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Research paper

Prefrontal cortex engagement during an fMRI task of emotion regulation as a potential predictor of treatment response in borderline personality disorder

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ABSTRACT

Background: Borderline personality disorder (BPD) is a severe mental illness, with high rates of co-morbid depression and suicidality. Despite the importance of optimizing treatment in BPD, little is known about how neural processes relate to individual treatment response. This study examines how baseline regional brain blood oxygen level dependent (BOLD) activation during a functional magnetic resonance imaging (fMRI) task of emotion regulation is related to treatment response following a six-month randomized clinical trial of Dialectical Behavior Therapy (DBT) or Selective Serotonin Reuptake Inhibitor (SSRI) treatment.

Methods: Unmedicated females with BPD ($N = 37$), with recent suicidal behavior or self-injury, underwent an fMRI task in which negative personal memories were presented and they were asked to distance (i.e., down-regulate their emotional response) or immerse (i.e., experience emotions freely). Patients were then randomized to DBT ($N = 16$) or SSRI ($N = 21$) treatment, with baseline and post-treatment depression and BPD severity assessed.

Results: BOLD activity in prefrontal cortex, anterior cingulate, and insula was associated with distancing. Baseline BOLD during distancing in dorsolateral, ventrolateral, and orbital prefrontal cortex (dlPFC, vlPFC, OFC) differentially predicted depression response across treatment groups, with higher activity predicting better response in the SSRI group, and lower activity predicting better response in the DBT group.

Limitations: All female samples.

Discussion: Findings indicate that greater prefrontal engagement during emotion regulation may predict more antidepressant benefit from SSRIs, whereas lower engagement may predict better response to DBT. These results suggest different mechanisms of action for SSRI and DBT treatment, and this may allow fMRI to guide individualized treatment selection.

1. Introduction

Borderline personality disorder (BPD) is a severe mental illness affecting over four million individuals in the United States alone (Lenzenweger et al., 2007). Depressive symptoms and suicidality are common in BPD (Rao and Broadbear, 2019). Over 60 % of individuals with BPD attempt suicide, and 10 % complete suicide (Brickman et al., 2014; Kullgren et al., 1986; Qin, 2011). BPD is also associated with one of the highest rates of healthcare utilization of any psychiatric disorder, highlighting the importance of targeted and effective treatment (Fertuck et al., 2007).

BPD is characterized by a pattern of instability in affect, impulse control, interpersonal relationships, and self-image. Individuals with BPD often experience depressed mood, intense anger, chronic emptiness, and engage in self-injurious behaviors, like suicide attempts and non-suicidal self-injurious behaviors (NSSI) (Linehan and Kehrer, 1993).

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Over the past decade, neuroimaging studies have examined neural correlates underlying emotion dysregulation and negative affect in BPD. When processing negative stimuli, individuals with BPD have heightened activation of the amygdala, hippocampus, and posterior cingulate cortex and attenuated engagement of prefrontal regions including, dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC), compared with healthy control subjects (HC) (Beblo et al., 2006; Donegan et al., 2003; Herpertz et al., 2001; Krause-Utz et al., 2014a; Krause-Utz et al., 2014b; Ruocco et al., 2013; Schmahl et al., 2006; Schulze et al., 2016; van Zutphen et al., 2015). Aberrant limbic-prefrontal connectivity has also been implicated (Schulze et al., 2016). Thus, treatments targeting normalization of these brain regions should result in symptom improvement.

Dialectical Behavior Therapy (DBT) has consistently been shown to be effective in treating mood-related symptoms in individuals with BPD (Cristea et al., 2017; DeCou et al., 2019; Salsman and Linehan, 2006; Stoffers-Winterling et al., 2022). DBT helps individuals with BPD develop skills related to mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness to manage their negative thoughts, emotions, and behaviors more effectively (Salsman and Linehan, 2006). Several studies have investigated changes in neural activation before and after treatment with DBT, and findings suggest that DBT can alter the neural underpinnings of BPD. Specifically, DBT was associated with downregulation of neuronal activity within limbic regions, including the insula and amygdala (Goodman et al., 2014; Schmitt et al., 2016; Schnell and Herpertz, 2007). It was also associated with increases in prefrontal recruitment (Ruocco et al., 2016) and prefrontal gray matter volume (Mancke et al., 2018), and enhanced functional connectivity between limbic and prefrontal regions (Schmitt et al., 2016; Uscinska and Bellino, 2018).

Selective serotonin reuptake inhibitors (SSRIs) have shown efficacy in treating symptoms of affect instability, depression, impulsivity, and hostility which are often present in individuals with BPD (Bozzatello et al., 2017; Mercer et al., 2009; Ripoll, 2022; Vita et al., 2011). Additionally, because of the high rate of depression, suicide attempts and self-injury in BPD, SSRIs are recommended (Bozzatello et al., 2017). Despite the potential benefits, there have been a limited number of randomized controlled trials examining the effects of SSRIs in reducing symptoms specific to BPD, and there are no documented neuroimaging studies examining the effects of SSRI treatment in BPD (Uscinska and Bellino, 2018). Although there have been no BPD specific neuroimaging studies examining SSRI effects to date, in depressed samples, antidepressant treatment is associated with a reduction in hyperactivity of limbic regions (i.e. amygdala, insula) when processing negative stimuli (Ma, 2015). Since hyperactivity of these regions is characteristic of BPD, SSRIs may target these underlying neural abnormalities, resulting in affective symptom improvement for those with BPD.

Though some progress has been made in understanding the neural processes targeted by treatment, little work has been done to identify predictors of differential treatment response. Identification of neurobiological markers indicating who will respond best to which treatment could lead to more personalized treatment and improve treatment response rate. The current study examined the neural correlates of negative emotion processing and regulation at baseline in unmedicated individuals with BPD with recent suicidal behavior or self-injury and investigated how these brain regions relate to treatment outcomes after participants are randomized into either 6 months of DBT or SSRI treatment. To capture the participants' ability to regulate their affect when presented with something emotionally triggering, we employed an fMRI task involving negative personal memories. During the fMRI task, participants were asked to immerse themselves in a negative memory, allowing themselves to freely feel any emotions or distance themselves from the negative memory, downregulating their emotional response. We predicted that the reappraisal condition would be associated with greater recruitment of prefrontal brain regions. Additionally, because prefrontal engagement is associated with effective emotional reappraisal, we predicted that individuals with greater prefrontal recruitment during distancing at baseline would show greater improvement in depressive symptoms as well as overall BPD symptom severity following treatment. Exploratory analyses will examine whether there is an interaction of treatment type and prefrontal engagement in predicting change in depressive symptoms and BPD symptom severity.

2. Methods

2.1. Sample

Participants ($N = 37$) were previously recruited by the Molecular Imaging and Neuropathology Division (MIND) at the New York State Psychiatric Institute (NYSPI)/Columbia Psychiatry to participate in a larger treatment study for BPD. All participants were required to meet DSM-IV criteria for BPD, as determined by the Structured Clinical Interview (SCID) for DSM-IV, parts I and II (First, 2014). Participants also had at least one suicide attempt, or suicide-related behavior, or episode of NSSI in the past 6 months, and a second suicide attempt, suicide-related behavior, or NSSI within the past two years. Suicide related behaviors were defined as: a.) aborted attempt as a self-destructive behavior with intent to die but stopped by the individual prior to the point where injury could begin; b.) interrupted attempt as a self-destructive behavior with intent to die but the behavior is interrupted by another person; c.) micro-overdose as taking more medication than prescribed or a larger dose than recommended in OTC medication in which the intent is not to die, but to sleep or to "not think"; d.) serious suicide ideation resulting in psychiatric hospitalization or ED or urgent care visit. Participants were English speaking, female, between 18 and 65 years of age, and clinically stable enough to be treated as an outpatient. Individuals were excluded from participation if they were unable to provide consent, had past or present bipolar I disorder, psychotic disorder, schizophrenic disorder, a current substance use disorder, uncontrolled medical illness, pregnant, breastfeeding, claustrophobic or had any condition contraindicated for neuroimaging. Participants were also excluded if they had previous failed treatment trials of DBT or fluoxetine. Participants were only included if they completed baseline fMRI and post-treatment behavioral measures. Only 37 fMRI participants met this criterion. A CONSORT diagram shows fMRI participant flow in the context of the larger treatment study (Fig. 1). A comparison of clinical and demographic characteristics between individuals who dropped out of the study and treatment group completers can be found in the supplemental materials (Table S2).

2.2. Overview of procedures for treatment portion of study

Participants were screened and randomized to either six months of DBT ($N = 16$) or SSRI ($N = 21$) treatment. Participants were evaluated on a bimonthly basis during the active phase of treatment. Participants were assigned by stratified random sampling, stratified by type of self-injury they reported in the past 6 months (NSSI vs. suicide attempt). Prior to start of treatment, those on medications began a medication taper and a 2-week washout period. Once deemed medication free for at least 2 weeks, those randomized to DBT started weekly individual DBT psychotherapy sessions and weekly skills group. For those randomized to the SSRI group, fluoxetine was started at 20 mg once daily (QD), increased up to a maximum dosage of 40 mg QD in four weeks. Those in the SSRI condition also received supportive clinical management, consisting of 30-minute sessions with the study psychiatrist at a minimum frequency of every two weeks; weekly if their condition was worsening. Supportive clinical management included psychoeducation about BPD, suicide and NSSI, assessment of side effects, suicide risk and mental status, review of procedures to follow during spikes in suicidal risk, and friendly support. Serum SSRI levels were drawn monthly to assess and monitor medication adherence.

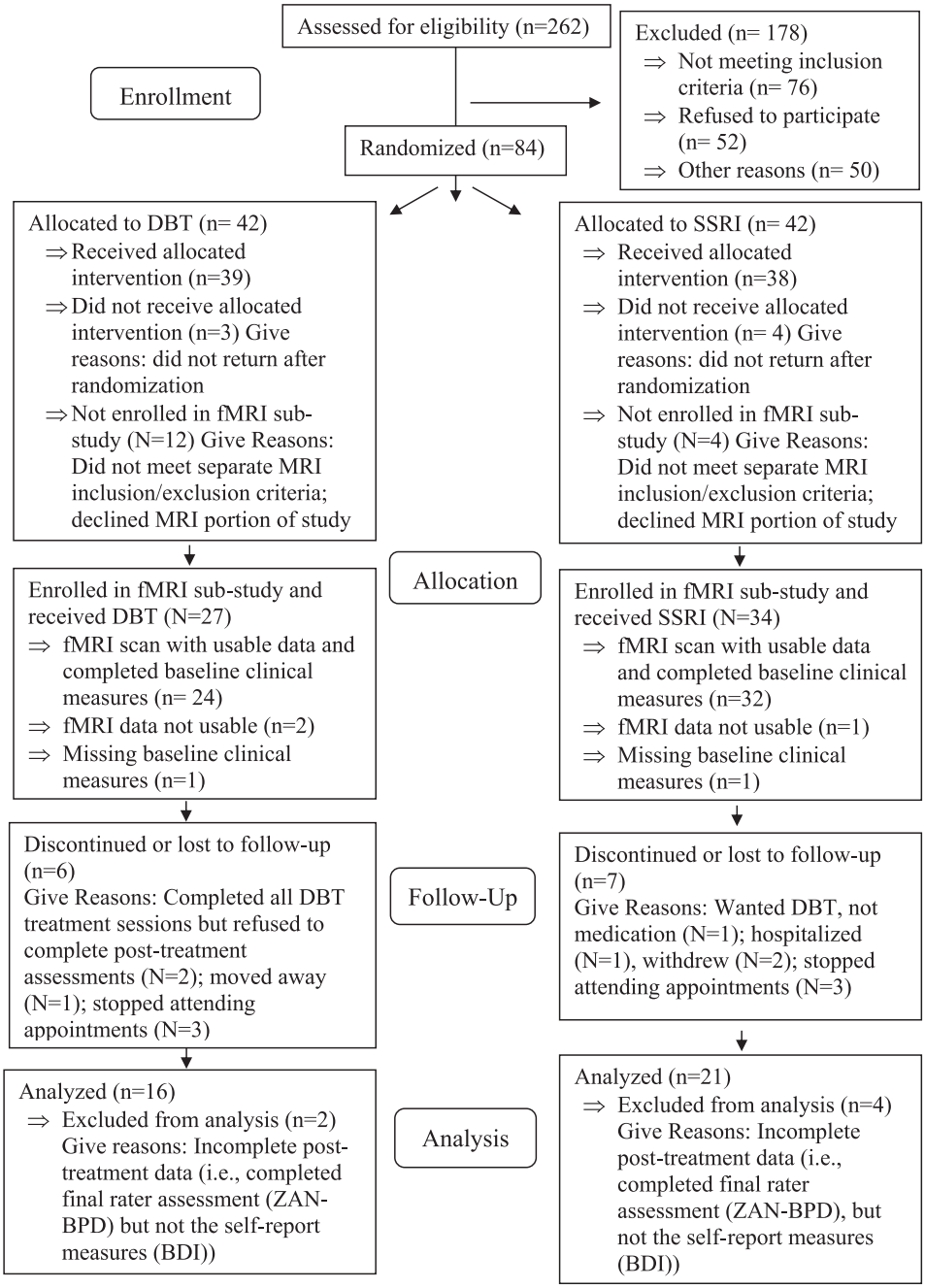

Fig. 1. Flow of participants through the fMRI portion of the trial.
Note: CONSORT Diagram. DBT: Dialectical Behavior Therapy. SSRI: Selective Serotonin Reuptake Inhibitor. fMRI: functional magnetic resonance imaging. The three participants who withdrew did not give a specific reason. Additional details on the clinical and demographic characteristics of the discontinued or lost to follow-up group can be found in the Supplement, along with a comparison to the DBT and SSRI groups included in the analysis.

All DBT therapists were Ph.D. level clinical psychologists intensively trained by the Behavioral Technology Transfer Group. They attended weekly DBT consultation team to ensure treatment precision and protect against drift. All treatment sessions were videotaped, and some used for supervision and to promote adherence. DBT adherence ratings were performed by an individual who received adherence rating training by the Linehan group. All therapists achieved DBT adherence.

2.3. Clinical measures

Participants completed a battery of assessments administered by trained Master's level psychologists at baseline and at the end of the 6 months of treatment. Clinical and demographic characteristics for the DBT and SSRI group at baseline and follow-up, as well as differences between the two groups at baseline are reported (Table 1). Axis I and II psychopathology was diagnosed using the *Structured Clinical Interviews for DSM-IV-TR* and the *Structured Clinical Interviews for DSM-IV Axis II Disorders* (First and Gibbon, 2004).

The primary outcome was depression severity and it was assessed using the *Beck Depression Inventory* (BDI) (Beck and Steer, 1984). The BDI is a 21-item self-report measure using a 4-point scale from 0 to 3, with higher scores indicating increased depression severity. Internal consistency of BDI has been reported to be high (Cronbach's alpha = 0.88) (Beck and Steer, 1984). BPD symptom severity was assessed using

Table 1
Demographic characteristics.

Scale or clinical characteristic	SSRI Group		DBT Group		DBT vs. SSRI
N	21		16		
	Mean	**SD (range)**	**Mean**	**SD (range)**	***p*-Value**
Age	27.1	6.77 (18–44)	28.81	10.13 (20–59)	$p = .51$
Education, years	15.38	1.71 (14–21)	15.88	1.86 (13–21)	$p = .44$
BDI T_1	29.86	9.60 (12–46)	28.56	10.73 (12–54)	$p = .71$
BDI T_2	18.38	12.41 (0–43)	15.13	13.22 (0–41)	
ZAN T_1	16.76	6.77 (4–28)	13.06	4.27 (7–21)	$p = .09$
ZAN T_2	10.1	4.54 (1–19)	8	5.71 (0–20)	
	t	**p-Value**	**t**	**p-Value**	***F*, p-value**
BDI T_1 vs. BDI T_2	4.5	$p < .001$	5.46	$p < .001$	$F_{1,35} = 0.29$, $p = .59$
ZAN T_1 vs. ZAN T_2	4.75	$p < .001$	3.04	$p = .008$	$F_{1,35} = 0.133$, $p = .57$
	%		**%**		**p-Value**
Sex (female)	100		100		
Prior suicide attempt	81		88		$p = .59$
Current MDD	81		63		$p = .21$
Lifetime MDD	86		75		$p = .21$
Current PTSD	24		19		$p = .71$
Race					$p = .93$
Asian	5		6		
Pacific Islander	5		0		
African American	10		14		
Caucasian	62		62		
Multiple	19		19		
Hispanic	10		25		$p = .21$

Note: BDI = Beck Depression Inventory. ZAN = the Zanarini Rating Scale for Borderline Personality Disorder. DBT = Dialectical Behavior Therapy. SSRI = Selective Serotonin Reuptake Inhibitor. SD = standard deviation. MDD = Major Depressive Disorder. T_1 = pretreatment T_2 = Posttreatment. A *t*-test was used for comparisons of continuous variables and chi-square test used for categorical variables. Linear regression was used to examine whether there was a main effect of treatment group on post-treatment scores, controlling for baseline scores.

the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) (Zanarini, 2003). The ZAN-BPD is a clinician administered assessment based on the DSM-IV criteria for BPD and it uses a five-point anchored rating scale of 0 to 4 to assess severity of the nine DSM-IV criteria for BPD. Internal consistency of the ZAN-BPD is reported to be high (Cronbach's $\alpha = 0.85$)(Zanarini, 2003).

2.4. Memory collection

In a pre-scanning testing session, a clinician asked participants to recall 8 upsetting memories from the last 6 months of their lives that made them feel sad, angry, or upset. If participants had difficulty, they were told that upsetting situations with family, friends and work are often sources of distress for people and if necessary, were asked to recall memories involving feeling ashamed, humiliated, rejected, misunderstood or hopeless. Participants rated each memory on a scale of 1–10 in terms of how initially distressing it was and its current intensity and vividness (all task memories were rated as a 7 or higher). The clinician and participant created brief phrases to be used as memory cues for the fMRI task. Participants provided 4 neutral memories for training purposes.

2.5. Memory task training

On 'immerse' trials, participants were told to see the situation in the first person and to feel any emotions that may arise. On 'distance' trials, participants were told to watch their memory unfold as if from a distance and to adopt the perspective of a reporter who is focused on the facts of their memory rather than its emotional details. Participants practiced the strategies with neutral memories, so they did not habituate to upsetting memories. Participants practiced distancing and immersing two memories aloud with an experimenter before practicing silently with two additional memories. All participants successfully described the strategy to the experimenter and verbalized how to distance themselves.

2.6. fMRI task

Participants completed four fMRI task runs, each comprised of four trials (Fig. 2). Each trial began with a memory cue (10 s) that prompted participants to recall the memory indicated. After a brief delay, the memory cue was presented with an instructional cue ('immerse' or 'distance') for 20 s, during which time participants either immersed or distanced themselves from their memory. After each trial, participants completed an active baseline task involving making button presses to indicate the direction of an arrow for 20 s (Stark and Squire, 2001). Participants were prompted to recall two memories twice per run, once with the immerse instruction and once with the distance instruction. Half of memories were presented with the immerse instruction first and half were presented with the distance instruction first. Stimuli were displayed using an LCD projector and a back-projection screen. Participants responded using a five-finger-button-response (Avotec Inc. and Resonance Technologies).

2.7. Analysis

2.7.1. fMRI acquisition

Whole-brain data were acquired on a GE 1.5 Tesla scanner (General Electric, Milwaukee, Wisconsin). Functional data were acquired with a T2*-sensitive EPI sequence (28 4 mm contiguous axial slices, TR = 2000 ms, TE = 34 ms, flip angle = 84°, FOV = 22.4 cm). Anatomical images were acquired with a T1-weighted SPGR scan (124 1.5 mm slices, TR = 19 ms, TE = 5 ms, FOV = 22 cm). All image processing and analyses were completed using FSL (Woolrich et al., 2009).

2.7.2. Preprocessing

The first four volumes of each functional scan were removed to avoid saturation effects. Preprocessing included slice time correction, motion correction, 120-second high-pass filter, bias field correction, and skull stripping. Normalized functional images were resliced to 3 × 3 × 3 mm voxels and smoothing with a Gaussian kernel of 6 mm. Functional images were registered to structural images with 6-degrees of freedom and then structural images were warped to the standard MNI space using a 12-degree affine registration implemented in FLIRT (Jenkinson et al., 2002). A nonlinear warp was also applied in FNIRT (Andersson et al., 2007). Visual checks were used to confirm there were no major artifacts or dropout, that field of view was appropriate and consistent, and to check for motion issues during the scan. All participants in the sample passed quality checks. Visual inspection also confirmed there were no registration failures during pre-processing in the sample.

2.7.3. Individual and group level fMRI analyses

First-level, second-level, and group analyses of blood oxygen level dependent (BOLD) signal were completed in FEAT within FSL (Woolrich et al., 2009). First level analyses included modeling memory recall, immerse condition, distance condition, and active baseline (arrows task) as boxcar regressors convolved with a canonical hemodynamic response function. Motion parameters and high-pass temporal filter parameters

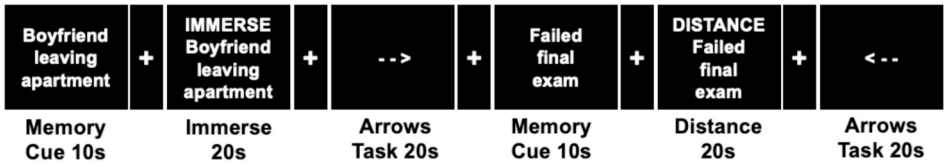

Fig. 2. Negative autobiographical memories task.
Note: s = seconds. Each trial begins with a memory cue for 10s that prompted participants to recall the memory. After an ISI ~2 s, the memory cue is presented with an instructional cue ('immerse' or 'distance') for 20 s, during which time participants either immersed or distanced themselves from their memory. Each presentation is followed by an arrows task where participants indicate the direction of the arrow. There are eight memories and four runs total. During each run, participants are presented with two memories twice, once with the immerse instruction and once with the distance instruction.

were included as nuisance regressors. Within-subject fixed effects models combined data across runs. Group level analyses used mixed-effects analysis to identify clusters (voxel $p < .001$; cluster $p < .05$). The distance > immerse condition was the focus of this study. To confirm treatment randomization was successful and determine if there were any baseline treatment group differences during our condition of interest (distance > immerse), we conducted a mixed effects model using a between-group contrast (DBT > SSRI and SSRI > DBT).

2.7.4. fMRI analyses: treatment type and clinical measures

Follow-up analyses were conducted in FSL. We examined the relationship between activation during the distance > immerse contrast and depression severity at post-treatment while controlling for baseline depression scores. Specifically, we conducted a mixed effects analysis with baseline BDI and post-treatment BDI as factors. The contrast of interest was post-treatment BDI. We also examined whether there was a relationship between activation during the distance > immerse contrast and the interaction of treatment type (DBT, SSRI) and post-treatment BDI. To do this we conducted a mixed effects analysis with the following factors: baseline BDI, post-treatment BDI, treatment type, and the interaction of treatment type and post-treatment BDI. The contrast of interest in this model was the interaction of treatment type and post-treatment BDI.

We completed the same analyses using the ZAN-BPD. To examine the relationship between activation during distance > immerse and post-treatment ZAN-BPD, we conducted a mixed effects analysis with baseline ZAN-BPD and post-treatment ZAN-BPD as factors. The contrast of interest was post-treatment ZAN-BPD. Additionally, to explore the relationship between activation during distance > immerse and the interaction of treatment type (DBT, SSRI) and post-treatment ZAN-BPD, we conducted a mixed effects analysis with the following factors: baseline ZAN-BPD, post-treatment ZAN-BPD, treatment type, and the interaction of treatment type and post-treatment ZAN-BPD. The contrast of interest in this model was the interaction of treatment type and post-treatment ZAN-BPD.

As an exploratory follow-up, we conducted a modified intent-to-treat analysis in which we used the 4-month BDI assessment scores for individuals who either discontinued before the 6-month mark or did not have a 6-month BDI. To examine how neural activation during distance>immerse related to the interaction of treatment type and depression severity at discontinuation or post-treatment, controlling for baseline depression scores, we conducted a mixed effects analysis with the following factors: baseline BDI, discontinuation/post-treatment BDI, treatment type, and the interaction of treatment type and discontinuation/post-treatment BDI. The contrast of interest for this model was the interaction of treatment type and discontinuation/post-treatment BDI.

Regional localizations were identified using the Harvard-Oxford Cortical and Subcortical atlases applied to the Montreal Neurological Institute (MNI)152 standard brain template (Collins et al., 1995; Mazziotta et al., 2001). Brain regions are reported and include the voxel coordinates (X, Y, Z) of the region's center of gravity (COG). The COG is calculated using a weighted average of the coordinates by the intensities within each brain region.

3. Results

3.1. Demographic and clinical characteristics of the sample

Clinical and demographic characteristics for the DBT and SSRI groups are reported in Table 1. At baseline, the two treatment groups did not differ on measures of age, education, attempt history, diagnosis, race, or depression severity (Table 1). Both DBT and SSRI treatments reduced depression severity from baseline to post-treatment (Table 1).

3.2. BOLD activation associated with cognitive reappraisal

In the distance > immerse contrast, distancing was associated with greater activation in orbital prefrontal cortex, operculum, anterior cingulate (ACC), dorsal striatum, insula, and paracingulate compared with the immerse condition (Fig. 3, Table 2). There were no baseline neural differences between the two treatment groups for the distance > immerse condition. In the immerse > distance contrast, there was greater activation in lateral occipital cortex and angular gyrus (Table S1).

3.3. BOLD activation during distancing and clinical outcomes

When analyzing the entire sample ($N = 37$), irrespective of treatment group, brain activity during the distance > immerse contrast was not related to post-treatment depression severity scores on the BDI.

There was a significant interaction of treatment type and post-treatment BDI scores with a cluster spanning the right dlPFC, ventrolateral prefrontal cortex (vlPFC), and orbital frontal cortex (OFC) (Table 3; Figs. 4a, 4b). For the SSRI group, greater activation in this

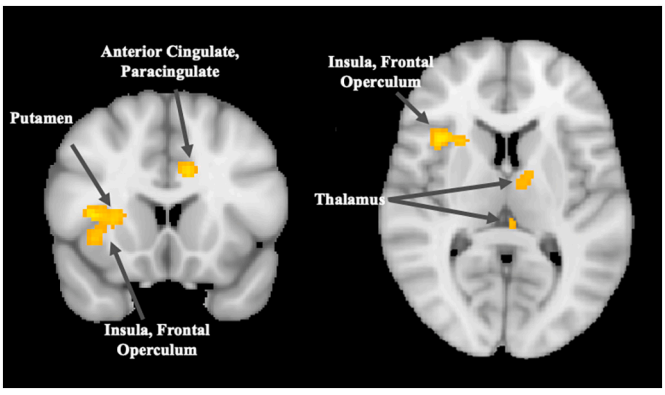

Fig. 3. Brain regions associated with distancing from negative autobiographical memories.
Note: $N = 37$. Thresholded activation 3.1 3.7. Brain regions for the distance > immerse contrast are shown above. Left image = coronal view; right = axial view. All analyses thresholded at voxel-$p < .001$, cluster-$p < .05$.

Table 2
Brain regions associated with distancing from negative autobiographical memories.

Brain region	k	Z-score	X	Y	Z
Brain stem	134	3.5	45.57	47.43	32.5
Central opercular cortex	11	3.47	22.73	67.45	36.27
Cingulate Gyrus, anterior division	132	3.53	49.08	72.23	50.48
Frontal operculum cortex	71	3.62	25.94	71.42	40.03
Frontal pole	37	3.5	57.43	83.11	46.89
Insular cortex	161	3.54	27.19	69.89	36.24
Left putamen	11	3.32	57.18	60.91	42
Left thalamus	41	3.25	47.83	55.49	39.37
Paracingulate gyrus	63	3.49	51.56	79.48	48

Note: N = 37. Brain regions listed are from the distance > immerse contrast. k = number of voxels, voxels 3 × 3 × 3 mm. X, Y, Z coordinates are for center of gravity (COG) for the region. The COG coordinates for the region are a weighted average of the coordinates by the intensities within the brain region. Z-score represents average Z-score for that region. Brain regions are listed based on a version of the Harvard-Oxford cortical and subcortical atlases, which only specifies right/left for certain subcortical regions. All analyses thresholded at voxel-p < .001, cluster-p < .05.

Table 3
Brain regions during distancing associated with differential treatment response.

Brain region	k	Z score	X	Y	Z
Orbital frontal cortex	76	3.40	24.57	77.38	32.39
Right frontal pole	63	3.28	23.00	83.02	33.62
Right inferior frontal gyrus, pars triangularis	135	3.51	18.40	77.72	37.79

Note: N = 37. k = number of voxels, voxels 3 × 3 × 3 mm. X, Y, Z coordinates are for center of gravity (COG) for the region. The COG coordinates for the region are a weighted average of the coordinates by the intensities within the brain region. Z-score represents average Z score for that region. Brain regions are listed based on the Harvard-Oxford cortical and subcortical atlases, which only specifies right/left for subcortical regions. BDI = Beck Depression Inventory. Brain regions listed are from an interaction analysis examining activation during the distance > immerse contrast associated with treatment type × BDI scores at post-treatment, controlling for baseline BDI scores. All analyses thresholded at voxel-p < .001, cluster-p < .05.

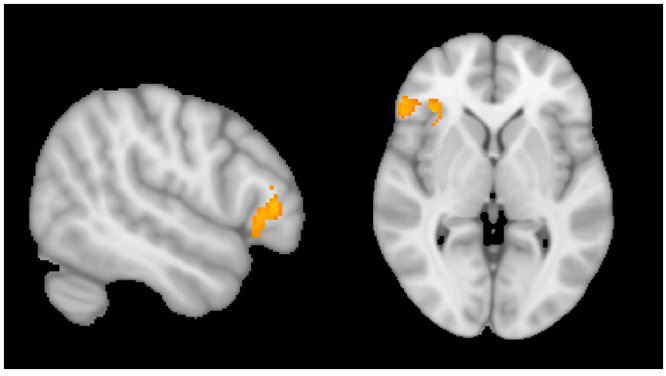

Fig. 4a. Activation in prefrontal cluster during distancing associated with differential treatment response.
Note: Thresholded activation images 3.1 3.7. N = 37. BDI = Beck Depression Inventory Cluster. Left image = sagittal view; right = axial view. All analyses thresholded at voxel-p < .001, cluster-p < .05. Activation in a cluster spanning the right dlPFC, vlPFC, and OFC differentially predicted BDI scores at post-treatment, while controlling for baseline BDI scores. Individuals with greater activation in dlPFC/vlPFC/OFC during distancing had with greater symptom improvement with SSRIs, while those with less dlPFC/vlPFC/OFC activation at baseline had greater improvement from DBT.

cluster was associated lower BDI scores post-treatment, indicating more improvement. The opposite was seen in the DBT group, with less prefrontal activation at baseline associated with lower BDI scores post-treatment, indicating greater reduction in depression symptoms (Fig. 4b). In our exploratory modified intent to treat analysis, there was similarly a significant interaction of treatment type and BDI scores with a cluster spanning the right vlPFC and OFC (Table S3). For the SSRI group, greater activation in vlPFC/OFC was associated lower BDI scores at 4 or 6 months. For the DBT group, less vlPFC/OFC activation was associated lower depression scores at 4 months or later (Table S3, Fig. S1).

When analyzing the entire sample, irrespective of treatment group, brain activity during the distance > immerse contrast was not related to post-treatment BPD severity scores on the ZAN-BPD. There was no interaction of treatment type and post-treatment ZAN-BPD scores.

4. Discussion

This is the first study to examine how neural activity during emotion regulation relates to differential treatment outcomes in females with BPD. Overall, reappraisal was associated with activation of prefrontal cortex, ACC, insula, thalamus, dorsal striatum, and parahippocampal gyri. Baseline dlPFC, vlPFC and OFC activation during emotion regulation trials differentially predicted treatment response of depressive symptoms, with higher activation predicting enhanced SSRI response and lower activation predicting enhanced response to DBT. These findings suggest that dLPFC, vlPFC and OFC activation may help delineate what treatment is likely to work optimally on depressive symptoms for a given individual.

dlPFC, vlPFC and OFC engagement during emotion regulation may be a neurobiological predictor of antidepressant treatment response. Individuals with greater dlPFC, vlPFC and OFC engagement during emotion regulation may have a better antidepressant response to SSRIs, while those with less engagement may benefit more from DBT. One explanation may be that elements of DBT treatment, like direct skills training in emotion regulation and distress tolerance, may increase dlPFC, vlPFC and OFC, resulting in improvement in mood following treatment. Prior data show that following DBT treatment, individuals with BPD had increased dlPFC engagement during an fMRI impulse control task (Ruocco et al., 2016), increased gray matter volume in prefrontal regions (Mancke et al., 2018), and increased prefrontal-limbic connectivity (Schmitt et al., 2016; Uscinska and Bellino, 2018). These neural changes are suggested to correspond with symptom improvement (Mancke et al., 2018; Ruocco et al., 2016; Schmitt et al., 2016; Uscinska and Bellino, 2018). Additionally, one study found that individuals who saw the greatest gains from DBT treatment, as assessed by reduction self-harm, were those with low dlPFC activity at baseline (Ruocco et al., 2016). If a core mechanism of DBT is increasing prefrontal engagement or connectivity during emotional processing, then individuals with low baseline activity in dlPFC, vlPFC and OFC may see the greatest mood benefits from DBT. In contrast, one reason individuals with high baseline dlPFC/vlPFC/OFC engagement may have benefited more from SSRIs is that antidepressants may improve mood through different brain targets (i.e., limbic regions). While there are no prior neuroimaging studies examining SSRI effects in BPD, metanalyses of antidepressant effects in depressed patients show that SSRI treatment was associated with decreased activity in regions of amygdala and insula when processing aversive stimuli (Ma, 2015). Since amygdala and insula hyperactivity is characteristic of BPD (Schulze et al., 2016), it is possible that reducing this hyperactivity is a key mechanism of antidepressant action of SSRI treatment (Ma, 2015). Thus, if SSRIs primarily improve mood in BPD by reducing limbic hyperactivity, then individuals with high dlPFC/vlPFC/OFC engagement at baseline may be predisposed to benefit more from SSRI treatment and have less improvement with DBT. Further research is needed to replicate these findings and to determine their basis.

This finding has a number of clinical implications for treating

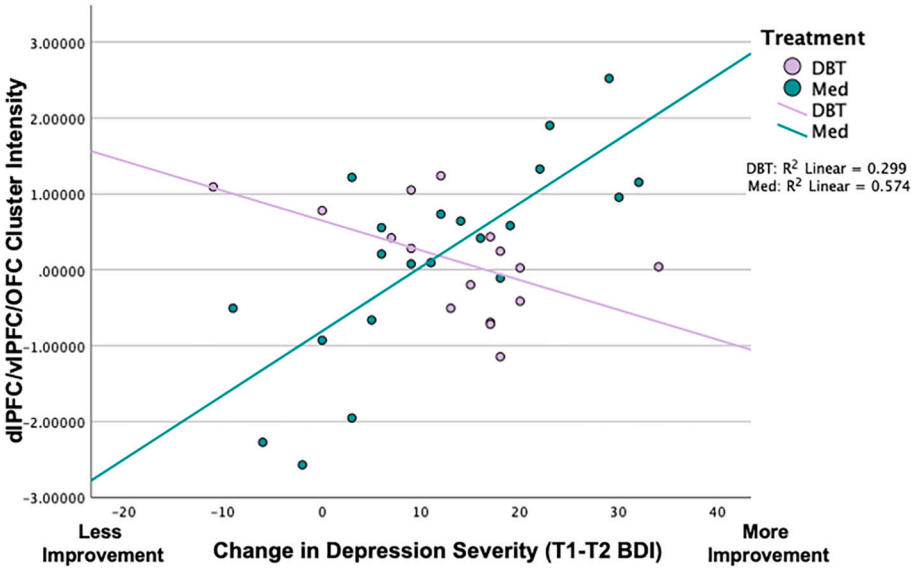

Fig. 4b. Activation of dlPFC, vlPFC, and OFC during distancing and change in depression severity by treatment type.
Note: N = 37. BDI: Beck Depression Inventory. DBT: Dialectical Behavior Therapy. SSRI: Selective Serotonin Reuptake Inhibitor. dlPFC: dorsolateral prefrontal cortex. vlPFC: ventrolateral prefrontal cortex. OFC: Orbital Frontal Cortex. Y-axis represents the average intensity of cluster spanning the dlPFC, vlPFC, and OFC during distancing. Higher intensity represents greater activation of regions during distancing. Larger change in depression severity (T1 BDI-T2 BDI) represents greater symptom improvement. Individuals with greater activation in dlPFC/vlPFC/OFC during distancing had with greater symptom improvement with SSRIs, while those with less dlPFC/vlPFC/OFC activation at baseline had greater from DBT.

depressive symptoms in females with BPD. Depressive symptomology is common in BPD and may increase the risk for suicidal behavior. Because of the high-risk nature of BPD, it is critical to identify factors that predict which treatment is most effective in improving mood symptoms. DBT involves a high financial cost and a substantial time investment from the patient (Murphy et al., 2020). DBT also has a high dropout rate, with more than one-fourth of patients ending treatment prematurely (Dixon and Linardon, 2020). Additionally, antidepressant medication is less effective in reducing depressive symptoms when MDD and BPD are co-occurring (Ceresa et al., 2021). Thus, identifying a neurobiological marker that can predict which patients would see more depressive symptom improvement from SSRIs vs. DBT would reduce patient burden, cost, and potentially increase treatment adherence and reduce dropout rates.

Baseline neural activity did not predict change in overall BPD symptom severity. BPD is a complex disorder with heterogeneous symptoms including impulsivity, anger, emotion dysregulation, identity disturbances, depressed mood, unstable interpersonal relationships, and self-injurious behaviors. The ZAN-BPD assesses BPD severity with one question for each of the nine DSM-IV criteria for BPD. Because of the heterogeneous nature of BPD symptoms, it is possible that neural activity is anchored to specific characteristics of the disorder (e.g., depressive symptoms, impulsivity, anger), and this may not be captured in the ZAN-BPD. Thus, future work should determine whether findings differ when using assessments specific to these different characteristics (e.g., impulsivity, aggression, etc.).

When examining the entire sample at baseline, females with BPD showed recruitment of several regions associated with adaptive emotion regulation. Specifically, reappraisal was associated with greater activation in regions of the prefrontal cortex, including frontal operculum and frontal poles, and the anterior cingulate. These regions are all implicated in cognitive control and reappraisal of negative emotional states (Ochsner and Gross, 2007; Ochsner et al., 2012), and are an integral part of effective emotional control. (Blumenfeld, 2002; Blumenfeld, 2010; Krause-Utz et al., 2014b; Ochsner and Gross, 2007; Ochsner et al., 2012). Meta-analyses indicate that individuals with BPD have less engagement of prefrontal regions compared with healthy controls when processing aversive stimuli, and this attenuated activation is associated with poor emotion regulation in BPD (Ruocco et al., 2013; Schulze et al., 2016). In addition to prefrontal structures, engagement of the thalamus, dorsal striatum (putamen), and insula were associated with distancing. The insula and paracingulate are involved in affective memory, attention, and processing of emotional stimuli, while the dorsal striatum is involved in reward processing (Blumenfeld, 2010; Morawetz et al., 2017; Ochsner et al., 2012; Song et al., 2017). Previous studies find that individuals with BPD have greater activation in insula and paracingulate during emotional regulation strategies than healthy controls, and this activation was associated with poorer emotion regulation abilities (Krause-Utz et al., 2014b; Schulze et al., 2016; van Zutphen et al., 2015). Hyperactivation of brain regions involved in reward processing (i.e., striatum, putamen, and thalamus) when processing negative stimuli has been documented in BPD compared with controls (Enzi et al., 2013; Krause-Utz et al., 2014b). While many regions in the greater limbic circuitry are involved in emotion regulation, the literature suggests that individuals with BPD generally have greater activation of these regions, or less deactivation of the regions, when attempting to downregulate their emotional response than healthy controls (Krause-Utz et al., 2014b; Schulze et al., 2016).

4.1. Limitations

While the sample size is comparable to other clinical studies (Schulze et al., 2016), one limitation of this study is the sample size within each treatment group. fMRI studies of clinical samples are often smaller than non-imaging studies due to many factors including more subject burden. Additionally, since this study required participants to remain in treatment for 6 months, this further added to the challenge of retaining a large sample. While we did have individuals who dropped out over the course of the study, our dropout rates were comparable to other RCTs (Dixon and Linardon, 2020). Another limitation is that the group that discontinued treatment had a higher rate of Hispanic participants than the SSRI treatment completer group. Future follow-up studies should strive to include more individuals within each treatment group and examine ethnic minority-specific barriers to retention.

Another limitation of this study is that the fMRI portion was completed with an all-female sample. Borderline personality disorder is

three times more common in females compared with males (Lenzenweger et al., 2007), and prior research has been predominately with female samples (Herpertz et al., 2018; Schulze et al., 2016). While the research to date does not report gender differences in prognosis and in treatment response (Schulze et al., 2016), future studies should include males to determine whether findings are generalizable to men with BPD or to populations with different clinical and demographic characteristics. Additionally, due to the high-risk nature of the sample, this treatment study did not include a non-treatment control group, and some pre-post clinical gains may be due to regression to the mean. Another limitation of the study is that there is no healthy comparison group. In order to understand BPD specific brain abnormalities, it is important to include clinical comparison samples in future studies. Future work should also examine whether there are neurobiological predictors of treatment response related to other BPD symptoms i.e., impulsivity or suicidal behavior.

4.2. Summary

dlPFC, vlPFC and OFC activation during emotion regulation pre-treatment may differentially predict antidepressant treatment response in females with BPD. This study is the first to suggest a biomarker for choosing SSRI versus DBT antidepressant treatment in BPD. Future work should seek to replicate this potential neurobiological predictor of treatment response, with the goal of more personalized care for this high-risk population.

CRediT authorship contribution statement

Christina A. Michel: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Noam Schneck:** Writing – review & editing. **J. John Mann:** Writing – review & editing. **Kevin N. Ochsner:** Writing – review & editing. **Beth S. Brodsky:** Writing – review & editing. **Barbara Stanley:** Writing – review & editing, Supervision.

Declaration of competing interest

JJM and BHS receive royalties from the Research Foundation for Mental Hygiene for commercial use of the C-SSRS. CAM, NS, BSB, and KNO have no conflicts to report. The design, preparation, review, and approval of the manuscript as well as the decision to submit the manuscript for publication was entirely done by the authors CAM, NS, BSB, KNO, JJM, and BHS.

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Clinical Trial registration information: “Treating Suicidal Behavior and Self-Mutilation in People with Borderline Personality Disorder” #NCT00533117.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.08.041.

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