlights patterns of functional brain connectivity. Front. Syst. Neurosci. 5:37. doi: 10.3389/fnsys.2011.00037

Abou Elseoud, A., Starck, T., Remes, J., Nikkinen, J., Törvensen, O., Kiviniemi, V., et al. (2010). The effect of model order selection in group ICA. Hum. Brain Mapp. 31, 1207–1216. doi: 10.1002/hbm.20929

Allen, E. A., Erhardt, E. B., Damaraju, E., Gruner, W., Segall, J. M., et al. (2011). A baseline for the multivariate comparison of resting-state networks. Front. Syst. Neurosci. 5:37. doi: 10.3389/fnsys.2011.00007

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., et al. (2005). Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol. Psychiatry 57, 1079–1088. doi: 10.1016/j.biopsych.2005.02.021

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., and Buckner, R. L. (2010). Functional-anatomic fractionation of the brain’s default network. Neuroimage 65, 550–562. doi: 10.1016/j.neuroimage.2010.02.005

Frontiers in Human Neuroscience www.frontiersin.org October 2013 Volume 7 Article 727 11
Menon, V., and Uddin, L. Q. (2010). Salience, switching, attention and control: a network model of insula function. Brain Struct. Func. 216, 635–667. doi: 10.1007/s00429-010-0262-0
Miller, D. D., Andreasen, N. C., O'Leary, D. S., Watkins, G. L., Bolea Ponto, L. L., Hulshoff, P. D., et al. (2001). Comparison of the effects of risperidone and haloperidol on regional cerebral blood flow in schizophrenia. Biol. Psychiatry 49, 704–715. doi: 10.1016/S0006-3223(00)01191-5
Minnabarriet, M. J., Fau, J., Nee, A. S., Tang, C. Y., and Siever, L. I. (2007). Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. Psychiatry Res. 150, 21–24. doi: 10.1016/j.pscychresns.2007.05.006
Neufeldt, I., Scholz, L., Kirsch, P., Harper, S. C., Böhm, M., Schmückle, C., et al. (2010). Affect regulation and pain in borderline personality disorder: a possible link to the understanding of self-injury. Biol. Psychiatry 68, 383–391. doi: 10.1016/j.biopsych.2010.04.015
Oldham, J. M. (2006). Borderline personality disorder and suicidality. Am. J. Psychiatry 163, 825–836. doi: 10.1176/appi.ajp.163.6.825
Palaniyappan, L., and Liddle, P. F. (2012). Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. J. Psychiatry Neurosci. 37, 17–27. doi: 10.1503/jpn.1100176
Phillips, M. L., Travis, M. J., Fagiolini, A., and Kapfer, D. J. (2008). Medication effects in neuroimaging studies of bipolar disorder. Am. J. Psychiatry 165, 513–520. doi: 10.1176/appi.amjpr.200707119
Schuckit, M. (1993). “The borderline patient, ” in Handbook of Psychiatric Drugs, ed. S. Aron (New York: Plenum Press), 398–410.
Sarey, W. W., Menon, V., Schlaug, A. F., Keller, J., Glover, G. H., Kenna, H., et al. (2007). Dissociable resting-state connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356. doi: 10.1523/JNEUROSCI.0577-06.2007
Skodol, A. E., Gunderson, J. G., Pfahler, B., Wollger, T. A., Livesley, W. J., Siever, L. J., et al. (2002). The borderline diagnosis: I. psychopathology, comorbidity, and personality structure. Biol. Psychiatry 51, 896–905. doi: 10.1016/S0006-3223(01)01524-0
Skodol, A. E., Stout, R. L., McGlashan, T. H., Grilo, C. M., Gunderson, J. G., Shea, M. T., et al. (1999). Co-occurrence of mood and personality disorders: a report from the Collaborative Longitudinal Personality Disorders Study (CLPS). J. Neurosci. 19, 106, 175–182. doi: 10.1523/JNEUROSCI.5587-01.2001
Smith, S. M., Fox, P. T., Miller, K. L., Glabos, D. C., Fox, P. M., MacKay, C. E., et al. (2009). Correspondence of the brain’s functional architecture during activation and rest. Proc. Natl. Acad. Sci. U.S.A. 106, 13250–13255. doi: 10.1073/pnas.0906898106
Smith, S. M., Miller, K. L., Mohseni, S., Xu, L., Auerbach, E. J., Woolrich, M. W., et al. (2012). Temporally-independent functional modes of spontaneous brain activity. Proc. Natl. Acad. Sci. U.S.A. 109, 1331–1336. doi: 10.1073/pnas.1121259109
Smoluk, M. J., Saliman, N., Wang, L., Smith, V., Lynch, T. R., Dagen, S. E., et al. (2011). Functional imaging of emotion reactivity in opioid-dependent borderline personality disorder. Pers. Disord. 2, 230–241. doi: 10.1037/ a0022228
Song, C., Rudi, V., Mühlan, M., Calhoun, V. D., Eichulu, T., Lüer, L., et al. (2007). Seizure changes of resting-state networks in individuals at risk for Alzheimer’s disease. Proc. Natl. Acad. Sci. U.S.A. 104, 18760–18765. doi: 10.1073/pnas.0704010104
Tafere, K. S., Seminowicz, D. A., and Drasen, K. D. (2009). Two systems of resting state connectivity between the insula and cingulate cortices. Hum. Brain Mapp. 30, 2731–2745. doi: 10.1002/hbm.20705
Tang, C. Y., and Siever, L. I. (2007). Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. Psychiatry Res. 150, 21–24. doi: 10.1016/j.pscychresns.2007.05.006
Torgerson, J. (2005). “Epidemiology, ” in The American Psychiatric Publishing Textbook of Personality Disorders, eds J. M. Oldham, A. E. Skokos, and D. S. Bender (Washington, DC: American Psychiatric Publishing), 129–142.
Uddin, L. Q., Inzlicht, M. S., Rybak, S., and Menon, V. (2011). Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. J. Neurosci. 31, 18788–18800. doi: 10.1523/JNEUROSCI.4405-11.2011
Williams, E. M., Suls, A., Gordon, E., and Menon, R. A. (2000). “Missing links” in borderline personality disorder: loss of neural synchrony relates to lack of emotion regulation and impulsive control. J. Psychiatry Neurosci. 25, 181–188.
Wold, R. C., Santambro, F., Vase, N., Schimid, M., Thomman, P. A., Bensmont, S. D., et al. (2011). Aberrant connectivity of resting-state networks in borderline personality disorder. J. Psychiatry Neurosci. 36, 402–413. doi: 10.1503/jpn.100193
Wood, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatry 64, 665–667. doi: 10.4088/JCP.v64n0607
Zhou, J., Griscius, M. D., Gorman, E. D., Grodens, M. E., Jiang, Y., Rabinovici, G. D., et al. (2010). Divergent network connectivity changes in behavioral variant frontotemporal dementia and Alzheimer’s disease. Brain 133(Pt. 5), 1352–1367. doi: 10.1093/brain/aap273
Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 29 May 2013; accepted: 12 October 2013; published online: 30 October 2014
Citation: Doll A, Sorg C, Manoliu T, Wöller H, Meng A, Förstl H, Zimmer C, Woods SW and Riedl V (2015) Shifted intrinsic connectivity of central executive and salience network in borderline personality disorder. Front. Hum. Neurosci. 7:273. doi: 10.3389/fnhum.2013.00727
This paper was submitted to the journal Frontiers in Human Neuroscience. Copyright © 2013 Doll, Sorg, Manoliu, Wollger, Meng, Förstl, Zimmer, Woods and Riedl. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.