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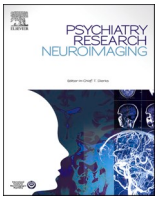

Article

Amygdala functional connectivity in borderline personality disorder

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ABSTRACT

Borderline personality disorder (BPD) is characterised by structural and functional brain alterations. Yet, there is little data on functional connectivity (FC) across different levels of brain networks and parameters. In this study, we applied a multi-level approach to analyse abnormal functional connectivity. We analysed resting-state functional magnetic resonance imaging (fMRI) data sets of 69 subjects: 17 female BPD patients and 51 age-matched psychiatrically healthy female controls. fMRI was analysed using CONN toolbox including: a) seed-based FC analysis of amygdala connectivity, b) independent component analysis (ICA) based network analysis of intra- and inter-network FC of selected resting-state networks (DMN, SN, FPN), as well as c) graph-theory based measures of network-level characteristics. We show group-level seed FC differences with higher amygdala to contralateral (superior) occipital cortex connectivity in BPD, which correlated with schema-therapy derived measures of symptoms/traits across the entire cohort. While there was no significant group effect on DMN, SN, or FPN intra-network or inter-network FC, we show a significant group difference for local efficiency and cluster coefficient for a DMN-linked cerebellum cluster. Our findings demonstrate BPD-linked changes in FC across multiple levels of observation, which supports a multi-level analysis for future studies to consider different aspects of functional connectome alterations.

1. Introduction

Borderline personality disorder (BPD) is characterised by commonly associated with emotional instability with fluctuating affects, irritability, and anger, but also low self-esteem, feelings of emptiness, or suicidality(Bohus et al., 2021). Magnetic resonance imaging (MRI) studies of function and structure in BPD show alterations in areas of the amygdala, anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (Schulze et al., 2016) In addition, meta-analysis of functional MRI (fMRI) studies also shows pathologies in the default mode network (DMN), including areas of the precuneus, and also associated areas of lateral temporal and orbitofrontal cortices (Visintin et al., 2016). Current neurobiological models of BPD therefore focus on fronto-limbic connectivity, suggesting that functional connectivity between amygdala and DLPFC is altered, and that this results in less control of emotions (Sicorello and Schmahl, 2021) This is supported by direct negative correlations of amygdala and frontal cortex connectivity with anger rumination and impulsivity, as two core symptoms of BPD (Mitolo et al., 2023)

A very recent review of resting-state fMRI studies in BPD has suggested both “selective” functional alterations in key hubs like amygdala, ACC, hippocampus, and prefrontal cortex as well as aberrant connectivity within and between prominent resting state networks like the DMN, but also salience network (SN) or central executive network (CEN) (Shafie et al., 2023). This points to a heterogeneity of approaches in resting-state fMRI data in BPD, because pathologies are analysed either focused on a single hub and its connections (e.g. amygdala, ACC) or looking at defined resting-state networks (e.g. DMN). In addition, recent studies also suggest that in addition to functional connectivity (FC), i.e. the correlation of time courses of the MRI signal, other parameters might offer additional insight. In particular, parameters based on graph theory such as clustering coefficients, global or local efficiency, or others (Xu et al., 2016) can describe and detect changes in network characteristics beyond traditional ROI-to-ROI analyses.

These different approaches can be combined to analyse network properties of the brain at different levels, including local or sub-networks, versus global indicators of network configuration.

In the present study, we attempt a comprehensive characterization of

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functional resting state networks in BPD by analysing resting-state fMRI in female patients with BPD and psychiatrically healthy female controls on three different levels. First, we use seed-based analysis to test the hypothesis that amygdala connectivity to other brain areas is disturbed in BPD. In an additional analysis, we used correlations with clinical scores (BSL scale for overall BPD pathology and measures derived from schema therapy-based assessments used in previous studies) in order to explore the relation to severity of clinical symptoms(Nenadic et al., 2020b). Second, we use independent component analysis (ICA) to isolate resting-state networks and then analyse intra-network and inter-network FC within and between the DMN, SN, and fronto-parietal (FPN) networks to test for FC reductions in these networks in BPD compared to HC Finally, we apply a graph-theory based approach to characterise resting-state network dysfunction in BPD as a measure of the connectedness or relation of nodes within these networks. and to test whether these differ from their counterparts in the HC group.

2. Methods

2.1. Subjects

For this study, we included 68 female subjects: 17 with borderline personality disorder (BPD) and 51 healthy controls (HC). All subjects gave written informed consent to a study protocol approved by the Ethics Committee of the Medical School of Friedrich-Schiller-University of Jena, Germany, in accordance with the Helsinki Declaration.

The study cohort overlaps with those of recently published structural MRI analyses which include details on recruitment (Nenadic et al., 2020a, 2020b). In brief, patients were recruited from in-patient and out-patient services of the Dept. of Psychiatry and Psychotherapy, Jena University Hospital, and had a DSM-IVR diagnosis of BPD, based on SCID-II screenings and subsequent SCID-II interviews for BPD section, carried out by a board-certified psychiatrist (I.N.). Based on a patient cohort with 17 female BPD patients, for which resting-state fMRI was available, we used an automated matching algorithm [10]to select 51 female, psychiatrically healthy subjects from recent imaging studies of the lab. All subjects were therefore female, and age did not differ ($t = -0.26148$, df = 29.862, p-value = 0.7955; 95 % CI: −2.42, 1.87) between BPD patients (mean 25 yrs, SD 3.66) and HC (mean 25.27 yrs, SD 4.01). BPD patients had axis I co-morbidities, including remitted major depression ($n = 9$), post-traumatic stress disorder ($n = 2$), avoidant personality disorder ($n = 2$), previous alcohol abuse ($n = 1$), and eating disorders ($n = 4$); 8 of these 17 BPD patients were on antidepressant medication. Healthy controls were recruited from the local community and were screened (using semi-structured interviews) for the absence of a current or previous psychiatric disorder (incl. substance abuse), which were defined as exclusion criteria. For both groups, additional exclusion criteria were: brain injury with loss of consciousness, neurological CNS disease, major uncontrolled medical diseases, pregnancy, and learning disability (operationalised as IQ<80, based on MWT-B assessments) (Lehrl et al., 1995).

We used German versions of the Borderline Symptom List (BSL-95) and schema-therapy derived inventories for traits (Young Schema Inventory, YSQ-2) and states (Schema Mode Inventory, SMI) to characterise symptom profiles. For an overview of demographic information and clinical scores see Table 1.

2.2. Data acquisition

All subjects underwent resting-state fMRI on a 3 Tesla MR system (Siemens Tim Trio; Siemens, Erlangen, Germany). Resting-state fMRI was acquired with eyes closed, with subjects instructed not to fall asleep (subjects were debriefed upon completion of fMRI). We obtained a series of 210 T2*-weighted whole-brain volumes over approx. 9 min, using a standard BOLD-sensitive EPI sequence (TR 2550 ms; TE 30 ms; flip angle 90°; whole-brain coverage with 45 contiguous axial slices, 3 mm thickness, without gap, 64×64 matrix; in-plane resolution 3 × 3 mm; field-of-view 192 mm×192 mm). In addition to the fMRI sequence, we acquired a high-resolution structural MRI for co-registration using a 3D MPRAGE sequence with 192 contiguous sagittal slices (1 mm thickness, TR 2300 ms; TE 3 ms; TI 900 ms; echo time 8.9 ms; flip angle 9°; matrix size 256×256; isotropic voxel dimensions of 1 × 1 × 1 mm).

Both functional and structural images series underwent quality assurance protocols, including visual inspection after the scan; none of the participants showed any artifacts or CNS pathologies.

2.3. Data analysis

For pre-processing and analysis of resting-state fMRI, we applied the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Images were first realigned using the SPM12 realign & unwarp procedure. Then they were co-registered and resampled to a reference image. The SPM12 slice-timing correction was used, as well as a normalization into standard MNI space. Smoothing was performed using spatial convolution with a Gaussian kernel of 4 mm FWHM. CONN's standard denoising pipeline was used, including correction for possible confounding effects like noise components, subject-motion, and outlier scans. BOLD signals were band-pass filtered and frequencies below 0.0008 Hz or above 0.09 Hz were removed.

2.4. Statistics

Three sets of analyses were calculated. First, we used a general linear model (GLM) implemented in CONN to test the hypothesis of a group main effect on bilateral amygdala functional connectivity with the rest of the brain. A threshold of $p < 0.05$ with cluster-level FDR correction implemented in CONN was applied. As groups were matched for age, we did not include age as co-variate in group main effect analyses.

Table 1
Overview of and group differences in sample demographics and clinical scores.

	N BPD / HC	BPD mean (SD)	HC mean (SD)	group difference (p)	group difference (p, FDR-corr.)	group difference (Cohen's d)
Age	17 / 51	25.00 (3.66)	25.28 (4.01)	0.804	0.804	−0.07
IQ (MWT-B)	14 / 50	104.57 (10.68)	103.48 (10.47)	0.732	0.804	0.10
YSQ-2 Emotional Deprivation	14 / 41	21.64 (5.40)	7.05 (2.97)	1.06e-17	**6.36e-17**	3.93
YSQ-2 Mistrust/Abuse	14 / 41	18.93 (7.60)	8.56 (3.91)	1.92e-08	**9.60e-08**	2.05
YSQ-2 Emotional Inhibition	14 / 41	17.29 (6.68)	8.20 (4.23)	2.25e-07	**6.75e-07**	1.84
SMI Detached Protector	14 / 41	3.47 (0.70)	1.55 (0.56)	1.33e-07	**5.32e-07**	3.22
BSL-95 Sum	13 / –	204.00 (46.07)	N/A	N/A	N/A	N/A

In addition, we performed an exploratory analysis on whether identified significant seed-based FC alterations were related to clinical ratings; for this purpose, we correlated significant FC parameters (beta values) with a) BSL scores, b) SMI state-based scores ("detached protector" mode), and c) YSQ trait-based scores (esp. emotional deprivation, mistrust/abuse, and emotional inhibition), both across the total sample and within each group (BPD, HC). In all analyses including continuous questionnaire scores within and across groups, age was included as a co-variate.

We did not use movement parameters as co-variates, but rather applied movement correction during pre-processing as to not decrease the degrees of freedom in GLMs with multiple co-variates / nuisance variables relying on limited sample size.

Second, we used GLM to test intra-network and inter-network connectivity (using the *conn_withinbetweenROItest* script in CONN, based on ICA analyses) for the (SN), DMN, and FPN.

Third, we tested for group-level differences in graph theory-based parameters, in particular global and local efficiency, average path length, and clustering coefficient as implemented in CONN.

3. Results

3.1. Seed-based amygdala connectivity

Left amygdala showed significantly reduced functional connectivity in BPD compared to HC with a cluster ($k = 43$) in the right superior lateral occipital cortex (see Fig. 1).

Right amygdala showed significantly reduced functional connectivity in BPD compared to HC with a cluster ($k = 52$) in the left superior lateral occipital cortex (see Fig. 2).

Peak voxel co-ordinates are given in Table 2 and location and extent of clusters is shown in Figs. 1 and 2, respectively.

The amygdala to occipital cortex connections did not correlate significantly with BSL-95 values in the BPD sample (amygdala left connectivity: $p = 0.7291$, amygdala right connectivity: $p = 0.6015$). For YSQ-2 and SMI correlations we found significant associations across the entire cohort (BPD and HC combined) for YSQ scores for emotional deprivation (amygdala left connectivity: $p = 0.00244$, amygdala right connectivity: $p = 0.0002037$), mistrust/abuse (amygdala left connectivity: $p = 0.029126$, amygdala right connectivity: $p = 0.004674$), and emotional inhibition (amygdala left connectivity: $p = 0.014982$, amygdala right connectivity: $p = 0.0002057$), as well as SMI "detached protector" mode (amygdala left connectivity: $p = 0.00291$, amygdala right connectivity: $p = 0.000985$). When analysing these correlations within BPD and HC separately, we did not find any significant correlations.

3.2. Intra-network functional connectivity

ICA-based analyses of intra-network connectivity for DMN, SN, and FPN did not show significant group differences (DMN: T(66)=0.23, $p = 0.822598$; T(66)=−0.72, $p = 0.472682$; T(66)=−1.16, $p = 0.249594$), and neither did inter-network connectivity analyses between these three selected networks (SN x DMN: T(66)=−0.37, $p = 0.712698$; SN x FPN: T

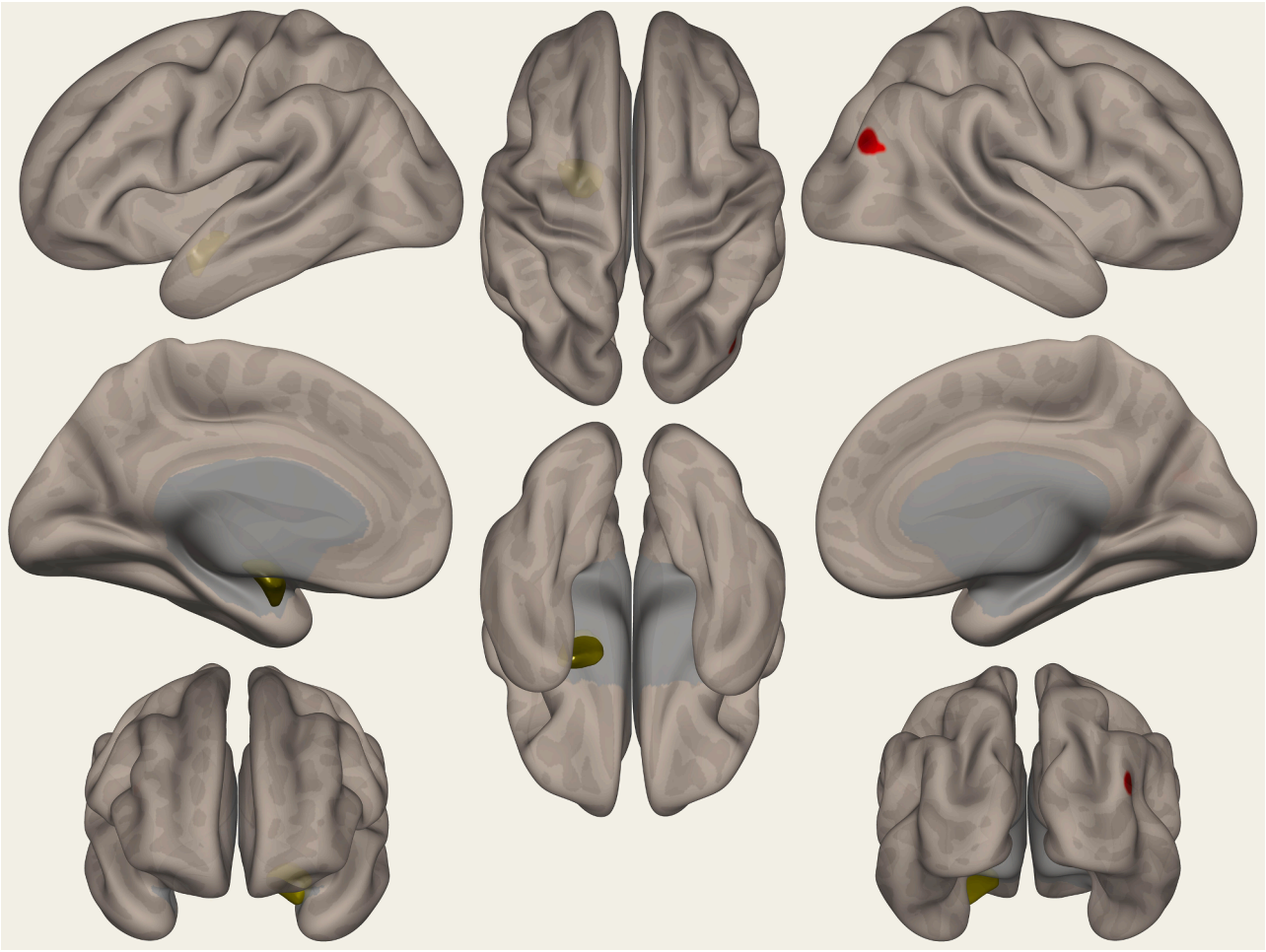

Fig. 1. Seed-based functional resting-state connectivity analysis of group differences between borderline personality disorder (BPD) vs. healthy controls (HC) subjects with left amygdala as seed; brain-wide association thresholded at $p < 0.05$ FDR-corrected.

Table 2
Results of seed-based analyses of functional resting-state connectivity contrasting higher connectivity in 17 female borderline personality disorder patients compared to 51 female healthy controls.

Seed region	Anatomical area (atlas labelling using …)	P (FDR cluster-level corrected)	Cluster size (voxels)	MNI Coordinates (maximum intensity voxel)
Left amygdala	Right lateral occipital cortex, superior division (100 %)	0.034881	43	+ 42 -72 + 30
Right amygdala	Left lateral occipital cortex, superior division (83 %)	0.014407	52	−26 -62 + 40

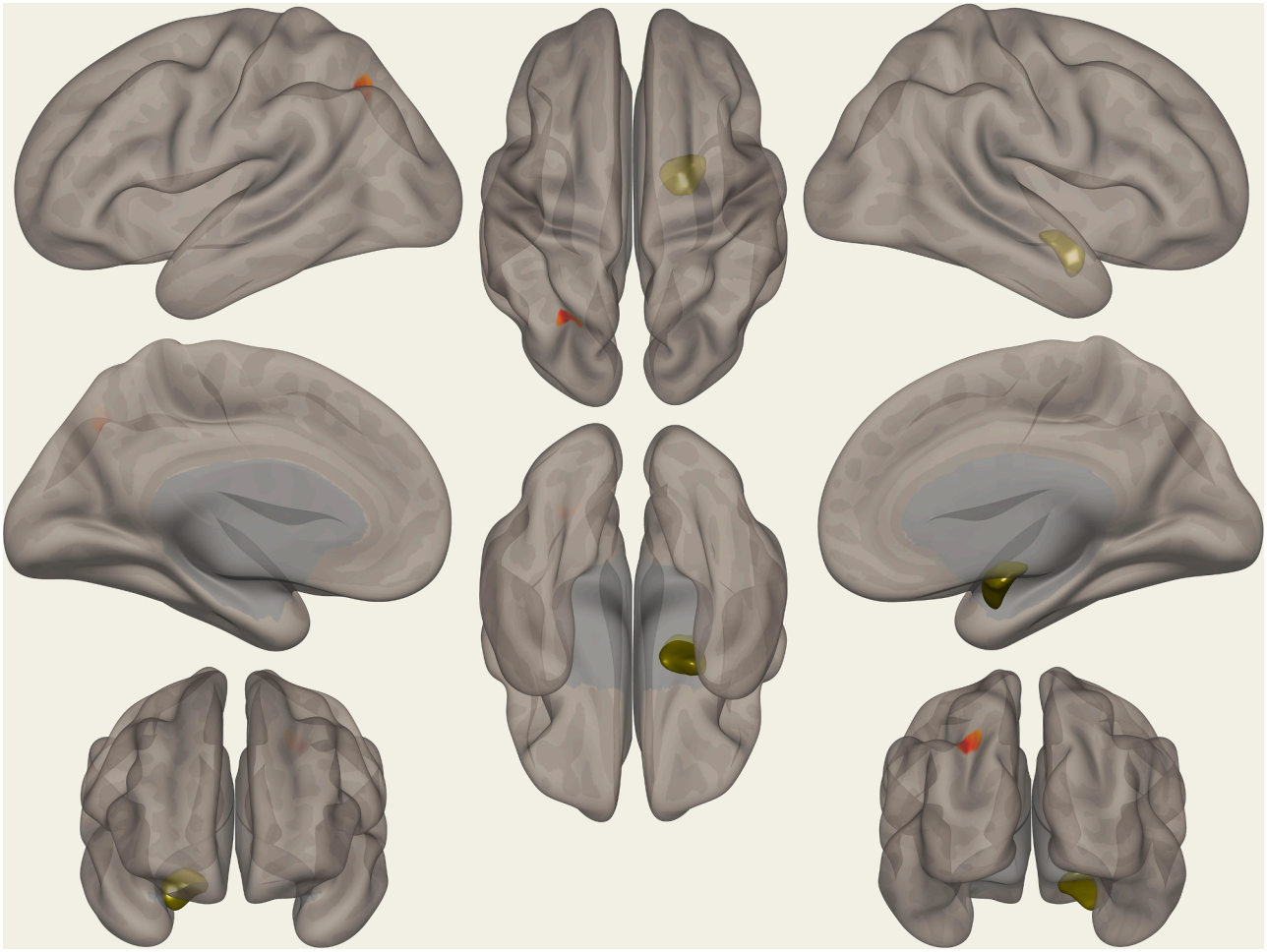

Fig. 2. Seed-based functional resting-state connectivity analysis of group differences between borderline personality disorder (BPD) vs. healthy controls (HC) subjects with right amygdala as seed; brain-wide association thresholded at $p < 0.05$ FDR-corrected.

(66)=−0.28, $p = 0.778086$; DMN x FPN: T(66)=−1.06, $p = 0.292636$).

3.3. Graph theory based functional connectivity analyses

Two cerebellar clusters associated with the DMN showed group-level differences in the DMN: for a right cerebellum cluster (maximum intensity voxel at 13, −47, −50) we found lower local efficiency ($p < 0.0001$) and lower clustering coefficient ($p < 0.0001$) and for a left cerebellum cluster (maximum at −10, −49, −48) we found a lower average path length ($p = 0.0001308$). In addition, a left cerebellum cluster (maximum at −37, −70, −41) in the FPN showed a higher cluster coefficient between groups ($p = 0.036724$). The cerebellar clusters are shown in Fig. 3.

4. Discussion

Our study used a multi-level analysis approach to resting-state fMRI, which addressed in parallel multiple perspectives of brain network dysfunction in BPD vs. healthy controls. Our main findings are group differences of FC between amygdala and (contralateral) superior occipital cortex and altered network parameters within the DMN. While both intra-network FC of the DMN and inter-network FC of the DMN to salience network or fronto-parietal network did not reach statistical significance, our graph theory-based analyses show group main effects for DMN global efficiency and cluster coefficients in DMN and FPN.

Our seed-based FC analysis of the amygdala showed aberrant connectivity to posterior occipital regions. Interestingly, this effect was bilateral, i.e. seen for both amygdalae, and related to contralateral occipital areas. While several previous studies have used seed-based approaches to FC in BPD, the heterogeneity of methods and in particular the focus/restriction to particular areas, is a limit to comparability across studies: for example, some studies identified direct proof of amygdala to DLPFC or medial PFC areas (Shafie et al., 2023). This effect, which was not observed in our study, was susceptible to changes following an emotion regulation intervention (Baczkowski et al., 2017). Altered activation in (middle) occipital cortices has emerged in a recent meta-analysis on the overlap between BPD with post-traumatic stress disorder and major depressive disorder (Schulze et al., 2019),

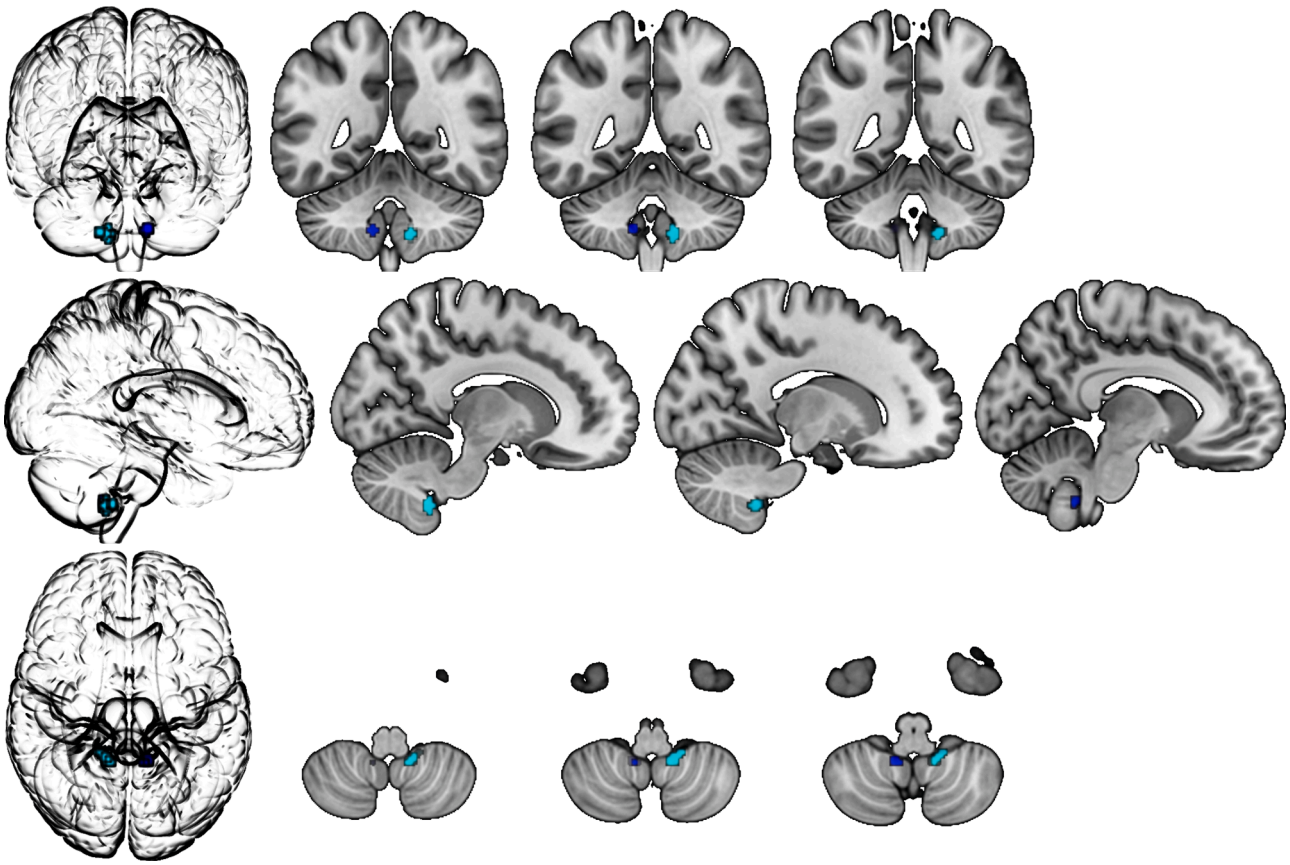

Fig. 3. Cerebellar clusters associated with the DMN network differences between BPD and HC for graph theory based measures (right cerebellum cluster (maximum voxel 13, −47, −50) for local efficiency ($p < 0.0001$) and clustering coefficient ($p < 0.0001$); left cerebellum cluster (maximum −10, −49, −48) for average path length ($p = 0.0001308$).

highlighting functional anatomies shared across diagnostic categories. The lack of correlation between clinical symptoms and this disturbed amygdala-occipital FC in our sample underlines the need for further research; our current analysis (which only included a subsample of the already limited cohort) thus also served to generate hypotheses for follow-up studies. While our sample size was limited, co-morbidities in our sample were similar to those reported in other fMRI studies (Shafie et al., 2023). This highlights a limitation of our study (but also most others in the field), i.e. the lack of specific ascription of this connectivity change to either the single diagnostic category or particular symptom(s). A putative interpretation of our finding can be drawn from recent studies of function connectivity between the amygdala and sensory cortical areas (Underwood et al., 2021), considering that sensory cortical areas might have a greater impact on emotional processing than previously assumed. Indeed, a few previous studies have identified occipital areas outside the ventral stream areas, which are typically implicated in facial emotion processing, to contribute to valence detection (Liu et al., 2021; Todorov and Engell, 2008) (Todorov & Engell, Soc CognAffect Neurosci 2008; Lidell et al., Biol Psychol 2017; see also meta-analysis in Liu et al., Neurosci Biobehav Rev 2021) and more recently in non-substance related addiction (Cheng and Liu, 2020).

Furthermore, a few recent studies have implied that the occipital cortex may play a role in key symptoms of BPD: like being a part of a large network showing an increase connectivity in BPD Patients listening to a narrative of directing moderate physical aggression towards others (Ueltzhöffer et al., 2019), increased connectivity of the right prefrontal cortex with bilateral occipital lobes in adolescent patients (Xiao et al., 2023) and an increased negative resting-state functional connectivity between the ventral ACC and medial occipital regions in BPD patients (Krause-Utz et al., 2014)

An fMRI study in adolescents with non-suicidal self-injury behaviour (regardless of diagnosis) showed a decreased functional connectivity between the amygdala and angular gyrus and occipital cortex (Schreiner et al., 2017), suggesting a transdiagnostic feature that could be investigated in further studies.

Additionally, a study on healthy subjects found evidence for repetition enhancement of amygdala functional connectivity with bilateral occipital cortex during nonconscious memory for negative items (Kark et al., 2016). In our sample we found a decreased functional connectivity which could point to a missing protective mechanism that contribute in healthy individuals to an effective emotional regulation.

Not all of the occipital areas mentioned above correspond to areas identified in our analysis (i.e. superior occipital cortices). This highlights the need of a more comprehensive approach to identifying the involvement of different visual cortical areas. For example, grey matter alternation (reduction in volume and thickness) of primary visual areas (Teicher and Samson, 2016) as well as structural connectivity alteration from the visual cortex towards other brain areas (Choi et al., 2012) have been associated with history of childhood parental abuse or violence, but its effect on secondary visual areas is not fully understood. A recent study that investigated the neurological underpinning of childhood maltreatment by looking into the associations between functional connectomes of large-scale brain networks, found visual network involvement in the prediction of childhood maltreatment evaluated through Childhood Trauma Questionnaire (Zhang et al., 2022). In addition, studies investigating dynamic changes of altered functional connectivity in BPD are still scarce(Westlund Schreiner et al., 2019).

The lack of correlation with clinical state or trait measures (BSL, YSQ, SMI) within the BPD group might be related to limited sample size and insufficient power to detect an association. While we find significant

associations between amygdala connectivity and trait measures across both groups, this finding is limited by the group differences and might be at least partially due to bi-modal tendency in distributions. We also need to consider that abnormal amygdala connectivity might be a result of trauma-related experiences, which was not sufficiently captured in our inventories.

Finally, our study also provides a first indication of altered network-level metrics captured by graph-theory based measures (in particular local efficiency and clustering coefficient). The identified cluster in the cerebellum approximately corresponds to an area of the cerebellum which has been shown to be intrinsically linked to the DMN (Habas et al., 2009). Given the preliminary nature of this finding, further replication is warranted. However, it is noteworthy that these statistically highly significant effects for graph-theory based measures occur in the absence of significant simple FC metric changes, as seen in the intra-network analysis of the DMN, SN, and FPN.

Among the limitations of our study are the small sample size, restriction to female study participants and comorbidities. Although the latter are a prevalent feature of most BPD patients (Bohus et al., 2021), there are studies that show a shared imbalance in functional networks in BPD and PTSD suggesting that both disorders represent a continuum with involvement of similar brain regions (with a different direction of activation) (Stopyra et al., 2023) but also disorder-unique functional activation patterns during emotion processing (Schulze et al., 2019). Small sample size and comorbidity may have contributed to our lack of significant network-level connectivity result in DMN and SN, which have been noted in most recent resting-state fMRI studies (Shafie et al., 2023; Visintin et al., 2016). While we find significant associations between amygdala connectivity and trait measures across both groups, this finding is limited by the group differences and might be at least partially due to bi-modal tendency in distributions. Finally, smoothing filter choice might influence results. In our present study, based on the small target structure and recent findings comparing different filter sizes for functional connectivity analyses indicating good applicability of medium sized filters (Alahmadi, 2021), we chose a 4 mm filter in line with these recent findings.

In conclusion, our study provides evidence for altered amygdala-occipital functional connectivity as well as changes in functional connectome topology of a DMN-associated cerebellar node, in the absence of intra- vs. inter-network FC changes. This demonstrates the utility of a multi-level approach in characterising functional connectivity changes in disorders like BPD. However, additional replication and extension of clinical phenotypes will be necessary to better understand the relation of particular facets of the disorder in relation to functional network changes.

CRediT authorship contribution statement

Laila Noor: Writing – original draft, Project administration, Conceptualization. **Jonas Hoffmann:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis. **Tina Meller:** Writing – review & editing, Visualization, Supervision, Methodology. **Christian Gaser:** Writing – review & editing, Supervision, Project administration, Data curation. **Igor Nenadić:** Writing – original draft, Supervision, Resources, Project administration, Data curation, Conceptualization.

Declaration of competing interest

The authors have no competing interests to declare.

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