8-1-2021

Effects of Dialectical Behavior Therapy on Body Modification in Borderline Personality Disorder

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EFFECTS OF DIALECTICAL BEHAVIOR THERAPY ON BODY MODIFICATION IN BORDERLINE PERSONALITY DISORDER

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

August 27, 2021

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ABSTRACT

Borderline Personality Disorder is a mood disorder characterized by emotional dysregulation, increased impulsivity, and increased self-harm. Recently, a positive correlation has been made relating number of body modifications (such as piercings, tattoos, and scarification) and severity of disease. Dialectical Behavior Therapy is the first-line treatment for Borderline Personality Disorder and has been found to significantly reduce engagement in another form of self-harming behavior (non-suicidal self-injury). However, the effects of Dialectical Behavior Therapy on body modification are not understood. **In this randomized control study, we will compare the effects of Dialectical Behavior Therapy, pharmacotherapy, or non-treatment on the number of body modifications in participants with untreated Borderline Personality Disorder.** Additionally, fMRI data will be obtained to better understand the neural mechanisms underlying engagement in body modification. This study will allow providers to better understand, recognize, and treat individuals with Borderline Personality Disorder who engage in frequent body modification.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Borderline Personality Disorder (BPD) is a mood disorder characterized by a pervasive pattern of instability in an individual's interpersonal relationships, personal identity, impulsivity, and affect.[1-3] These characteristics are further outlined by the DSM-V Diagnostic Criteria for BPD (Table 1), of which an individual must meet five out of nine criteria in order to be diagnosed.[3] When studied in the general United States population, epidemiologic studies suggest that the prevalence of BPD has a broad range, occurring in anywhere from 0.5%-5.9% of the population with a median prevalence of 1.35%.[4-6] Yet when studied in a clinical setting, this prevalence increases to 15-25%, demonstrating that a large portion of the population goes undiagnosed and thus untreated.[7]

Table 1. DSM-V Diagnostic Criteria for Borderline Personality Disorder

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
1. Frantic efforts to avoid real or imagined abandonment. (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance misuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
5. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

Source: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, 2013, American Psychiatric Association.

Even though BPD is underdiagnosed in the United States, a substantial amount of research has been conducted to identify the most efficacious treatment options for patients who are ultimately diagnosed with BPD. Current evidence does not support the use of pharmacotherapy alone in BPD, but the use of pharmacotherapy to target specific BPD symptoms such as affective dysregulation, impulsive-behavioral dysregulation, paranoia, or dissociation has been shown to be effective.[1] For example, Selective Serotonin Reuptake Inhibitors (SSRIs) such as fluoxetine, sertraline, and venlafaxine have been found to decrease affective dysregulation and impulsive-behavioral dysregulation, while neuroleptics such as haloperidol have demonstrated effectiveness in managing symptoms of behavioral dysregulation, paranoia, and dissociation.[1]

Rather than pharmacotherapy alone, the current first-line treatment for BPD is psychotherapy. Dialectical Behavior Therapy (DBT), a form of psychotherapy developed by Dr. Marsha Linehan in the 1990s, has the most evidence for the treatment of BPD.[1,2,8] DBT involves four components: a weekly skills training group, a weekly hour-long individual psychotherapy session, telephone consultation between sessions as needed, and a weekly therapist consultation team meeting.[8] Most trials evaluating the efficacy of DBT in the treatment of BPD have been 12 months in duration, though studies are underway to evaluate the efficacy of six-month programs as an alternative for patients.[9] Ultimately, the goal of DBT is to allow for people with BPD to be able to self-recognize maladaptive behavior, and then apply both problem-oriented and supportive techniques to better manage their behavior.[8,10]

One kind of maladaptive behavior is described in criterion 5 of the DSM-V criteria for the diagnosis of BPD: the engagement in recurrent suicidal gestures, or threats, or non-suicidal self-injury (NSSI) such as skin cutting, scraping, scratching, burning, or scarring.[3] It has been hypothesized that recurrent self-harm in BPD may be due to altered pain perception. In experimental paradigms where individuals with BPD were exposed to painful physical stimuli, researchers not only found a generalized reduction of pain perception in the group of participants with BPD, but they also found that those who engaged in either NSSI or indirect self-injury demonstrated an increased pain threshold and endurance compared to healthy control participants.[11,12] Functional magnetic resonance imaging (fMRI) has been used to extend these behavioral findings to understand the underlying neural mechanisms. In one such study, patients with BPD demonstrated an increased response in the dorsolateral prefrontal cortex (dlPFC) and deactivation in the anterior cingulate and amygdala when exposed to painful thermal stimuli.[13]

In addition to understanding the behavioral and neural mechanisms of NSSI, it is important to consider the ways in which it may be possible to treat or reduce engagement in these self-harming behaviors. A recent study has aimed to better understand the effects of 12 weeks of DBT compared to treatment as usual in a group of people with BPD who engaged in frequent NSSI.[14] In this study, treatment as usual was defined as non-DBT treatment that participants were participating in prior to study initiation (outpatient psychotherapy, residential crisis intervention, pharmacotherapy, self-help, and non-specific community-based treatment).[14] While there was no significant change in pain threshold identified following 12 weeks of DBT, it did appear that there were significant

changes in neural mechanisms. When analyzing the amygdala, these researchers found a neural deactivation in response to painful stimuli at baseline, which was no longer present in participants who received treatment with DBT.[14] This research suggests that DBT may alter the neural mechanisms underlying pain response, as well as reduce engagement in NSSI.[15]

To this point, most research has focused primarily on either suicidal behavior or NSSI, with little insight into a subset of different behaviors deemed "body modification." Body modification is defined as "the process of purposefully altering previously unaltered parts of the body"[16] and may include engagement in activities such as piercings, tattooing, scarification, pubic hair removal, or cosmetic surgery.[17] Specific body modifications, such as tattooing, have been found to be associated with a diagnosis of personality disorder, yet were previously only anecdotally related to BPD specifically.[18] More recently, the number of BPD features or severity of disease and total number of body modifications have been positively correlated.[17] Given the dearth of research within this area of BPD, there lacks a firm understanding of the etiology or neural circuitry underlying this relationship. Further research is needed to identify if individuals with BPD who engage in frequent body modification demonstrate an increased pain threshold and endurance like those who engage in frequent NSSI. Additionally, while it is understood that DBT can be utilized to reduce a patient's engagement in suicidal behaviors or NSSI,[15,19-22] we do not know the effect of DBT on engagement in body modification in patients with BPD. Ultimately, while body modification does not appear to be inherently harmful as is NSSI or suicidal behavior, researchers do not yet have a firm understanding of the motivation for, underlying neural mechanisms of, and effects of

treatment on body modification in people with BPD. This information will be an important diagnostic and prognostic tool for clinicians to utilize when treating individuals with BPD.

1.2 STATEMENT OF THE PROBLEM

The effect of DBT on engagement in body modification as well as the underlying neural mechanisms of pain response in people with BPD, has not yet been adequately studied. It is worthwhile to explore this topic so that providers can gain a better understanding as to whether the treatment modality recommended for suicidal behavior and NSSI, is also beneficial for patients engaging in frequent body modification or if it modifies their engagement in body modification. Additionally, by further understanding the possible relationship between pain response and engagement in body modification, providers will be better equipped to discuss the etiology of this behavior with their patients.

1.3 GOALS AND OBJECTIVES

This randomized controlled trial (RCT) serves to look at the effects of 12 weeks of DBT compared to pharmacotherapy alone or no treatment on the mean number of body modifications and pain response in patients with previously untreated BPD. Patients diagnosed with BPD who have engaged in body modification frequently within the past six months and who are not currently receiving BPD-directed therapy (either pharmacotherapy or behavioral therapy such as DBT) will be recruited for this study. Baseline measurements of number of body modifications will be obtained using the Body Modification Questionnaire (BMQ), as well as pain tolerance as measured by QST, and neural response as measured by fMRI. Participants will be randomized into one of three

groups: DBT, pharmacotherapy, and non-treatment. DBT will be provided by a single post-doctoral student and pharmacotherapy will be prescribed by the site's Principal Investigator (PI), Dr. Fineberg. Following 12 weeks, the baseline measurements will be repeated to evaluate the effects of the randomized intervention.

1.4 HYPOTHESIS

Among adults diagnosed with BPD there will be a significant reduction in mean number of body modifications following completion of 12 weeks of Dialectical Behavior Therapy compared to groups randomized to pharmacotherapy or no treatment.

1.5 DEFINITIONS

Body Modification: process of purposefully altering previously unaltered parts of the body and may include engagement in activities such as piercings, tattooing, scarification, pubic hair removal, or cosmetic surgery.

Dialectical Behavior Therapy (DBT): a form of psychotherapy developed in the 1990s with the most evidence-based support for the treatment of BPD.

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Chapter 2 – Review of the Literature

2.1 INTRODUCTION

An exhaustive literature search was conducted between July 2020 and August 2021 using Ovid, MEDLINE, PubMed, Scopus, APA PsycBooks, and APAPsycExtra. Terminology used in the primary literature search included "Borderline Personality Disorder" OR "DBT" AND "body modification" OR "tattoo" OR "body piercing" OR "scarification". Additional search terms included "Dialectical Behavior Therapy", "DBT", "pain", "pain processing", "pain threshold", "pain response", "pain adaptation", "altered pain response", "fMRI", "functional magnetic resonance imaging", "magnetic resonance imaging", "trauma", "NSSI", "non-suicidal self-injury", "childhood abuse", "childhood trauma", "quantitative sensory testing", "method of limits", "age", and "impulsivity". Studies were deemed relevant based on their title and subsequent review of their abstracts. The full article for each relevant study was obtained, reviewed, and if relevance remained, were included in this study's literature review. Additional resources and studies were obtained by utilizing those referenced in sources already deemed relevant to this study. The studies included in this literature review were those with a study population of individuals between the ages 11-65 years old and participants diagnosed with either a personality disorder or borderline personality disorder. The designs of studies included were randomized control trials, non-randomized trials, meta-analyses, systematic reviews, and case reports.

2.2 REVIEW OF EMPIRICAL STUDIES ABOUT THE RELATIONSHIP BEING STUDIED

2.2.1 *DBT as the first-line treatment for BPD*

DBT was first developed by Dr. Linehan in the 1990's to treat people with BPD.[1] It is based on cognitive behavioral therapy and utilizes multiple components in order to help individuals better manage emotional, behavioral, and interpersonal dysfunction. DBT typically consists of one year of weekly skills training groups, weekly hour-long individual psychotherapy sessions, telephone consultation between sessions as needed, and weekly therapist consultation team meetings.[2] More specifically, the skills training group aims to make people with BPD aware of common behavioral skill deficits related to self-identity, interpersonal relationships, emotion control and awareness, thoughts of abandonment, and impulsivity.[2] It then uses training modules in four key areas (core mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance) to teach these individuals to recognize maladaptive thoughts or actions and to learn new non-maladaptive, more effective coping methods to respond.[2]

A great deal of research has been conducted to identify the effectiveness of DBT in reducing severity of BPD symptoms and engagement in suicidal behavior or NSSI. One of the first studies conducted was by Dr. Linehan in 1991, and it compared the effects of DBT to no treatment in parasuicidal people with BPD.[3] Parasuicidal behavior was defined in this study as "any intentional, acute self-injurious behavior with or without suicidal intent, including both suicide attempts and self-mutilative behaviors."[3] This study found that there was a significant decrease in the engagement in parasuicidal behavior in individuals that were randomized to the DBT arm compared to no treatment.[3] There have been numerous studies since these initial investigations that have provided empiric evidence supporting the efficacy of DBT in the treatment of BPD.[4-9] Most recently, a meta-analysis was completed to assess the effects of various psychological

therapies in people diagnosed with BPD.[4] Included in the review were RCTs which compared a variety of psychotherapy modalities, primarily DBT and mentalization-based treatment (MBT) to treatment as usual (either community treatment or any treatment which was not the experimental treatment being studied) or a waiting list. Findings from this analysis revealed that "DBT was more effective at reducing BPD severity, self-harm, and improving psychosocial functioning,"[4] than other forms of treatment. This evidence has provided the framework for the American Psychiatric Committee Practice Guidelines, which currently recommend psychotherapy as the first-line treatment for BPD.[10]

2.2.2 *Non-suicidal self-injury (NSSI) in individuals with BPD*

The DSM-V outlines the diagnostic criteria for BPD (Table 1); patients must meet five of nine criteria to receive a diagnosis of BPD. Criterion five describes engagement in recurrent suicidal gestures or threats, or self-mutilating behavior such as NSSI or body modification. NSSI can include behaviors such as cutting, burning, scratching, self-hitting, head banging, bone breaking, hair pulling, nail biting that results in bleeding, or interfering with wound healing.[11] Engagement in NSSI occurs in a higher percentage of people with BPD[12] and has a prevalence from around 4-5.9% of the general adult US population.[11] Many studies have found that prior to NSSI, individuals typically endorse negative feelings or emotions such as sadness and frustration, but that there is a significant improvement in these emotions following completion of NSSI.[13-16] This data suggests that NSSI serves as a method for people with BPD to achieve immediate relief from stressors and negative emotions.

2.2.3 *Body modification in patients with BPD*

Unlike NSSI, little research has been conducted to better understand a subset of self-mutilating behavior considered under criterion five of the DSM-V diagnostic criteria for BPD known as "body modification." As previously discussed, body modification is the process of purposefully altering the body through either permanent or non-permanent methods such as piercing, tattooing, scarification, pubic hair removal, or cosmetic surgery.[17,18] While other non-painful and non-permanent methods of body modification (wearing thick makeup) have been found to be related to BPD,[19] this paper will focus primarily on painful and permanent body modifications.

Prior research has demonstrated a correlation between body modification and different forms of psychological and personality disorders.[20-24] Since this relationship was demonstrated, physicians and researchers have anecdotally reported a positive correlation between BPD specifically and repeated engagement in forms of body modification such as piercing and tattooing.[25,26] These claims have been further supported by research conducted by Manuel and Retzlaff who studied the relationship between psychopathology and tattooing in 8,574 prison inmates.[27] These researchers found a significant correlation between BPD pathology and engagement in tattooing.[27] More recently, researchers have demonstrated a statistically significant correlation between the total number of body modifications a person engages in and the number of BPD features that they demonstrate.[17] This research demonstrates that like NSSI and suicidal behavior, there is likely a relationship between engagement in body modification and diagnosis of BPD. However, unlike NSSI and suicidal behavior, there is no research to date demonstrating if DBT has any effect on further engagement in body modification or if body modification leads to relief of negative stressors or emotions.

2.2.4 *Altered pain response in patients with BPD*

As researchers have gathered evidence supporting the relationship between BPD and engagement in suicidal behavior, NSSI, and body modification, they have also begun to research the etiology of this behavior. Prior studies have demonstrated that engagement in such behavior may likely be related to a key feature of BPD: hyposensitivity to pain.[28] This concept has been further studied through the application of painful stimulation using various modalities, which include the following: thermal stimuli (Cold Pressor Test or other methods of applying heat stimuli),[29-36] tactile or mechanical stimuli (Tourniquet Pain Test, small incisions, or electrical stimulation via probes),[31,37-41] or injections.[38] When utilizing these modalities in order to elicit a pain response in participants, these studies have consistently found that compared to healthy control participants, individuals with BPD report decreased pain ratings,[30-35,37,38] demonstrate an increased pain threshold (point which onset of pain is reported),[30,31,34,35,38-41] are able to adapt to pain faster,[29] and tend to demonstrate a higher level of tolerance for pain (point at which participants physically withdraw from a painful stimulus).[42] Additional research has demonstrated that this reduction in response to and perception of painful stimuli in people with BPD is further reduced during periods of increased stress.[31,39] In sum, this data allows researchers to conjecture that there may be a relationship between these decreased pain thresholds and increased pain tolerance, and engagement in potentially painful behaviors such as NSSI or body modification.

2.2.5 *Functional magnetic resonance imaging (fMRI) to evaluate alterations in pain processing in patients with BPD*

While it is established that people with BPD report an increased pain threshold[30,31,34,35,38-41] and greater tolerance for pain,[42] it is important to understand the underlying neural processing of pain and how this may differ in BPD. Researchers have combined fMRI with various methods intended to cause physical or imagined pain in order to evaluate the underlying pathways and structures involved in pain processing in healthy control subjects. These studies have revealed that there is significant activation in both the anterior cingulate cortex (ACC),[43,44] dorsolateral prefrontal cortex (dlPFC),[45] primary and secondary somatosensory cortex, and anterior and posterior insula.[46]

Prior research has helped to elucidate the potential roles which these brain regions may play in processing information. Research conducted by Sakagami and Watanabe, suggests that the dlPFC is responsible for integrating "cognitive and motivational context to enable adaptive goal-directed behavior." [47] Yet while integrating information to guide behavior is one role of the dlPFC, it serves several additional functions such as adaptive decision making, action planning, and self-control.[48,49] A systematic review completed by Apkarian, Bushnell, Treede, and Zubieta provides evidence that the primary and secondary somatosensory cortexes, insular cortex, and ACC are activated in response to both physical painful stimuli and emotional pain.[50]

Schmahl, Bohus, Esposito, et al evaluated how the neural processing of pain may differ in a group of individuals with BPD.[35] They accomplished this through a case-control study in which they recruited 12 females diagnosed with BPD and 12 healthy age-matched female controls.[35] These participants were exposed to heat stimuli using a TSA-II sensory tester and underwent an fMRI scan using a 1.5 Tesla MRI scanner. Image analysis demonstrated that when comparing participants with BPD to healthy controls,

there was a significant difference in activity in the dlPFC, posterior parietal cortex (PPC), ACC, and amygdala.[35] More specifically, participants with BPD demonstrated lower activity in the right PPC and increased activity in the left dlPFC during the early phase of temperature stimulation.[35] During the late phase of temperature stimulation, there was less activity in the perigenual region of the ACC, left temporal pole, and right amygdala.[35] This study demonstrates that when exposed to painful stimuli, there is increased activity in the left dlPFC and decreased activity in the ACC in people with BPD compared to healthy control participants.

While additional research is required in order to provide more than just speculation, it is important to consider what alterations in these specific brain regions may mean or how they may contribute to BPD symptomatology. Prior research has demonstrated that increased connectivity between the ventral striatum and dlPFC during reward conditions serves to reinforce behavior.[51] Meanwhile, Schmahl, Bohus, Esposito, et al. demonstrate an increase in dlPFC activity during the early stages of painful stimuli in participants with BPD.[35] Taking both findings together may suggest a mechanism of positive reinforcement mediated by the enhanced connectivity between the ventral striatum and the dlPFC and subsequent activation of dlPFC in response to painful stimuli. This may help to explain why people with BPD continue to engage in behavior which elicits a similar pain response.

Additionally, Schmahl, Bohus, Esposito, et al. found there to be decreased activity in the ACC during the late stage of temperature stimulation in participants with BPD compared to healthy control participants.[35] Given the role of the ACC in processing both physical and emotional pain,[50] this finding may suggest a modified pain response in

people with BPD such that they are able to acclimate to pain faster. While this is one possible explanation, one could imagine that this may also be demonstrative of an altered pain response like that found in patients with chronic or clinical pain conditions. The Apkarian, Bushnell, Treede, and Zubieta meta-analysis found data to suggest a decreased activation of the primary and secondary somatosensory cortexes, insular cortex, and ACC during noxious stimuli in participants with a clinical pain condition compared to normal participants.[50] When considering these findings, one could speculate that people with BPD may repeatedly engage in painful behavior due to changes in the neural mechanisms responsible for processing pain, like that seen in chronic pain conditions.

2.2.6 *Effects of DBT on pain sensitivity and pain processing*

It is understood that DBT is the first-line treatment for BPD symptomatology (including engagement in NSSI and suicidal behavior)[10] and that individuals with BPD demonstrate alterations in brain activation in response to painful stimuli,[35] but recent studies have been conducted in order to learn more about the relationship between these variables. Niedtfeld, et al. compared participants with BPD receiving DBT treatment, participants with BPD receiving treatment as usual, and healthy control participants in order to further understand the effects of DBT on pain sensitivity and the "affect-regulating function of pain."[52] All BPD participants met DSM-IV criteria for BPD, and all engaged in frequent NSSI during the six months prior to study participation. This study included two fMRI scans separated by 12 weeks during which participants were subjected to both photos and temperature stimuli. This study found that like prior studies, there is a deactivation of the amygdala in response to painful stimuli, but that this was no longer present after 12 weeks, in patients enrolled in DBT.[52] Additionally, Niedtfeld, et

al. found that individuals with BPD demonstrated a decreased sensitivity to painful stimuli, but that this was not normalized following DBT.[52] In sum, these researchers were able to reproduce prior findings of reduced sensitivity to pain in people with BPD and the ability of DBT to normalize pain-mediated affect regulation, but were unable to provide evidence that DBT has an effect on altering pain sensitivity in BPD.[52]

2.3 REVIEW OF STUDIES TO IDENTIFY POSSIBLE CONFOUNDING VARIABLES

The first confounding variable to be controlled for is medical history. This study will exclude participants with the following conditions: any serious medical or neurological illness, traumatic brain injury, schizophrenia, bipolar (Type I) disorder, current Major Depressive Disorder (MDD) within the past 6 months, developmental disorders such as Attention Deficit Disorder (ADD) or Attention Deficit Hyperactive Disorder (ADHD), chronic pain disorder, peripheral neuropathy, loss of consciousness, or a substance use disorder. It is important to control for these diagnoses for several reasons as outlined by the DSM-5.[53] Serious medical or neurological illnesses can lead to personality changes, some developmental conditions (ADD or ADHD) can lead to challenges with identity, and individuals with a substance use disorder or episodes of MDD and bipolar disorder can have in-the-moment behavior almost identical to that of BPD.[53] These conditions have the possibility to confound this study's sample size and inadvertently allow for the recruitment of patients with diagnoses other than BPD, making it important to exclude these conditions.

A second variable which will be controlled for is medication use. This study will control for medications by excluding the following: chronic NSAID use, opioids, opioid

replacement therapy (such as methadone, suboxone, buprenorphine, or naltrexone), topiramate, lamotrigine, lithium, benzodiazepines, and muscle relaxants. More specifically, because this study is looking at pain tolerance and endurance, potential participants who engage in chronic NSAID use (daily use for greater than one year) will be excluded.[54]

A third category of possible confounding variables for which will be controlled for includes demographics such as age, sex, race, and education. Prior research conducted by Vizgaitis and Lenzenweger found that women endorsed a greater number and variety of body modifications compared to men in their sample.[17] Because of this, it is important to make sure that sex is controlled for by attempting to recruit a sample consisting of approximately equal numbers of males and females. A second demographic important to control for is age, due to its possible effect on impulsivity. To date, some studies have illustrated that there appears to be increased impulsiveness in younger adults, with a reduction of this impulsivity and a subsequent reduction in suicidal behavior as individuals with BPD get older.[55-57] Yet despite this evidence, some research refutes this, with data suggesting that there is no statistically significant difference in impulsiveness, suicidal behavior, or self-harm in younger versus older adults.[58] Each of these studies divided their participants into either two (younger and older adults),[56] three (young, middle-aged, and older adults),[57,58] or four groups (adolescents, young adults, middle-aged adults, and old adults).[55] Given significant discrepancy in data, this current study will control for age by only allowing for the recruitment of participants between the ages of 18 and 65.

A final possible confounding variable is history of childhood abuse or trauma. In a retrospective study looking at individuals with BPD admitted to an inpatient psychiatric unit, a significant correlation was made between prolonged childhood sexual abuse and rate of engagement in NSSI, number of suicide attempts, cigarette smoking, alcohol use, and sexual impulsivity.[59] This data suggests that in people with BPD, a history of childhood sexual abuse may lead to an increased likelihood of later engaging in self-injurious or painful behavior. Since this study is looking at painful forms of body modification, one could suspect that childhood trauma could be a potential confounding variable. In order to assess for history of childhood trauma, the Early Trauma Inventory–Self Report-short form (ETISR-SF) will be completed at the baseline visit. Data from this questionnaire and any differences in trauma history that exists between treatment groups will be considered during data analysis and interpretation.

2.4 REVIEW OF RELEVANT METHODOLOGY

2.4.1 *Study Design*

2.4.1.1 DBT Program

Participants enrolled in this study will be randomized to one of three conditions: 12 weeks of outpatient DBT, pharmacotherapy alone, or non-treatment. While DBT programs are traditionally outpatient and one year in duration, inpatient programs of a shorter duration have also been found to be effective. Bohus, et al. conducted a pilot study in which they established and evaluated the efficacy of a 12-week inpatient DBT treatment program.[60] Analysis of their data demonstrated that after 12 weeks of inpatient DBT, patients demonstrated a decrease in self-injury, dissociation, anxiety, global stress, and improvement in depressive symptoms.[60]

These results were further supported by a trial which enrolled female participants diagnosed with BPD (who engaged in NSSI or had one suicide attempt within the past 2 years) into a 12-week inpatient DBT program.[61] These researchers compared this treatment group to a control group of participants diagnosed with BPD who were on a waiting list to enroll in DBT.[61] In this trial conducted by Bohus, et al., the inpatient DBT program followed DBT guidelines as set forth by Linehan and included the following: individual therapy (2 hours/week), group skills training (2 hours/week), group psychoeducation (1 hour/week), peer group meetings (2 hours/week), mindfulness group (1 hour/week), individual body-oriented therapy (1.5 hour/week), and therapist team consultation meetings (2 hours/week).[1,61] Results from this study demonstrated that following 12 weeks of inpatient DBT, patients demonstrated reductions in self-injury, greater clinical improvement, and improvements in "dissociation, depression, anxiety, interpersonal functioning, social adjustment, and global psychopathology."[61]

While researchers have demonstrated a benefit from 12 weeks of inpatient DBT in people with BPD, researchers are now beginning to evaluate the efficacy of outpatient DBT programs of reduced duration.[62-64] One such group of researchers were able to demonstrate a "partial remission" (as demonstrated by statistically significant improvements in the Beck Depression Inventory, Symptom Checklist, and Borderline Symptom List 95) in people with BPD following 12 weeks of DBT in a day clinic setting.[63] A similar study employed a 14-week outpatient DBT program for individuals with BPD, and found a significant reduction of the severity of borderline symptoms after study completion.[62] This research demonstrates that outpatient intensive (12 to 14 weeks)

DBT programs can also be successful in improving and managing symptoms in people with BPD.

2.4.1.2 fMRI Procedure

All participants enrolled in this study will complete two fMRI sessions, one session at baseline prior to randomization and the second session after completion of the 12-week intervention. In a study conducted by Niedtfeld, et al., BPD participants receiving DBT treatment, were compared to those receiving treatment as usual and to healthy control subjects.[52] These participants completed two fMRI sessions (using a 3T MRI scanner), one session at baseline and a second session 12 weeks later.[52] This study was successful in finding significant differences in brain activation in the dlPFC and left amygdala, which were no longer present after 12 weeks of treatment with DBT.[52]

2.4.1.3 Pain Thresholds

Quantitative sensory testing (QST) is frequently utilized in order to evaluate an individual's temperature threshold and pain response.[65] The method of limits is one technique that can be applied and is a standard for conducting QST.[66] This method was first used by Fruhstorfer, Lindblom, and Schmidt in order to compare "thermal sensibility" in subjects with neurological disorders compared to healthy control subjects.[67] Frushstorfer used a thermostimulator and constant current source in order to determine warm, cold, heat pain, and cold pain thresholds in participants.[67] To determine the warm and cold thresholds, the thermostimulator was first applied to subjects' skin and they were asked to reverse a switch when they felt the stimulator getting warm.[67] Once they did this, the current would reverse, causing the stimulator to become cool.[67] Subjects were then advised to reverse the switch a second time once they began to feel the

stimulator getting cold.[67] This was continued for a total of two minutes, during which time the temperatures at which the switch was reversed were recorded.[67]

Once the warm and cold thresholds were established, each subject's cold pain and warm pain thresholds were determined. To do so, a baseline temperature of 30°C was applied to the subjects' skin and this temperature was decreased at a rate of either 1.0°C/second or 1.5°C/second (depending on the skin area).[67] Subjects were advised to activate the switch when the stimulus was painful, which reversed the current. Temperature was then increased at a rate of either 1.0°C/second or 1.5°C/second, and subjects were again asked to activate the switch when the stimulus was perceived as painful.[67] This method was found to be successful in quickly and reliably determining temperature thresholds in study subjects. The method of limits has been used to evaluate temperature perception at various parts of the body (volar distal forearm, thenar eminence, lower medial calf, and lateral dorsal foot).[68] Recommendations from current research, suggest using a baseline temperature of 32°C and a 1°C/second rate of temperature change.[68]

Heat pain and cold pain thresholds have been studied in BPD using similar methods.[52] Like the method established by Fruhstorfer, Lindblom, and Schmidt, one recent study conducted by Niedtfeld, et al. delivered temperature stimuli to the skin of participants using a Thermal Sensory Analyzer II.[52] They utilized a baseline temperature of 38°C, which was either increased or decreased at a rate of 2°C/second in order to apply three ascending and three descending temperature stimuli, and patients were asked to press a button once they perceived the stimulus to be painful.[52] Using this information,

these researchers were then able to determine an individualized painful stimulus which would be administered during each participant's fMRI scan.[52]

2.4.2 *Study Setting*

DBT has been found to be an effective treatment regimen for patients with BPD in both inpatient and outpatient settings.[4,6,7,60-64,69] There does not appear to be data demonstrating that either setting is preferred. When administered on an outpatient basis, studies have frequently included selection criteria stating that participants must live within a certain radius in order to maximize engagement in further outpatient DBT sessions and to limit rate of attrition.[61]

2.4.3 *Selection Criteria*

Participants must meet DSM-V criteria for BPD as outlined in Table 1.[53] Additionally, both the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-I and SCID-II)[70] and the Diagnostic Interview for Personality Disorders (DIPD) BPD questions[71] will be utilized to confirm that study participants meet the diagnostic criteria for BPD. Participants who meet ≥5/9 of the DIPD criteria will be included. The age range of eligible participants is 18-65 years of age. Comparable studies have included similar age ranges and typically have an average age of 29-30 years old.[31,38,54,72]

Participants that engage in frequent body modification will be selected and included in this study. Prior studies looking at self-mutilating behavior and NSSI demonstrate a wide variability in what is considered "frequent" or "recent" behavior. In one study looking at NSSI in individuals with BPD, participants were required to have a history of "at least three incidents of self-mutilating behavior, in the absence of pain, within the past 2 years,"[31] while a similar study, required participants to have engaged in

NSSI at least once within the past month.[54] Other comparable studies do not specify that its participants needed to engage in a specific number of self-injurious behaviors or NSSI in order to be eligible for participation. One of these studies found that there was a range from one single episode to up to eight times per month (with an average of 3 times per month),[38] while another found that its participants "committed NSSI at least once per week during the preceding 6 months."[41] In general, when evaluating the severity of a disease, clinicians typically rate a patient's symptoms on a scale of mild, moderate, or severe. Yet current research demonstrates that there does not yet exist a standardized method for classifying individual's frequency or recency of NSSI or body modification into one of these categories in order to determine severity of behavior (mild, moderate, or severe). Because of this, our study will model itself after St. Germain and Hooley[54] and require that participants have engaged in body modification at least once within the past month.

Each participant's past medical history will be carefully reviewed to determine study eligibility. Exclusion criteria will include the following: history of any serious medical or neurological illness, traumatic brain injury, schizophrenia, bipolar (Type I) disorder, current Major Depressive Disorder (MDD) within the past 6 months, developmental disorders such as Attention Deficit Disorder (ADD) or Attention Deficit Hyperactive Disorder (ADHD), chronic pain disorder, peripheral neuropathy, loss of consciousness, or a substance use disorder. It is important to control for these diagnoses for several reasons as outlined by the DSM-5.[53] Additionally, these exclusionary medical conditions are those which are widely excluded from previous peer-reviewed articles of similar topics and study designs.[29,35,39,41,52,72-75]

Medications are permitted in this study but must not be modified within four weeks of screening for study eligibility. Excluded medications include the following: chronic NSAID use (daily use for greater than one year), any opioids (within the past three months prior to study enrollment), opioid replacement therapy (such as methadone, suboxone, buprenorphine, or naltrexone), topiramate, lamotrigine, lithium, benzodiazepines, and muscle relaxants. The list of excluded medications and requirement for medication stability for four weeks prior to screening is based on the protocols set forth by prior peer-reviewed studies of similar study populations and outcomes.[38,41,54,72]

2.4.4 *Exposure*

This study will randomly assign study participants to one of three treatment groups for 12 weeks: DBT, pharmacotherapy alone, and non-treatment (treatment as usual). As previously discussed, DBT is the first-line treatment for BPD and seeks to teach individuals with BPD improved techniques to manage interpersonal problems.[76,77] Typically, DBT programs are of a 12-month duration, but additional research has demonstrated that 12 weeks of either inpatient or outpatient DBT has been effective in the management and improvement of BPD symptoms.[60-64] Given the substantial data to support the utilization of DBT in the treatment of BPD, this will be one treatment group within this proposed study.

A second group of participants within this study will be assigned to pharmacotherapy alone. While DBT is the first-line therapy for the treatment of BPD,[76] providers will often utilize pharmacotherapy in order to assist with the management of specific symptoms. The APA Practice Guidelines has stated that pharmacotherapy may help reduce the severity of specific symptoms in BPD such as affective instability,

impulsivity, and self-destructive behavior,[76] all of which likely play a role in an individual's engagement in NSSI or body modification. The APA guidelines provide recommendations for specific pharmacotherapy options, with the first-line pharmacotherapy option being SSRIs such as fluoxetine and sertraline.[76] Other second-line pharmacotherapy options include monoamine oxidase inhibitors (MAOIs) such as phenelzine or tranylcypromine and mood stabilizers (lithium, carbamazepine, or valproate).[76]

The third and final treatment group included in this study will be a non-treatment or treatment as usual group. Similar peer-reviewed studies have included non-treatment groups, which serve as a control group of participants.[7,61] In one study conducted by Psieczney and Connor, participants in the treatment as usual group still received clinical case management from multidisciplinary case managers.[7] This study design allowed for a control group, but was ethical in that it still allowed for weekly contact with participants and care in the form of "engagement, ongoing assessment, planning, linking with community resources, consultation with carers, assistance expanding social networks, collaboration with medical staff, advocacy, individual counseling, living skills training, psychoeducation and crisis management."[7] Another strategy that has been employed is to consider participants on a waitlist for study treatment as control participants, until they were able to receive study treatment.[61] When an individual was on this waitlist, they were not allowed to enroll in DBT programs, but were allowed to engage in "some form of professional mental health care", which included inpatient psychiatric units.[61]

2.4.5 *Outcomes*

The primary outcome of this study will be number of body modifications, as determined by the Body Modification Questionnaire (BMQ). This is a 118-item questionnaire that was developed by Vizgaitis and Lenzenweger and allows participants to provide information on body modifications such as piercings, tattoos, scarifications, pubic hair removal, and cosmetic surgery.[17] The BMQ will be administered during screening (as a condensed version), at baseline, and following 12 weeks of intervention. In addition to the BMQ, information pertaining to how frequently and for how long a participant has engaged in body modification will be obtained.

Additionally, this study will have several secondary outcomes including temperature threshold and pain response, which will be analyzed using QST delivered through a probe administering thermal stimuli to participants during fMRI scans. As established by prior studies, participants will receive a customized hot and cold painful stimulus through a Thermal Sensory Analyzer II probe.[52] With this stimulus, pain response, pain thresholds, and pain endurance will be analyzed at baseline and after 12 weeks of assigned intervention. While these painful stimuli are administered, an fMRI scan will be completed at both baseline and after 12 weeks of intervention. This fMRI data will be novel in that no fMRI data has yet to be obtained in individuals with BPD who engage in frequent body modification. This study will ultimately aim to evaluate if like prior studies, there is a significant difference in activity in the dlPFC, posterior parietal cortex (PPC), ACC, and amygdala when individuals with BPD are exposed to painful stimuli,[35] or alternatively, if this pattern of activity somehow differs in individuals with BPD who engage in frequent body modification. The activities of these brain regions in response to painful stimuli will be re-evaluated following 12 weeks of

intervention, to determine if like prior studies, participants enrolled in DBT demonstrate changes from baseline patterns of brain activation.[52]

This study will also assess childhood trauma using the Early Trauma Inventory–Self Report-short form (ETISR-SF),[78] which will be administered at baseline. This interview consists of 27 items and evaluates physical, emotional or sexual abuse, general traumatic experience, and the most serious trauma prior to 18 years old.[78] Prior studies have demonstrated that increased cases and amount of abuse has a positive correlation with number and severity of BPD symptoms.[79] Having this baseline information will allow for the evaluation and interpretation of any possible differences in childhood abuse history that may exist between groups.

One additional outcome to be assessed at both baseline and following 12 weeks of intervention will be the function and awareness of body modification. An interview modeled after that designed by Klonsky will be utilized.[13] This interview will assess (i) history of body modification, (ii) consequences of the body modification, (iii) affect-states before and after the body modification, and (iv) reason for the body modification.[13] An example of possible options for consequences, affect-states, and reasons provided to participants has been provided in Appendix A. This interview will allow for the evaluation of how aware participants are about their body modifications, and the emotions which they are experiencing prior to, during, and after engaging in the behavior.

Appendix A: Responses for Interview regarding consequences, reasons, and affect-states related to body modification

Consequences	**Reasons**	**Affect-States**
I experience an adrenaline rush	To express to others how I am feeling	Angry (at others)
Distracts me from memories	To fit in with my peer-group	Angry (at self0)
Marks are left on my skin	To let others know what I	Sad

	am going through	
Family members become concerned for me	To cope with/avoid memories of negative childhood experiences	Afraid
Close friends become concerned for me	To release emotional pressure that builds up inside of me	Excited

2.4.6 *Sample Size and Statistical Tests*

To determine the appropriate sample size of this study, precedence set forth by prior comparable studies, NIH Exploratory/Developmental Research Grant Award (R21) monetary allowances, and Cohen's d effect sizes were all considered. Goodman, et al. conducted a similar study in which they evaluated fMRI pre- and post-12-months of DBT in individuals not previously receiving treatment.[74] These researchers hypothesized that participants with BPD would demonstrate statistically significant changes in amygdala activation and improved emotion regulation following 12 months of DBT.[74] This study utilized a sample size of 22 participants (11 controls and 11 participants diagnosed with BPD) and found a significant change in amygdala activity over time in the BPD group.[74] While this represents a small sample size, Goodman, et al. were able to demonstrate significant between-group differences in a similar population of participants and with similar interventions as those set forth by this proposed study.[74]

A second study conducted by Niedtfeld, et al. utilized fMRI to assess the changes in pain thresholds and appraisal of pain in participants with BPD after completing 12 weeks of DBT, compared to participants with BPD undergoing treatment as usual and a healthy control group.[52] This study recruited a total sample size of 66 participants in total and hypothesized that pain-mediated affect regulation would normalize, and that pain sensitivity would be reduced in participants with BPD following completion of 12 weeks

of DBT.[52] With this sample size, these researchers were successful in elucidating significant differences in amygdala activation and inhibitory coupling of the left amygdala and dACC pre- and post-12 weeks of DBT.[52] Niedtfeld, et al. acknowledge their small sample size and the effects which this had on their study's statistical power, but also comment on the difficulties they faced in recruiting BPD participants that did not have prior experience with DBT.[52]

In reviewing the protocols and sample sizes set forth by fMRI studies researching similar populations of participants with similar research questions, the sample sizes have ranged from 12-93 participants.[31,35,52,73-75] While these sample sizes are small and do not allow for the detection of a small or medium effect size, it is often challenging for researchers to recruit a larger number of participants given the population of desired participants and exclusion criteria set forth. This study will calculate its sample size based off the guidelines set forth by these previous peer-reviewed and published papers, as well as monetary restrictions which come with completing a study under an R21 grant.

The data collected by this study will be analyzed using IBM Statistical Package for the Social Sciences (SPSS) Software version 28, a software program which allows for the analysis of research data sets and will allow for the completion of a 3x2 repeated measures ANOVA.[30,52,73] A univariate repeated-measures ANOVA will allow for the evaluation of whether or not there is a statistically significant difference in total body modifications (as assessed by the BMQ) amongst treatment groups over the duration of the 12-week period.[80] While other studies have utilized additional software programs such as Statistica,[74] SPSS is the statistical software that is most frequently used by researchers at this study's site.

2.5 CONCLUSION

This extensive literature review was successful in providing background information to support and design the current study. There is a substantial number of peer-reviewed articles which provide supporting evidence that individuals with BPD engage in body modification. While the underlying etiology, neural mechanisms, and effect of DBT on this behavior has not yet been studied, similar studies have been conducted looking at NSSI in BPD. These peer-reviewed studies will be utilized as described in order to model our study, its interventions, and outcomes.

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Chapter 3 – Study Methodology

3.1 STUDY DESIGN

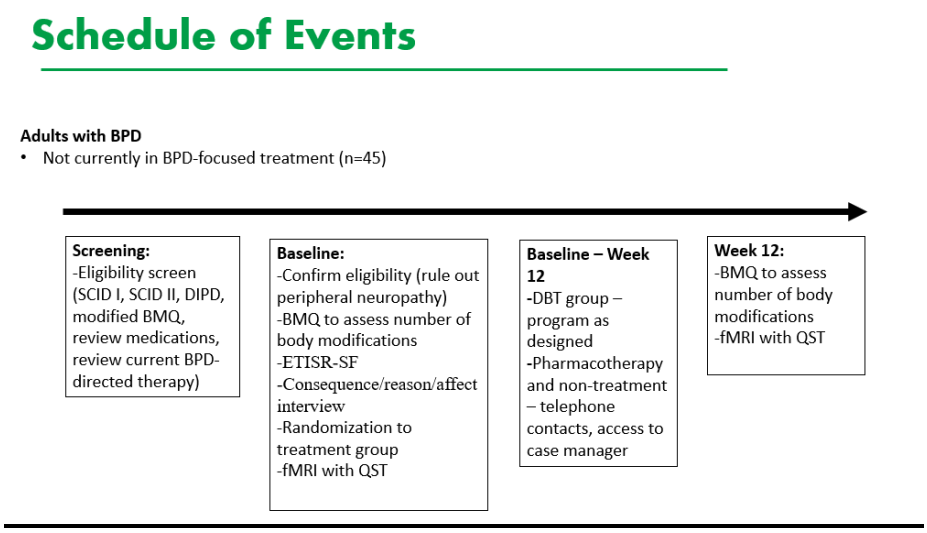
The proposed study is a RCT that will be conducted in New Haven, Connecticut and which will investigate the effects of randomization to 12 weeks of DBT compared to groups randomized to 12 weeks of pharmacotherapy alone or 12 weeks of no treatment, on mean number of body modifications, as measured by the BMQ, in patients who have engaged in frequent body modification within the past six months and who are not currently receiving BPD-directed therapy (either pharmacotherapy or behavioral therapy such as DBT). A condensed version of the BMQ will be administered at screening to determine possible eligibility, and the full version will be completed at both baseline (prior to randomization) and following the completion of 12 weeks of the assigned intervention. The full version will be used in order to assess for mean change in the number of body modifications. DBT will be administered by one post-doctoral student at this site who will have completed formal DBT training and has had experience treating patients with BPD. The schedule for DBT will follow that set forth by previous research and the current standard. It will consist of weekly skills training groups, weekly hour-long individual psychotherapy sessions, telephone consultation between sessions as needed, and weekly therapist consultation team meetings.

The participants who are randomized to the pharmacotherapy group will be prescribed medication by the site's PI, Dr. Fineberg, who is a clinical Psychiatrist with extensive experience treating patients with BPD. These participants, in addition to those randomized to the non-treatment (treatment as usual) group, will be asked to return to the study's lab in New Haven, Connecticut once weekly for an hour-long session during

which they will meet with the study coordinator and/or the study PI in order to discuss community resources, to address any medical needs or concerns, to evaluate need for social support, to provide resources for life skills training, to discuss crisis management, and to review psychoeducation resources. All three treatment groups will also have once weekly phone calls in order to discuss treatment compliance (if applicable), adverse events, medication changes, or health changes.

The study will also aim to investigate the association between randomization to 12 weeks of DBT compared to groups randomized to pharmacotherapy or no treatment on pain perception, tolerance, and endurance. Quantitative sensory testing (QST) using the method of limits will be utilized to determine the cold and warm perception thresholds for each participant. The Thermal Sensory Analyzer II will be the thermal device used in this study. This probe will be placed over the participant's left forearm and will deliver thermal stimuli. The baseline temperature delivered through the probe will be 32°C, which will be increased or decreased at a rate of 1°C/second with a minimum temperature of 10°C and maximum temperature of 50°C. Each participant will be asked to press a button as soon as they perceive the stimulus as either getting warmer or colder, and again when they perceive it as becoming painful. The temperature will then be either increased or decreased at a rate of 3°C/second in order to return to the baseline temperature of 32°C. The painful stimulus will be documented for each individual participant, and they will be instructed that they will receive 60% of this level of stimulus throughout the fMRI session. Participants will then receive either the baseline temperature (32°C) or the individualized painful temperature stimulus throughout the fMRI scan. A schedule of events has been outlined in Appendix B and is included below.

Appendix B: Schedule of Events



Given the nature of the study design and intervention, both study participants and study staff (PI, research assistants, and site's psychologist who will be administering DBT) will be notified of the assigned intervention following random assignment. A trained neuroradiologist associated with Yale University will be responsible for analyzing the MRI images and the site's PI will be responsible for interpreting the fMRI data. The neuroradiologist will remain blinded to treatment allocation throughout the study. Randomization software will be utilized to randomly assign participants amongst the three groups (DBT, pharmacotherapy alone, or no treatment) equally.

3.2 STUDY POPULATION AND SAMPLING

This study will enroll individuals with clinically diagnosed BPD who are not currently receiving BPD-directed therapy (either pharmacotherapy or behavioral therapy such as DBT) and who have engaged in frequent body modifications within the past six months. Participants included in this study must be within the ages of 18-65, able to speak and write in English as assessed during screening procedures by study staff, able to provide informed consent, and able to travel to New Haven, Connecticut for study visits.

Participants will be eligible for this study if they are not currently using any medications or not currently using any of the medications outlined in the list of "Excluded Medications" (Table 2). Participants must meet criteria for BPD as outlined by the DSM-V diagnostic criteria as assessed using the SCID I, SCID II, and Diagnostic Interview for BPD. Participants must demonstrate a significant number of total body modifications in their lifetime, with at least one body modification within the past month. Initial interviews to assess for eligibility will be completed by study staff and research assistants, with final confirmation of eligibility completed by the site's PI.

Participants will be excluded from this study if they are currently receiving BPD-directed therapy (either pharmacotherapy or behavioral therapy such as DBT). This study will allow for a history of participation in behavioral therapy such as DBT. If the participant has either in the past or is currently receiving treatment for another psychiatric diagnosis, they can still possibly participate in the study given that there have not been medication changes within four weeks of screening (a list of included and excluded medications is provided in Table 2). Participants with a history of any serious medical or neurological illness, chronic pain disorder, schizophrenia, bipolar (Type I) disorder, current Major Depressive Disorder (MDD) within the past six months, developmental disorders such as Attention Deficit Disorder (ADD) or Attention Deficit Hyperactive Disorder (ADHD), peripheral neuropathy, traumatic brain injury, or loss of consciousness are not eligible to participate in this study. Participants with a history of a substance use disorder or who have a positive urine toxicology screen on the day of MRI scans will be excluded.

Participants that have contraindications to MRI, such as claustrophobia or metal implant(s) not MRI compatible, are not able to participate in this study. For those participants that are female and of childbearing potential, they will be provided information regarding risk of MRI in pregnancy prior to all scans and offered the option of a urine pregnancy test before proceeding with the completion of the MRI scans. A list of all inclusion and exclusion criteria is provided in Table 2.

Table 2. Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Age 18-65 • Clinical diagnosis of BPD as defined by DSM-V criteria. • Able to speak and write in English. • Able to provide informed consent. • Able to travel to New Haven, Connecticut for study visits. • No current BPD-directed pharmacotherapy or behavioral therapy (such as DBT). • Unmedicated patients are eligible to participate. Any medication that does not belong to the list of "excluded medications" are deemed acceptable for this study.	• Currently receiving BPD-directed therapy (either pharmacotherapy or behavioral therapy such as DBT). • Contraindications to MRI, such as claustrophobia or metal implant(s) not MRI compatible. • Medical history: any serious medical or neurological illness, chronic pain disorder, schizophrenia, bipolar (Type I) disorder, current MDD (no episode in the past 6 months), developmental disorders (ADD or ADHD), peripheral neuropathy, or substance use disorder. • History of traumatic brain injury (TBI) or loss of consciousness. • Positive urine toxicology screen for drugs of abuse on day of MRI scans. • Medication change within 4 weeks of study screening. • Excluded medications: chronic NSAID use, opioids, opioid replacement therapy (such as methadone, suboxone, buprenorphine, or naltrexone), topiramate, lamotrigine, lithium, benzodiazepines, muscle relaxants. Chronic NSAID use is defined as daily use for greater than one year.

The inclusion and exclusion criteria set forth aims to recruit a sample which controls for possible confounding demographics. If this study is unable to recruit 75% of the planned sample in the first year, these criteria will be slightly modified in order to maximize study enrollment. One such modification would allow for the recruitment of participants with a history of MDD within the past year but not within the past three months. The second modification would allow participants to have an outpatient prescription for an as needed benzodiazepine, but they would not be permitted to use the benzodiazepine within one day of their scheduled fMRI scans.

3.3 SUBJECT PROTECTION AND CONFIDENTIALITY

This study protocol and all recruitment materials will be reviewed and approved by the Yale University Human Investigation Committee (HIC). Data for this study will be collected by study staff at the Connecticut Mental Health Center (CMHC) and the Yale Magnetic Resonance Research Center (MRRC). Study staff and research assistants must be added to the Yale HIC approved protocol and will be required to complete HIPAA Compliance training before engaging in study-related activity.

Each study participant will be assigned a unique study identifier during the phone screening and all identifying information will be replaced with this identifier. A paper record will be used to connect each participant's personal identifying information with the coded, unique study identifier. This record will be kept in a locked filing cabinet in the PI's locked office, with access granted to only the PI and select members of the research team. All study data will be entered into computer files using the participant's unique study identifier, and a paper copy will be printed. This data will be stored in

locked cabinets located in the PI's locked office and in password-protected files through a Yale University approved database (Yale Secure Box).

3.4 STUDY RECRUITMENT

This study will recruit its participants using Yale HIC approved advertisements included in local newspapers, posters throughout New Haven, New Haven bus ads, and Facebook ads. The Yale New Haven Hospital Psychiatry Department and CMHC will be provided study information and advised that they are able to provide appropriate patients with study information and study site contact information. A list of potential participants who respond to advertisements and endorse interest in the study will be stored in a secure Yale University managed database (Yale Secure Box).

Study staff and research assistants will contact the individuals listed in the database by either telephone or encrypted email in order to schedule a time to or to complete a phone screening to assess eligibility. All participants that respond to or participate in a phone screening will receive a unique study identifier that will replace all personal identifying information. During the phone screen, participants will be assessed for study eligibility through a series of questions which assess for all other inclusion and exclusion criteria as listed in Table 2. Participants will be screened for BPD specific traits using the SCID I, SCID II, and DIPD. Screening for lifetime and recent (past 6 months) engagement in body modification will be done using an abbreviated BMQ. If a participant is found to be eligible according to the initial phone screening procedure, they will be asked to schedule their baseline visit during which eligibility will be further evaluated before proceeding. Each participant will be assessed for peripheral neuropathy using a Semmes-Weinstein monofilament at the baseline visit. If a participant meets all

inclusion criteria, no exclusion criteria, and the PI deems eligible, then they will be able to proceed to randomization.

3.5 STUDY VARIABLES AND MEASUREMENTS

In this RCT, the independent variable or primary intervention is treatment assignment. Treatment assignment will be divided such that participants will be randomly assigned to one of three groups: DBT, pharmacotherapy alone, and non-treatment. DBT is the primary outcome measure, with pharmacotherapy as a comparison group, and the non-treatment group as a control. The main outcome or dependent variable will be the mean change in body modifications as measured through the BMQ. This main outcome variable will be measured as a continuous variable at both baseline and the 12-week follow-up visit. In addition to the BMQ, information pertaining to how frequently and for how long a participant has engaged in body modifications over their lifetime will be obtained at baseline.

Multiple secondary outcome variables will be the studied as well. The first secondary outcome variable will be the change in neural activation in response to painful stimuli as assessed by fMRI at two timepoints: baseline and post-intervention (12 weeks). An additional secondary outcome will be change in pain perception, threshold, and endurance in response to painful stimuli as measured by the Quantitative Sensory Testing Task (QST) at two timepoints: baseline and post-intervention (12 weeks). A third covariate will be the Early Trauma Inventory–Self Report-short form (ETISR-SF) which will be administered at baseline in order to evaluate each participant's trauma history, as this may contribute to study results. Finally, at both baseline and study completion, an interview assessing consequence, reason, and emotional affect related to body

modification will be conducted. This will allow for a better understanding of each participant's awareness of their engagement in body modification, as well as the emotions which they experience before, during, and after this behavior.

There are several categories of confounding variables which will be accounted for and controlled for within this study. The first category of confounding variables consists of medical history. This will be controlled for by excluding participants that meet criteria for the following: history of any serious medical or neurological illness, traumatic brain injury, schizophrenia, bipolar (Type I) disorder, current Major Depressive Disorder (MDD) within the past 6 months, developmental disorders such as Attention Deficit Disorder (ADD) or Attention Deficit Hyperactive Disorder (ADHD), chronic pain disorder, peripheral neuropathy, loss of consciousness, or a substance use disorder.

A second category of confounding variables consist of medication use. Participants on certain medications (chronic NSAID use, opioids, opioid replacement therapy, topiramate, lamotrigine, lithium, benzodiazepines, and muscle relaxants) will be excluded from this study to limit confounding. Given that participants may have concomitant psychiatric conditions that are not exclusionary and for which they may be receiving pharmacotherapy, there may be a combination of participants in the DBT group who are either taking or not pharmacotherapy that is not DBT-directed therapy. This pharmacotherapy may consist of the same medications as those being prescribed in the pharmacotherapy group of this study. A third category of confounding variables consist of demographics which include age, sex, race, and education.

3.6 METHODOLOGY CONSIDERATIONS

3.6.1 *Blinding of Intervention*

Due to the intervention being utilized in this study, it will not be possible for this to be a double-blind RCT. Both participants and investigators (PI, individual administering DBT for this protocol, and research assistants) will be notified of each participant's randomization. The site's neuroradiologist responsible for analyzing the fMRI images will remain blinded to intervention allocation throughout the study.

3.6.2 *Blinding of Outcome*

Due to the intervention being utilized in this study, it will not be possible to maintain blinding of study outcome. As discussed, personnel responsible for analyzing fMRI data will remain blinded to intervention allocation throughout the study.

3.6.3 *Assignment of Intervention*

Participants who provide informed consent at the screening visit and who are eligible for this study will be randomized to a treatment arm after the baseline evaluation of number of body modifications using the BMQ, pain response, and fMRI. This study will use randomization software to randomly assign eligible participants amongst the three intervention groups equally. Once baseline measures are completed, a research assistant will enter the participant's unique identifier into the randomization software and this will reveal if the participant has been randomized to 12 weeks of DBT, 12 weeks of pharmacotherapy alone, or no treatment.

3.6.4 *Adherence*

Adherence to study intervention will be assessed during weekly telephone contacts made by site personnel. The site staff completing this call will be unblinded to intervention allocation and will be able to assess for compliance. If a participant is assigned to the DBT intervention, they will be asked if they have attended that week's

skills training group, psychotherapy session, and therapist consultation team meeting. If a session has been missed, this will be documented along with the reasoning for missing the session, and the participant will be instructed of the importance of attending all study visits. If the participant is assigned to the pharmacotherapy intervention, they will be asked about any missed doses that they may have had that week. They will also be asked to count the number of pills that they have remaining of their prescribed medication, this number will be documented, and compliance will be calculated. Lastly, if a participant has been randomized to the control group with no treatment, these weekly calls will solely be to check in regarding an adverse event and/or any medication changes that may have been prescribed by an outside provider. During telephone contacts with the DBT and pharmacotherapy, groups adverse events and/or medication changes will also be assessed.

3.6.5 *Monitoring of Adverse Events*

This protocol presents minimal risk to participants and adverse events are not anticipated. The questionnaires used in this study may cause participants to experience feelings of distress due to the questions being posed, but no lasting effects are anticipated. MRI is considered a safe procedure given that the guidelines set by the United States Food and Drug Administration (FDA) pertaining to magnet strength and exposure will be adhered to throughout the study. Additionally, all participants will be provided with an MRI safety questionnaire which will assess for the presence of and safety of any metal devices, electronic implants, or ferromagnetic materials that may be present on their person. All participants will be required to remove metal objects from their pockets and any clothing that may contain metal prior to the scan. As an added precaution, each

participant will be asked to walk through a metal detector to ensure that all metal objects have been removed. All females of child-bearing potential will be offered a urine pregnancy test to complete prior to the scan. It is anticipated that some participants may begin feeling uncomfortable or anxious during the scan. If this occurs, it is acceptable to request discontinuation of the scan. These feelings typically resolve on their own quickly with no intervention required.

Although adverse events are unlikely and not anticipated to occur, study staff will contact participants weekly by telephone to complete a health check-in throughout the 12-week course of the study. Staff will assess for any changes in health or any serious or life-threatening and unanticipated events that may have occurred. While not expected, if any such event occurs, the PI will be notified of the event as soon as study personnel are informed, study activities will be put on hold, and a written report of the incident will be provided to the Yale HIC for review.

3.7 DATA COLLECTION

Each participant will complete a telephone screening questionnaire with research personnel. When contact is made with a participant, they will be assigned a unique study identifier which will be associated with a particular participant for the duration of the study. The phone screening, baseline, and 12-week follow-up questionnaires will be administered through an online survey and analytics tool (Qualtrics) that is approved by Yale Web Services, secure, and utilized by Yale School of Medicine. This system allows personnel to complete screening documents on behalf of participants, but also allows participants to have the ability to complete self-report measures. The data obtained from

these surveys will be converted to encrypted computer files and paper versions that will be kept locked in filing cabinets and kept confidential.

The fMRI data obtained through this study will be collected at the Yale MRRC (300 Cedar St., New Haven, CT) and stored on their secure servers. A Siemens 3.0 Tesla Prisma Fit MRI scanner with a 64-channel head coil for simultaneous multi-slice data collection will be used. Imaging sequences collected will include a Localizer, 3D T1 and T2 acquisitions ($1mm^3$), single five-minute resting state BOLD scan (multi band $2mm^3$), and the task (temperature stimulation) with BOLD scan. Subjects will respond using a 2x2 button box synchronized to the task presentation software. Each scan will be labeled with the participant's unique study identifier and no identifiable information. A copy of the MRI scan will be converted onto a CD-ROM allowing it to be reviewed by the site's neuroradiologist. Once analyzed, the CD will be stored in locked filing cabinets in the PI's office and will only be accessed by study personnel. The information regarding the scan's results will be shared with only one designated research assistant involved with this protocol for analysis.

3.8 SAMPLE SIZE CALCULATION

The sample size for this proposed study has been based on both the sample size utilized in previous peer-reviewed fMRI studies investigating patients with BPD, but also the budget provided by the NIH Exploratory/Developmental Research Grant Award (R21). While it is important to utilize studies that have already been reviewed and published as a basis for the sample size calculation for this proposed study, it is also important to consider the monetary logistics. In order to fund this proposed study, we will apply for the NIH Exploratory/Developmental Research Grant Award (R21). The R21

grant is intended to encourage exploratory and developmental research by providing monetary support for exploratory, novel studies. It provides researchers with eligible projects a budget that may not exceed $275,000 over the span of two years, with no more than $200,000 allowed to be requested in any single year. This grant does not require any preliminary data, although it may be included if available. The budget provided by the R21 grant will be used to pay the annual salary for a post-doctoral student that will be leading study visits (DBT), data collection, data analysis, and all additional miscellaneous study tasks. With an annual salary of $60,000 and the Yale University fringe cost, this will be an estimated annual cost of $76,500. We will consider splitting the time of this post-doctoral student with another lab in order to help fund their salary. Doing so will allow us additional funds in order to pay the salary of the neuroradiolost who will be analyzing the study's fMRI scans. This protocol will also require that we hire a research assistant to help with study-related tasks (recruitment, IRB protocol submissions, data entry, etc.) three to four days per week, which we estimate to be an annual cost of $19,125 when considering an annual salary of $37,500 and a Yale fringe cost of $10,312. When considering the annual cost of the salaries for both a post-doctoral student and research assistant, we anticipate that we will have an estimated remainder of $83,750 over the span of two years for study equipment, supplies, and subject compensation. This study is a longitudinal fMRI study that will require subjects to undergo two MRI scans over the span of 12 weeks, with each scan costing an estimated $500. This study will also compensate participants $50 per MRI visit.

This study will be analyzed using a 3x2 repeated measures ANOVA. The guidelines set by Cohen have provided the following benchmarks for effect sizes: small

(f=0.1), medium (f=0.25), and large (f=0.4). G*Power was used to determine sample sizes using these effect sizes and a pre-determined power of 0.8 and alpha of 0.05. This study would require a sample size of 12 participants to achieve a large effect size, 27 participants for a medium effect size, and 150 participants for a small effect size given the above parameters.

Given that this is an exploratory and novel project that would likely be funded by an R21 grant as described above, the sample sizes provided by the G*Power analysis are not achievable through this grant. The sample size proposed for this study will be 45 participants, who will be evenly divided into the three treatment groups (DBT, pharmacotherapy, and no treatment). This sample size is based on the sample sizes utilized in similar peer-review projects and is realistic given funding limitations. It is hoped that the preliminary data from this pilot study can be used to apply for an R01 grant which would allow for a larger budget and ultimately a larger sample size.

3.9 ANALYSIS

The data collected by this study will be analyzed using SPSS Software version 28. The primary outcome (mean change in body modifications) and secondary outcomes (pain perception, threshold, and tolerance) will be evaluated using a 3x2 repeated measures ANOVA. The between-subjects factor is the study intervention (DBT, pharmacotherapy alone, or non-treatment) and the within-subjects factor is the time point that data is obtained (baseline and 12 weeks). These will be analyzed for each of the dependent variables (number of body modifications, pain perception, pain threshold, and pain tolerance).

For image pre-processing, we will convert the DICOM files to .nii format, crop the first five runs, and motion correct. Pre-processing steps are done on a Linux platform employing in-house code in conjunction with SPM and FSL utilities. Images will then be registered to stripped MPRAGE images (using BioImage Suite). All comparisons will be checked and edited for motion balance. To test our hypotheses, we will test the effect of pain on limbic (amygdala and ACC) and prefrontal (dlPFC and BA8) brain regions given the involvement of these areas in emotion processing in BPD.[1] These regions of interest (ROI) will be defined using automatic segmentation methods, such as FreeSurfer. We will use a general linear model (GLM) to test regressors of interest in Matlab. All GLMs will be computed at the subject level, with resulting B-weights entered into second level analyses (to compute between-group and between-condition comparisons), as in a random-effects model. The false discovery rate method will be used to correct for multiple comparisons.

3.10 TIMELINE AND RESOURCES

The proposed study will take place over the span of two years as allowed for by the R21 grant. If recruitment is delayed due to restrictive inclusion criteria, these criteria will be modified as described above. The Yale MRRC located in the Anlyan Center at 300 Cedar St., New Haven, CT will be utilized in order to acquire and store fMRI data. We will rely heavily on our colleagues and local neuroradiologist for the evaluation and interpretation of fMRI data. Office space will be provided by the PI of this study (Dr. Fineberg) located at CMHC (34 Park St., New Haven, CT 06519).

3.11 References

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Chapter 4 – Conclusion

4.1 Advantages

BPD has been estimated to effect anywhere from 0.5%-5.9% of the general population.[1,2] For years, there has existed anecdotal evidence of a connection between BPD and increased engagement in both NSSI and body modification.[3] It has not been until recently that researchers have published data which has formed a quantitative connection between severity of BPD and number of body modifications completed.[4] One major advantage of this study is that it focuses on a topic which, to date, does not have robust peer-reviewed literature. While researchers have proposed possible underlying neural mechanisms for NSSI in people with BPD and the effects of DBT on this behavior, no data has yet been published which studies these concepts as they are related to body modification in BPD. This project represents a novel topic in which researchers do not yet have much quantitative data or a firm understanding.

A second advantage of this study is that it is a RCT. RCTs are considered the gold standard in evaluating the efficacy of a specific treatment modality. By proposing an RCT, this study allows for the equal and random assignment of participants to each intervention group in order to avoid any possible or inadvertent biases that may arise with alternative study designs.

4.2 Disadvantages

While this study certainly has several advantages, disadvantages are present as well. One disadvantage of this study is the study's proposed sample size. According to G*Power, this study would require a sample size of 12 participants to achieve a large effect size, 27 participants for a medium effect size, and 150 participants for a small

effect size. Due to monetary constraints set forth by the R21 grant, which would fund this study, a sample size of 45 participants has been proposed. While this is certainly a small sample size and does not achieve the statistical power needed to detect small effects, this sample size does not vary significantly by the precedent set by previous studies of comparable populations[5-10] and would allow for medium effects to be detected. Depending on the results of this proposed study, future studies may consider recruiting a larger population size in order to achieve the desired sample of 150 participants and to detect the smallest effects which may be missed in this study.

A second disadvantage of this study is that there will not be a way to make the experiences of each treatment group identical. As discussed, the DBT group will be engaged in weekly skills training groups, weekly hour-long individual psychotherapy sessions, telephone consultation between sessions as needed, and weekly therapist consultation team meetings.[11] In comparison, the pharmacotherapy and non-treatment groups will only have once weekly hour-long sessions during which they can request community or educational resources, address any medical concerns, and discuss crisis management techniques. While this will allow for these two groups to have contact with study staff throughout their study participation, it will not equate to the amount of time that the DBT group will spend engaging with site staff. This should be considered when interpreting this study's results, and future studies may want to consider other methods to control for this discrepancy.

4.3 Clinical Significance

This study will serve to provide novel, quantitative data on the effects of DBT on the engagement in body modification in people with BPD. Additionally, this data will

help to develop a better understanding of this behavior's underlying neural mechanisms, may demonstrate that there is utility in the engagement in body modifications (provide relief from stressors, improve negative emotions, provide a sense of self, etc.), and will likely prompt future research on this topic. With this data, healthcare providers will be better able to recognize body modification in their patients and understand how DBT may affect their patients' engagement in this behavior. Additionally, this study's findings will assist providers in being able to better discuss this behavior with their patients and provide their patients with more information on why they may be drawn to engage in such behavior. Ultimately, this study's results will not only educate healthcare providers, but also people with BPD who engage in frequent body modification.

4.4 Future Directions

This proposed research study serves as a foundation for future studies aimed to investigate similar populations of patients and ask similar research questions. It may be interesting for future studies to delve further into the evaluation of the different types of body modifications, in order to evaluate if treatment influences this. For instance, if the results from this study do not demonstrate that 12 weeks of DBT result in a statistically significant overall reduction in engagement in body modification, it would be interesting to evaluate the different types of body modifications that study participants endorsed at the end of the 12-week period. Perhaps it is found that there is a significant reduction in the number of permanent body modifications, which are focused on in this study (piercing, tattooing, cosmetic surgery, etc.), but that there is an increase in non-permanent body modifications (hair cutting, hair coloring, or thick make-up application). Such results may suggest that treatment with DBT may have an overall effect on reducing

painful, permanent behaviors, but that it does not affect engagement in non-painful, non-permanent body modifications which may serve as a way for people with BPD to obtain a sense of self.

A second consideration for future studies is that many individuals who do not meet the diagnostic criteria required for a diagnosis of BPD, also engage in frequent body modifications. It may be interesting for future researchers to design a study similar to the one proposed, but which also recruits two additional groups of participants: those that do not have any underlying psychiatric diagnoses but engage in frequent body modifications and those with psychiatric diagnoses other than BPD who engage in frequent body modifications. This study would allow for the comparison of these three groups, allowing researchers to evaluate any potential differences in baseline demographics, response to DBT, pain response, and the underlying neural mechanisms present. This would provide researchers and clinicians more information about how and why body modifications may vary amongst different groups of individuals.

4.5 References

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Appendix A: Responses for Interview regarding consequences, reasons, and affect-states related to body modification

Consequences	**Reasons**	**Affect-States**
I experience an adrenaline rush	To express to others how I am feeling	Angry (at others)
Distracts me from memories	To fit in with my peer-group	Angry (at self0)
Marks are left on my skin	To let others know what I am going through	Sad
Family members become concerned for me	To cope with/avoid memories of negative childhood experiences	Afraid
Close friends become concerned for me	To release emotional pressure that builds up inside of me	Excited

Appendix B: Schedule of Events

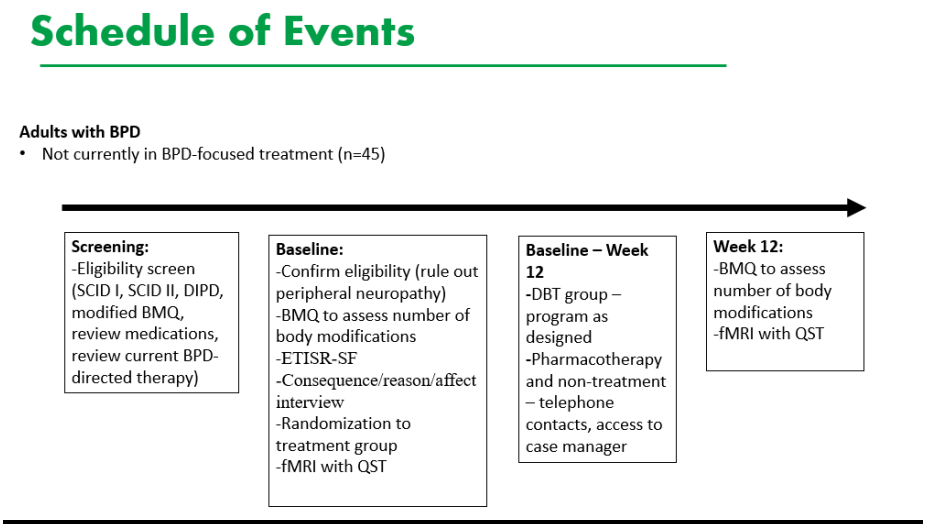

Table 1. DSM-V Diagnostic Criteria for Borderline Personality Disorder

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
10. Frantic efforts to avoid real or imagined abandonment. (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
11. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
12. Identity disturbance: markedly and persistently unstable self-image or sense of self.
13. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance misuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
14. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
15. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
16. Chronic feelings of emptiness.
17. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
18. Transient, stress-related paranoid ideation or severe dissociative symptoms.

Source: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, 2013, American Psychiatric Association.

Table 2. Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Age 18-65 • Clinical diagnosis of BPD as defined by DSM-V criteria. • Able to speak and write in English. • Able to provide informed consent. • Able to travel to New Haven, Connecticut for study visits. • No current BPD-directed pharmacotherapy or behavioral therapy (such as DBT). • Unmedicated patients are eligible to participate. Any medication that does not belong to the list of "excluded medications" are deemed acceptable for this study.	• Currently receiving BPD-directed therapy (either pharmacotherapy or behavioral therapy such as DBT). • Contraindications to MRI, such as claustrophobia or metal implant(s) not MRI compatible. • Medical history: any serious medical or neurological illness, chronic pain disorder, schizophrenia, bipolar (Type I) disorder, current MDD (no episode in the past 6 months), developmental disorders (ADD or ADHD), peripheral neuropathy, or substance use disorder. • History of traumatic brain injury (TBI) or loss of consciousness. • Positive urine toxicology screen for drugs of abuse on day of MRI scans. • Medication change within 4 weeks of study screening. • Excluded medications: chronic NSAID use, opioids, opioid replacement therapy (such as methadone, suboxone, buprenorphine, or naltrexone), topiramate, lamotrigine, lithium, benzodiazepines, muscle relaxants. Chronic NSAID use is defined as daily use for greater than one year.

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