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Neurocircuitry associated with symptom dimensions at baseline and with change in borderline personality disorder

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ABSTRACT

Borderline personality disorder (BPD) is a serious illness associated with chronic suffering and self-injurious behavior. Parsing the relationships between specific symptom domains and their underlying biological mechanisms may help us further understand the neural circuits implicated in these symptoms and how they might be amenable to change with treatment. This study examines the association between symptom dimensions (Affective Disturbance, Cognitive Disturbance, Disturbed Relationships, and Impulsivity) and amygdala resting-state functional connectivity (RSFC) in a sample of adults with BPD (n = 18). We also explored the relationships between change in symptom dimensions and change in amygdala RSFC in a subset of this sample (n = 13) following 8 weeks of quetiapine or placebo. At baseline, higher impulsivity was associated with increased positive RSFC between right amygdala and left hippocampus. There were no significant differences in neural change between treatment groups. Improvement in cognitive disturbance was associated with increased positive RSFC between left amygdala and temporal fusiform and parahippocampal gyri. Improvement in disturbed relationships was associated with increased negative RSFC between right amygdala and frontal pole. These results support that specific dimensions of BPD are associated with specific neural connectivity patterns at baseline and with change, which may represent neural treatment targets.

1. Introduction

Borderline personality disorder (BPD) is characterized by symptoms such as affective instability, difficulties in interpersonal relationships, and non-suicidal self-injury (NSSI; American Psychiatric Association, 2013). BPD is a serious mental illness, with approximately 75% of individuals with BPD having made at least one suicide attempt in their lifetime (Soloff et al., 1994; Wedig et al., 2012). There is an urgent need for more effective treatment options.

Since BPD is a clinically heterogeneous disorder, development of personalized approaches to allow treatment plans to be tailored around a patient's individual characteristics will be critical important for advancing the field. For example, Ingenhoven and colleagues conducted a meta-analysis and a very large effect size for mood-stabilizers in the treatment of impulsive dyscontrol and anger; a large effect size on anxiety, and a moderate effect size on depression. Antipsychotics has a moderate/large effect on anger and a moderate effect size on cognitive-perceptual symptoms. Antidepressants were shown only to have a small effect on depression and anxiety (Ingenhoven and Duivenvoorden, 2011). The importance of recognizing the specificity of treatments for improving different symptom dimensions within BPD has received increasing recognition (Nelson and Schulz, 2011) and aligns with the National Institute of Mental Health's (NIMH) strategic research priorities regarding greater precision in the treatment of mental illness (NIMH, 2017). To advance these initiatives, research is needed to understand the neurobiological mechanisms that underlie specific symptom profiles and how these biological mechanisms change with clinical improvement. This approach can serve to identify biological treatment targets and contribute to development of a neurobiologically-informed approach in providing personalized intervention for BPD.

The use of functional magnetic resonance imaging (fMRI) has shed light on the neural networks implicated in BPD. One common theme has been that individuals with BPD often show increased amygdala activation compared to controls in the context of negative emotional stimuli (Baskin-Sommers et al., 2015; Herpertz et al., 2001; Schulze et al., 2016). Research examining functional connectivity, as measured

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by the correlation of blood oxygen level dependent (BOLD) response between regions of the brain from either resting-state or task fMRI data, may be compromised in patients diagnosed with BPD. Previous studies that have examined functional connectivity during tasks involving fearful face viewing and emotional distraction (Cullen et al., 2011; Krause-Utz et al., 2017), found that patients with BPD may be more susceptible to have a hypersensitive response to negatively-valenced information. Similarly, Salvador and colleagues found that those with BPD showed increased functional connectivity at rest (RSFC) between limbic regions (the amygdala and hippocampus) and the anterior cingulate cortex (ACC; Salvador et al., 2016).

Taking a step beyond these studies identifying circuitry associated with an overarching BPD diagnosis, some neuroimaging researchers have begun to parse the heterogeneity of BPD by examining the associations between neural measures and BPD symptoms. For instance, one study found that BPD patients with dissociative symptoms had lower RSFC between amygdala and fusiform gyrus, but higher RSFC between amygdala and right middle and superior temporal gyri and left inferior lobule (Krause-Utz et al., 2017). Additionally, trait aggression in males with BPD (but not females) has been associated with decreased amygdala-dorsolateral prefrontal cortex (PFC) and orbitofrontal cortex (OFC) connectivity and increased amygdala-thalamus connectivity (Herpertz et al., 2017). Continued research along these lines is needed to further develop our understanding of how symptom dimensions are modeled in the brain and how they may be altered with treatment. These studies identifying functional connectivity patterns associated with BPD diagnosis and with specific dimensions of BPD provide a foundation for the next phase of work geared toward probing the how the neural circuits underpinning specific dimensions of BPD might change with treatment.

The present study sought to contribute to the existing literature by investigating the neurocircuitry associated with symptom dimensions and mechanisms of change in BPD. In this pilot study, we incorporated neuroimaging procedures into the protocol of a subset of participants completing a double-blind, placebo-controlled trial (Black et al., 2014). The goals of this neuroimaging portion of the study were to (1) identify the neurocircuitry associated with symptom dimensions within a sample of BPD patients, (2) measure how change in neurocircuitry is associated with change in BPD symptom dimensions, and (3) explore whether these relationships between change in neurocircuitry and symptom dimensions differ between medication and placebo groups. Given that previous work has implicated anomalous amygdala functioning within BPD, this study focused on amygdala-centered networks and limited analyses to brain regions within specific limbic and cortical structures implicated in affective processing, behavioral and emotional regulation, interpersonal functioning, and cognitive control. These regions included the subgenual ACC, OFC, basal ganglia, thalamus, insula, opercula, and cingulate gyrus. Based on the functions of the intrinsic connectivity networks (ICNs) indicated by Laird and colleagues (Laird et al., 2011), we hypothesized that amygdala RSFC with these regions would be associated with specific BPD symptom dimensions (Affective Disturbance associated with amygdala-ACC and parahippocampal gyri RSFC, Cognitive Disturbance with amygdala-thalamus, basal ganglia, insula, and cingulate RSFC, Impulsivity with amygdala-parahippocampal gyri, thalamus, basal ganglia, ACC, and OFC RSFC, and Disturbed Relationships with amygdala-ACC and insula RSFC).

2. Method

2.1. Participants

Adults aged 18–45 years were recruited from the University of Minnesota (UMN) location of a larger multi-site clinical trial (Black et al., 2014) to complete pre- and post-treatment MRI scanning. Participants were required to meet DSM-IV criteria for a diagnosis of BPD. The inclusion/exclusion criteria for the larger study has previously been published (Black et al., 2014), which included no current diagnosis of major depressive disorder, posttraumatic stress disorder, panic disorder, or obsessive-compulsive disorder, or history of psychotic disorder. Individuals were also excluded if they had a primary neurological condition, were cognitively impaired, were medically unstable, had a history of lack of response to an atypical antipsychotic, were pregnant or lactating, were acutely suicidal, or had current substance dependence or recent abuse of opiates, amphetamine, barbiturates, cocaine, or hallucinogens. Additionally, participants could not be taking psychotropic medication with the exception of ≤ 1.0 mg/day of benzodiazapines or anticholinergics for sleep. Participants also could not begin psychotherapy for the duration of the study. For the present study, additional criteria required participants to not have any magnetic resonance imaging (MRI) contraindications. Participants who met criteria for the larger study at the UMN site and had no MRI contraindications were invited to participate in pre- and post-treatment MRI scanning. All participants completed written informed consent. This study was approved by the UMN Institutional Review Board.

2.2. Assessments

All participants completed the Diagnostic Interview for DSM-IV Personality Disorders (Zanarini et al., 1996) in addition to a number of clinical measures, which included the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) (Zanarini et al., 2003). The ZAN-BPD includes subscales of Affective Disturbance, Cognitive Disturbance, Impulsivity, and Disturbed Relationships. This scale was administered at baseline, which took place approximately 2 weeks prior to the treatment trial, and again after 8 weeks of one of three randomized conditions: (1) placebo, (2) 150 mg/daily quetiapine, and (3) 300 mg/daily quetiapine. The subscales of the ZAN-BPD were used as symptom dimensions to examine their association with neurocircuitry. The ZAN-BPD contains nine items that correspond to each of the BPD diagnostic criteria in the DSM-IV and DSM-5. Participants and clinicians each rated the presence of each symptom on a scale of 0–4, with a higher score indicating higher severity with 36 being the highest total score. Three items comprise the Affective Disturbance subscale (highest score of 12), two items comprise the Cognitive Disturbance subscale (highest score of 8), two items comprise the Impulsivity subscale (highest score of 8), and two items comprise the Disturbed Relationships subscale (highest score of 8). We used the self-report data for the present study. Cronbach's alpha between clinician and participant ratings for each of the subscales ranged from 0.77 to 0.93 for baseline (0.91 for total score) and 0.85 to 0.93 for post-treatment (0.97 for total score).

2.3. MRI acquisition

Each participant completed a baseline (completed shortly before beginning treatment study) and post-treatment MRI (following 8 weeks of medication trial) scan using identical acquisition parameters on a Siemens 3T Tim Trio scanner located at the Center for Magnetic Resonance Research at the University of Minnesota. A T1-weighted high-resolution magnetization prepared gradient echo (MPRAGE) sequence was used to acquire whole-brain anatomical images with repetition time = 2530 ms, echo time = 3.65 ms, inversion time = 1100 ms, flip angle = 7°, field of view = 256 mm, voxel size 1 mm isotropic, generalized, autocalibrating, partially parallel acquisition acceleration factor (GRAPPA) = 2. The resting-state functional magnetic resonance imaging (rsfMRI) scans were acquired using 180 contiguous echo planar imaging (EPI) whole brain volumes with repetition time = 2000 ms, field of view = 220 mm, voxel size = 3.44 × 3.44 × 4 mm, and 34 slices. For the duration of the scan, participants were instructed to relax with their eyes closed and remain awake. The duration of the rsfMRI scan was approximately six minutes. A field map was also collected with compatible parameters as the

rsfMRI for use in preprocessing.

2.4. MRI preprocessing

The T1 data were processed using FreeSurfer version 5.3 (surfer.nmr.mgh.harvard.edu), which included brain extraction and parcellation of data into anatomically-based regions of white and gray matter. Using methods published previously (Cullen et al., 2014), this output was visually inspected on a slice-by-slice basis and manually corrected when necessary. These preprocessed data were registered to the rsfMRI data using bbregister (surfer.nmr.mgh.harvard.edu/fswiki/bbregister).

We used tools from the FMRIB Software Library (FSL; fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and custom developed tools in MATLAB (MathWorks; mathworks.com/products/matlab/) to preprocess the rsfMRI data. Preprocessing steps included brain extraction, motion correction, and a denoising procedure that incorporated RETROICOR (Glover et al., 2000) to remove physiological noise caused by cardiac and respiratory cycles and linear trends. We used the field map to correct for magnetic field inhomogeneity-induced geometric distortion. White matter (WM) and cerebrospinal fluid (CSF) were created using FreeSurfer, aligned to each participant's rsfMRI data, and their mean time series were extracted. We regressed each brain voxels' time series on eight nuisance variables, which included WM, CSF, and the six motion parameters. We completed data scrubbing following the method published by Power et al. (2012), which excluded any volume with a DVARS value exceeding 8 (% BOLD signal change * 10) and/or a framewise displacement (FD) value exceeding 0.5 mm (Power et al., 2012). The previous volume and the two following volumes were also excluded. Individuals who had greater than 30% of their volumes excluded in either the baseline or post-treatment rsfMRI scan ($n = 0$) were excluded from further analyses.

We used anatomically based regions of interest (ROIs) of the right and left amygdala that were generated using FreeSurfer to conduct RSFC analyses. We registered each individual's right and left amygdala ROIs to their preprocessed rsfMRI data and extracted the mean time series of voxels in these regions. We used these time series as primary regressors in a general linear model analysis of all other voxel time series (separately for right and left), which resulted in whole brain connectivity maps. Prewhitening, spatial smoothing with a 5 mm kernel, and registration to anatomical data and standard space (Montreal Neurological Institute 152), were also completed.

2.5. MRI analysis

We used AFNI's *3dRegAna* (Cox, 1996) to complete whole-brain linear regression analyses with the whole brain connectivity maps generated during the first level analyses. First, we investigated the association between BPD symptom dimensions and amygdala RSFC at baseline. We conducted separate analyses for each of the four ZAN-BPD subscales (Affective Disturbance, Cognitive Disturbance, Impulsivity, and Disturbed Relationships) as the main regressor. To limit the number of comparisons, we chose a priori to exclude voxels outside of components 1–5 from Laird and colleagues (Laird et al., 2011), multiplying the output of *3dRegAna* by a mask that was created using WFU PickAtlas (Lancaster et al., 2000, 1997; Maldjian et al., 2004, 2003). The Laird et al. components 1–5 consist of limbic and medial-temporal areas, subgenual ACC, OFC, basal ganglia, thalamus, insula, opercula, and cingulate gyrus. We used AFNI's *3dClustSim* and the *AutoCorrelation Function* to perform a cluster-based thresholding approach to correct for multiple comparisons. We used an initial $p < 0.005$, with a cluster size of $\alpha < 0.05$ [uncorrected for multiple tests (right and left amygdala)].

We also conducted analyses to identify significant clusters whose change in response to treatment corresponded to change in the four ZAN-BPD subscales. We calculated pre- versus post-treatment change in amygdala RSFC for each subject by subtracting the pre-treatment amygdala RSFC *z*-score maps from the post-treatment amygdala RSFC *z*-score maps using *fslmaths*. This provided us with a map representing amygdala RSFC change for each person. We also calculated change in each symptom dimension by subtracting the pre-treatment score from the post-treatment score for each subject. We then proceeded to run *3dRegAna* for the change in right and change in left amygdala *z*-score maps with each symptom dimension change score as a regressor. This was followed by multiplying the *3dRegAna* output by the WFU PickAtlas-created mask described above followed by *3dClustSim* with *AutoCorrelation Function* to perform a cluster-based thresholding approach to correct for multiple comparisons. We used an initial $p < 0.005$, with a cluster size of $\alpha < 0.05$ [uncorrected for multiple tests (right and left amygdala)].

We extracted the average *z*-score values of each cluster that was significant following *3dClustSim* by using each cluster as a mask for every individual. This was done to inspect the data for outliers and to determine whether RSFC analyses needed to be repeated after excluding outliers. R Statistical Software was used to calculate Pearson's *r* to understand the magnitude of the correlations between RSFC and symptom dimensions and to create figures. In the case of ZAN-BPD scores that violate the assumption of normality, Spearman's *r* was also used to understand the magnitude of correlations. To further correct for multiple comparisons, we used a Bonferoni correction to set a more stringent *p*-value of 0.0065. This is to correct for a total of 8 comparisons for each set of analyses (ZAN-BPD subscale baseline vs. RSFC and ZAN-BPD subscale change vs. RSFC change). This accounts for each of the four ZAN-BPD subscales and also the separate right and left amygdala analyses.

3. Results

3.1. Demographic and clinical characteristics

A total of 19 participants with BPD had complete and usable baseline neuroimaging data and clinical measures. Fourteen of these participants also completed a post-treatment MRI scan and clinical measures. One participant was excluded from analyses because of extreme *z*-score values for RSFC analyses, yielding 18 participants in the baseline analyses and 13 participants in the change analyses. Demographic information of the study cohort is found in Table 1.

3.2. Baseline symptom dimensions associated with neurocircuitry

Higher scores on the Impulsivity subscale of the ZAN-BPD were positively associated with RSFC between right amygdala and a cluster in the left hippocampus (low scores were associated with low RSFC while high scores were associated with greater positive RSFC; $r = 0.754$, $p = 0.0003$) (Fig. 1). Due to baseline Impulsivity scores violating the assumption of normality, Spearman's *r* was calculated, which yielded a similar finding; $r_s = 0.773$, $p = 0.0002$. There were no other significant correlations between either amygdala RSFC and the clinical measures.

3.3. Change in symptom dimensions associated with change in neurocircuitry

Of 13 adults with BPD with usable pre- and post-treatment MRI scans, 4 individuals were prescribed 150 mg of quetiapine once daily, 1 was prescribed 300 mg of quetiapine once daily, and 8 were prescribed placebo. Given the overall small sample size, both of the quetiapine groups as well as the placebo group were included in the change analyses. Thus, results are more of a reflection of change in a symptom dimension in general rather than change in a symptom dimension due to an intervention. With all groups combined, greater decreases in Cognitive Disturbance scores were associated with change in RSFC between the left amygdala and left temporal fusiform and

Table 1
p-values represent paired-samples *t*-test comparing pre- and post-treatment values.

Demographic characteristics	Baseline (n = 18)	Post-treatment (n = 13)	Post-treatment quetiapine (n = 5)	Post-treatment placebo (n = 8)
Age (mean years ± SD)	29.29 ± 7.37			
Gender (male/female/other)	5/12/1			
Global Axis of Functioning (mean ± SD)	65.83 ± 4.91	71.46 ± 5.59	70.4 ± 5.50	72.13 ± 5.92*
ZAN-BPD Total Score (mean ± SD)	15.61 ± 5.98	6.92 ± 6.49*	5.6 ± 3.36*	8.00 ± 7.95*
ZAN-BPD Affective Disturbance (mean ± SD)	7.28 ± 2.37	3.31 ± 2.66	2.6 ± 1.52**	3.75 ± 3.20*
ZAN-BPD Cognitive Disturbance (mean ± SD)	3.33 ± 2.14	1.77 ± 2.28**	1.4 ± 1.14	2.00 ± 2.83**
ZAN-BPD Impulsivity (mean ± SD)	1.33 ± 1.37[a]	0.69 ± 1.25	0.4 ± 0.89	0.88 ± 1.46
ZAN-BPD Relationship Difficulties (mean ± SD)	3.72 ± 2.02	1.31 ± 0.86	1.2 ± 0.84*	1.38 ± 0.92*

[a] Significant difference between males and females (males = 1.00 ± 0.707, females = 1.58 ± 1.564, p = 0.015).
* $p < 0.05$.
** $p < 0.001$.

parahippocampal gyri (increased negative RSFC for greater improvements in Cognitive Disturbance; $r = -0.900$, $p < 0.001$) (Fig. 2). Further, this held when using Spearman's R due to change in Cognitive Disturbance violating the assumption of normality; $r_s = 0.909$, $p < 0.001$. Greater decreases in Disturbed Relationships were associated with change in RSFC between right amygdala and right frontal pole (increased positive RSFC for greater improvements in Disturbed Relationships; $r = 0.871$, $p < 0.001$). See Fig. 3 for more information (Fig. 3).

4. Discussion

Despite the small sample size of the present study, our findings highlight the potential utility of this approach and generate hypotheses for future work. While highly preliminary, the present study provides evidence of potentially unique patterns of neural circuitry that may correspond to specific symptom dimensions in BPD at baseline and/or in response to change following treatment. Further, this study uses conservative methods to minimize the effect of motion and also focuses on particular brain regions by applying a mask, thereby limiting the number of comparisons. We also implemented a non-Gaussian approach in our analyses. An additional strength of this study is the double-blind study design and inclusion of both placebo and quetiapine groups in the analyses. This provides us with the ability to understand the mechanisms of change associated with symptom dimensions independent from a specific treatment, particularly since we found that

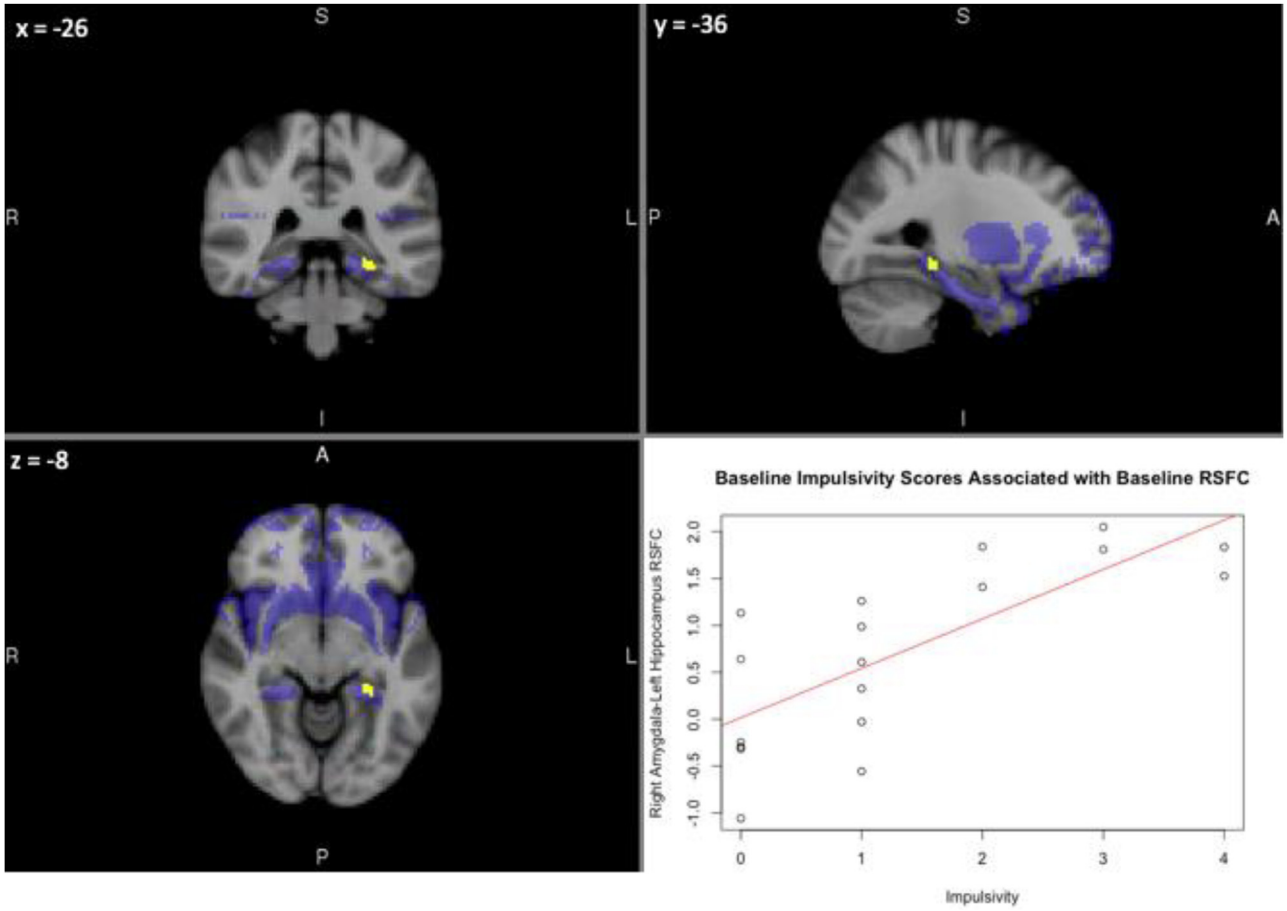

Fig. 1. Higher scores on the Impulsivity dimension on the ZAN-BPD scale was associated with greater positive RSFC between the right amygdala and left hippocampus (yellow). Areas shaded in blue represent the regions included in the mask. Coordinates are in MNI space and are the location of the peak voxel for each cluster. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

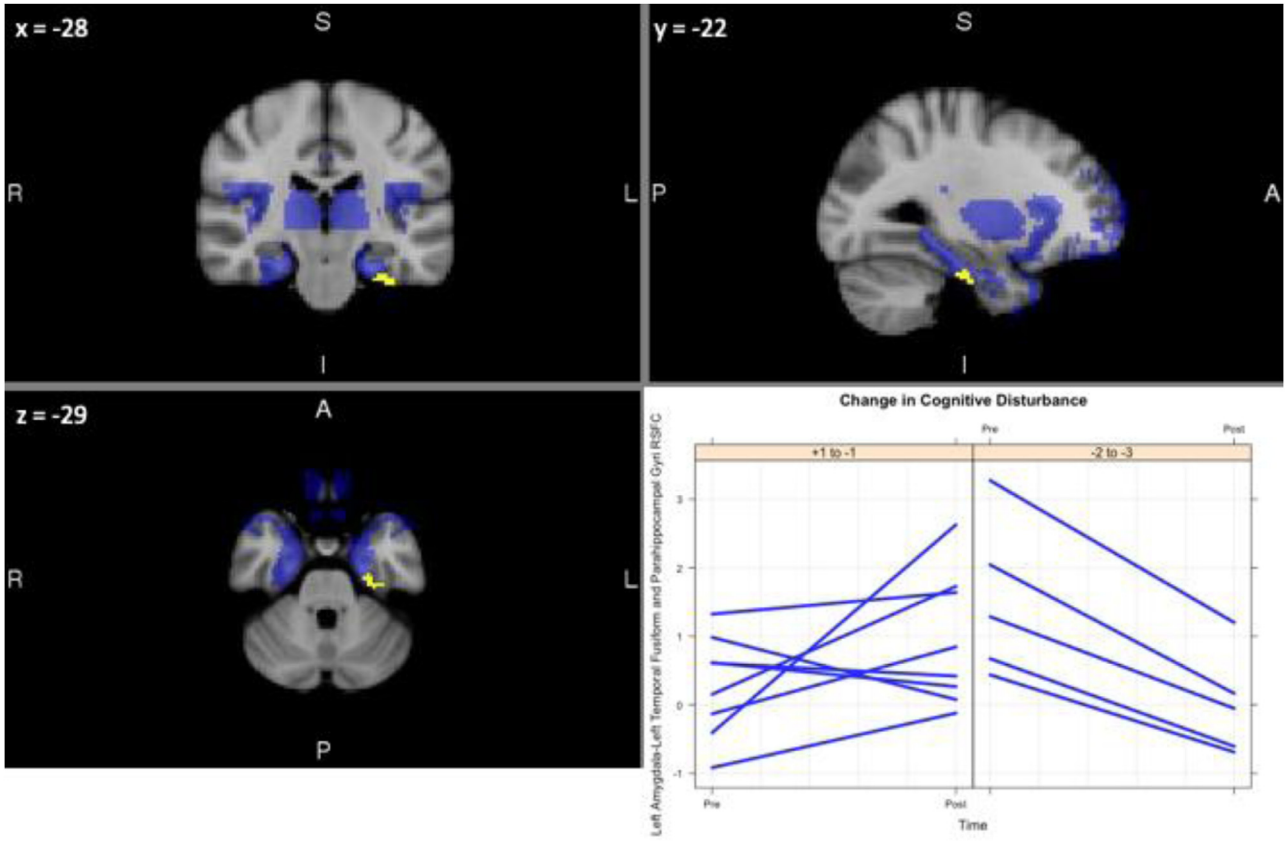

Fig. 2. The plot depicts the change in RSFC for each participant. Positive values represent an increase while negative represent a decrease in Cognitive Disturbance scores. Those who had a greater reduction in scores on the Cognitive Disturbance dimension on the ZAN-BPD scale also had a greater decrease in positive RSFC between the left amygdala and left temporal fusiform and parahippocampal gyrus (yellow). Areas shaded in blue represent the regions included in the mask. Coordinates are in MNI space and are the location of the peak voxel for each cluster. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

group membership did not impact the relationship between RSFC change and symptom dimension change.

While there has been demonstrated success in treating BPD using psychotherapy, such as dialectical behavioral therapy (DBT; Linehan, 1993), Systems Training for Emotional Predictability and Problem Solving (STEPPS; Black et al., 2004), Schema Therapy (Young et al., 2003), Object Relations (Clarkin et al., 2006), and Mentalization-based treatment (Bateman and Fonagy, 2004), many patients also require psychopharmacological intervention. However, at present, no medications have been approved by the United States Food and Drug Administration (FDA) for the treatment of BPD. Having effective medication options for BPD is valuable for those who may have limited access to qualified therapists and may provide added benefit to those also engaging in an empirically supported psychotherapy. Given the risks and personal and societal impact associated with BPD, clinicians, patients, and families need access to a full array of evidence-based, comprehensive treatment options. Thus far, research aimed at medication use in BPD has primarily focused on reducing overall BPD symptoms rather than fully appreciating the heterogeneity of the different symptom dimensions within the disorder.

Building on previous research, the present study examined the neurocircuitry associated with four key symptom dimensions of BPD: Affective Disturbance, Cognitive Disturbance, Disturbed Relationships, and Impulsivity. At baseline, higher Impulsivity scores were associated with increased RSFC between right amygdala and left hippocampus. Improvements in Cognitive Disturbance following 8 weeks of placebo or quetiapine were associated with increased positive RSFC between the left amygdala and left temporal fusiform and parahippocampal gyri. Further, greater improvement in Disturbed Relationships was associated with increased negative RSFC between the right amygdala and right frontal pole. These relationships did not differ based on whether participants were in the placebo or medication group.

The Impulsivity dimension of the ZAN-BPD includes behaviors such as self-injury and/or suicide as well as excessive drinking and high spending. At baseline, higher scores on this dimension were associated with higher right amygdala-left hippocampus RSFC. Increased functional connectivity TFC during a stress induction task between the amygdala and hippocampal/parahippocampal gyrus has been associated with emotional abuse early in life (Fan et al., 2015) and has also been found following a psychosocial stressor and during a fear conditioning paradigm (Kruse et al., 2018). Further, increased amygdala-hippocampal connectivity has been found in previous studies of BPD during both rest and during emotional stimuli (Cullen et al., 2011; Krause-Utz et al., 2017; Salvador et al., 2016). Impulsive behaviors such as self-injury and substance abuse often occur in the context of a stressor that contributes to a negative affective state (Dir et al., 2013). Relatedly, one study found increased connectivity between the amygdala and hippocampus was associated with increased trait sensitivity to aversive events, which leads to increased levels of arousal and attention (Hahn et al., 2010). Future research may benefit from investigating impulsivity specifically within the context of negative emotion (e.g. Negative Urgency). This would expand our understanding of the role of impulsivity in BPD while recognizing that these symptoms may manifest differently within certain affective states. Further, while there were no associations between change in Impulsivity and RSFC change, this may be due to the fairly limited magnitude of change pre- and post-treatment. This may be the result of having low scores on this scale to begin with, ineffectiveness of the treatment conditions in reducing

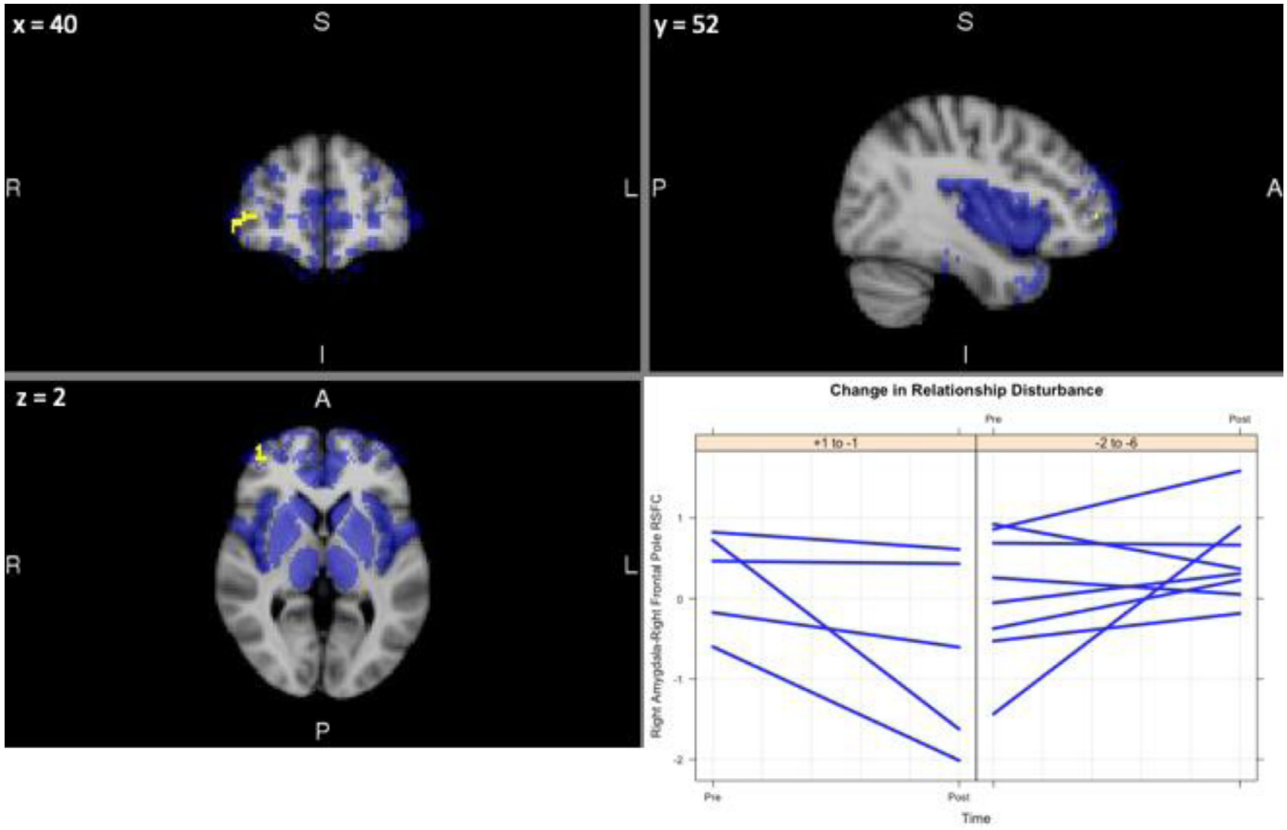

Fig. 3. The plot depicts the change in RSFC for each participant. Positive values represent an increase while negative represent a decrease in Disturbed Relationships scores. Those who had a greater reduction in scores on the Disturbed Relationships dimension on the ZAN-BPD scale also had an increase in positive RSFC between the right amygdala and right frontal pole (yellow). Areas shaded in blue represent the regions included in the mask. Coordinates are in MNI space and are the location of the peak voxel for each cluster. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

impulsivity, and our small sample size in general.

The Cognitive Disturbance dimension within the ZAN-BPD assesses the presence of the BPD symptoms of identity disturbance, paranoia, and dissociation. The present study found that those who showed greater improvement within this dimension also showed increased negative RSFC between the left amygdala and left temporal fusiform and parahippocampal gyrus. In contrast to previous work finding that dissociation within BPD was associated with lower RSFC between the amygdala and fusiform gyrus (Krause-Utz et al., 2017), we did not find an association between these two constructs at baseline. As illustrated in Fig. 2, we instead found that a reduction in Cognitive Disturbance (which includes dissociation) appeared to be associated in a decrease of RSFC between these regions. This is more consistent with studies that have found increased amygdala connectivity with temporal fusiform and parahippocampal gyri in response to emotional faces in patients with social anxiety disorder and among adolescents and young adults with NSSI (Frick et al., 2013; Westlund Schreiner et al., 2017). While it is possible that the inclusion of other symptoms in addition to dissociation within our measure may obscure our interpretation and explain our disparate findings compared to those of Krause-Utz and colleagues, these findings provide support for the continued exploration of the role of this circuit in dissociative symptoms.

The Disturbed Relationships dimension includes avoidance of abandonment and intense and unstable relationships. Improvement in this symptom dimension was associated with increased positive RSFC between the right amygdala and right frontal pole. While this is consistent with previous research finding increased amygdala-frontal connectivity following neurofeedback training in both healthy controls and in BPD patients (Paret et al., 2016a,b), it is unclear how this specifically relates to interpersonal relationships. It is possible that the difficulties in interpersonal relationships may be a significant source of distress among those with BPD and lead to exacerbation of other symptoms.

4.1. Limitations

Similar to previous work, the most significant limitation of the present study is its small sample size. Thus, despite having three different treatment groups (placebo, 150 mg quetiapine, and 300 mg quetiapine), we were unable to fully examine the role of this particular treatment on symptom improvement or RSFC change. However, this may also be beneficial as findings regarding symptom change may be generalized to other types of intervention rather than restricted to quetiapine. Similarly, our sample size in addition to the uneven number of male versus female participants limited our ability to examine the effect of gender on our analyses.

We also want to acknowledge that while we found significant associations between change in RSFC and change in symptom dimensions, the number of participants who showed greater change is limited. This is particularly the case for our finding showing an association between RSFC change and disturbed relationships change. As illustrated in Fig. 3, there are few participants who showed a substantial increase in RSFC over time. Thus, this finding warrants additional caution with regard to drawing meaningful conclusions.

4.2. Conclusions

BPD has often been conceptualized as being difficult to treat, particularly when considering medication options. However, much of the existing research has focused on the disorder as a whole rather than seeking to better understand its heterogeneity. This preliminary study

found evidence for differing patterns of amygdala connectivity at rest for different symptom domains, particularly Impulsivity, Cognitive Disturbance, and Disturbed Relationships. By understanding how different symptoms and their improvement are associated with brain functioning, we may be able to more effectively select interventions that target these deficits.

CRediT authorship contribution statement

Melinda Westlund Schreiner: Data curation, Formal analysis, Methodology, Validation, Writing - original draft, Writing - review & editing. **Bonnie Klimes-Dougan:** Writing - review & editing. **Bryon A. Mueller:** Writing - review & editing, Conceptualization, Resources, Supervision, Validation, Methodology, Data curation, Formal analysis. **Katharine J. Nelson:** Writing - review & editing. **Kelvin O. Lim:** Writing - review & editing, Conceptualization, Resources. **Kathryn R. Cullen:** Writing - review & editing, Conceptualization, Resources, Supervision, Validation, Methodology, Data curation, Formal analysis.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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