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Amygdala Resting State Connectivity Differences between Bipolar II and Borderline Personality Disorders

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Amygdala · Bipolar disorder · Borderline personality disorder · Corticolimbic functioning · Neuroimaging

Abstract
Background: Borderline personality disorder (BPD) and bipolar II disorder (BD II) have significant clinical overlap, leaving the potential for diagnostic inaccuracies and inadequate treatment recommendations. However, few studies have probed for clinical and neurobiological differences between the two disorders. Clinically, some prior studies have linked BPD with greater impulsivity and more frequent negative affective shifts than BD II, whereas previous neuroimaging studies have highlighted both similar and distinct neural abnormalities in BPD and BD II. Notably, no prior study has specifically targeted cortico-limbic neural differences, which have been hypothesized to underlie these core clinical differences. ***Methods:*** Individuals with BPD (n = 14) and BD II (n = 15) completed various clinical measures and a resting state functional imaging scan at 3T. Whole-brain amygdala resting state functional connectivity (RSFC) was compared between the two groups. ***Results:*** Relative to the BD II group, BPD participants reported significantly higher levels of impulsivity, trait anxiety, more frequent negative affective shifts, greater interpersonally reactive affective instability, lower overall functioning, and were characterized by lower amygdala-middle frontal gyrus RSFC. Lower amygdala-middle frontal gyrus RSFC was associated with greater impulsivity, trait anxiety, affective shifts, interpersonal affective reactivity, and functional impairment. ***Limitations:*** The current study consisted of small sample sizes and lacked a control group. ***Conclusions:*** This preliminary study suggests that amygdala-frontal RSFC may distinguish BPD from BD II. These results may guide future work aimed at identifying neural markers that can help disentangle these two disorders, leading to greater diagnostic accuracy and appropriate treatment implementation.

Introduction

The relationship between borderline personality disorder (BPD) and bipolar II disorder (BD II) remains the subject of debate [1]. Some researchers have suggested that there is significant overlap between the two disorders

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[2], whereas others have asserted that they have distinctly different clinical phenomenologies, courses, etiologies, and responses to treatment [3]. Highlighting such differences, these researchers have emphasized that inaccurately diagnosing borderline patients with bipolar disorder may lead to unnecessary and ineffective treatment with pharmacotherapy and may prevent borderline patients from receiving appropriate psychotherapeutic treatments.

Regarding potential differences in the clinical phenomenology of BPD versus BD II, BPD has been associated with higher levels of impulsivity compared to BD II [4], and affective instability in BPD has been found to be both qualitatively and quantitatively different from that in BD II [5, 6]. In particular, BD II patients may experience more intense positive affect, whereas BPD patients may have more frequent negative affective shifts as well as overall greater self-reported maladaptive emotion regulation strategies [5–7]. Additionally, BPD patients report more interpersonally reactive affective instability compared to those with BD II [6]. This suggests that those with BPD may demonstrate greater impairments in self-regulation compared to those with BD II, which may also be reflected by distinct neural substrates.

The neural signatures of these self-regulation deficits likely involve aberrant functioning of corticolimbic neural circuits, as higher levels of impulsivity and difficulties with regulating negative emotions have been associated with weaker amygdala-prefrontal functional connectivity [8–10]. These circuits are also consistently implicated in both BPD and BD II. Specifically, a meta-analysis found that individuals with BPD show stronger amygdala responses and less recruitment of the dorsolateral prefrontal cortex when processing negative emotional information compared to healthy controls [11]. Most studies examining the neural correlates of aberrant emotion processing in BD have focused on BD I or combined BD I and BD II groups. However, a study exclusively targeting BD II found that, relative to healthy controls, BD II participants in a depressed state showed blunted amygdala-ventrolateral prefrontal cortex, amygdala-orbitofrontal cortex, and amygdala-dorsolateral prefrontal cortex functional connectivity during an emotion processing task [12].

Despite the clinical significance of being able to accurately diagnose BPD versus BD II, which can often be difficult due to the common overlap in clinical presentation, very few studies have directly compared similarities and differences in neural functioning between these two disorders. One study comparing the two disorders using an emotional Stroop task found that both BD (bipolar subtype was not specified) and BPD groups exhibited decreased dorsolateral prefrontal cortex activity and increased ventral lateral prefrontal cortex activity compared to healthy controls. However, the two clinical groups also demonstrated differences, with the BD group showing greater dorsomedial prefrontal cortex activity versus the BPD group, and the BPD group showing less amygdala activity versus the BD group [13]. Together, these studies suggest that both BD II and BPD are characterized by impaired corticolimbic functioning during processing of negative emotional information and that these disorders may have both overlapping and distinct patterns of corticolimbic dysregulation.

While differences in the types of task and stimuli used to probe emotion processing deficits in these two disorders may lead to heterogeneous results, researchers have circumvented these issues by using resting state functional magnetic resonance imaging (fMRI) to examine corticolimbic functioning. This allows for the examination of pervasive corticolimbic alterations that may be independent of symptom provocation. Resting state studies comparing individuals with BPD versus healthy controls have found that individuals with BPD show lower amygdala-medial prefrontal cortex, amygdala-ventral anterior cingulate cortex, and amygdala-orbitofrontal cortex resting state functional connectivity (RSFC) [8, 14]. One of these studies also found that lower amygdala-medial prefrontal cortex RSFC was associated with higher levels of self-reported impulsivity and emotion dysregulation [14]. However, others have failed to find reduced amygdala-medial prefrontal cortex RSFC in BPD [15], and one study has reported *increased* connectivity between the amygdala and anterior cingulate cortex [16].

With respect to BD II, mirroring the task-based fMRI literature, most resting state studies have focused on BP I disorder exclusively or combined BP I and BD II disorder groups, despite documented clinical and neurobiological differences between the two disorder subtypes (e.g., [17, 18]). Of the few studies focusing on BD II disorder, one study specifically probing amygdala RSFC failed to find amygdala-prefrontal RSFC differences compared to healthy controls [19], while other studies have targeted other large-scale networks outside of the amygdala [20–22]. Specifically, these studies have found that individuals with BD II show greater temporo-insular network connectivity, but decreased cerebellar-central executive network connectivity [20], cerebellar-default mode network connectivity [22], and medial prefrontal voxel-mirrored homotopic connectivity [21]. To date, only one RSFC

study has compared individuals with BPD versus BD disorder, and found that individuals with BD (bipolar subtype was not specified) showed increased connectivity between a number of large networks compared to those with BPD, including social salience (dorsal anterior cingula cortex, anterior insula)-frontoparietal (dorsolateral prefrontal cortex, lateral parietal cortex) networks, social salience-precuneus networks, social salience-ventromedial prefrontal cortex networks, and default mode (medial prefrontal cortex, posterior cingulate cortex)-precuneus networks [23]. However, this study did not assess group differences in amygdala-based networks.

Given the sparse number of studies directly comparing BPD versus BD II disorder, the goal of this study was to replicate and extend prior work by assessing differences in clinical phenomenology as well as probing potential group differences in amygdala RSFC. Prior work has shown that individuals with BPD exhibit greater levels of impulsivity and have more frequent affective shifts [4–6], and disruptions in corticolimbic neural circuits have been demonstrated to underlie these deficits [8–10]. Thus, we hypothesized that individuals with BPD would show weaker amygdala-frontal cortex RSFC compared to the BD II group. Additionally, we predicted that symptomatology characteristic of BPD (e.g., greater impulsivity) would correlate with reduced amygdala-frontal cortex RSFC.

Methods

Participants and Procedures

Participants were 29 females aged between 18 and 45 years, assessed as part of an fMRI study examining neural correlates of affective instability in BPD and BD II. Participants were recruited through Craig's List and referrals from clinicians affiliated with McLean Hospital. After providing informed written consent to a protocol approved by the Partners Health Care IRB, participants were evaluated using the Revised Diagnostic Interview for Borderlines (DIB-R) [24], the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV) [25], and the Structured Clinical Interview for DSM-IV Disorders (SCID-IV) [26]. To be eligible for the study, BD II participants had to meet criteria for BD II disorder as assessed by the bipolar module of the SCID-IV, and BPD participants had to have a DIB-R score of ≥8 and meet DSM-IV criteria for BPD. Exclusion criteria included: (1) lifetime diagnosis of organic mental disorder or psychotic disorder (schizophrenia, schizoaffective disorder, or mood disorder with psychotic features); (2) diagnosis of substance dependence or alcohol dependence; (3) current alcohol use exceeding 14 drinks per week and/or binge alcohol use; (4) substance abuse within the last 6 months; and (5) meeting diagnostic criteria for both BPD and BD. After establishing study eligibility during a screening session, participants were invited for a separate imaging session, which took place at the McLean Imaging Center.

Demographic and Clinical Measures

Prior to completing neuroimaging, participants were assessed with a series of clinical instruments, including the Affective Lability Interview for Borderline Personality Disorder (ALI-BPD), the Impulsivity-Venturesomeness-Empathy Questionnaire (IVE Questionnaire), the Barratt Impulsivity Scale (BIS-II), the Beck Depression Inventory (BDI-II), the Montgomery-Asberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), and the Spielberger State-Trait Anxiety Inventory (STAI). In addition, study staff provided a Global Assessment of Functioning (GAF) score for each participant [27] and rated the socioeconomic status of each subject using the Hollingshead-Redlich Scale [28]. The ALI-BPD is a 9-item clinician-administered instrument designed to measure different dimensions of affective instability over the last week and has been shown to differentiate BPD from BD [5]. The instrument asks the interviewer to rate affective changes in each dimension in terms of both frequency and intensity, including the percentage of affective changes that are interpersonally reactive on a 5-point scale ranging from 0 (0–10% of the time) to 4 (90–100% of the time). The IVE Questionnaire is a 63-item self-report questionnaire that provides discrete measures of impulsivity, venturesomeness, and empathy [29]. The BIS-II is a 45-item self-report measure that is commonly used to measure impulsivity which includes 3 subscales: Cognitive Impulsivity, Motor Impulsivity, and Non-Planning Impulsivity [30]. The BDI-II is a 21-item self-report measure that assesses depression severity over the last 2 weeks. It has been widely used to measure depression in both clinical and non-clinical samples [31]. The MADRS is a 10-item clinician-rated scale that assesses a range of depressive symptoms and has shown to be an efficient and practical measure of depression [32]. The YMRS is an 11-item clinician administered measure of manic symptom severity [33]. The STAI is a self-report measure widely used to measure anxiety in adults; it includes two 20-item scales, one measuring the more temporary condition of "state" anxiety and the other measuring the more general and long-standing quality of "trait" anxiety [34].

Imaging Acquisition

Each participant completed a 6 min and 47 s resting state scan. Imaging datasets were acquired on a Siemens Tim Trio 3.0 Tesla MRI scanner with a 32-channel head coil. Resting state functional data were acquired using a T2*-weighted gradient-echo, echoplanar pulse sequence. We collected 41 contiguous coronal slices (TR = 2.5 s, TE = 30 ms; FOV = 224 × 224 mm, matrix = 64 × 64, slice thickness = 3.5 mm). A high-resolution T1-weighted anatomical image was also collected and served as an anatomical map for the functional images (TR = 20 s, TE = 2.15 ms, FOV = 240 mm; matrix = 166 × 256 mm; flip angle = 12, slice thickness = 1.3 mm).

fMRI Analysis

The first 5 of each participant's resting state functional data were dropped to allow for magnetic field stabilization. The resting state functional data were preprocessed in SPM12, according to the following steps: slice-time correction, realignment, normalization to Montreal Neurological Institute (MNI) space and resampling to 2 × 2 × 2 mm voxels and smoothing with a 6-mm kernel. The artifact detection tool box was used to identify outlier data points, which were defined as volumes that exceeded a global mean intensity of 3 SDs away from the mean intensity across functional runs, or a composite threshold of 0.5 mm framewise displacement.

Table 1. Demographic and clinical variables

Variable	BD II	BPD	*p* value
Age, years, mean ± SD	28.13±7.19	26.43±6.65	0.40
SES, mean ± SD	2.20±0.676	2.43±1.22	0.89
GAF, mean ± SD	57.93±4.30	51.71±3.93	<0.001
Education, mean ± SD	15.79±1.25	14.93±1.77	0.71
Treatment, % (*n*)			
Ever psychiatrically hospitalized	13.3 (2)	64.3 (9)	<0.01
Ever therapy	100 (15)	92.9 (12)	0.13
Current medication, % (*n*)			
Stimulant	13.3 (2)	21.4 (3)	0.94
Antidepressant	26.6 (4)	57.1 (8)	0.10
Mood stabilizer	53.3 (8)	35.7 (5)	0.34
Antipsychotic	6.7 (1)	0 (0)	0.33
Anxiolytic	13.3 (2)	14.2 (2)	0.94

Additional pre-processing steps and whole-brain RSFC analyses were conducted using the CONN toolbox [35]. Physiological noise from white matter and cerebrospinal fluid was estimated and regressed out for each participant using the CompCor method [36]. In a first-level general regression model, detrending, modeling of outlier images along with the 3 translation and 3 rotation parameters, plus one composite motion parameter indexing the maximum scan-to-scan movement and the ComCor corrections, were conducted simultaneously. Next, a temporal band-pass filter of 0.008–0.09 Hz was applied to the time series. The time series was extracted from a right and left amygdala seed region. The amygdala seed regions were taken from the Harvard-Oxford maximum likelihood probabilistic atlas provided in the CONN toolbox [37–39]. The time series of the left and right amygdala were separately correlated with each voxel in the brain. The whole-brain correlation maps (r) were subsequently normalized using a Fisher's z transformation. Finally, these normalized correlation maps were used to calculate all group-level statistics.

Statistics

Wilcoxon rank-sum tests or χ^2 analyses were used to evaluate potential between-group baseline demographic variables, clinical history variables, and clinical scales, including in: (1) mean YMSRS scores; (2) mean MADRS scores; (3) mean STAI-State Anxiety and STAI-Trait Anxiety scores; (4) mean scores on the impulsivity, venturesomeness, and empathy scales of the IVE Questionnaire; (5) mean overall and individual subscale scores of the BIS-11; and (6) ALI borderline frequency and intensity subscale scores and scores on the ALI item measuring reactivity of mood. Cohen's d values were computed to evaluate effect sizes of putative group differences. With respect to the imaging analyses, two independent sample t tests were conducted to compare differences between the group with BPD versus the BD II group on right and left amygdala – whole-brain RSFC. All RSFC results were considered significant if they passed a voxel threshold $p < 0.005$ cluster corrected to a family-wise error rate of $p < 0.05$. Additionally, we conducted correlations between group differences in amygdala RSFC and clinical measures.

Results

Demographics and Clinical Characteristics

Fourteen participants met study criteria for BPD and 15 participants met study criteria for BD II. A participant from the BPD group was dropped from all imaging analyses due to a brain abnormality. Table 1 summarizes demographic and clinical characteristics for each study group. There were no significant differences between groups with respect to age, education, or socioeconomic status. The BD II group had a significantly higher GAF score than the BPD group, but both groups had mean scores within the range specifying "moderate symptoms" or "moderate impairments in social, occupational, or school functioning." Several participants in each group were taking psychiatric medications (stimulants, antidepressants, mood stabilizers, or anxiolytics), but the groups did not differ with respect to medication usage. Significantly more participants in the BPD group had a history of psychiatric hospitalization (64.3 vs. 13.3%, $\chi^2 = 9.12$, $p < 0.01$). For the BPD group, past history of major depression ($n = 1$), post-traumatic stress disorder ($n = 1$), eating disorder ($n = 1$), panic disorder without agoraphobia ($n = 1$), and panic disorder with agoraphobia ($n = 2$) were reported. In the BD II group, past history of obsessive-compulsive disorder ($n = 1$), eating disorder NOS ($n = 1$), binge eating disorder ($n = 1$), body dysmorphic disorder ($n = 1$), and agoraphobia without panic ($n = 1$) were reported.

Clinical Measures

As detailed in Table 2, significant group differences were found on the IVE-Impulsiveness subscale, the STAI-Trait Anxiety, ALI-Frequency subscale, the ALI-Reactivity subscale, and GAF scores. Mean scores on the impulsivity scale of the IVE were almost twice as high for subjects with BPD compared to subjects with BD II (14.3 vs. 8.7; $p = 0.001$; Cohen's d value: 1.47). Additionally, individuals with BPD reported ~18% higher trait anxiety levels (STAI-Trait Anxiety) compared to those with BD II (57.5 vs. 47.9; $p = 0.014$; Cohen's d value: 1.00). Moreover, those with BPD endorsed ~39% more frequent affective shifts (ALI-Frequency; 8.2 vs. 5.5; $p = 0.03$; Cohen's d value: 0.70) and reported twice as high interpersonal affective reactivity (ALI-Reactivity; 2.5 vs. 1.3; $p = 0.006$; Cohen's d value: 1.05). There was also a non-significant trend for individuals with BPD to report more severe depressive symptoms (BDI-II, $p = 0.08$, Cohen's d value: −0.74). However, there were no significant group differences on the YMRS, MADRS, HAM-A, STAI-State Anx-

Table 2. Clinical phenomenology scores in BD II and BPD subjects

Variable	BD II	BPD	*Z*-score	*p* value	Cohen's *d*
YMRS, mean ± SD	2.5±2.2	2.4±1.9	0.13	0.91	0.09
MADRS, mean ± SD	9.0±5.8	12.2±10.2	0.62	0.56	–0.40
Beck Depression Inventory II, mean ± SD	14.3±8.9	22.9±13.9	1.73	0.08	–0.74
State Trait Anxiety Scale-1, mean ± SD	36.8±9.7	42.6±13.0	1.29	0.20	–0.51
State Trait Anxiety Scale-2, mean ± SD	47.9±10.6	57.5±8.5	2.43	0.014	–1.00
ALI Borderline Frequency Scale, mean ± SD	5.5±3.8	8.2±3.9	2.12	0.03	–0.70
ALI Borderline Intensity Scale, mean ± SD	6.2±3.9	6.9±3.2	0.99	0.29	–0.20
ALI Reactivity Item, mean ± SD	1.3±1.0	2.5±1.1	2.83	0.006	–1.20
IVE Impulsivity Scale, mean ± SD	8.7±3.8	14.3±3.7	3.31	0.001	–1.53
IVE Venturesomeness Scale, mean ± SD	9.7±3.2	10.2±3.5	0.29	0.35	–0.14
IVE Empathy Scale, mean ± SD	13.3±3.7	13.9±3.9	0.79	0.34	–0.16
BIS-11 Total, mean ± SD	69.7±12.9	75.6±12.8	0.85	0.11	–0.46
BIS-11 Attention, mean ± SD	18.5±3.9	19.9±4.1	0.61	0.18	–0.35
BIS-11 Motor, mean ± SD	23.3±5.8	25.1±6.0	0.79	0.21	–0.31
BIS 11 Non-planning score, mean ± SD	27.9±5.4	30.6±5.3	1.46	0.09	–0.51

iety, BIS-II, IVE-Empathy, IVE-Venturesomeness, and ALI-Intensity scales.

Finally, owing to the fact that the mean GAF score was significantly higher for the BD II group relative to the BPD group, four separate hierarchical regression analyses were run to test whether the factor group (dummy coded) predicted STAI-Trait Anxiety, ALI borderline frequency subscale, ALI reactivity scores, and IVE impulsivity when accounting for GAF scores. To this end, GAF scores were entered in the first step, followed by group (dummy coded) in the second steps. For the STAI-Trait Anxiety ($\Delta R^2 = 0.229$, $\Delta F[1.26] = 7.91$, $p < 0.0090$), ALI reactivity ($\Delta R^2 = 0.145$, $\Delta F[1.26] = 5.27$, $p < 0.030$), and IVE impulsivity measures ($\Delta R^2 = 0.214$, $\Delta F[1.26] = 9.08$, $p < 0.006$), the adjusted group difference was significant. For the ALI borderline frequency subscale, the adjusted group difference failed to reach significance ($\Delta R^2 = 0.114$, $\Delta F[1.26] = 3.34$, $p = 0.077$).

Group-Level fMRI Results

Relative to the BD II group, BPD participants showed lower right amygdala-right middle frontal gyrus connectivity (54, 24, 28, 306 voxels, $Z = 4.04$, FWE $p = 0.000045$; Cohen's d value = 3.47) and right amygdala-left middle frontal gyrus (–44, 10, 32, 132 voxels, $Z = 4.03$, $p = 0.032$; Cohen's d value = 2.25; Fig. 1). There were no other significant group differences in right amygdala whole-brain connectivity and there were no significant group differences in left amygdala whole-brain connectivity. Given that there were significant group differences in GAF, STAI-Trait Anxiety, ALI frequency, ALI reactivity, and IVE-Impulsiveness, we conducted two follow-up hierarchical regression analyses to test whether the factor group (dummy coded) predicted right amygdala-right middle frontal gyrus and right amygdala-left middle frontal gyrus RSFC when accounting for these clinical differences. The clinical measures were entered in a first step, followed by group in the second step. Group differences in right amygdala – right middle frontal gyrus RSFC ($\Delta R^2 = 0.292$, $\Delta F = [1.21] = 31.54$, $p < 0.001$) and right amygdala – left middle frontal gyrus RSFC ($\Delta R^2 = 0.450$, $\Delta F = [1.21] = 33.07$, $p < 0.001$) remained significant even after controlling for clinical differences.

Correlations between RSFC and Clinical Measures

Given that there were group differences in ALI-Frequency, ALI-Reactivity, and IVE-Impulsiveness, STAI-Trait Anxiety, GAF, and amygdala-middle frontal gyrus RSFC, we examined whether individual differences in these clinical measures and amygdala-middle frontal gyrus RSFC were correlated (Fig. 2). Across the BPD and BP-II groups, decreased right amygdala-middle frontal gyrus RSFC was associated with greater levels of impulsivity ($r = –0.54$, $p = 0.003$, Pearson's correlation), interpersonal affective reactivity (*Rho* = –0.59, $p = 0.001$, Spearman's correlation), and trait anxiety ($r = –0.54$, $p = 0.003$, Pearson's correlation) as well as lower overall general functioning ($r = 0.46$, $p = 0.01$, Pearson's correlation). There was a non-significant trend with decreased right amygdala-right middle frontal gyrus RSFC also being associated with more frequent affective shifts ($r = –0.37$, $p = 0.05$, Pearson's correlation). Additionally, decreased

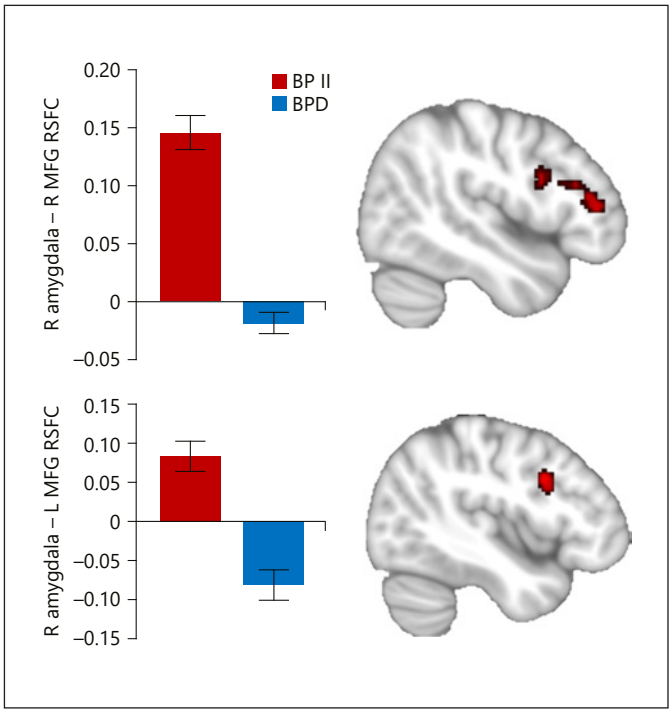

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Fig. 1. Individuals with BP II showed greater right (R) amygdala – right MFG connectivity and right amygdala – left MFG compared to those with BPD. BP II, bipolar II disorder; BPD, borderline personality disorder; MFG, middle frontal gyrus.

right amygdala-left middle frontal gyrus RSFC was associated with increased interpersonal affective reactivity (*Rho* = –0.49, $p = 0.008$, Spearman's correlation). Associations between right amygdala-right middle frontal gyrus and impulsivity, interpersonal affective reactivity, as well as trait anxiety survived Bonferroni correction for multiple comparisons (10 tests, corrected $p < 0.005$). All other correlations did not survive multiple comparison corrections.

Discussion

Our primary aim was to extend the limited studies comparing the clinical phenomenology and underlying neurobiology of BPD versus BD II. Consistent with prior work [4–6], we found that individuals with BPD reported higher levels of impulsivity, more interpersonally reactive affective instability, and more frequent affective shifts. Additionally, we found that individuals with BPD reported higher levels of trait anxiety compared to the BD II group. While no prior studies have specifically compared trait anxiety differences between the two groups, one study reported that having a BPD diagnosis was associated with higher levels of anxiety-related symptoms on the Hamilton Rating Scale for Depression compared to having just a BD II diagnosis [40]. Notably, all clinical phenomenological differences between the two disorders survived when controlling for group differences in GAF scores, except for frequency of affective shifts, which dropped to a trend level.

With respect to the neuroimaging results, the BPD group showed weaker amygdala-middle frontal gyrus RSFC compared to the BD II group. Additionally, decreased amygdala-middle frontal gyrus was associated with higher levels of impulsivity, interpersonal affective reactivity, and trait anxiety, as well as lower overall general functioning. These group differences in amygdala RSFC also survived when accounting for differences in clinical self-report measures and GAF scores, indicating that the weaker fronto-limbic connectivity was not just an epiphenomenon of group differences in clinical profile (or stated differently, the imaging data had incremental predictive validity). These results are consistent with prior work in clinical and non-clinical populations showing that weaker amygdala-frontal cortex connectivity is associated with higher levels of impulsivity and greater self-reported difficulties in regulating negative emotions [8–10]. These findings are also consistent with reports (including from the current sample) that individuals with BPD are characterized by greater impulsivity and more difficulties with emotion regulation [4, 7]. Given the clinical differences between these disorders and studies demonstrating that corticolimbic deficits underlie these clinical facets, it is likely that they may be characterized by weaker amygdala-frontal cortex RSFC in BPD versus BD II.

However, results of the current study must be interpreted within the context of several limitations. First, the study was designed as a pilot study and thus represents an initial investigation of RSFC differences between the two clinical groups; accordingly, sample sizes were small and the design did not include a healthy control group. Second, most participants in both study groups were taking psychiatric medication, including mood stabilizers and anxiolytics. In order to ensure ecological validity, we intentionally did not exclude participants taking psychiatric medications. Third, each study group contained some comorbidity, which could potentially have influenced between-group comparisons. Fourth, with respect to the clinical phenomenological differences, we did not correct for multiple comparisons. Despite these limitations,

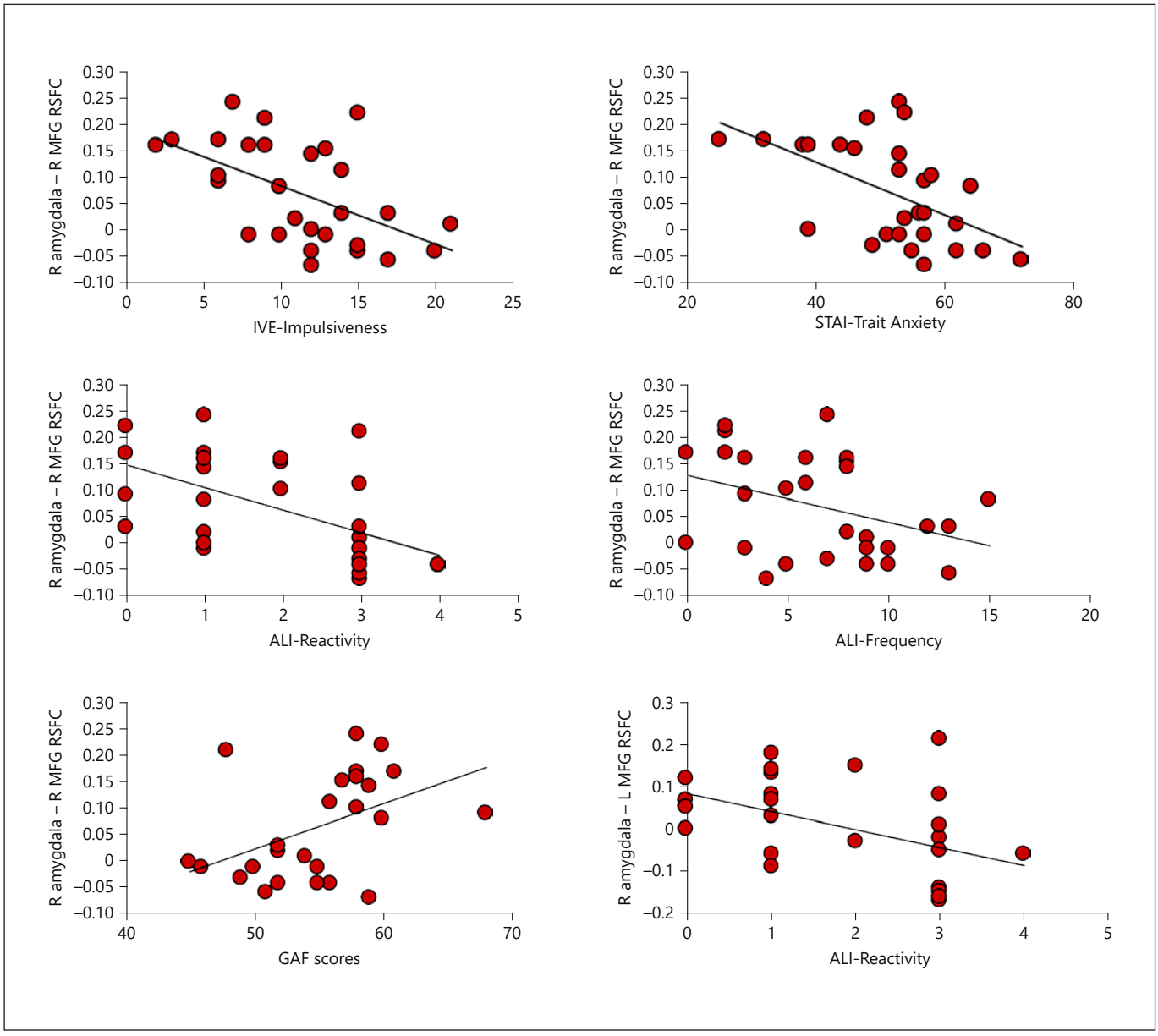

Fig. 2. Across the BP II and BPD groups, decreased right (R) amygdala – right MFG was associated with increased impulsivity (IVE-Impulsiveness), trait anxiety (STAI-Trait Anxiety Inventory), affective shifts (ALI-Frequency, Affective Lability Interview), and interpersonal affective reactivity (ALI-Reactivity), but decreased GAF. Additionally, decreased right (R) amygdala – left MFG was linked to higher interpersonally affective reactivity (ALI-Reactivity). BP II, bipolar II disorder; BPD, borderline personality disorder; MFG, middle frontal gyrus; GAF, global assessment of functioning.

study findings provide a preliminary examination of potential amygdala-based RSFC differences, which may guide future studies aiming to differentiate the two disorders to ensure more timely and accurate clinical diagnoses and subsequent implementation of appropriate treatments.

Statement of Ethics

All subjects in this study provided written informed consent. The study protocol was approved by the Partners Health Care Institutional Review Board.

Disclosure Statement

Over the past 3 years, D.A.P. has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Posit Science, and Takeda and an honorarium from Alkermes for activities unrelated to the current study. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. All other authors report no biomedical financial interests.

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Author Contributions

As the principal investigator of the study Dr. D. Bradford Reich generated the initial proposal for the study. He recruited all subjects for the study, performed all diagnostic assessments, assisted in analysis of study data, and co-authored the study manuscript. Dr. Emily L. Belleau performed the analysis of all imaging data and co-authored the study manuscript. Dr. Christina M. Temes performed the analysis of study clinical data. Dr. Atilla Gonenc participated in analysis of all imaging data. Dr. Staci A. Gruber supervised the collection of all clinical measures for subjects, supervised administration of neuroimaging, and contributed to the study design. In addition, she participated in revisions of the study manuscript. Dr. Diego A. Pizzagalli performed oversight of administration of the study and analysis of all study data. In addition, he participated in revisions of the study manuscript.

References

1 Coulston CM, Tanious M, Mulder RT, Porter RJ, Malhi GS. Bordering on bipolar: the overlap between borderline personality and bipolarity. Aust N Z J Psychiatry. 2012 Jun;46(6):506–21. Available from: https://doi.org/10.1177%2F0004867412445528

2 Perugi G, Hantouche E, Vannucchi G, Pinto O. Cyclothymia reloaded: A reappraisal of the most misconceived affective disorder. J Affect Disord. 2015 Sep;183:119–33.

3 Paris J, Black DW. Borderline personality disorder and bipolar disorder: what is the difference and why does it matter? J Nerv Ment Dis. 2015 Jan;203(1):3–7.

4 Bøen E, Hummelen B, Elvsåshagen T, Boye B, Andersson S, Karterud S, et al. Different impulsivity profiles in borderline personality disorder and bipolar II disorder. J Affect Disord. 2015 Jan;170:104–11.

5 Reich DB, Zanarini MC, Fitzmaurice GM. Affective lability in bipolar disorder and borderline personality disorder. Compr Psychiatry. 2012 Apr;53(3):230–7.

6 Reich DB, Zanarini MC, Hopwood CJ, Thomas KM, Fitzmaurice GM. Comparison of affective instability in borderline personality disorder and bipolar disorder using a self-report measure. Personal Ment Health. 2014 May;8(2):143–50.

7 Bayes A, Parker G, McClure G. Emotional dysregulation in those with bipolar disorder, borderline personality disorder and their comorbid expression. J Affect Disord. 2016 Nov 1;204:103–11.

8 Baczkowski BM, van Zutphen L, Siep N, Jacob GA, Domes G, Maier S, et al. Deficient amygdala-prefrontal intrinsic connectivity after effortful emotion regulation in borderline personality disorder. Eur Arch Psychiatry Clin Neurosci. 2017 Sep;267(6):551–65.

9 Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan KL. Amygdala-frontal connectivity during emotion regulation. Soc Cogn Affect Neurosci. 2007 Dec;2(4):303–12.

10 Coccaro EF, Sripada CS, Yanowitch RN, Phan KL. Corticolimbic function in impulsive aggressive behavior. Biol Psychiatry. 2011 Jun 15;69(12):1153-9.

11 Schulze L, Schmahl C, Niedtfeld I. Neural correlates of disturbed emotion processing in borderline personality disorder: A multimodal meta-analysis. Biol Psychiatry. 2016 Jan;79(2):97–106.

12 Vizueta N, Rudie JD, Townsend JD, Torrisi S, Moody TD, Bookheimer SY, et al. Regional fMRI hypoactivation and altered functional connectivity during emotion processing in nonmedicated depressed patients with bipolar II disorder. Am J Psychiatry. 2012 Aug;169(8):831–40.

13 Malhi GS, Tanious M, Fritz K, Coulston CM, Bargh DM, Phan KL, et al. Differential engagement of the fronto-limbic network during emotion processing distinguishes bipolar and borderline personality disorder. Mol Psychiatry. 2013 Dec;18(12):1247–8.

14 Balducci T, Gonzalez-Olivera JJ, Angeles-Valdez D, Espinoza-Luna I, Garza-Villarreal EA. Borderline personality disorder with cocaine dependence: Impulsivity, emotion dysregulation and amygdala functional connectivity. Front Psychiatry. 2018;9:328.

15 Krause-Utz A, Veer IM, Rombouts SA, Bohus M, Schmahl C, Elzinga BM. Amygdala and anterior cingulate resting-state functional connectivity in borderline personality disorder patients with a history of interpersonal trauma. Psychol Med. 2014 Oct;44(13):2889–901.

16 Salvador R, Vega D, Pascual JC, Marco J, Canales-Rodríguez EJ, Aguilar S, et al. Converging medial frontal resting state and diffusion-based abnormalities in borderline personality disorder. Biol Psychiatry. 2016 Jan;79(2):107–16.

17 Baek JH, Park DY, Choi J, Kim JS, Choi JS, Ha K, et al. Differences between bipolar I and bipolar II disorders in clinical features, comorbidity, and family history. J Affect Disord. 2011 Jun;131(1-3):59–67.

18 Caseras X, Murphy K, Lawrence NS, Fuentes-Claramonte P, Watts J, Jones DK, et al. Emotion regulation deficits in euthymic bipolar I versus bipolar II disorder: a functional and diffusion-tensor imaging study. Bipolar Disord. 2015 Aug;17(5):461–70.

19 Gong J, Chen G, Jia Y, Zhong S, Zhao L, Luo X, et al. Disrupted functional connectivity within the default mode network and salience network in unmedicated bipolar II disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2019 Jan;88:11–8.

20 Yip SW, Mackay CE, Goodwin GM. Increased temporo-insular engagement in unmedicated bipolar II disorder: an exploratory resting state study using independent component analysis. Bipolar Disord. 2014 Nov;16(7):748–55.

21 Wang Y, Zhong S, Jia Y, Zhou Z, Zhou Q, Huang L. Reduced interhemispheric resting-state functional connectivity in unmedicated bipolar II disorder. Acta Psychiatr Scand. 2015 Nov;132(5):400–7.

22 Luo X, Chen G, Jia Y, Gong J, Qiu S, Zhong S, et al. Disrupted cerebellar connectivity with the central executive network and the default-mode network in unmedicated bipolar II disorder. Front Psychiatry. 2018 Dec;9:705.

23 Das P, Calhoun V, Malhi GS. Bipolar and borderline patients display differential patterns of functional connectivity among resting state networks. Neuroimage. 2014 Sep;98:73–81.

24 Zanarini MC, Gunderson JG, Frankenburg FR, Chauncey DL. The Revised Diagnostic Interview for Borderlines: discriminating BPD from other axis II disorders. J Pers Disord. 1989;3(1):10–8.
25 Zanarini MC, Frankenburg FR, Sickel AE, Yong L. The Diagnostic Interview for DSM-IV Personality Disorders. Belmont (MA): McLean Hospital; 1996.
26 Ventura J, Liberman RP, Green MF, Shaner A, Mintz J. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). Psychiatry Res. 1998 Jun;79(2):163–73.
27 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) Washington: American Psychiatric Association, 2000.
28 Hollingshead AB. Two Factor Index of Social Position. New Haven (CT): Yale University; 1965.
29 Eysenck SB, Eysenck HJ. Impulsiveness and venturesomeness: their position in a dimensional system of personality description. Psychol Rep. 1978 Dec;43(3 Pt 2):1247–55.
30 Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol. 1995 Nov;51(6):768–74.
31 Beck AT, Steer RA, Brown GK. Beck Depression Inventory Manual. 2nd ed. San Antonio (TX): The Psychological Corporation; 1996.
32 Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979 Apr;134(4):382–9.
33 Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978 Nov; 133(5):429–35.
34 Spielberger CD. Manual for the State-Trait Anxiety Inventory (Form Y). Palo Alto (CA): Consulting Psychologists Press; 1983.
35 Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012;2(3):125–41.
36 Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage. 2007 Aug;37(1):90–101.
37 Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, et al. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry. 2005 Jul;162(7):1256–65.
38 Goldstein JM, Seidman LJ, Makris N, Ahern T, O'Brien LM, Caviness VS Jr, et al. Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. Biol Psychiatry. 2007 Apr;61(8):935–45.
39 Makris N, Goldstein JM, Kennedy D, Hodge SM, Caviness VS, Faraone SV, et al. Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophr Res. 2006 Apr; 83(2-3):155–71.
40 Wilson ST, Stanley B, Oquendo MA, Goldberg P, Zalsman G, Mann JJ. Comparing impulsiveness, hostility, and depression in borderline personality disorder and bipolar II disorder. J Clin Psychiatry. 2007 Oct;68(10): 1533–9.