Title: Isolating Mechanisms in the Treatment of Borderline Personality Disorder

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RESEARCH STRATEGY

SIGNIFICANCE

Recent NIMH priorities regarding treatment development for psychological disorders provide guidance toward creating efficient, cost-effective, and ultimately disseminable interventions. First, the NIMH Research Domain Criteria[19] (RDoC) initiative challenged researchers to translate evidence from basic science in order to elucidate core fundamental processes that cut across diagnoses and can become the focus of treatment. This priority is beginning to take shape in the form of transdiagnostic treatment protocols that purportedly target common mechanisms maintaining symptoms across a range of disorders. Although transdiagnostic approaches appear to have promise in reducing symptoms[43, 44], the fact that they consist of multiple components makes it difficult to draw conclusions regarding the "active ingredients" in treatment. To address this problem, NIMH is currently prioritizing experimental therapeutics trials aimed at isolating the effects of an intervention's putative mechanism of action as a means to scale-down treatment protocols and facilitate dissemination. Additionally, treatment specificity informed by patients' presenting severity may also represent a way to scale interventions, thereby increasing their portability. Borderline personality disorder (BPD) is a costly, debilitating, and understudied condition[1, 2, 3] that may particularly benefit from the application of these research initiatives. Extant treatments for BPD are explicitly designed to address the most severe, life-threatening presentations, despite the fact that most individuals diagnosed with this disorder never attempt suicide or require inpatient hospitalization[13]. Further, these treatments are intensive and consist of multiple components, impeding dissemination efforts and making it difficult to determine which treatment strategies are impacting outcomes. Finally, high rates of comorbidity with anxiety and depressive disorders[8, 9] may underscore the utility of a transdiagnostic approach for the treatment of BPD.

Extant Treatments for BPD: Over the past twenty years, treatment protocols addressing the severe life-threatening dysregulation characterizing BPD have emerged. Dialectical Behavior Therapy (DBT)[4] has accumulated considerable empirical support and treatments such as Transference-Focused Therapy (TFT)[6], Mentalization-Based Treatment (MBT)[5], Schema-Focused Therapy (SFT)[7], and General Psychiatric Management (GPM)[17] also appear promising (for a review, see: Neacsiu & Linehan[20]). These approaches are all intensive, long-term (usually at least 1 year), and have, understandably, focused on targeting the life-threatening and therapy-interrupting behaviors that often characterize this disorder. BPD, however, is a heterogeneous disorder with diagnostic criteria that can be combined to create over 300 unique symptom presentations[18]; to date, no treatments have been explicitly designed with lower risk presentations of BPD in mind. Patients presenting with less severe symptoms of BPD, referred to in this application as "lower-risk BPD", may represent a unique opportunity to explore core, mechanistic deficits as they are less likely to display life-threatening behavior that may shift the focus of treatment to safety.

BPD as an Emotional Disorder: As noted above, BPD demonstrates high rates of comorbidity with anxiety and depressive disorders (lifetime estimates as high as 75%[8,9]), prompting some authors to suggest that similar underlying mechanisms may characterize these disorders[10, 11,12]. In fact, anxiety and depressive disorders, as well as BPD more recently, have been referred to as emotional disorders as a way to highlight the common role of emotions and emotion dysregulation in their development and maintenance. Specifically, emotional disorders are characterized by frequent and intense negative emotions, aversive reactions to these emotional experiences, and subsequent efforts to escape or avoid them[14]. Focusing on functional similarities across emotional disorders may provide a useful, theoretically informed heuristic to guide treatment for individuals presenting with lower-risk BPD that is consistent with RDoC priorities.

Although the term emotional disorder is most often associated with anxiety and depressive disorders[21], there is ample evidence suggesting that BPD is characterized by similar processes[15]. To summarize, individuals with BPD indeed demonstrate frequent, strong negative emotions[23, 24, 25, 26, 27, 28], find such emotional experiences aversive, and engage in attempts to avoid them[29, 30, 31, 32]. In fact, the behavioral dysfunction associated with BPD is thought to function as avoidance of intense negative emotion; for example, self-harm, substance use, and binge eating (common in BPD) have long been conceptualized as intentional efforts to reduce or escape from emotional pain[33, 34, 35, 36, 37, 38, 39]. Additionally, emerging factor analytic work suggests that the interpersonal difficulties seen in BPD represent a lower-order factor moderated by emotional dysregulation[42], further suggesting that emotional difficulties are at the heart of BPD symptoms. For example, the interpersonal chaos that follows from frantic attempts to avoid abandonment (a BPD diagnostic criterion) can be conceptualized as efforts to avoid the strong emotions that may result as a function of the abandonment, rather than the abandonment itself. Unfortunately, these avoidant strategies backfire, ultimately leading to increased negative emotions and intensified BPD symptoms[40]. In addition to functional similarities with other emotional disorders, structural research supports the notion that BPD shares substantial underlying

temperamental variance with anxiety and depressive disorders, represented largely by a neuroticism factor[12, 41]. Finally, there also appear to be similar biological mechanisms (e.g., hyperexcitability of limbic structures, coupled with disrupted or limited inhibitory control by cortical structures[86, 87]) shared amongst BPD and other emotional disorders.

Treatment Mechanisms of Action: One potential target in the treatment of emotional disorders is deficits in emotional tolerance. This target is identified as Linehan's[4] theoretical priority for treating individuals presenting with less severe BPD symptoms. Additionally, targeting emotional tolerance is the core putative mechanism in the Unified Protocol[16] (UP), a recently developed transdiagnostic treatment that was explicitly designed to address the range of emotional disorders. The UP consists of multiple treatment components purported to reduce negative reactions to emotions making it difficult to draw conclusions regarding the unique role of each component. Similarly, DBT (Linehan's treatment for BPD) contains some skills aimed at this mechanism and other skills that may be counter to increasing emotional tolerance (e.g., distraction) but necessary for safety in suicidal individuals. Outcome data suggests that both the UP and DBT lead to symptom improvement across a range of emotional disorders[22,42,43,44,47].

A common strategy across both of these treatments is asking patients to behave in ways that are counter to their emotional urges; this is referred to as opposite action in DBT and countering emotion-driven behaviors in the UP. The inclusion of this strategy in these treatments draws from a long tradition in more basic emotion science suggesting that the most fundamental way to change an emotion is through altering the action-tendencies associated with it[88,89,90,91,92]. It is hypothesized that acting inconsistent with emotion-driven urges leads to reductions in the intensity of the activating emotion; in turn, increased ability to regulate one's emotions (e.g., reducing their intensity through acting inconsistent to them) is thought to lead to greater tolerance of emotions as they occur. Despite, its inclusion in both the UP and DBT, the role of acting counter to emotion-driven behavioral urges in reducing emotional intensity and increasing emotional tolerance has not been explored empirically in the context of a therapeutic intervention for emotional disorders.

Single-Case Experimental Designs: Single-case experimental designs[84] (SCEDs) are powerful and cost-efficient tools to explore mechanisms. Advantages of SCEDs include high internal validity, and strong potential conclusions regarding the effects of a specific intervention strategy. SCEDs offer the opportunity to explore reasons for inter-subject variability using flexible and responsive experimental strategies. This approach leads, ultimately, to more effective treatment development, and has been employed in prior research testing novel interventions for emotional disorders[70, 71] and BPD-relevant behaviors including self harm[73, 81].

Study Overview: The proposed work will utilize the advantages of SCEDs, across two study phases, to explore the effects of behaving counter to emotional urges on emotional intensity (target) and emotional tolerance (outcome). Consistent with an experimental therapeutics approach, the purpose of Phase I is to explore whether acting inconsistent with emotion-driven behavioral urges (EDBs) leads to reductions in the intensity of emotional experiences, a notion postulated by the developers of leading treatments for emotional disorders but that has never been tested empirically. To this end, participants with lower-risk BPD will take part in an alternating treatment design (ATD; Barlow & Hayes, 1979[50]) that elegantly uses individual subjects as their own control by rapidly alternating two experimental conditions within the individual. In the first condition, participants will be instructed to act inconsistent with EDBs following an emotion induction while in the second condition, they will instructed to act consistent with their EDBs. These two conditions will be rapidly and randomly alternated across 6 sessions. The effects of these conditions will be explored for several discrete emotions (anxiety, sadness, anger, and shame). It is hypothesized that, across emotions, when participants are instructed to act inconsistent (versus consistent) with their EDBs, they will demonstrate greater reductions in the discrete emotion induced using convergent indices (self-report, and behavioral). Identifying core mechanisms relevant across diagnostic boundaries is important for treatment refinement such that focused treatments can be more easily disseminated and implemented by frontline clinicians.

Phase II will also utilize SCED, in this case a multiple baseline design, in order to explore the effect of a brief intervention focused specifically on countering emotion-driven behavioral urges on reducing the frequency of EDBs, reducing emotional intensity, and increasing emotional tolerance. Again, participants in this phase will be individuals with lower-risk BPD. The initial baseline phase (2 weeks or 4 weeks in duration) serves as a control condition to establish frequency of EDBs and levels of emotional intensity and emotional tolerance in the absence of any intervention, and potentially demonstrate that change occurs when and only when the experimental phase begins[84]. The focused countering EDBs intervention will consist of four 50-minute individual weekly sessions. Following the four-week intervention phase, participants will enter a 4-week follow up period. Real-time occurrence of EDBs will be monitored through the use of ecological momentary assessment methods, which are ideal for obtaining information about frequently occurring behaviors.

Measuring EDBs on a smart-phone will allow us to record EDBs as they occur naturally in real time, thereby augmenting ecological validity. This design will allow us to explore whether an intervention focused solely on countering EDBs (as opposed to multi-component interventions that include this strategy) indeed enacts change in the frequency of EDBs, intensity of affect experienced, and emotional tolerance. Although measures of BPD symptoms will be collected, the effect of countering EDBs on BPD symptoms will be exploratory.

INNOVATION.

1. Given the heterogeneity of BPD presentations, treatment tailored to the presenting level of severity may represent an important way to increase efficiency and cost-effectiveness in approaching this disorder. To date, no treatments have been developed explicitly for individuals meeting criteria for BPD without severe behavioral dyscontrol (e.g., lower-risk BPD).
2. Despite an abundance of empirical support for the conceptualization of BPD as an emotional disorder, this case has only recently been explicitly made[15]. There is extensive literature regarding the underlying mechanisms maintaining symptoms in emotional disorders; as such, understanding BPD as an emotional disorder provides a theoretically informed heuristic to guide a treatment approach aimed at individuals presenting with lower-risk BPD.
3. Distillation of the mechanism(s) of action thought to address a core deficit in BPD in the context of a laboratory study (Phase I of the proposed study) may further inform the simplification of psychosocial interventions aimed at BPD, thereby enhancing dissemination efforts. Additionally, a preliminary exploration of whether a brief EDB-focused intervention (Phase II of the proposed study) indeed enacts changes in the frequency of EDBs and whether these changes impact intensity of affect will provide necessary ecological validity regarding the importance of this mechanism.
4. Finally, conceptualizing BPD as an emotional disorder also underscores its high rates of comorbidity with anxiety and depressive disorders, which are characterized by similar deficits in emotional processing. This suggests that the extensive comorbidity amongst BPD and other emotional disorders might be better served through treatment strategies that address several disorders simultaneously by targeting common deficits. After establishing that acting inconsistent to EDBs leads to improvements in a putative maintaining factor in emotional disorders (deficits in emotional tolerance) in the context of patients with lower-risk BPD, next steps will involve confirming the transdiagnostic utility of this strategy in other emotional disorders.

APPROACH

Preliminary studies on acting counter to EDBs as a mechanism of symptom reduction: In the context of BPD, the UP was recently used to treat four patients (meeting the proposed study's inclusion/exclusion criteria for lower-risk BPD) in an open series of cases[22]. Patients received 16 weekly sessions and were treated by the applicant and a supervised graduate student. All participants evidenced pre- to post-treatment improvements on BPD symptoms, as measured by Zanarini Rating Scale for Borderline Personality Disorder- Self-report Version[51] (ZAN-BPD: SVR); the effect size for change in BPD symptoms was large (ES_{sg} =1.06) with a confidence interval that did not include 0. However, more germane to the present proposal, patients also displayed large pre- to post-treatment changes in their self-reported tendency to pursue goal-oriented behavior even when distressed (DERS-Goals, ES_{sg} = .77) and their ability to control emotion-driven impulsive behavior (DERS-Impulse Control, ES_{sg} = 1.06), as measured by the Difficulties in Emotion Regulation Scale (DERS)[53]. These changes suggest that countering EDBs is responsive to treatment; limitations of this small-scale pilot study prevent isolation of the role of this mechanism in the reduction of BPD symptoms. For example, the UP is a multi-component intervention and it was administered in its entirety, precluding our ability to isolate the effects of the Countering EDBs module specifically on the DERS and ZAN-BPD-SRV. The proposed project will address these limitations by exploring whether acting inconsistent to EDBs indeed impacts its purported mechanisms, reduced emotional intensity (Phase I), and whether the Countering EDBs module from UP indeed leads to reductions in EDBs and emotional intensity (Phase II).

Research Design:

Study Design- Phase I of the proposed study will utilize an alternating treatment design (ATD) aimed at isolating the effects of an unstudied treatment component contained in several existing transdiagnostic treatments on putative mechanisms maintaining symptoms of emotional disorders. The role of acting inconsistent with emotion-driven behavioral urges (EDBs) in reducing the intensity of emotional experiences will be examined by rapidly alternating two experimental conditions (acting consistent vs. inconsistent with an induced emotion) within the individual. Phase II will also use a SCED (a multiple baseline approach) to explore whether a brief intervention focused solely on acting inconsistent to EDBs indeed leads to change in the frequency of EDBs and the intensity of experienced affect using real-time assessment techniques (EMA).

Clinician-rated, self-reported, and behavioral measures of BPD symptoms and emotional tolerance will also be administered weekly and/or at major assessment time-points (pre-baseline, pre-intervention, post-intervention, and post-follow-up). The baseline period (2 or 4 weeks in duration) will serve as the control condition, allowing us to observe whether change on variables of interest occur only when the intervention is applied. This project is very much in line with the PI's mentor's and collaborator's work developing and testing treatments for BPD (Dr. Marsha Linehan) and investigating mechanisms of action in existing interventions (Dr. David H. Barlow).

Study Setting: All study sessions will be conducted at CARD, which is one of the largest research clinics devoted to emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Study Population: Participants will include 32 men and women who are at least 18 years of age. *Phase I* will include 24 participants meeting DSM diagnostic criteria for BPD (as determined by the DIPD[54], see Study Measures below) and *Phase II* will include 8 individuals diagnosed with BPD (per the DIPD); samples of this size are customary for SCEDs (see detailed description of power in the Data Analysis section below). Following long-standing procedures for clinical trials at CARD, participants in both phases who are on psychotropic medications will be included if they are willing to maintain a constant dosage throughout study sessions. This avoids problems with reluctance to discontinue or difficulty with discontinuing, and also the confounding of outcomes from initiation of medication during treatment. Because of the difficulty maintaining a consistent dose for PRN medications that are taken as needed per the patient's discretion, participants on PRN psychotropic medications will be excluded. Medication usage will be assessed weekly in order to control for any changes that may arise (described below). Additionally, participants in Phase II must also be willing to refrain from any additional psychosocial treatment during the course of the study and have their own smartphone.

Exclusion criteria. Exclusion criteria in this study provide the basis for determining whether participants are demonstrating lower-risk BPD symptoms. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the participant and will consist primarily of conditions that would require prioritization for immediate treatment (e.g., severe suicidality or substance dependence). Specifically, these conditions include: (a) current *DSM-5* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk (intent) and (c) current or recent (within 3 months) history of drug dependence. Individuals will also be excluded if their emotional symptoms are due to a medical/physical condition in which case alternative treatment would be clinically indicated.

Patient flow and feasibility. Participants will primarily be recruited from local treatment sites currently reporting an overflow of BPD patients; these include the intake and referral offices at Massachusetts General Hospital and the McLean Hospital (see letters of support from clinical faculty at these institutions in Other Attachments). Additionally, participants will be recruited through CARD's general client population. CARD completes over 1000 new patient screenings per year of which approximately 15% endorse symptoms of BPD; rather than refer these individuals out for BPD treatment elsewhere, they will be sent to this study for further assessment. Finally, we will also advertise specifically for the study in locations and publications commonly advertising treatment studies. These recruitment procedures are consistent with a recent data collection at CARD that enrolled 50 individuals with BPD (and comorbid Bulimia Nervosa) over the course of 4 years in the context of an NIMH-funded Career Development Award (PI: Thompson-Brenner). Further, while recruiting for a small pilot study, 4 patients meeting the current study's eligibility criteria were recruited from the above sources in a two-month period (2 from CARD, 1 from McLean Hospital, and 1 from Massachusetts General Hospital). Recruitment at this rate during the proposed project would be sufficient to achieve enrollment goals.

Participant Retention: In both phases, participants that discontinue will be replaced. However, we will employ procedures during both study phases to reduce potential dropout. First, at the baseline assessment, the PI will personally meet with participants to provide them with a plan for discussing any concerns as they arise throughout the study. Specifically, participants will be informed that they should first address concerns directly with study staff (IEs) or the PI. In cases where patients may not feel comfortable addressing the PI directly, Dr. David Barlow (the mentor on this study and Director Emeritus of the clinic) may be involved to resolve concerns with patients. This will establish a positive working alliance with the research "team." Additionally, study staff will be flexible in re-scheduling missed sessions within reasonable limits. These procedures recommended by Marsha Linehan and others involved in treating patients with BPD and co-occurring disorders[55] and will be overseen by Dr. Linehan, a close collaborator on this project with

extensive experience treating BPD.

Diagnostic Assessment (Phases I and II). Upon referral to the study, participants will complete a brief telephone screening; patients eligible following the initial screening will be scheduled for an in-person appointment in which informed consent will be obtained and the baseline assessment will be conducted to confirm inclusion/exclusion criteria. Diagnostic measures will include: (1) Diagnostic Interview for DSM-IV Personality Disorders- Borderline Module[54] (DIPD-IV). The DIPD-IV is well-established and widely used diagnostic interview of personality disorders with good inter-rater and test–retest reliability. This measure will be used to establish inclusion criteria for BPD participants and exclusion criteria for the anxiety disorder comparison subjects. (2) Anxiety Disorders Interview Schedule-5[57] (ADIS-5). The ADIS-5 is a semi-structured diagnostic interview designed to establish reliable DSM-5 anxiety, mood, somatoform and substance disorders. For each current diagnosis, interviewers assign a 0-8 clinical severity rating (CSR) that indicates their judgment of the degree of distress and impairment associated with the disorder (0=none to 8=very severely disturbing/disabling, scores of 4 and above reflect clinical threshold diagnoses). This measure will be used to establish study exclusion criteria (e.g., substance dependence, bipolar disorder).

PHASE 1: ATD Component Procedures. Twenty-four participants will be included in the ATD component of this study. There are four discrete emotions (anger, sadness, anxiety, and guilt) under investigation and participants will be randomly assigned to complete study procedures for only one emotion. Six participants will be assigned to each emotion condition. Following usual and customary procedures for ATDs, the first participant for each discrete emotion will comprise the main experiment with the subsequent participants serving as replications. Each participant will be presented with six emotion inductions (focused on the emotion related to their assigned condition), occurring on six separate days over the course of two weeks. In order to maximize clinical relevance, emotional stimuli used in the emotion inductions will be tailored to each individual by instructing participants to write about a time in the past two months in which they felt the particular emotion being induced. This strategy has been successfully implemented previously by the PI to induce strong emotions in individuals with BPD[78]. Prior research has suggested that using idiographic stimuli (vs. standardized stimuli) results in greater emotional reactivity in individuals with BPD[48] and anxiety disorders[93]. Prior to the first emotion induction in the first session, study staff will assist participants in developing a list of situations, occurring in the past two months, that brought up the emotion consistent with the condition to which the participant is assigned. Participants will be asked to rate the emotional intensity of each situation (on a 1-100 scale consistent with subjective units of distress[59]) and six situations rated above 60 (to ensure sufficiently strong emotion is induced) will be chosen as the basis for the emotion induction writing assignments.

Following each emotion induction, participants will be instructed to either act consistent or inconsistent with the emotion induced; instructions will be randomly alternated so that each participant will act consistent during 3 sessions and act inconsistent during 3 sessions. The randomization schedule will be such that one condition will not be presented more than two times in a row. Participants will be informed that "the goal of this project is to test out two different strategies for coping more effectively with emotions in order to ascertain the most effective strategy for you." The two conditions will both be presented as credible and effective strategies to the participants in order to minimize any biased results due to expectancy effects. The specific instructions for acting inconsistent and consistent with EDBs following the mood induction will based on idiosyncratic action urges associated with the induced emotions. For example, the guilt induction may elicit action urges to withdraw/hide and/or (albeit less commonly) lash out in an effort to deflect blame[49]. Acting inconsistent to urges to withdraw may involve making plans with friends (via phone or email) or making small talk with confederates while acting inconsistent to urges to lash could include writing thank you notes to loved ones or engaging in an act of kindness. Study staff will assess for idiosyncratic emotion-driven action urges after the emotion induction to craft appropriate behavioral instructions relevant for the individual.

An important advantage of SCEDs is that the flexible nature of these studies and the immediate availability of results allows for the real-time alteration of procedures in order to obtain an effect on the putative mechanism of action[88]. In this case, if we fail to find reductions in the intensity of the induced emotion by asking participants to act inconsistent with their reported action urges, we may, for example, extend the purview of behaviors to include emotion-consistent/inconsistent posture, and tone of voice[4]. Making these changes informs the development of interventions by evaluating various strategies to manipulate putative mechanisms. The strategies tested can be confirmed by replication and also associated with individual characteristics. Participants will be paid $40 per session for a total of $240 for completing the entire six study sessions.

Phase I Assessment. The DIPD-IV and ADIS-5 (described above) will be used to confirm inclusion and exclusion criteria. The primary dependent variable in Phase I is the intensity of the discrete emotion induced.

Three convergent indices (self-report, behavioral, and physiological) will be used. **Self-report:** The Positive and Negative Affective Schedule-Expanded Form (PANAS-X[52]) includes subscales measuring the intensity of the four discrete emotions represented in this study (fear, sadness, guilt, and anger). A Manipulation Check will be included asking participants to rate the extent to which they feel they were adherent to the prescribed strategy (acting consistent vs. inconsistent). **Behavioral:** The Facial Expression Coding System[58] (FACES) is a rater-coding system that yields information regarding the frequency, intensity, and duration of facial expressions. Participants' facial expressions will be video recorded throughout all study procedures and all tapes will be subsequently coded by trained undergraduate research assistants. The applicant will receive standard training in this protocol by Dr. Sloan, its creator and a collaborator on this project.

PHASE II: **Multiple Baseline with Phase Change Procedures:** Participants (8) will be randomized to a 2- or 4-week initial baseline period. The baseline period will consist of assessment only, described in detail below. Following the initial baseline period, participants will receive 4 weekly 50-minute sessions of an intervention; this duration of treatment is consistent with clinical experience at our center indicating that this is an adequate amount of exposure to given UP modules. The Countering EDBs Module from the UP will be used as the basis for session content as the modular approach of the UP allows for the delivery of just this treatment topic isolation. Randomization to baseline phases of differing lengths will allow us to explore whether change on variables of interest occurs when and only when the intervention is applied. *Phase II Treatment Quality Assurance.* The PI (applicant) will serve as the study therapist. The PI is a licensed clinical psychologist with over eight years of experience with adults with BPD. Additionally, the PI is fully certified as an expert in the delivery of the UP. All therapy sessions will be audiotaped and will all be rated for adherence and competence ratings by an expert rater. Most importantly for the current project, integrity measures will assess for allowed and disallowed techniques within the UP to ensure only information regarding countering EDBs is presented as a means to isolate this putative mechanism. Descriptive statistics on fidelity measures will be obtained.

Phase II Assessment. During all periods (baseline and intervention), participants will be asked to complete a daily log of EDBs and emotional intensity using SymTrend, a software developed specifically for real-time data collection. Participants will be trained in using their personal smart-phone to complete these daily logs on SymTrend. Participants who do not own a smart-phone will be excluded from this study; based on consultation with collaborator Dr. Rosenthal who routinely conducts research using EMA and recent studies utilizing these methods at CARD, we anticipate very few participants will be excluded do to this criterion. Participants will be asked to self-initiate an entry whenever they are experiencing strong emotions (at least once per day) and will be asked to rate the intensity of their emotional experience. One hour after self-initiating the entry, participants will be prompted by text message via SymTrend to indicate whether they engaged in EDBs or acted inconsistent to emotional urges, as well as to rate their current emotional intensity. SymTrend will automatically send text messages everyday at mid-day to remind participants to self-initiate entries when feeling a strong emotion. Additionally, participants will receive a text-message reminder once a week prompting them to complete a longer self-report battery. Participants will have the option to complete the logs and questionnaire battery on a computer rather than smart phone, should they prefer. Phase II assessment measures will include: **Diagnostic Measures.** As in Phase I, the DIPD-IV and ADIS-5 (described above) will be used to confirm inclusion and exclusion criteria. **Major Assessment Measures.** Major assessments will be completed at four time-points: pre-baseline period, pre-intervention period, post-intervention, and post-follow up. These assessments will include: (1) Zanarini Rating Scale for Borderline Personality Disorder[51] (ZAN-BPD). The ZAN-BPD is a continuous clinician-rated scale designed to address change in BPD symptoms by rating severity of the diagnostic criteria across a 1-week time frame. The ZAN-BPD has demonstrated high levels of reliability and validity. (2) Paced Auditory Serial Addition Task- Computerized Version[64] (PASAT-C). The PASAT-C is behavioral measure that has been used with BPD participants as assess willingness to engage in goal-directed behavior while experiencing distress[69] and will be used as a behavioral indicator of acting inconsistent with EDBs. **Weekly Measures.** As noted above, patients will be prompted to complete a self-report battery via text-message from SymTrend on a weekly basis. The battery will include the (1) self-report version of the ZAN-BPD (ZAN-BPD-srv) and the (2) Multidimensional Experiential Avoidance Questionnaire[60] (MEAQ). The MEAQ is a self-report measure that will be used to assess emotional tolerance. The MEAQ has demonstrated high internal consistency and validity. Finally, (3) changes in medication will be tracked. **Daily Measures.** As described above, participants will be asked to self-initiate entries when experiencing a strong emotion. These entries will involve completing the PANAS-X and then, one hour later, completing a series of structured questions regarding engagement in EDBs, followed by an additional PANAS-X.

Participants will receive a $50 payment for each clinician-rated assessment they complete (pre-baseline, pre-intervention, post-intervention, and post-follow-up). Additionally, participants can earn a $100 bonus for a ≥ 80% compliance rate with smart-phone entries and weekly questionnaires (up to $300 total). Similar studies at our Center (e.g., utilizing daily EMA across 12 weeks in individuals engaging in non-suicidal self-injury) have demonstrated a 90% compliance rate with daily assessments using the bonus incentive.

	Time of Administration				
	Pre-baseline period	*Weekly*	*Pre-intervention*	*Post-intervention*	*Post Follow-Up*
Clinician-rated measures					
DIPD-IV	X				
ADIS-5	X				
Major Assessments					
ZAN-BPD (clinician-rated)	X		X	X	X
PASAT-C (behavioral task)	X		X	X	X
Weekly Measures					
MEAQ	X	X	X	X	X
ZAN-BPD (self-report version)	*X*	*X*	*X*	*X*	*X*
Medication tracking form	X	X	X	X	X
Daily Measures					
PANAS-X and EDB questions					

Phase II Assessment Quality Assurance. Independent Evaluator (IE) Qualifications. Clinician-rated measures (DIPD-R, ZAN-BPD, Mini-ADIS) will be administered by graduate level IEs at a pre-baseline period assessment, a pre-intervention assessment, a post-intervention assessment, and a post-follow up assessment. IEs will be trained to reliability on the DIPD-R and ZAN-BPD by the PI who will have previously completed training on these measures with Dr. Mary Zanarini, author of these measures and a collaborator on this project. Further, all graduate students at CARD receive rigorous training and meet strict certification criteria in the administration of the ADIS-5, which would be completed prior to their participation on the current study. For more information regarding this training process, see Brown and colleagues[68]. *Reducing IE drift.* All assessments will be audio recorded and the PI will rate 15% of randomly selected interviews at regular intervals. If reliability falls below criteria, IEs will be retrained. Reliability statistics will be included in publications. Because all participants in Phase II will be in active treatment, it will not be necessary for IEs to remain blind. Additionally, we fully expect that some patients' BPD symptoms may not improve after only four sessions (as our primary focus is our ability to manipulate the putative mechanism of EDBS), thus reducing concerns about IE bias regarding the favorability of the intervention. Data Entry Procedures. Both patient self-report measures and IE measures will be completed directly on smart-phones (participant self-report) or tablet computers (IE entries) that will transfer data directly into secure databases using SymTrend's online survey program; this will greatly reduce human errors that occur by manually entering data. See Safety/confidential section for data safety information.

Participant Safety and Confidentiality: PHASES I & II. The PI, working closely with her mentor, will carefully monitor the safety of participants. During Phase I, the PI will conduct a risk assessment following each study session to ensure that participants are safe to leave the laboratory after each emotion induction session. In the unlikely event that participants report increased risk, they will be encouraged to contact their existing treatment provider (Phase I does not preclude ongoing treatment) or will be given referrals if they do not have one. If risk is imminent, every measure will be taken to ensure participant safety (e.g., safety plan, hospitalization) in a manner consistent with customary clinical care at CARD. Because Phase II examines the effects of an intervention, participants will be asked to refrain from additional treatment during the baseline, treatment, and follow-up periods. It is important note that inclusion/exclusion criteria reflects the lower-risk BPD patients of interest in this study and these patients should be able to tolerate all periods of Phase II. Safeguards will be in place in the unlikely event that patients deteriorate. First, weekly questionnaire data will be examined as it is returned for indicators of clinical deterioration – email notifications will alert the PI to incoming data. Endorsement of increased suicidal ideation on the ZAN-BPD-srv (ratings of 2 or higher on item 5) will trigger a formal risk assessment; this will be conducted with 24 hours of receipt of the data. Issues of clinical deterioration and safety will be discussed during ongoing mentoring meetings with Dr. Barlow, who has also agreed to be available by cell for emergencies. Following long-standing customs of research studies at our Center, any patients deteriorating (as determined by a > 6 point increase on the ZAN-BPD-srv) in any study phase will be brought to the attention of current clinical director of CARD, Dr. Lisa Smith (who is not

involved with this study and can objectively evaluate the patient) to determine if the patient should be removed from the study to receive alternative, or more intensive care. The PI and Dr. Barlow will coordinate care, either at CARD or elsewhere, for participants withdrawn due to deterioration. After completion of the study, *all* participants will be given a written list of referrals and instructions to contact study staff if they would like assistance with securing additional treatment. It should be noted that patients in dire need of additional treatment (likely due to deterioration because only stable patients will be recruited) will have been withdrawn at this point; this is a longstanding procedure within collaborator Dr. Linehan's lab for providing resources to patients completing research trials. Participants' confidentiality will be carefully guarded and respected. Data will be coded with participant numbers, with all identifying information removed. Data with identifying information will be stored in locked cabinets and electronic data will be password protected on secure CARD servers.

DATA ANALYSIS: PHASE I & II. *Phase I Data Analyses:* Hypotheses regarding differential outcomes between the two strategies (acting consistent versus inconsistent) will be evaluated using a combination of classical methods of idiographic data-analysis and modern non-parametric statistical techniques. We will first plot parallel lines representing intensity of emotion as a function of each individual strategy. These will be directly compared as to changes in level and slope. In addition to customary visual observation (often, functions in ATDs yield non-overlapping datasets), more quantitative evaluations will also be employed by conducting non-parametric randomization and bootstrap tests of the mean differences between the two conditions[82]. The non-parametric statistical analyses will be conducted using the Single-Case Randomization Tests package[61] (SCRT) within the R statistical framework. Randomization tests will be conducted regarding levels of mean change in self-reported emotional intensity and clinician-rated facial emotional intensity from post-induction to post-regulation condition (acting consistent/inconsistent). Results from these non-parametric randomization tests will be used in conjunction with the visual observations for each individual to draw conclusions regarding the effect of acting counter to EDBs on the intensity of emotion relative to acting consistent with emotional urges.

Phase I, Hypothesis 1: When instructed to respond to induced emotions by acting inconsistent to emotional urges, participants will demonstrate greater reductions in the intensity of their emotions compared to acting consistent with their emotional urges. Similar patterns of results are expected across all discrete emotions induced.

Phase II Data Analyses: The multiple baseline and phase change design will make between- and within-subjects analysis possible[72]. By applying different baseline lengths across individuals, between-series comparisons will be possible to determine if changes in EDBs, emotional intensity, and emotional tolerance occur when and only when the intervention is applied[85]. The phase change (baseline phase to treatment phase) process will allow for within-series comparisons to examine concomitant changes in EDBs, emotional intensity, and emotional tolerance when treatment is present compared to when it is absent within individuals. For both between-and within-subjects comparisons, we will first plot parallel lines representing changes in these variables over time for each individual. These will be directly compared in terms of changes in level and slope to determine if differences seen are due to phase change[88]. We will also conduct non-parametric randomization tests of mean differences in EDBs, emotional intensity, and emotional tolerance as a function of phase using the SCRT[61] within the R statistical framework. Results from these tests will be used with visual inspection of data to draw conclusions regarding effects of the intervention on frequency of EDBs, emotional intensity and emotional tolerance. We will also explore maintenance effects of our intervention by examining stability in EDBs, emotional intensity, and emotional tolerance during the follow-up phase. Finally, as an exploratory analysis, we will examine phase effects (baseline, treatment, follow-up) on clinician rated and self-reported BPD symptoms.

Phase II, Hypothesis I: Individuals will demonstrate change in self-reported frequency of EDBs, intensity of emotion (PANAS) and tolerance of emotions (MEAQ), as well as behavioral willingness to act inconsistent with emotional urges (PASAT-C) only after treatment is applied. *Phase II, Hypothesis II:* Change in these variables will be maintained during a 4-week follow up period. *Phase II, Hypothesis III:* In this exploratory analysis, we hypothesize that clinician-rated and self-reported BPD symptoms (ZAN-BPD, ZAN-BPD-srv) will decrease when and only when the intervention is applied, and only for patients who demonstrate reduction in EDBs.

Power Analyses. Sample size in SCEDs refers to the number of observations collected. In Phase I, 35 observations (ratings of emotional intensity) will be collected for each emotion under study (18 acting consistent with emotional urges and 18 acting inconsistent); this will yield 180 total observations with 90 in each condition. Phase II will result in 88 observations for weekly measures and 616 observations for daily

measures. These numbers of observation will make possible detection of medium effect sizes across both phases.

Timeline Timetable: Support is requested for 4 years in order to successfully complete both phases of the project, which are integral to the applicant's training goal to gain expertise in exploring mechanisms of action in treatment. Year 1 of the project will be dedicated to acquiring advanced training in the assessment of physiological and behavioral indictors of emotion to corroborate self-report data and for training study staff. Recruitment and data collection for Phase I will take place in Year 2. Recruitment and data collection for Phase II will begin in the 9th month of Year 2 and continue through Year 3. Additionally, in Year 3, data analyses will be started and an R01 application for a larger-scale efficacy trial examining the effect of countering EDBs on BPD symptoms will be submitted. A larger N will make possible longitudinal repeated-measurement of treatment mediators and exploration of moderators (e.g., severity). Finally, Year 4 will be used to complete data analyses, prepare manuscripts, and re-submit the R01 application.