Title: 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 major depression and suicidality. Despite the importance of optimizing treatment in BPD, little is known about how neural processes relate to individual treatment response. The present 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 randomized clinical trial of six months of Dialectical Behavior Therapy (DBT) or Selective Serotonin Reuptake Inhibitor (SSRI) treatment.

Methods: Unmedicated individuals with BPD (N=35), reporting suicidal behavior or self-injury in the prior six months, underwent an fMRI task in which negative personal memories were presented and they were asked to either distance (i.e., experience the memory from a third-person perspective, a regulation strategy) or immerse (i.e., experience the memory from a first-person perspective). Patients were then randomized to six months of either DBT (N=16) or SSRI (N=19) treatment. Baseline and post-treatment depression severity was scored.

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

Discussion: The present findings indicate that greater dlPFC and vlPFC engagement during emotion regulation may predict more antidepressant benefit more from SSRI treatment, whereas lower engagement may predict more antidepressant response to DBT treatment. These results

suggest different antidepressant mechanisms of action of SSRIs and DBT that may allow pretreatment fMRI to guide individualized antidepressant treatment selection.

Keywords: fMRI, borderline personality disorder, DBT, SSRI, randomized clinical trial, depression

Introduction

Borderline personality disorder (BPD) is a severe mental illness affecting over four million individuals in the United States alone (Lenzenweger et al., 2007). 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. Impaired emotion control in BPD contributes to depressed mood, intense anger, chronic emptiness, and self-injurious behaviors, like suicide attempts and non-suicidal self-injurious behaviors (NSSI) (Linehan and Kehrer, 1993). 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 following treatment.

Methods

Sample

Participants (N=35) 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 18-65 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 35 of the original 57 participants met this criterion.

Overview of Procedures for Treatment Portion of Study

Participants were screened and randomized to either six months of DBT (N=16) or SSRI (N=19) 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.

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.

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 0-3, 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).

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.

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.

fMRI Task

Participants completed four fMRI task runs, each comprised of four trials (Figure 1). Each trial began with a memory cue (10 seconds) 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 seconds, 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 seconds (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).

Analysis

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 4mm contiguous axial slices, TR=2000ms, TE=34ms, 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).

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 6mm. 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.

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 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 $p < 0.001$; cluster $p < 0.05$). The distance > immerse condition was the focus of this study. To confirm treatment randomization was successful, an analysis was run to determine if there were any baseline treatment group differences in brain activation during these contrasts.

fMRI Analyses: Treatment Type and Clinical Measures

Follow-up analyses were conducted in FSL examining relationship between activation during the distance>immerse contrast and depression severity at post-treatment while controlling

for baseline depression scores. The BDI was used to assess depression severity at baseline and after 6 months of treatment. Analyses were then conducted in FSL examining the interaction of treatment type x depression severity at post-treatment, controlling for baseline depression scores. 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.

Results

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 posttreatment (Table 1).

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), parahippocampal gyri, dorsal striatum, insula, and paracingulate compared with the immerse condition (Figure 2). In the immerse>distance contrast, there was greater activation in lateral occipital cortex (Table S1). There were no baseline neural differences between the two treatment groups.

BOLD Activation during Distancing and Clinical Outcomes

When analyzing the entire sample (N=35), 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 and ventrolateral prefrontal cortex (vlPFC) (Table 3; Figure 3a,3b). For the SSRI group, greater activation in dlPFC/vlPFC was associated lower BDI scores post-treatment, indicating more improvement. The opposite was seen in the DBT group, with less dlPFC/vlPFC activation at baseline associated with lower BDI scores post-treatment, indicating greater reduction in depression symptoms (Figure 3b).

Discussion

This is the first study to examine how neural activity during emotion regulation relates to differential treatment outcomes in individuals with BPD. Overall, reappraisal was associated with activation of prefrontal cortex, ACC, insula, thalamus, dorsal striatum, and parahippocampal gyri. Baseline dlPFC and vlPFC 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 and vlPFC activation may help delineate what treatment is likely to work optimally for a given individual.

dlPFC and vlPFC engagement during emotion regulation may be a neurobiological predictor of antidepressant treatment response. Individuals with greater dlPFC and vlPFC 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 and vlPFC, 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 and vlPFC might benefit most from DBT. In contrast, one reason individuals with high baseline dlPFC/vlPFC 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 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.

When examining the entire sample at baseline, 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 OFC, 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 parahippocampal gyri, thalamus, dorsal striatum (caudate, putamen), and insula were associated with distancing. The insula, paracingulate and parahippocampal gyri 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, paracingulate, and the hippocampus 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).

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. Despite these constraints, future follow-up studies should strive to include more individuals within each treatment group.

Another limitation of this study is that it was completed with an all-female sample. Borderline personality disorder is much commoner in females compared with males (3:1) (Lenzenweger et al., 2007), and prior research has been predominately with female samples (Schulze et al., 2016). While the research to date does not report gender differences in prognosis and in treatment response (Schulze et al., 2016), but studies with male samples should be conducted to determine whether this study's findings are generalizable to men with BPD or to populations with different clinical and demographic characteristics. 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.

Summary

dlPFC and vlPFC activation during emotion regulation pre-treatment may differentially predict antidepressant treatment response in 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.

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References

Andersson, J.L., Jenkinson, M., Smith, S., 2007. Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2. FMRIB Analysis Group of the University of Oxford 2, e21.

Beblo, T., Driessen, M., Mertens, M., Wingenfeld, K., Piefke, M., Rullkoetter, N., Silva-Saavedra, A., Mensebach, C., Reddemann, L., Rau, H., 2006. Functional MRI correlates of the recall of unresolved life events in borderline personality disorder. Psychological medicine 36, 845-856.

Beck, A.T., Steer, R.A., 1984. Internal consistencies of the original and revised Beck Depression Inventory. Journal of clinical psychology 40, 1365-1367.

Blumenfeld, H., 2002. Neuroanatomy through clinical cases.

Blumenfeld, H., 2010. Neuroanatomy overview and basic definitions. Neuroanatomy.

Bozzatello, P., Ghirardini, C., Uscinska, M., Rocca, P., Bellino, S., 2017. Pharmacotherapy of personality disorders: what we know and what we have to search for. Future neurology 12, 199-222.

Brickman, L.J., Ammerman, B.A., Look, A.E., Berman, M.E., McCloskey, M.S., 2014. The relationship between non-suicidal self-injury and borderline personality disorder symptoms in a college sample. Borderline personality disorder and emotion dysregulation 1, 1-8.

Collins, D.L., Holmes, C.J., Peters, T.M., Evans, A.C., 1995. Automatic 3-D model-based neuroanatomical segmentation. Human brain mapping 3, 190-208.

Cristea, I.A., Gentili, C., Cotet, C.D., Palomba, D., Barbui, C., Cuijpers, P., 2017. Efficacy of psychotherapies for borderline personality disorder: a systematic review and meta-analysis. Jama psychiatry 74, 319-328.

DeCou, C.R., Comtois, K.A., Landes, S.J., 2019. Dialectical behavior therapy is effective for the treatment of suicidal behavior: A meta-analysis. Behavior therapy 50, 60-72.

Donegan, N.H., Sanislow, C.A., Blumberg, H.P., Fulbright, R.K., Lacadie, C., Skudlarski, P., Gore, J.C., Olson, I.R., McGlashan, T.H., Wexler, B.E., 2003. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. Biological psychiatry 54, 1284-1293.

Enzi, B., Doering, S., Faber, C., Hinrichs, J., Bahmer, J., Northoff, G., 2013. Reduced deactivation in reward circuitry and midline structures during emotion processing in borderline personality disorder. The World Journal of Biological Psychiatry 14, 45-56.

Fertuck, E.A., Makhija, N., Stanley, B., 2007. The nature of suicidality in borderline personality disorder. Primary Psychiatry.

First, M.B., 2014. Structured clinical interview for the DSM (SCID). The encyclopedia of clinical psychology, 1-6.

First, M.B., Gibbon, M., 2004. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II), Comprehensive handbook of psychological assessment, Vol. 2: Personality assessment. John Wiley & Sons, Inc., Hoboken, NJ, US, pp. 134-143.

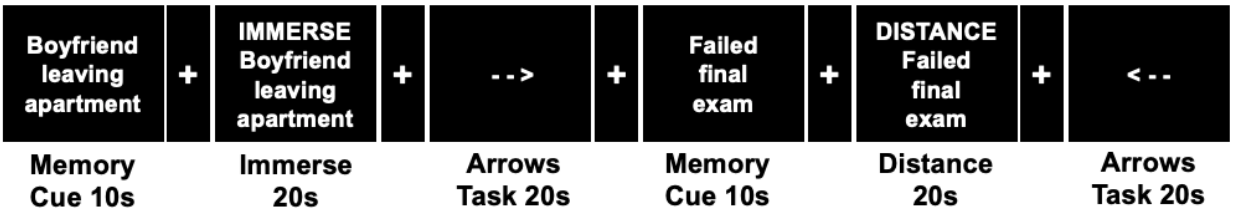
Goodman, M., Carpenter, D., Tang, C.Y., Goldstein, K.E., Avedon, J., Fernandez, N., Mascitelli, K.A., Blair, N.J., New, A.S., Triebwasser, J., 2014. Dialectical behavior therapy alters emotion regulation and amygdala activity in patients with borderline personality disorder. Journal of psychiatric research 57, 108-116.

Herpertz, S.C., Dietrich, T.M., Wenning, B., Krings, T., Erberich, S.G., Willmes, K., Thron, A., Sass, H., 2001. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. Biological psychiatry 50, 292-298.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825-841.
Krause-Utz, A., Veer, I., Rombouts, S., Bohus, M., Schmahl, C., Elzinga, B., 2014a. Amygdala and anterior cingulate resting-state functional connectivity in borderline personality disorder patients with a history of interpersonal trauma. Psychological medicine 44, 2889-2901.
Krause-Utz, A., Winter, D., Niedtfeld, I., Schmahl, C., 2014b. The latest neuroimaging findings in borderline personality disorder. Current psychiatry reports 16, 1-13.
Kullgren, G., Renberg, E., Jacobsson, L., 1986. An empirical study of borderline personality disorder and psychiatric suicides. The Journal of nervous and mental disease 174, 328-331.
Lenzenweger, M.F., Lane, M.C., Loranger, A.W., Kessler, R.C., 2007. DSM-IV personality disorders in the National Comorbidity Survey Replication. Biological psychiatry 62, 553-564.
Linehan, M.M., Kehrer, C.A., 1993. Borderline personality disorder. Clinical handbook of psychological disorders 2.
Ma, Y., 2015. Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. Molecular psychiatry 20, 311-319.
Mancke, F., Schmitt, R., Winter, D., Niedtfeld, I., Herpertz, S.C., Schmahl, C., 2018. Assessing the marks of change: how psychotherapy alters the brain structure in women with borderline personality disorder. Journal of Psychiatry and Neuroscience 43, 171-181.
Mazziotta, J., Toga, A., Evans, A., Fox, P., Lancaster, J., Zilles, K., Woods, R., Paus, T., Simpson, G., Pike, B., 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 356, 1293-1322.
Mercer, D., Douglass, A.B., Links, P.S., 2009. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. Journal of personality disorders 23, 156-174.
Morawetz, C., Bode, S., Derntl, B., Heekeren, H.R., 2017. The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: A meta-analysis of fMRI studies. Neuroscience & Biobehavioral Reviews 72, 111-128.
Ochsner, K.N., Gross, J.J., 2007. The neural architecture of emotion regulation. Handbook of emotion regulation 1, 87-109.
Ochsner, K.N., Silvers, J.A., Buhle, J.T., 2012. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Annals of the new York Academy of Sciences 1251, E1-E24.
Qin, P., 2011. The impact of psychiatric illness on suicide: differences by diagnosis of disorders and by sex and age of subjects. Journal of psychiatric research 45, 1445-1452.
Ripoll, L.H., 2022. Psychopharmacologic treatment of borderline personality disorder. Dialogues in clinical neuroscience.
Ruocco, A.C., Amirthavasagam, S., Choi-Kain, L.W., McMain, S.F., 2013. Neural correlates of negative emotionality in borderline personality disorder: an activation-likelihood-estimation meta-analysis. Biological psychiatry 73, 153-160.
Ruocco, A.C., Rodrigo, A.H., McMain, S.F., Page-Gould, E., Ayaz, H., Links, P.S., 2016. Predicting treatment outcomes from prefrontal cortex activation for self-harming patients with borderline personality disorder: a preliminary study. Frontiers in human neuroscience 10, 220.

Salsman, N., Linehan, M.M., 2006. Dialectical-behavioral therapy for borderline personality disorder. Primary Psychiatry 13, 51.
Schmahl, C., Bohus, M., Esposito, F., Treede, R.-D., Di Salle, F., Greffrath, W., Ludaescher, P., Jochims, A., Lieb, K., Scheffler, K., 2006. Neural correlates of antinociception in borderline personality disorder. Archives of general psychiatry 63, 659-666.
Schmitt, R., Winter, D., Niedtfeld, I., Herpertz, S.C., Schmahl, C., 2016. Effects of psychotherapy on neuronal correlates of reappraisal in female patients with borderline personality disorder. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 1, 548-557.
Schnell, K., Herpertz, S.C., 2007. Effects of dialectic-behavioral-therapy on the neural correlates of affective hyperarousal in borderline personality disorder. Journal of psychiatric research 41, 837-847.
Schulze, L., Schmahl, C., Niedtfeld, I., 2016. Neural correlates of disturbed emotion processing in borderline personality disorder: a multimodal meta-analysis. Biological psychiatry 79, 97-106.
Song, S., Zilverstand, A., Song, H., d'Oleire Uquillas, F., Wang, Y., Xie, C., Cheng, L., Zou, Z., 2017. The influence of emotional interference on cognitive control: A meta-analysis of neuroimaging studies using the emotional Stroop task. Scientific reports 7, 2088.
Stark, C.E., Squire, L.R., 2001. When zero is not zero: the problem of ambiguous baseline conditions in fMRI. Proceedings of the national Academy of Sciences 98, 12760-12766.
Stoffers-Winterling, J.M., Storebø, O.J., Kongerslev, M.T., Faltinsen, E., Todorovac, A., Jørgensen, M.S., Sales, C.P., Callesen, H.E., Ribeiro, J.P., Völlm, B.A., 2022. Psychotherapies for borderline personality disorder: a focused systematic review and meta-analysis. The British Journal of Psychiatry, 1-15.
Uscinska, M., Bellino, S., 2018. Treatment-induced brain plasticity in borderline personality disorder: review of functional MRI studies. Future Neurology 13, 225-238.
van Zutphen, L., Siep, N., Jacob, G.A., Goebel, R., Arntz, A., 2015. Emotional sensitivity, emotion regulation and impulsivity in borderline personality disorder: a critical review of fMRI studies. Neuroscience & Biobehavioral Reviews 51, 64-76.
Vita, A., De Peri, L., Sacchetti, E., 2011. Antipsychotics, antidepressants, anticonvulsants, and placebo on the symptom dimensions of borderline personality disorder: a meta-analysis of randomized controlled and open-label trials. Journal of clinical psychopharmacology 31, 613-624.
Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. Neuroimage 45, S173-S186.

Appendix

Figure 1 *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 ~2s, the memory cue is presented with an instructional cue ('immerse' or 'distance') for 20s, 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.

Table 1 Demographic Characteristics

Scale or Clinical Characteristic	**Total Sample**		**SSRI Group**		**DBT Group**	
N	35		19		16	
	Mean	**SD (Range)**	**Mean**	**SD (Range)**	**Mean**	**SD (Range)**
Age	27.8	8.16 (18-59)	26.95	6.20 (18-44)	28.81	10.13 (20-59)
Education, Years	15.71	1.76 (13-21)	15.58	1.71 (14-21)	15.88	1.86 (13-21)
BDI T_1	29.14	10.73 (12-54)	29.63	8.95 (12-45)	28.56	10.73 (12-54)
BDI T_2	15.94	12.11 (0-43)	16.63*	11.41(0-43)	15.13*	13.22 (0-41)
	%		**%**		**%**	
Sex (Female)	100.00		100		100	
Prior Suicide Attempt	83		79		88	
Current MDD	71		79		63	
Lifetime MDD	89		90		88	
Race						
Asian	6		5		6	
Pacific Islander	3		5		0	
African American	11		11		14	
Caucasian	60		58		62	
Multiple	20		21		19	
Hispanic	17		11		25	

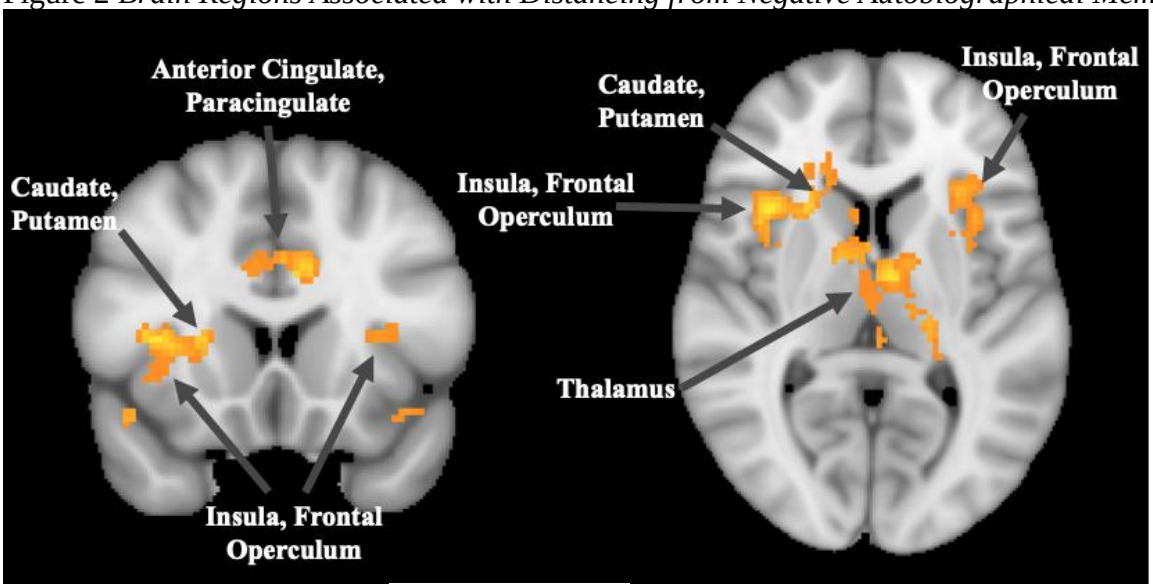
Note: BDI= Beck Depression Inventory. SD= standard deviation. MDD= Major Depressive Disorder. $T_{1=}$ pretreatment T_2=Postreatment. * Reduction if depression severity (p<.001) from T_1 to T_2 for both DBT and SSRI treatment groups (p<.001).

Table 2 *Brain Regions Associated with Distancing from Negative Autobiographical Memories*

Brain Region	**k**	**Z-score**	**X**	**Y**	**Z**
Brain Stem	187	3.50	46.28	48.47	31.34
Central Opercular Cortex	41	3.41	36.05	66.34	38.73
Cingulate Gyrus, anterior division	279	3.52	46.94	72.74	50.42
Cingulate Gyrus, posterior division	12	3.35	41.83	44.33	36.5
Frontal Operculum Cortex	155	3.53	43.06	71.56	40.14
Frontal Orbital Cortex	177	3.38	60.01	76.33	32.19
Frontal Pole	61	3.50	57.31	82.66	44.43
Insular Cortex	321	3.54	37.70	69.02	37.68
Left Caudate	33	3.45	52.12	61.15	44.85
Right Caudate	17	3.34	39.88	67.12	40.82
Left Putamen	24	3.32	57.21	63.38	41.71
Right Putamen	10	3.55	32.40	70.30	37.6
Left Thalamus	239	3.41	48.66	56.20	39.54
Right Thalamus	57	3.31	43.30	56.68	39.37
Paracingulate Gyrus	107	3.49	49.15	79.54	48.13
Parahippocampal Gyrus, anterior division	10	3.37	51.90	52.60	25.8
Parahippocampal Gyrus, posterior division	26	3.35	53.42	49.81	27.23
Temporal Pole	99	3.48	20.17	69.33	31.36

Note: 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.

Figure 2 *Brain Regions Associated with Distancing from Negative Autobiographical Memories*



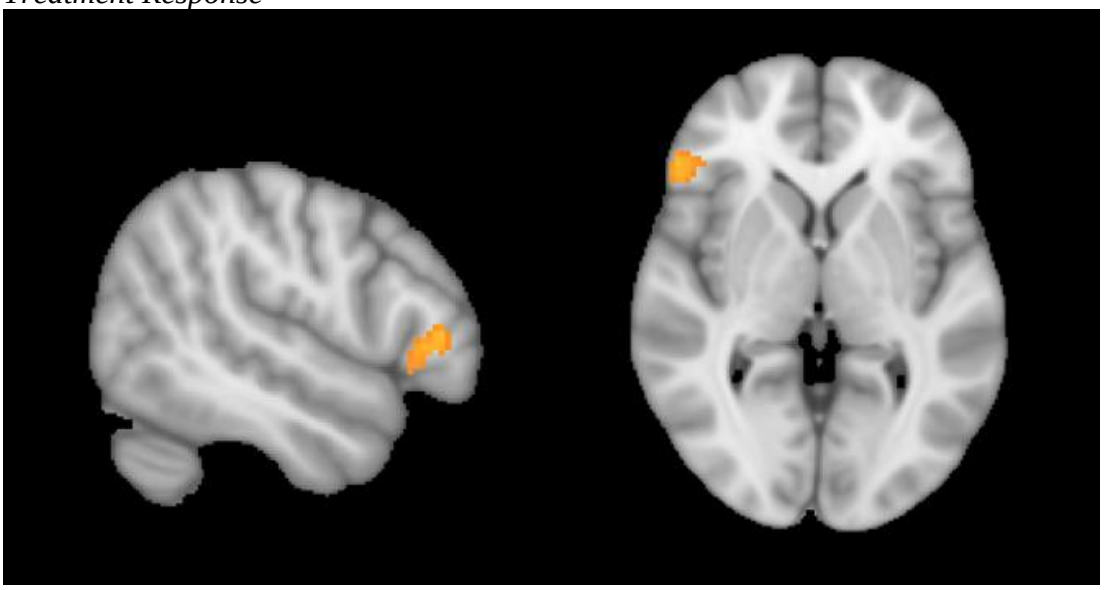
Note: Thresholded activation 3.1 5.3. Brain regions for the distance>immerse contrast are shown above. Left image =coronal view; right =axial view. All analyses thresholded at voxel-p<0.001, cluster-p <0.05.

Table 3 *Brain Regions During Distancing Associated with Differential Treatment Response*

Brain Region	**k**	**Z score**	**X**	**Y**	**Z**
Right Frontal Pole	26	3.25	21.42	81.27	35.46
Right Inferior Frontal Gyrus, pars triangularis	104	3.52	18.69	77.87	37.25

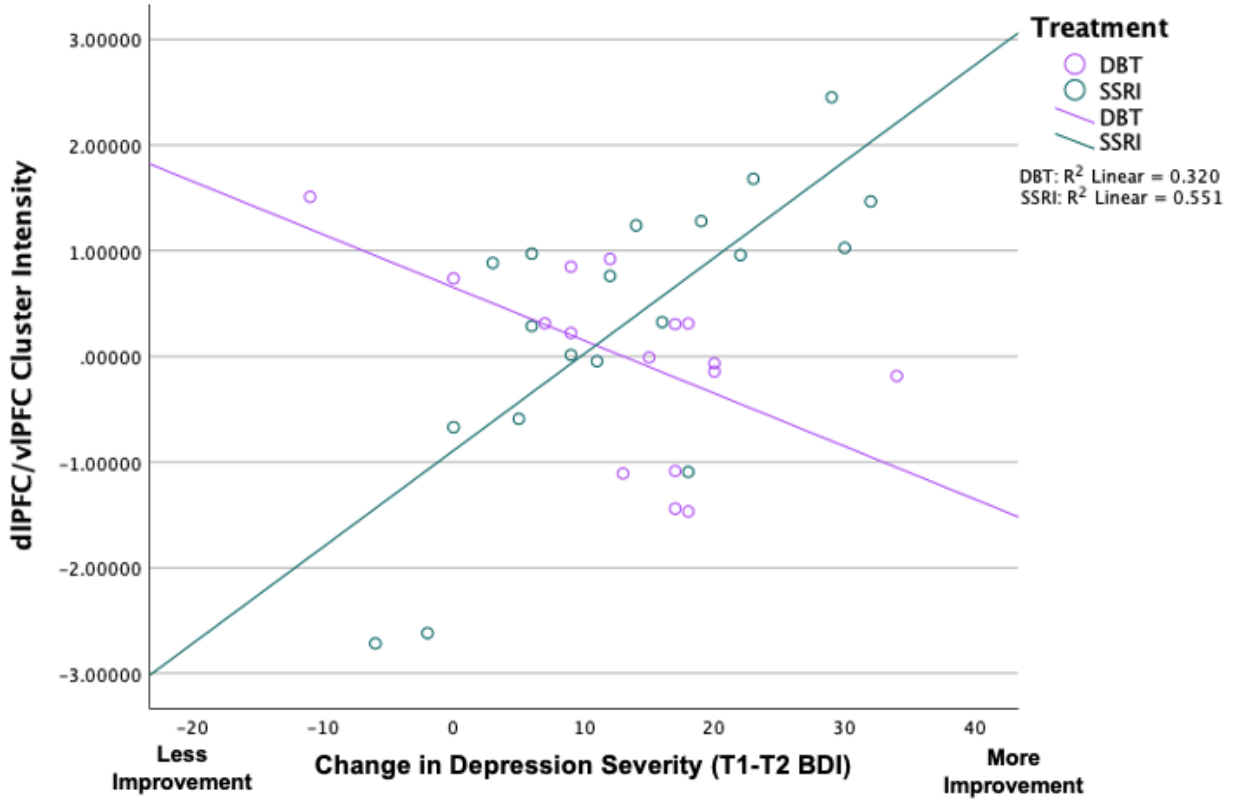
Note: k=number of voxels, voxels 3×3×3 mm. X, Y, Z coordinates are for center of gravity (COG) for the region. The COG coordinates for the region are a weighted average of the coordinates by the intensities within the brain region. Z-score represents average Z score for that region. Brain regions are 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 x BDI scores at post-treatment, controlling for baseline BDI scores.

Figure 3a *Activation in Prefrontal Cluster During Distancing Associated with Differential Treatment Response*



Note: Thresholded activation images 3.1 5.3. N=35. BDI= Beck Depression Inventory Cluster. Left image=sagittal view; right =axial view. All analyses thresholded at voxel-p<0.001, cluster-p <0.05. Activation in a cluster spanning the right dlPFC and vlPFC differentially predicted BDI scores at posttreatment, while controlling for baseline BDI scores. Individuals with greater activation in dlPFC/vlPFC during distancing had with greater symptom improvement with SSRIs, while those with less dlPFC/vlPFC activation at baseline had greater improvement from DBT.

Figure 3b *Activation of dlPFC and vlPFC During Distancing and Change in Depression Severity by Treatment Type*



Note: N=35. BDI: Beck Depression Inventory. DBT: Dialectical Behavior Therapy. SSRI: Selective Serotonin Reuptake Inhibitor. dlPFC: dorsolateral prefrontal cortex. vlPFC: ventrolateral prefrontal cortex. Y-axis represents the average intensity of cluster spanning the dlPFC and vlPFC 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 during distancing had with greater symptom improvement with SSRIs, while those with less dlPFC/vlPFC activation at baseline had greater from DBT.