Cognitive Reappraisal Training Targeting Emotion Circuits As a Therapeutic Intervention in Borderline Patients
PI: Harold W Koenigsberg, MD
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RESEARCH STRATEGY

A. Significance

A.1. Borderline Personality Disorder and its Treatment Challenges

Borderline Personality Disorder (BPD) is a prevalent and enduring psychiatric condition found in approximately 2% to 5.9% of the population [1, 2] and 20% of hospitalized psychiatric patients. Suicide rates of approximately 10% have been reported [3]. One of the most prominent clinical features of BPD is extreme mood shifts [4-6] occurring in response to external social/emotional events [7-9]. The emotional instability in BPD contributes to many of the most disabling, even life-threatening, symptoms of the disorder, including suicidality, outbursts of intense anger, and seriously impaired role functioning [10]. The severity of the BPD symptom profile, its prevalence, chronicity and high burden upon health care services [11-13] make the development of effective and accessible treatment for BPD a high priority. Although several psychological treatments show promise [1417] and medications are of value in ameliorating certain specific symptoms [18, 19], no medications are currently indicated to treat the BPD syndrome [19] and extant psychological treatments have small effect sizes, are resource intensive and of limited availability [20, 21]. The development of new treatment approaches is therefore essential. Neuroimaging is useful in treatment development to identify neural mechanisms underlying key symptoms, guide targeted treatments and assess their impacts.

A.2. Cognitive Reappraisal as Therapeutic Focus

Intense, unstable or prolonged emotional reactions to psychosocial events characterize BPD, contributing to high levels of distress, disturbed relationships and impaired role functioning. Reducing affective instability (AI) in BPD is important to the successful treatment of the disorder because of the central role of AI in BPD's most disabling and life-threatening symptoms [4, 5, 10]. Thus, the enhancement of emotion regulation is central to the treatment of BPD. A growing body of research has characterized the dynamics of emotion regulation [22]. A number of classes of regulation strategies have been described, including changing the situation (e.g., avoiding stressful situations), attentional redeployment (e.g., diverting attention away from the stressor), cognitive change, and modulating one's emotional response (e.g., suppressing the expression of emotion) [23-25]. Cognitive change in particular is one of the most highly adaptive and versatile classes of regulation strategies, with cognitive reappraisal (CR) representing a particularly valuable strategy for implementing cognitive change [25]. CR entails re-construing a situation in such a way as to alter its emotional valence.

Two CR tactics have been described as a means of operationalizing reappraisal [26, 27]. The first, *distancing,* is a strategy in which the subject construes the emotional situation as psychologically distant – i.e. calmly, objectively, and not emotionally relevant personally, or far away in time or place, so as to reduce its negative valence. This is the mechanism, for example, which underlies the "clinical distancing" that enables an emergency room physician to function effectively even in the face of intensely upsetting situations. The second is *reinterpretation* – a strategy in which the subject creates a different (e.g., more benign) narrative for a situation to change its valence (e.g. re-conceptualizing bad performance on a test as a "learning opportunity", rather than as a marker of failure) [28] [26, 27].

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Overall, cognitive reappraisal has been demonstrated to be a particularly effective strategy. Individuals who use cognitive reappraisal, in comparison to other regulation strategies, show a *better sense of well-being, enhanced social relationships, better memory and less cardiovascular sympathetic arousal* [25, 29, 30]. In particular, the *distancing tactic* of CR had the *largest effect size* (d=.45) [31] of various emotion regulation strategies examined [22]. Further, a direct comparison of distancing and reinterpretation CR tactics has shown that longitudinal training in distancing uniquely yields significant reductions in perceived stress in daily life [26]. We have previously shown that BPD patients show impairments in cognitive reappraisal associated with anomalous neural activation when attempting to reappraise-by-distancing (see **C.1.3.1.** for previous results). They fail to engage the top-down cortical regions typically employed by healthy subjects (HCs) and do not downregulate amygdala activity as HCs do [32]. This observation motivated us to explore whether BPD patients could be trained to enhance the effectiveness of cognitive reappraisal-by-distancing, the central aim of our recently completed NIMH funded study (R01 MH077813). In this study, we demonstrated that with 5 sessions of focused cognitive reappraisal-by-distancing (CRD) training, BPD patients were able, when reappraising negative pictures (vs. just looking), to reduce activity ($p=0.03$, one-tailed) in the picture induced negative emotion signature (PINES) network, a whole-brain pattern derived through machine learning that is sensitive and specific to picture induced negative emotion [33]. PINES activation increases monotonically with subjectively reported levels of negative emotion. This network is more sensitive and specific for emotional reactions to negative pictures than other regions associated with negative emotion alone, such as the amygdala, insula, salience network and default mode network. In addition to the decreased PINES response, we found that, behaviorally, subjects showed a decrease in ratings of negative valence after training ($p <0.03$).

This body of work convinced us to pursue development of focused cognitive reappraisal training as a novel approach to the treatment of BPD, either as a stand-alone treatment or in concert with evidence-based treatments for BPD. To accomplish this objective, we propose the current R61/R33 study. In the **R61 phase**, the proposed study will develop and manualize an enhanced form of focused cognitive reappraisal training, building upon the model explored in our previous work, will confirm that the manualized treatment can be delivered adherently, will demonstrate that this treatment influences targeted behavioral measures and specific hypothesized circuits, and will identify an optimal dose for the treatment. Should we demonstrate that the intervention can significantly influence activity in the targeted neural circuits, we will proceed to examine the R61determined optimal dose in the **R33 phase** of the study. In this phase, we will confirm that the treatment can be delivered reliably with good therapist adherence and patient acceptance, and will examine whether the treatment will have a beneficial effect on clinical outcome measures, including measures of overall BPD symptom score, affective lability, mood, impulsivity, and perceived stress. In addition this phase will allow us to replicate, in a new sample, that the treatment influences the target neural networks identified in the R61 phase, and to test whether change in clinical outcome measures correlate with changes in target circuit activation and behavioral reappraisal response. We will also examine the near-term durability of the treatment effect by re-assessing the clinical outcome measures *1 and 4 months* after the end of the treatment.

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A.3. From Proximal Target Engagement to Symptom Change: Modeling the Effects of Treatment

The ultimate objective of the proposed treatment for BPD is to reduce the disabling symptoms of the disorder that contribute to personal distress, interpersonal impairments and social role dysfunction. These key symptoms include affective instability, unstable patterns of relating to others, impulsivity, inappropriate anger, self-destructive behaviors and inconsistent experience of self in terms of values, goals and beliefs. Affective instability, the tendency for emotions to be excessively reactive to events, rapidly shifting from one emotion state to another, reaching high levels of intensity and being slow to return to baseline, is an especially critical symptom of BPD. We have previously shown that many of the symptoms of BPD, including suicidal threats, gestures and acts, inappropriate anger, chronic emptiness and identity disturbances, are correlated with affective instability [10].

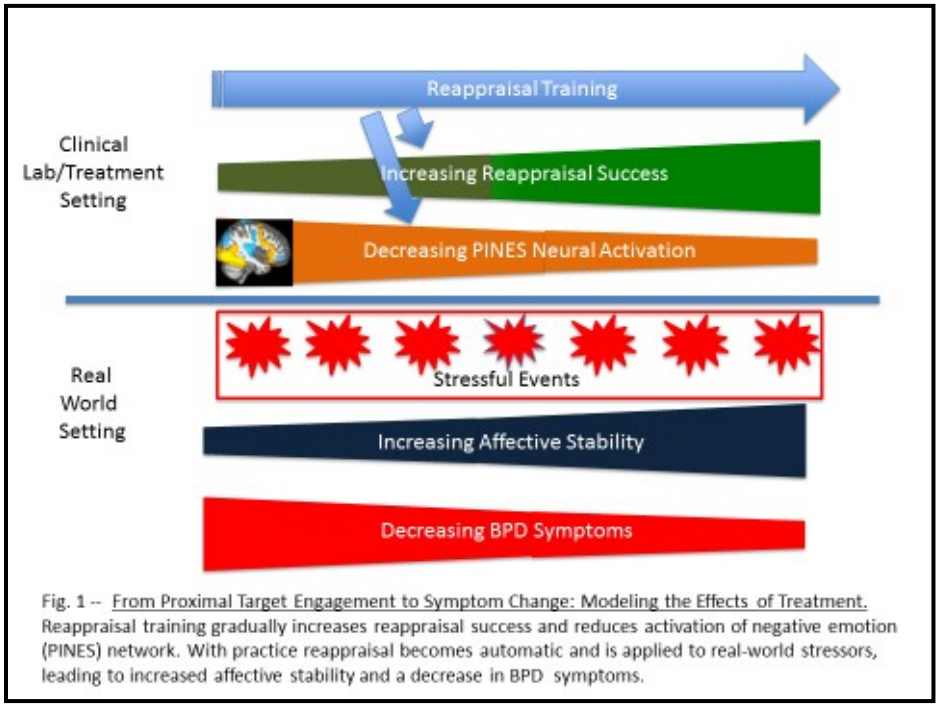

Fig. 1 -- From Proximal Target Engagement to Symptom Change: Modeling the Effects of Treatment. Reappraisal training gradually increases reappraisal success and reduces activation of negative emotion (PINES) network. With practice reappraisal becomes automatic and is applied to real-world stressors, leading to increased affective stability and a decrease in BPD symptoms.

Hence we propose a treatment that directly aims to reduce affective instability by enhancing the emotion regulation skill of cognitive reappraisal (CR). From moment to moment, the effective use of CR should reduce the intensity with which negative stimuli are experienced and reduce activity in the PINES network. On the basis of the findings from our previous study (see **A.2**. above and **C.1.3.3.** below), we predict that CR training will lead to: 1) reduced PINES activation during negative picture reappraisal and 2) a reduction in behavioral ratings of negative valence (improved reappraisal success). Of the two, we expect that neural response will be the more sensitive measure of the proximal training effect because it is less subject to demand expectations and reporting bias.

Our prior work demonstrated that with 5 sessions of CR training, subjects reduced their negative ratings of aversive pictures not only when reappraising, but also when simply looking at the negative pictures. This suggests that as reappraisal is repeatedly practiced, it becomes automatically utilized even when not explicitly directed. We therefore expect that CR techniques will generalize beyond the treatment setting and be implicitly activated as subjects contend with emotionally stressful events in their daily lives (Fig. 1). This will lead to a decrease in affective instability and a consequential decrease in the BPD symptoms linked to affective insatiability: suicidal threats gestures and acts, inappropriate anger, chronic emptiness and boredom, and identity disturbances. These hypotheses will be explicitly tested in the R33 phase.

A.4. Studies of Cognitive Reappraisal Enhancement

A number of recent studies have examined the degree to which individuals can be trained to enhance cognitive reappraisal. These studies employed a variety of training

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techniques including: longitudinal mentor guided training in the lab, smart-phone based home practice focusing on daily life events, and practice providing counseling to others using reappraisal, delivered over an internet platform. The duration of training varied from one to three weeks, with session frequencies ranging from every 3 to 5 days to daily. Five of the seven studies examined healthy subjects [26, 34-37] and one each examined those with social anxiety [38] or high levels of neuroticism [29]. Most studies focused upon the reinterpretation tactic, but in their study of healthy subjects, Denny et al [26] compared training in reinterpretation and in distancing. They reported a robust reduction in self-reported negative affect relative to the control condition in both the distancing and reappraisal training conditions, with the *effect in the distancing group greater than in the reappraisal group*. Moreover, the distancing group showed a decrease in perceived stress following training. Overall, training in CR across these various studies appeared to be effective and was associated with symptom improvement. None of these studies examined BPD and only one defined a group based upon a clinical symptom [38].

While we are unaware of any studies, other than our own preparatory work (see C.1.33), directly examining the effect of focused CR training on neural activity, one study examined regional BOLD activity as a predictor of outcome in cognitive-behavioral treatment (CBT) of subjects with generalized anxiety disorder and panic disorder [39]. The authors report that, during a task in which subjects were instructed to “keep up” or “reduce” their emotional reactions, which the authors characterize as a reappraisal task, activation in the right hippocampus and left uncus during “keep up”, and in the left transverse temporal gyrus, left anterior insula, right and left superior temporal gyrus, left supramarginal gyrus, left precentral gyrus, left superior frontal gyrus, and right substantia nigra during “reduce” predicted, using a random forest model, outcome to CBT treatment. Goodman and colleagues [40] reported that BPD patients who received 12-months of Dialectical Behavior Therapy (DBT) showed reduced amygdala activation to emotional pictures and an improvement in total score in the self-reported Difficulties in Emotion Regulation Scale (DERS, [41]). One component of DBT is the development of emotion regulation skills, although cognitive reappraisal is not explicitly taught. Nevertheless this study provides some support for the hypothesis that CR training may be valuable for BPD patients. The current proposed study will, however, test the hypothesis that focused CR training, as a highly targeted intervention, may shorten the time to clinical change.

Although these findings are highly encouraging, there are some important limitations to this literature. Few studies used objective measures of reappraisal utilization and effectiveness, instead relying primarily on self-reports. One of these studies involving assessment of neural activity showed that repeated CR-by-distancing training uniquely attenuated amygdala activity one week following training [37], but that study was confined to healthy subjects and examined massed CR practice over two days, rather than longitudinal training. **Critically for the current application, are no reports of CR-specific treatments that have been manualized and there is no data on optimal dose**. Further, significantly, no CR training study has examined BPD, the paradigmatic condition of emotional dysregulation. Thus, **several important knowledge gaps remain: 1) can patients with BPD be trained to improve their ability to regulate emotion and improve symptoms and functional outcome by targeted CR training, 2) what are the neural mechanisms by which CR is enhanced through focused training, and 3) what is the optimal form of such training in terms of technique and dose?** Addressing these knowledge gaps**,** the present study is positioned to translate cognitive reappraisal training into an addition to the therapeutic armamentarium for BPD, efficiently targeted to known mechanisms of emotion regulation, and impacting the key symptom domains of BPD. It may also have wider application to other disorders marked by affective instability.

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B. Innovation

The proposed study is highly innovative in several respects. First, it is the only study to develop and test a new treatment for BPD that is based upon the highly adaptive emotion regulatory strategy of cognitive reappraisal. Further, it is the only study to test this treatment intervention on a proximal target defined on the basis of predicted neural and behavioral markers of cognitive reappraisal, i.e. reduced activation of signature negative affect neural circuits, increased activation of top-down emotion control circuits and behavioral measures of reappraisal success. This provides a sensitive test of the effectiveness of the intervention and can confirm that clinical benefits arise from theoretically understood mechanisms. This also will be the first study to examine the effect of reappraisal training upon clinical symptoms and perceived stress in BPD patients, the paradigmatic disorder of emotion dysregulation. In fact, to our knowledge, this is the only study to examine the efficacy of reappraisal training in any clinical diagnostic group. Finally this proposal is the first to develop a manual for the reliable delivery of training in cognitive reappraisal.

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C. Approach

C.1 Prior Work

C.1.1 Studies of the Phenomenology of Affective Instability in BPD. Our group has pursued a research program focused on understanding the nature of affective instability and emotion regulation in BPD. We have characterized its phenomenology in BPD [42], examined its relationship to the suicidality and interpersonal dysfunction in the disorder [10] and contrasted affective instability in BPD to that of bipolar disorder [43]. We have continued to further refine the affective instability construct [44].

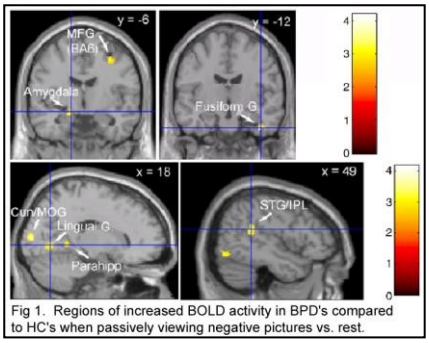

Fig 1. Regions of increased BOLD activity in BPD's compared to HC's when passively viewing negative pictures vs. rest.

C.1.2. Neuroimaging Studies of Passive Emotion Processing in BPD. We contrasted patterns of BOLD activation between 19 BPD patients and 17 HC subjects while they passively viewed emotional images [45]. When viewing negative International Affective Pictures System (IAPS) pictures compared to rest, BPD patients showed greater activity than HCs in the amygdala, fusiform gyrus, primary visual areas, superior temporal gyrus (STG) and premotor areas (Fig 1), whereas healthy controls showed greater activity in the insula, middle temporal gyrus and dorsolateral prefrontal cortex.

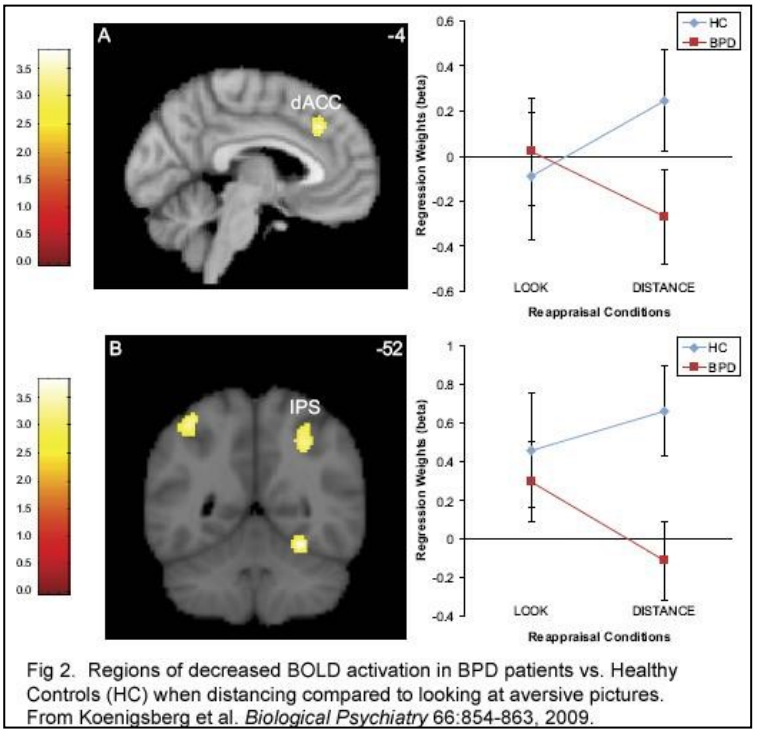

Fig 2. Regions of decreased BOLD activation in BPD patients vs. Healthy Controls (HC) when distancing compared to looking at aversive pictures. From Koenigsberg et al. *Biological Psychiatry* 66:854-863, 2009.

C.1.3. Neuroimaging Studies of Emotional Dysregulation in Borderline Patients To understand the basis for the emotional dysregulation in BPD, we conducted a study (R01MH077813) examining two hypotheses: (1) that BPD patients were emotionally dysregulated because they could not effectively bring to bear the common and highly adaptive emotion regulating mechanism of cognitive reappraisal by distancing (see A.2.), and (2) that BPD patients were emotionally dysregulated because they could not habituate as healthy subjects could, to repeated encounters with negative emotional stimuli.

C.1.3.1. (1) Neuroimaging Studies of Reappraisal by Distancing in BPD. The first goal of this previous R01 study was to compare neural activation between BPD and HC subjects and the psychopathological control group of AvPD patients as they employed CRD when viewing aversive emotional pictures. We published findings contrasting 18 BPD patients and 16 HC's [32]. When distancing compared to looking, BPD patients did not activate the dorsal ACC (dACC) and intraparietal sulci (IPS) as strongly as HC's

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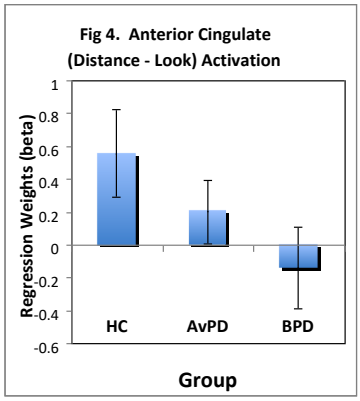

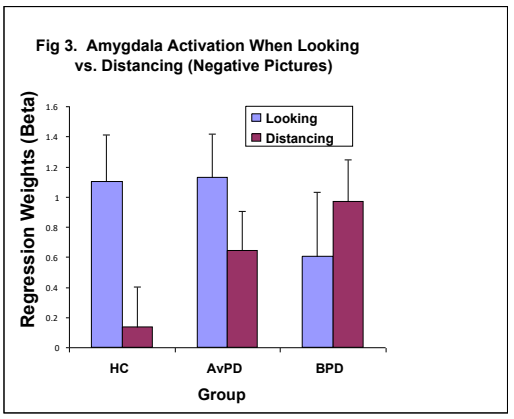

(Fig. 2), did not downregulate the amygdala to the extent that HC's did and activated the superior temporal sulcus (STS) and superior frontal gyrus more strongly than HC's. This study was the first imaging study, to our knowledge, to contrast cognitive reappraisal processes in BPD patients and healthy controls. To determine whether the effects we observed were characteristic of personality disorders in general or more specific to BPD, we included the AvPD group in the comparison (19 BPD, 20 AvPD and 18 HC's). Examination of the effect of distancing (vs. looking) in amygdala when viewing aversive images showed a significant Condition (distance vs. look) X Group interaction ($F(2,54)=4.85$, $p=.01$). Post hoc tests demonstrated that for HC's there was significantly less amygdala activity when distancing vs. looking ($F(1,18)=9.05$, $p=.008$) and for AvPD's the effect was in the same direction but less marked ($F(1,19)=3.66$, $p=.07$), while BPD's do not show a reduction in amygdala activity ($F(1,17)=1.20$, NS) (Fig. 3). Correspondingly, in the ACC (4,34,22) we found the greatest increase in activation from looking to distancing in HC's, the least in BPD's, with AvPD's intermediate (Fig. 4).

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C.1.3.2. (2) Neuroimaging Studies of Habituation to Single Repeat Viewing in BPD vs HC's. Our second goal in this study was to determine whether there are differences between BPD, AvPD and HC subjects in the degree to which neural networks habituate or sensitize to emotional stimuli. We found [46] in a sample of 19 BPD subjects, 23 AvPD subjects**,** and 25 HC subjects that, as hypothesized, only the HC subjects habituated to repeated viewing of the aversive pictures showing reduced negative affect ratings (t=2.71,df=24,p<0.01, one-tailed). HC's, but not BPDs showed increased activity of the dorsal anterior cingulate cortex (dACC) when viewing repeat vs novel aversive pictures (156 voxel cluster, p<.05, k=150, FWE, Fig.5). Importantly, activation in this region was negatively correlated with affective instability (ALS score) for HC and BPD patients (r=-.038, p >0.04 and r=-0.56, p<0.01, one-tailed, respectively, Fig. 6).

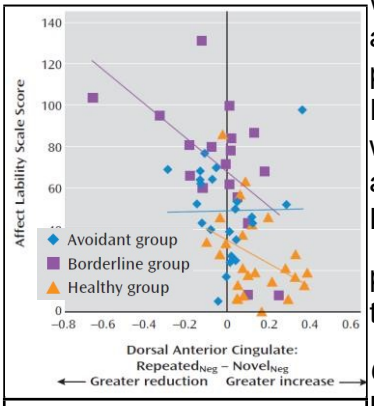


Fig. 6. Affective instability inversely correlates with dorsal anterior cingulate activity for HCs

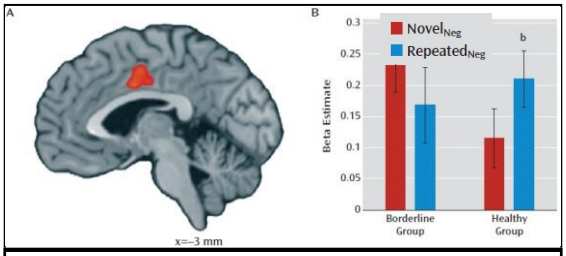
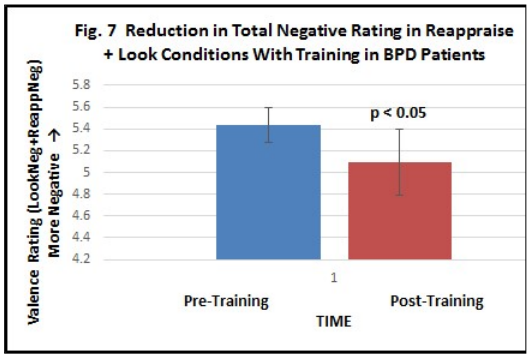


Fig. 5. BPD patients fail to increase dorsal anterior cingulate activity to repeat viewings of negative images

C.1.3.3. Preparatory Studies of Reappraisal Training in BPDs Having demonstrated that BPD patients could not down-regulate amygdala activity and could not engage top-down regulatory networks as healthy volunteers could when attempting cognitive reappraisal-by-distancing (see C.1.3.1 above and [47]), we carried out a study (R01 MH077813) to determine <u>whether focused training could enhance reappraisal</u> in BPD, examining neural circuits implicated in reappraisal. BPD subjects (N=19), and healthy volunteers (HC; N=18) performed a cognitive reappraisal-by-distancing task 5 times: at baseline while fMRI images were acquired, then for three additional training sessions, and again on a 5th session when fMRI images were once again acquired. The sessions were separated by 2-3 days each. The reappraisal-by-distancing task, similar to the task to be employed in the present proposal (**see more detailed description below**), comprised 3 conditions presented in random order, in which subjects received the instruction either: 1) to apply reappraisal-by-distancing when viewing negative emotional pictures (Reappraise-Negative Condition; RNeg), 2) to simply look at a negative picture, self-monitoring feelings induced by the picture (Look-Negative Condition; LNeg), or 3) to simply look at a neutral picture, self-monitoring the feelings present (Look-Neural Condition; LNeu). Following each picture presentation, the subject was prompted to rate how negative they were feeling on a scale from 1 (least negative) to 5 (most negative), after they carried out the instruction. A total of 90 trials (30 each condition) were presented each day, with different pictures each day. We selected pictures that involved interpersonal interactions. The *reappraisal training* carried out each day consisted of two parts and followed a standardized script. First the subjects read a brief description of the distancing strategy written in lay language and were encouraged to discuss their understanding of the strategy and ask questions of the experimenter. Subjects practiced distancing with several pictures, describing their thought process to the experimenter and receiving feedback to help shape their performance. Second,



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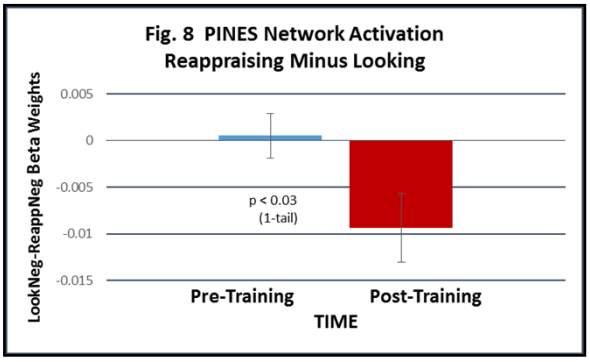
they performed the distancing tactic on 20 practice pictures before beginning the 3-condition reappraise by distancing task described above.

Analysis of the behavioral data demonstrated a decrease from baseline to session 5 in negative valence ratings in the BPD group in the Look-Negative as well as the Reappraise-Negative condition, suggesting the possibility that the effect of reappraisal training carried over to the Look condition, even without conscious intention. This observation is particularly encouraging in terms of *training generalizability*, since it suggests that training in distancing may facilitate its *automatic engagement*, without need for deliberate intent. We found (see fig 7) that the total negative valence ratings for RNeg and LNeg showed a significant decrease post-training ($p < 0.05$, twotailed). In terms of neural activity, we hypothesized that effective reappraisal of negative affective pictures would result in a downregulation of activity in a network known to represent a sensitive and specific neural signature responsive to viewing aversive negative pictures, the PINES network [33]. We found that, as expected, after reappraisal training BPD patents showed decreased PINES activity when reappraising (vs. looking) relative to pre-training, with a large effect size ($d=0.73$, $p<0.03$, one-tailed; see Fig. 8). *Thus, we found that with 5-days of reappraisal-by-distancing training BPD patients were able to significantly improve their ability to downregulate activity in the brain network activated by negative emotion, and behaviorally to reduce how negatively they rated aversive pictures.*



C.2. Overall Design

The present proposal follows the R61/R33 experimental medicine model to refine and test a proposed clinical intervention for BPD patients, training in reappraisal-by-distancing, in terms of its ability to influence hypothesized neural and behavioral targets and, once that is established, to demonstrate its ability improve clinically relevant outcome measures.

C.2.1. R61 Phase. Specifically, in the R61 phase we will determine whether reappraisal training will have an effect upon hypothesized proximal neural targets (see below) and behavioral measures (assessed by means of our imaging task; **C.2.6.**), further develop our treatment manual and will test 3 doses of the treatment with BPD patients -- treatment delivered 2 times a week for 2, 4 and 6-weeks. The reappraise-treatment condition will be contrasted with a control condition (**C.2.7.2**). Therapist's adherence to the manual will be assessed.

Based upon an extensive body of research on the neural correlates of cognitive reappraisal [48-50], we expect reappraisal training focused upon down-regulating reactions to negative emotional pictures to influence the neural pattern that reflects processing of negative emotional pictures, the PINES signature. The PINES is a particularly appropriate target, because it has been shown to vary monotonically with subjective emotion ratings and has been shown to be specific to picture induced negative emotion [33]. Moreover, we found in our preparatory study (C.1.3.3) that reappraisal training was associated with a significant reduction in activation of this region. Hence our milestone for R61 success will be based upon change in the PINES network (see C.2.2). Although not specified as milestones, we will also examine

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ROI's identified in the reappraisal literature: the amygdala, and the top-down control regions: the ventrolateral prefrontal cortex (VLPFC), the dorsolateral prefrontal cortex (DLPFC), the dorsomedial prefrontal cortex (DMPFC), the dorsal anterior cingulate cortex (dACC), and the posterior parietal cortex (PPC) [48]. In addition, we will examine behavioral reappraisal success. The effect of reappraisal training upon all of these targets will be monitored at baseline and at weeks 2, 4 and 6 by means of our fMRI reappraisal task (see **C.2.6**. below).

C.2.2. Milestones to Proceed to R33 Phase and Optimal Dose Determination. We have selected milestones for the present study, cognizant of the need to achieve a balance: criteria sufficiently stringent to insure that a target-based treatment is genuine on the one hand, yet which also guards against discarding an important treatment advance on the other. Ultimately, the goal of reappraisal training is to improve subject's ability to reduce their negative emotional reactions to aversive cues, which we expect (and will test in the R33 phase) to improve their ability to handle stress and to reduce the clinical symptoms of BPD. We hypothesize that such clinical improvements would be associated with an improved ability to downregulate activity in the negative emotion responsive brain regions. As described above, with training, we expect to see an improvement in downregulation of the PINES network response to negative pictures. Our prior studies (see **C.1.3.3**) suggest that the neuroimaging measures are more sensitive to change than the behavioral measures – the effect size of 5days of training on PINES activity was large (d =0.73), while the effect on behavioral ratings of negative valence, though significant, was small (d=0.15). We did not see an increase in activity of the top-down control regions with training in the BPD, although after training the BPD's maintained activity in these regions at baseline levels in contrast to HC's whose activity decreased, possibly because of increased efficiency. Thus it is possible that, unlike HC's, BPD's do not have the ability to upregulate these regions, but rather bring about decreased PINES activity through enhancement of "bottom-up" regulatory processes. These questions require further exploration.

The milestone to proceed to the R33 phase is based on a statistically significant difference between the experimental and the control conditions. Should all three doses be found to be significantly superior to the control condition, the dose that shows the largest effect size will be considered for the R33 phase. Among doses with similar or same effect size the one that requires the fewer number of weeks will be selected.

C.2.3. R33 Phase. In this phase we will examine, in a new sample of BPD patients, the effect of the optimal treatment dose (R61) upon clinically relevant symptom measures of BPD. In addition, using the same techniques as in the R61 phase we will repeat assessment of the effect of treatment upon PINES network activation, activation of the top-down control regions and behavioral measures of negative valence during reappraisal, (see C.2.5). **This component of the R33 phase specifically addresses reproducibility as a priority in this research design**. We will obtain subjective reports, using established measures (e.g. DERS *and ERQ*, see C.3.3), of the extent to which specific emotion regulation strategies, including reappraisal-by-distancing, were used by each subject at baseline and following treatment. We will record drop-out rates and obtain subjective measures of treatment acceptability and relevance by the subjects and monitor therapist adherence to the manual. To assess short-term durability of treatment, we will obtain re-assessment of the clinical measures *one and four months* after treatment completion. These R33 phase measures will enable us to assess the clinical effectiveness and feasibility of the treatment and to replicate the neural and behavioral effects

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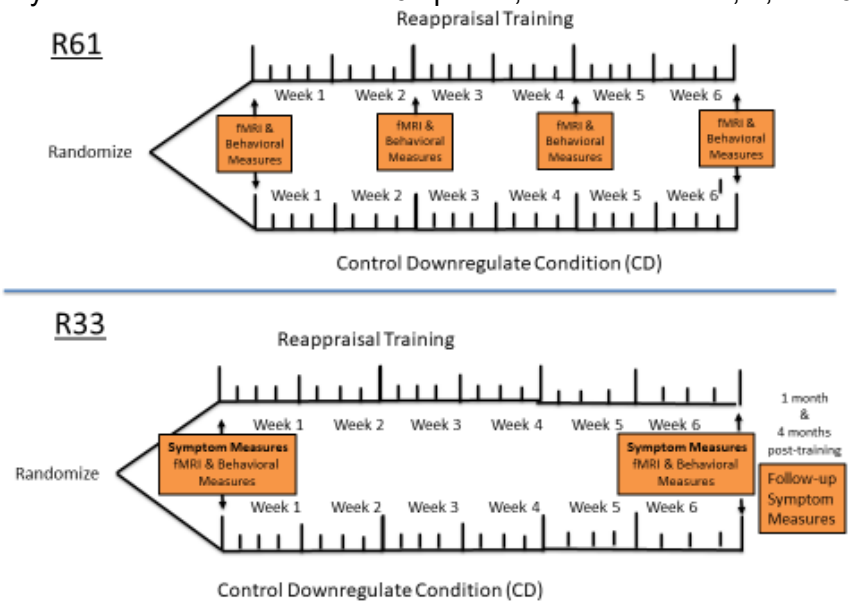
identified in the R61 phase in a distinct population. Finally, we will examine whether change in the targeted neural processes is correlated with clinical symptom change.

C.2.4. Overview of the Treatment and Control Conditions in the R61 and R33 phases

The same treatment and control conditions will be used in both R61 and R33 phases, differing only in dose delivered. In the R61 phase, three doses – 2, 4, and 6 weeks -- of 2 times a week



treatment and control sessions will be studied. In the R33 phase the 6-week dose will be employed. In the R61 phase, all subjects will be seen for 6-weeks, with the full battery of assessments, including fMRI imaging, carried out at baseline and the 2, 4, and 6 week time points. We considered the alternative model in which separate subject cohorts receive 2, 4 and 6 weeks of treatment. However, we believe that any possible benefit to be gained by having subgroups with the 3 pre-designated treatment durations, is outweighed by the increased power and opportunity for within subject comparisons available in the single cohort 6-week staged-dosing model that we will use.

The reappraisal-by-distancing treatment (described in section **C.2.7.1** below) is an extension of the method developed by Ochsner [51] and employed by our group in two published studies [32, 52] and three R01 grant studies. Our group is experienced in these methods, having trained over 60 subjects in the distancing strategy. The treatment control condition will be *Downregulate (CD),* an alternative regulation strategy (see C.2.7.2), well-matched to the experimental condition [22, 23]. Subjects in both conditions will practice an emotion regulation task: either reappraisal-by-distancing or the control task, while viewing emotional pictures 2 sessions a week for 2- , 4- or 6-weeks. They will receive the same battery of behavioral and task-based imaging assessments at the 2-, 4, and 6-week points. Subjects in both treatment and control groups will view the same number pictures and have the same number of contact hours with the trainer.

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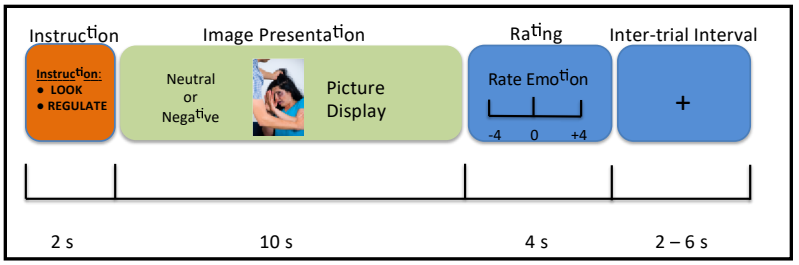
C.2.5. The imaging tasks During fMRI imaging subjects from both treatment and control groups will carry out a task assessing their neural and behavioral responses to instructions to down-regulate negative emotions by either distancing, or expressive suppression. The imaging task is one that we have considerable experience with, having employed it in published work [47, 53] and over the last ten years in three R01 studies. It is modeled after that of [51]. Subjects will be asked to view affective pictures under 3 conditions: 1) look at neutral pictures, 2) look at negative pictures, and 3) regulate reactions to negative pictures. Each picture will be shown for 10 seconds and preceded with an instruction ("Look" or "Regulate"), which will appear on the screen for 2 seconds. Subjects will be told that when they see the "Regulate" instruction, they should employ reappraisal-by-distancing (treatment group) or *downregulate* (active control group). The "Look" instruction will be paired with neutral and negative pictures; "Regulate" with negative pictures only, since an instruction to emotionally down-regulate reactions to neutral pictures would be confusing. The order of the instruction/picture pairings will be randomized. Each picture is followed by a rating screen at which time subjects rate the valence of their reaction to the picture after carrying out the instruction on a 9-point scale (from -4 to 4) using an fMRI compatible slider. The rating screen will appear for 4 sec followed by an inter-trial screen that will be present for a jittered 2 – 6 sec. There will be 40 trials for each of the 3 conditions for a total of 40 minutes, divided into 4 runs of 10 minutes each.



Prior to the baseline imaging task scan, subjects are familiarized with the 2 instructional conditions by the experimenter, using standardized scripts for the treatment and control conditions. Subjects in both conditions will be instructed that in the "Look" condition, they should simply look at the picture and be aware of whatever spontaneous emotions arise. For those in the CRD treatment group, training for the "Regulate" condition consists of two parts. First, the subjects will read a brief description of the distancing strategy. The following description of the strategy in lay language is presented: "*view the photos **in a very neutral way, knowing that you are not personally involved**, and/or imagine that the pictured events happened far away or a long time ago. As you view each pictured event, what is **important** is that you cut all personal ties to the event in a way that any negative emotional reaction is decreased as much as possible.*" In our experience, BPD subjects readily understand the strategy explained in this way. Subjects will next practice distancing to a series of IAPS slides, not subsequently used in the scanning sessions. The experimenter will have the subject describe aloud how he/she implements distancing, slide-by-slide, and will assist the subject to shape effective strategies. The subject will next practice the distancing task in a block of 20 trials presented outside the scanner on a laptop computer. The training for subjects in the downregulate (CD) control group will be the same, except that subjects will be instructed that when they see the "Regulate" prompt they should *use whatever emotion regulation strategy works for them to reduce their negative feelings*. As for the treatment group subjects, the researcher will shape their behavior in 5 trials, *having them draw upon their experience*, and they will practice for 20 trials outside the scanner before beginning the imaging task. Subjects will be specifically instructed not to close their eyes or look away from the images in any of the conditions.

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C.2.6. Distancing-Training and Downregulate Control Condition in R61 and R33 Phases

Training in distancing and in the suppression-control condition will be the same in both R61 and R33 phases, except that in the R33 phase only a single dose, the optimal dose (number of sessions) determined in the R61 phase will be employed.

C.2.6.1. Cognitive Reappraisal-by- Distancing (CRD) Training. We present here a brief summary of Distancing Training, which is more fully described in our treatment manual (see Appendix). Training is carried out in two 45 minute sessions a week. In the initial session, the experimenter reviews the description of distancing (see C.2.6.) and explains that the training sessions are designed to help the subject become efficient in using emotion regulation-by-distancing, emphasizing that it is an important skill to develop since it can be helpful in dealing with distressing situations in daily life. Subjects will then engage in an interactive distancing practice to 5 negative emotion pictures. In this practice, the trainer asks the subject to describe their thought process as they carry out the distancing task, using this opportunity to engage collaboratively with the subject, making suggestions (drawn from those in the treatment manual) to enhance the process, e.g. *"Try looking at the scene from a neutral position, distancing as though you are a newspaper reporter collecting information for a story."* In each session, following this period of guided instruction, subjects intensively practice, by viewing 40 negative pictures on the laptop, distancing to 20 and carrying out the "look' instruction to 20. This laptop practice is similar to imaging task described above (**C.2.6**.), except that it does not include the Look-Neutral condition. In order to foster carryover of the developing distancing skill beyond the lab, subjects will be encouraged in each session to watch for emotional situations in their daily life where the distancing strategy might be useful. Ten to 15 minutes of each session will be allocated for a review of those real-world situations, considering whether distancing is the optimal strategy and how it might be employed. This CRD training program is based upon the model that we employed to train 60 subjects in our prior R01 study, modified by *an increase in the number of sessions and adding generalization to real-world situations component*.

C.2.6.2 Control Downregulate (CD) Condition. *We addressed a number of considerations to identify a control condition that would be credible and well-matched to the experimental condition, would be neutral in its neural and behavioral effects and would not be detrimental to subjects. We chose a condition in which subjects are told we will help them build upon their own natural way of downregulating negative feelings to disturbing situations by giving them focused practice, using negative pictures, during a training period. See the control treatment manual (see Appendix) for fuller description. While we appreciate that this control condition has the drawback of heterogeneity, the fact that it draws upon what our symptomatic subjects are already doing speaks the the neutrality of its effect. We will monitor the strategies subjects are actually using by asking them to report the specific strategies they use. Our concern over the heterogeneity is also mitigated by the fact that many successful BPD psychotherapy research studies have used the heterogeneous "treatment-as-usual" control condition successfully.*

Like CRD training, CD training is carried out in two 45-minute sessions a week. It will involve viewing the same negative and neutral pictures on a laptop and comparable contact and engagement with a trainer, as in the reappraisal training condition. Moreover*, the fMRI task for the CD condition parallels that of the training condition, incorporating the same set of neutral and negative pictures and cognitive demands*. In the first session, subjects are instructed that they will learn how to regulate negative emotions by getting practice with the strategies that come naturally to them. Each session will follow the same structure as the CRD training, with description of the CD strategy, practice and behavior shaping with 5 negative pictures, independent practice with 20 look-negative and 20 suppress-negative trials, and discussion of use of the technique in real world settings.

C.3. Design Considerations

C.3.1. Choice of Affect-Induction Stimuli. Pictures employed in the fMRI tasks and the training tasks will be negative and neutral valence images from the International Affective Pictures System (IAPS [55]) and the Nencki Affective Pictures system (NAPS;[56]), stimuli widely used in emotion research, which have normed valence and arousal ratings. The assignment of images to scan day (baseline, 2-,4-,or 6- weeks in R61 or baseline and endpoint in R33) and the assignment of negative images to the look or regulate conditions will be counterbalanced among subjects.

C.3.2. Choice of Regions of Interest for Imaging Analyses. We will assess negative reactivity by examining activation of the Picture Induced Negative Emotion Signature (PINES) network. We selected this network because its activation has been demonstrated to be specific to and monotonically proportional to subjective reactions to the negative picture stimuli we are employing. Moreover, it has been shown to outperform the three ROI's, the amygdala, insula and ACC, and seven whole brain networks, including the salience, default and somatomotor networks, commonly associated with negative affect [33]. Although PINES network activation is our primary neural outcome measure, we will also separately examine activity in each of the above specific ROI's and in the salience, default and somatosensory networks. Although not primary outcome measures, we will also examine the effect of training upon the top-down control regions implicated in cognitive reappraisal that have been highlighted in the meta-analysis by Buhle et. al. [48]: the dorsolateral prefrontal cortex (dlPFC), the ventrolateral PFC (vlPFC), the posterior dorsomedial PFC (dmPFC) and the posterior parietal cortex (PPC).

C.3.3 Outcome Measures. R61: The primary outcome measure will be change in PINES network activity. Other outcome measures will be change in activity in the top-down control regions described above and in behavioral valence ratings of the image stimuli during reappraisal. **R33:** The primary outcome measure will be change in BPD symptomatology (total score in the Zanarini Rating Scale for Borderline Personality, self-report (ZAN-BPD, [57])). Secondary outcome measures will be the ZAN_BPD sector scores, Affective Lability Scale total (ALS, [58], Perceived Stress Scale (PSS; [59]),Difficulty in Emotion Regulation Scale Scores (DERS; [41]), Beck Depression Scale score (BDI) and State-Trait Anxiety Scale Score (STAXI).

C.3.4 Rationale for Eye Gaze and Pupilometry Measures. Eye gaze direction will be assessed in both R61 and R33 phases to determine whether changes in BOLD activity during regulate conditions are associated with diversion of gaze [60] away from emotionally salient portions of the pictures. Change in pupil diameter (regulate-look) will be recorded during each scan, as an index of cognitive effort [61].

C.4.0 Specific Design and Methods

C.4.1 Subject Inclusion and Exclusion Criteria for R61 and R 33 Phases

C.4.1.1 Inclusion Criteria. Male and female BPD subjects 18 to 55 years old meeting criteria for DSM-5 Borderline Personality Disorder and not meet criteria for Schizotypal personality disorder (SPD)**.** Subjects meeting criteria for a non-IV substance use disorder more than 6 months prior to enrollment will not be excluded. Subjects meeting criteria for past PTSD will not be excluded unless they are currently experiencing symptoms. All subjects will be free of psychotropic medications for 2 weeks (6 weeks for fluoxetine) and will not be in current psychotherapy. We will monitor our recruitment rate every three months during the course of the R61 and R33 phases and should extrapolation of these rates suggest that we will not meet our recruitment goals we are prepared to liberalize the inclusion criteria to allow patients who are currently taking psychotropic medications or are in psychotherapy, so long as there has been no change in mediation or psychotherapy over the preceding two months. In this case, medication type and dosage and psychotherapy type and duration will be recorded and available for

subsequent analyses. Educational level will be recorded and will be available as a covariate in the analyses. Subjects will be medically healthy.

C.4.1.2. Exclusion Criteria. Subjects will not meet criteria for Schizotypal Personality Disorder (SPD). SPD is excluded to avoid a possible confound from the restricted affect that characterizes SPD. BPD subjects will not meet DSM-5 criteria for past or present bipolar I disorder, schizophrenia, schizoaffective disorder, substance dependence, organic mental syndromes, head trauma, CNS neurological disease, or seizure disorder. Subjects currently meeting DSM-5 criteria for PTSD will be excluded, unless they are in remission or not currently experiencing symptoms. Subjects currently meeting criteria for major depressive disorder will also be excluded (except as described above). However, since depression is commonly associated with BPD (Koenigsberg et al., 1999), too stringent a depression exclusion criteria would yield a clinically atypical BPD sample. For this reason, BPD patients with Axis I depressive disorders other than major depression and those with a past history of major depression, will not be excluded. *Suicidal subjects will not be excluded, unless referral to a higher level of care is deemed clinically necessary by the evaluating clinician*. Subjects must not have met criteria for a substance use disorder for 6 months prior to entry into the study. All subjects must be free of significant medical illness. They may not have a pacemaker, surgical clips, any metallic implants, or shrapnel fragments that would contraindicate MRI scanning. Pregnant women will be excluded.

C.4.2. Sample Size, Recruitment and Assessment

C.4.2.1 Sample Size. ***R61 Phase:*** (see Power Analysis C.4.5.1). *49* BPD subjects will be recruited each for the training and control groups to acquire *39* subjects in each group allowing for a 20% loss for drop out and fMRI movement artifact. ***R33 Phase:*** 65 BPD subjects will be recruited each for the training and control groups to obtain 51 subjects per group, allowing for 20% loss.

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C.4.2.2 Recruitment: Subjects will be recruited by newspaper, radio, and social media advertisements and by referral from the psychiatry outpatient department at Mount Sinai Medical Center, the Center for the Intensive Treatment of Personality Disorders at Mount Sinai West, and the Bronx VA Medical Center. We are confident that we can meet recruitment goals for both R61 and R33 as our Mood and Personality Disorders Research Program at Mount Sinai, which has been engaged in neurobiological research studies of BPD for over 30 years, has extensive experience in recruiting borderline personality disorder patients for research. Recently we have augmented our recruitment strategy by including additional clinical sites and by engaging an experienced research recruitment company, Bump Digital Marketing (Toronto, Ontario), to develop targeted website ads and a recruitment landing page for our studies. (See **2.5 Recruitment and Retention Plan** for detailed recruitment strategy.)

Table 1 – Assessment Measures

	R61				R33		
Assessment	Baseline	Week 2	Week 4	Week 6	Baseline	Termination	Follow-up 1 & 4 months.
SCID-5	X				X		
SIDP	X				X		
Medical Hx. & Exam	X				X		
Blood Count	X				X		
Metabolic & Electrolyte Panel	X				X		
TSH, T4, Serology	X				X		
Routine Urinalysis	X				X		
Urine Drug Screen	X	X	X	X	X	X	
Affective Lability Scale (ALS)	X	X	X	X	X	X	X
Difficulty in Emotion Regulation Scale (DERS)	X	X	X	X	X	X	X
Dissociative Experiences Scale (DES)	X	X	X	X	X	X	X
Beck Depression Rating Scale (BDS)	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X
Speilberger State-Trait Anxiety Inventory (STAI)	X	X	X	X	X	X	X
Zanarini Rating Scale for BPD (ZAN-BPD)	X	X	X	X	X	X	X
Emotion Regulation Questionnaire (ERQ)	X	X	X	X	X	X	X
Perceived Stress Scale (PSS)	X	X	X	X	X	X	X
Shipley IQ Scale	X				X		
Crowne_Marlowe Social Desirability Scale (CMSDS)	X				X		
Life Events Check-List (LEC-5)	X	X	X	X	X	X	X
Childhood Trauma Questionnaire (CTQ)	X				X		

C.4.2.3. Assessments All subjects receive the diagnostic, medical, self-report assessments and ratings indicated in Table 1. Assessors will be blind to training assignment. Research diagnoses (DSM-5) are made by means of semi-structured interviews, the SADS and SID-P, administered by experienced interviewers (masters or doctoral level clinical psychologists). We have achieved an interrater reliability kappa of .81 for diagnosing BPD.

C.4.2.4. Sex as a biological variable. Based on prior experience we expect to recruit equal numbers of males and females. We will examine the effect of gender upon all findings.

C.4.3 Procedures for Individual Subjects

C.4.3.1 Timeline of Procedures. For both R61 and R33 Phases: Following consent, subjects will be seen for an initial session for baseline clinical interviews and self-report

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instruments (Table 1). Subjects will receive a medical evaluation (see Table 1) and will be randomized (1:1) to CRD training or CD control *conditions using a randomization scheme in random blocks of 2, 4 and 6. An online, electronic randomization system will be implemented by the study statistician.* The medical evaluation will take place at the Clinical Research Unit (CRU) (1468 Madison Avenue, 1st floor). This will include routine blood tests (complete blood count, metabolic and electrolyte panel, thyroid function tests, and a routine urinalysis. The urine drug screen will be administered in our office (1399 Park Avenue) on the day of your Medical Evaluation. On a separate day, subjects will carry out the baseline imaging task (see C.2.6). **For R61 Phase:** Within about 2 weeks of baseline scan, subjects will begin the manualized CRD-training or control CD training, which will continue for 6 weeks. At 2-, 4- and 6- weeks, subjects will receive an fMRI scan similar to the baseline scan (different image sets will be employed for each scan, counterbalanced for sequence among scans across subjects) and the assessment measures as indicated in Table 1. **For R33 Phase:** The procedures will be as in the R61 phase except that training will last for 6 weeks. Following the last session, subjects will receive the termination assessments, including fMRI, as indicated in Table 1. Subjects will return approximately *1- and 4- months* after their last session for follow-up (see Table 1).

C.4.3.2 Regulation-Training Procedures, Adherence Assessment and Refinement of the Treatment Manuals for both R61 and R33 Phases

Regulation-training (for CRD and CD) will be carried out, guided by the appropriate training manual (see appendix for manuals). It will be carried out by a clinical psychologist, who will be instructed in the manualized treatments by HWK or BTD (authors of the treatment manuals). All treatment sessions will be video and audio recorded. The treatment sessions will be done in person via the approved e-prime program, and remotely via the approved PowerPoint slides Teleconference supervision for the trainers will be available from HWK or BTD. To assess adherence, one random session will be recorded from 20% of the treatments for review by HWK or BTD (see adherence rating scale in appendix to training manual) and additional supervision will be provided if low adherence (defined by consensus of HWK and BTD) is identified. **The Specific Aim R61-1 of training manual development will be achieved by periodic reviews conducted by HWK and BTD with the training psychologist**, at 4 month intervals, at which time proposed modifications of the manuals will be considered.

C.4.4. Addressing Missed Sessions and Premature Drop-out

We will implement a number of measures to minimize drop out over the 6-week training period. These include careful planning of a session schedule that is optimally convenient for the subject, educating the subject about the importance of regular attendance and telephoning subjects after missed sessions to encourage attendance at the next session and to troubleshoot factors that might interfere with attendance. (See also section **2.5 Recruitment and Retention Plan**)

C.5. Behavioral Data Analysis

C.5.1 R61 Phase. Analyses for **Aims R61-2a and R61-2b** are described in image analysis (C.6.4, below). **Aim R61-2c:** *Data will be checked for normality and appropriate transformations will be applied to normalize them.* Data analysis will primarily use linear mixed models, incorporating fixed effects for Training Group (CRD and ES), Session, and Trial Type (Look Neutral, Look Negative, and Regulate Negative), and their interactions, as well as a random effect consisting of an intercept for each participant. We will examine additional models that incorporate and estimate random-effects slope variance across participants on the time effect (i.e., Session). Outcome variables will be repeated measures in self-reported negative affect and reappraisal success (defined as the Look Negative minus Regulate Negative behavioral valence rating at each Session*). Although we do not anticipate large differences in*

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baseline characteristics between the groups, given that the trial is randomized, we will include variables that are strongly unbalanced at baseline (p< 0.01) as covariates in our models.

C.5.2 R33 Phase. Aim R33-1: The primary outcome measure is the Zanarini total score (ZTS;[57]). We compare the change in ZTS from baseline to end of treatment (EOT) between groups by *mixed effect models with group, time and their interaction as fixed effects*. A similar analysis will be carried out for the additional outcome measures specified in C.3.3. (Table 1), *using the Holm's procedure for* correction for multiple comparisons. **Aim R33-2**: The analysis will be as for R61 Aims R61-2 a,b and c. **Aim R33-3**: The analysis is described in imaging analysis section C.6.3. **Aim R33-4:** As above, we will use linear mixed models to examine change in ZTS as the outcome variable. Bonferroni corrections will be applied for multiple clinical outcome measures. P-values throughout will be 0.05, two tailed. *All analyses will be conducted according to the intent-to-treat principle for both the R61 and the R33 phase. As a sensitivity analysis we will also consider models that adjust for the number of sessions actually received. Missing data will be assumed as MAR. Under this assumption, a mixed model approach that uses all available information will yield reasonable estimates of the effect sizes.*

C.6. Image Acquisition and Analysis

C.6.1 Image Acquisition. Participants will all be scanned 4 times in the R61 Phase (0, 2, 4, 6 weeks) or 2 times in the R33 Phase (Baseline, End-of-Treatment [EOT]) using the same 3 Tesla Siemens Skyra MRI system equipped with a 16-channel head coil. For each scan session, 4 series of 550 T2*-weighted images will be acquired during the 4 runs of the emotion regulation task using a multi-band echo-planar imaging sequence sensitive to the blood oxygenation level-dependent (BOLD) signal (multi-band factor = 7; repetition time = 1200 ms; echo time = 35 ms; flip angle = 60º; field of view = 228 mm^2; matrix = 108 × 108; slice thickness = 2.1 mm; 70 slices). A high-resolution anatomical image will be acquired with a T1-weighted magnetization-prepared rapid gradient echo (MP-RAGE) sequence.

C.6.2 Image Preprocessing. The 4 time series of T2*-weighted images acquired during the emotion regulation task at each time point will be separately motion corrected and co-registered to the respective MP-RAGE image. Time series with more than 1 voxel of motion (≥ 2.1 mm) or rotation (≥ 2.1°) will be discarded. Next, to optimize the images for cross-session contrasts of treatment effects, the week 2, week 4, and week 6 time series will be separately co-registered to the week 0 series (R61) and the EOT time series will be co-registered to the baseline series (R33). The coregistered sets of time series will then be jointly normalized to the Montreal Neurological Institute template and smoothed with a 6-mm Gaussian kernel. **C.6.3 First-Level Modeling of Individual Treatment Effects.** General linear models (GLM) will be conducted individually for each participant to jointly fit the week 0, 2, 4, and 6 time series (R61) or the baseline and EOT time series (R33). Beta weights will be fit to regressors for the 3 trial events of interest (Look Neutral, Look Negative, and Regulate Negative) and 2 trial events of no interest (Instruction, Rating), as well as 6 motion parameters [62], convolved with the hemodynamic response function [63]. Appropriate linear contrasts will be applied to the beta weights for Regulate Negative events minus Look Negative events in week 2, week 4, and week 6 (all versus week 0) in the R61 phase and EOT versus baseline in the R33 phase. The resultant contrast maps represent the effects of treatment on whole-brain activation for emotion regulation. To estimate the effect of treatment specifically on PINES network activation, the contrast maps will be scaled by the PINES weight map (downloaded from Chang_PLoSBiology_PINES) by calculating the voxel-wise dot product of the two maps. The effect of treatment on neural activation in emotion-specific regions (e.g., amygdala) and top-down control regions (e.g., dlPFC) will be modeled using the unweighted contrast maps together with masks derived from the "aal.002" atlas for automatic anatomic labeling [64] and the meta-analysis conducted by Buhle et. al. [48].

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C.6.4 Second-Level Analysis of Group Differences in Treatment Effects. Random-effects GLM will use two-sample t-tests to compare the neural effects of reappraisal-by-distancing (CRD) and control training. The 3 contrast maps (weeks 2, 4, 6) for each participant in the R61 phase and the EOT versus baseline contrast map for each participant in the R33 phase will be entered as dependent variables in separate GLM in which gender, age, education level, and pre-treatment ALS score will serve as covariates. The speculative purpose of the R61/R33 mechanism justifies setting the alpha level at a relatively liberal value of $p<0.05$ and a cluster threshold of 50 contiguous voxels. The hypothesized effects of treatment would be supported by findings of significant reductions in PINES activation for emotion regulation in the CRD training compared to the CD control training condition at either weeks 2, 4, or 6 or at EOT. *The decision to proceed to the R33 phase is based on finding a statistically significant difference in reduction in PINES activation between the CRD and control conditions*. EOT versus baseline contrast maps for all participants in the R33 phase will be entered into a GLM that will use multiple regression to test for differential changes in activation in the regions of interest associated with improvement on clinical outcome variables for distancing training compared to the control condition. The 3 regressors will include: (1) % change in clinical outcome variable; (2) dichotomous treatment type variable; and (3) an interaction term (i.e., product), which identifies activation change related to differential response to the two treatments. The regressors will be centered on zero.

C.7. Power Analyses:

R61 Phase: The primary outcome measures are decreases from baseline in PINES network activity in the REGULATE (vs. LOOK) conditions in CRD training vs. the CD condition at the 2-, 4-, and 6-week treatment doses. A significant effect at any dose will meet milestone criteria. In our previous work (see C. 1.3.3 above), we obtained a strong effect size of d = 0.73 for 5 days of training. We will, however, power the current study at a more moderate power of d = *.65* to increase our detection sensitivity. We can achieve this at α = 0.05 (*two*– tailed), power = 0.80 with an n = *39* per group (G-Power 3.1). **R33 Phase:** The primary outcome measure for the R33 is the effect of CRD-training upon BPD relevant symptoms, assessed by the Zanarini Rating Scale (see C.4.2.3). A meta-analysis of randomized controlled clinical trials of psychotherapy for BPD reported an effect size of 0.56 for seven stand-alone trials employing BPD-relevant outcomes [65]. Powering to detect an effect size of 0.*56* with a power of 0.80 at *two*-tailed α = 0.05 requires 51 subjects per group.

C.8 Potential Study Complications and Alternative Outcomes

R61 or R33: Recruitment Shortfall: We will closely monitor the rate of subject recruitment. If the rate at the 3- or 6-month time points, extrapolated, suggests that the recruitment goals will not be met, we will implement the measures described in **section 2.5 (Recruitment and Retention Plan),** including, modifying exclusion criteria to allow entry of subjects currently on psychotropic medication and /or in psychotherapy, provided that dose or session frequency has not changed in the prior 2 months. Treatment will be recorded and entered as a covariate in analyses**. R61:** Alternative Outcomes: It is possible that, contrary to our hypothesis, CRD-, will not be superior to CD-training in reducing PINES activity. While such a finding would not meet milestone criteria, this observation would motivate future research to further explore the active features of CD (as well as nonspecific factors) in the treatment of BPD.

D. Resource Sharing Plan

Data obtained in this study will be shared via the National Database for Clinical Trials related to Mental Illness. Upon study enrollment the following information will be collected to permit generation of a GUID for each participant: sex, first name, last name, middle name, date of birth, and city/municipality of birth. Submission of descriptive/ raw data will be accomplished semi-annually and other data will be submitted upon publication or conclusion of the study. A

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plain language description of the data sharing plan will be incorporated into the informed consent. Descriptive data will be submitted to the NDCT semiannually (January 15 and July 15) and will be checked for accuracy before submission and after submission. All other data will be provided at the time of publication or at the end of the grant, whichever comes first. We will share positive and negative results specific to the study cohorts. We will disseminate findings from this study via publications in peer-reviewed journals and presentations at national and international meetings. We will make our treatment manuals available to interested clinicians. In addition we will present our findings to lay borderline advocacy groups such as TARA and Emotions Matter, groups with which we currently have ongoing relationships.

E. Sources of Materials

Diagnostic and assessment information is obtained by interviews of the subject by trained clinicians and raters and by the use of standardized rating questionnaires. Medical assessment involves a history and physical examination of the subject as well as blood samples, urine samples, an EKG and a chest x-ray if indicated. Brain anatomic information is obtained by an MRI scan and functional brain activity by an fMRI scan conducted by our group. Eye gaze and pupilometry data is obtained using the NordicNeuroLab, (Milwaukee, WI) eye gaze fMRI compatible system. All of this material will be obtained specifically for research purposes.

F. Potential Risks

No short-term risks have been reported for MRI. Some people have claustrophobic reactions in the MRI scanners. An individual will be present to reassure the subject and aid in relaxing, but should the subject wish, the MRI scanning can be stopped immediately. Because of possible risks from metallic objects in the scanner magnetic field, subjects with surgical clips or metallic prostheses (such as artificial hip or knee), a pacemaker or any metal implants or shrapnel in the body, may not participate in the study. The effect of fMRI scanning upon the fetus has not been studied. Consequently pregnant women will not be permitted to participate in the study. There are no known risks associated with eye gaze measurement. Subjects may experience distress when viewing some negative-valence emotional pictures, but such distress is expected to be transient. The negative-valence emotional pictures used in this study are comparable to those seen in newspaper or television news programs. The blood drawing carried out as part of the medical screening has the small risk of bruising or infection at the site. The cognitive training programs of cognitive reappraisal-by-distancing (CRD) and the control downregulate condition (CD) are not expected to have adverse effects, however it is possible that subjects will become more upset or experience exacerbations of symptoms, or inappropriate apply regulation strategies during the course of the treatment. Training sessions will be video and audio recorded. There is the risk of embarrassment if there is a breach of confidentiality with respect to personal information included in study assessments or the video recordings of training sessions. All of the above are research risks, as these procedures are not part of treatment.

F.1 Adequacy of Protection against Risks

F.1.1 Recruitment and Informed Consent

Subjects who express interest in the study will receive a phone pre-screening evaluation, followed by a screening evaluation by Dr. Koenigsberg (PI) or a designated colleague. Research-eligible candidates will approached by a research MD or a delegate trained by him for consent to participate. Consent will be obtained after the potential subject has expressed interest in participating and after the study has been explained to the subject by the researcher. Consents will be obtained at the Icahn School of Medicine at Mount Sinai or the James J Peters VA Medical Center in a private office setting by the principal investigator or a delegate approved by the Mount Sinai and/or JJPVA IRBs. After the protocol is described to the subject and the subject's questions are answered, the subject will be asked to summarize the procedures that he/she will undergo and to describe 2 risks involved in the study to confirm understanding. A

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checklist will be used for this purpose by the person obtaining consent. Informed consent will be documented by means of an informed consent form approved by the Mount Sinai and/or James J Peters VA IRBs and signed by the subject and the researcher who obtains the consent. BPD subjects are cognitively intact and have no impairment in reality testing, however, if there is any doubt about a BPD subject's capacity to give consent, a psychiatrist independent of the study will assess the subject to determine whether they understand the study and can give informed consent.

F.1.2 Protection against Risks

Should a subject become anxious or have a claustrophobic reaction in the scanner, a member of the research team will be available to reassure them and aid them in relaxing. Subjects will be informed that the scanning will be stopped immediately should they wish it. Subjects are prescreened at two points in time – when they sign the informed consent and again just prior to scanning – to insure they have no metallic implants. Women will receive a pregnancy test to exclude subjects who are pregnant. Trained technicians will draw blood, using sterile technique to minimize risk of bruising or infection the structural MRI scans of all subjects will be routinely reviewed by a neuroradiologist at the Mount Sinai Hospital and subjects will be informed of clinically significant incidental findings. If indicated, we will refer them for medical or neurological follow-up.

A number of protections are implemented to minimize psychological risks. At the time of initial rating, subjects will be routinely screened for suicidal ideation, employing the Columbia Suicide Severity Rating Scale (C-SSRS). If present, the subject will be assessed by a research psychiatrist or clinical psychologist and, as clinically indicated, will be referred for treatment or emergent evaluation and treatment. *If there is no clinical indication for emergent treatment or referral, subjects with suicidal ideation will not be excluded*. Subjects will also be provided with a 24-hour emergency phone number to contact one of our research psychiatrists at any time during the course of the study. The CRD and CD training will be carried out by a clinical psychologist and procedures for handling any emergent crises are incorporated in the treatment manuals. These include reassessment with the Columbia Suicide Rating Scale, consultation with a study psychiatrist, referral for additional treatment, or for emergency evaluation. To minimize adverse reactions to the images employed in the study, subjects will be informed of the general nature of the negative pictures prior to participation and told that they may ask any image to be turned off at any time in the study. An individual will be present to provide reassurance for subjects who find any pictures upsetting.

Serious adverse events and any harm to a subject that is, in the opinion of the investigator, unexpected and at least probably related to the research procedures will be reported to the Mount Sinai and James J Peters VA Medical Center IRB's within 5 days and other adverse events as required by the IRB's. All adverse events will be reported to study Data Safety Monitoring Board (DSMB, see below) and to the NIH in the annual progress report. The principal investigator will monitor all adverse events continuously throughout the study.
The following procedures will be employed to protect confidentiality: Data, including session recordings, will be stored in locked cabinets and password-protected computer files. No published reports will identify any subject individually. Each subject will be assigned a coded identifier that will be used to associate stored data with each subject. Subjects' names will be entered initially on the telephone screening forms when subjects inquire about the study. These names will then be removed from the forms and replaced with a coded identifier. Subsequent questionnaires and forms will not have identifiers that can be linked to the subject other than the coded identifier. Diagnostic interviewers will only enter coded identifiers on their notes and forms. The only forms that will contain the subjects names and identifying information will be the consent forms which will be stored separately in a locked file and in the research chart (if the patient has a medical chart at Mount Sinai or the James J Peters VA Medical Center a copy will also be placed in that chart), and the medical screening examination and medical lab tests

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which will be stored separately in a locked file in the research office and in the Clinical Research Center (CRC). The list associating subject's names with coded identifiers will be maintained separately from the data and in a locked file.

F.1.3 Potential Benefits of the Proposed Research to Human Subjects and Others

By determining whether BPD patients can be trained to use the cognitive reappraisal strategy of distancing to more effectively control their negative reactions to aversive stimuli and to normalize their neural activity when employing this strategy, this study can provide proof of concept that reappraisal-by-distancing training can help BPD patients better regulate their emotions. This would provide a neurobiological rationale for the use of cognitive distancing training as a novel approach in the psychotherapy of BPD. In providing information directly relevant to psychotherapeutic practice, this study may enhance the treatment of BPD, a prevalent and difficult to treat disorder. The research will not be of immediate benefit to the participants (apart from the benefits of thorough psychiatric and medical evaluations). Since risks involved in this study are small, and the potential benefit in the treatment BPD is substantial, the benefit to risk ratio is favorable.

F.1.4 Data and Safety Monitoring Plan. A Data and Safety Monitoring Plan will be implemented for this study. A central component of this plan will be A Data Safety and Monitoring Board (DSMB), which will consist of 3 experienced clinicians, *independent of the present study*, who will meet every 6 months to review risks and adverse events. The DSMB may recommend modifications to the study design to address any possible safety issues. In the event of safety issues deemed unaddressable, the DSMB may recommend study closure. In addition to the planned 6 month reviews, DSMB may also been convened at any time at the discretion of the study investigators or institutional review board, should urgent safety concerns arise.

Data quality and security will be monitored on a continuous basis by the data management research coordinator. Interim reviews of the imaging and physiological data will be conducted quarterly to insure data integrity. **Any data collected remotely will be through HIPAA-Compliant Zoom accounts to ensure the protection of participants personal information**

G. Dissemination Plan for both the R61 and R33 Phase

This study will be registered under ClinicalTrials.gov as outlined in the NIMH policy. Results information will be submitted to ClinicalTrials.gov following the timelines of the policy. Results from the study will also be disseminated via presentation at national meetings and submitted for publication in peer-reviewed journals. The informed consent for this study will include a specific statement indicating posting of clinical trial information at ClinicalTrials.gov. The Icahn School of Medicine at Mount Sinai has an internal policy in place to insure clinical **trials registration and results reporting are in compliance with policy requirements.**

H. Compensation

The compensation for the control condition is:

Session	**Length**	**Compensation**
Screening Interview	1 hr	$25
Clinical Interview	2-3 hr	$40
2 Questionnaire Packets	~1 hr per packet	$25 for each packet
Consent & Medical Evaluation Visit	1 hour	Not compensated for – can keep results of medical evaluation
Behavioral Battery	1 hour	$40
Training day + baseline fMRI session	2 hour (1 hr training, 1 hour fMRI)	$100
Week 1-Week 6	45 minutes, twice a week for 6 weeks	No charge for the training sessions

Training in Cognitive Reappraisal by Distancing with clinical psychologist		
End of Week 6 fMRI + behavioral battery check in	2 hour (15 min refresher, 45 min battery, 1 hour fMRI)	$100
1 and 4 month follow-up	1-2 hours each	$40 for each session
Total of 20 visits over 6-8 weeks	23 ~ 25 hours	$435

The compensation for the training condition is

Session	**Length**	**Compensation**
Screening Interview	1 hr	$25
Clinical Interview	2-3 hr	$40
2 Questionnaire Packets	~1 hr per packet	$25 for each packet
Consent & Medical Evaluation Visit	1 hour	Not compensated for- can keep results of medical evaluation
Behavioral Battery	1 hour	$40
Training day + baseline fMRI session	2 hour (1 hr training, 1 hour fMRI)	$100
Week 1-Week 6 Training in Cognitive Reappraisal by Distancing with clinical psychologist	45 minutes, twice a week for 6 weeks	No charge for the training sessions
End of Week 6 fMRI + behavioral battery check in	2 hour (15 min refresher, 45 min battery, 1 hour fMRI)	$100
1 and 4 month follow-up	1-2 hours each	$40 for each session
Total of 20 visits over 6-8 weeks	23 ~ 25 hours	$435

I. COVID considerations

During COVID-19 we would like to implement remote and social distancing measures to ensure staff and participant safety. The first two screening interviews and clinical assessments can be done over HIPAA-Compliant Zoom. If the participant has to come in person, they will be provided with a lab laptop and HIPAA-Compliant Zoom and placed in a separate room as the coordinator or clinical psychologist in order to social distance.

The consent form can be done on iOpen and the coordinator goes through the consent form with the participant over HIPAA-Compliant Zoom. If the participant has to come in person, they can use paper consent but will still social distance by using HIPAA-Compliant Zoom on a lab laptop. All self-report questionnaires can be done on Qualtrics for a remote option, or in person on paper in separate rooms.

For training days with the clinical psychologist, clinical training can be done in person or over a HIPAA-Compliant Zoom. Training done in person will be via the approved e-prime program, and remote sessions will be via the approved power point

fMRI sessions, these cannot be done remotely as they require lab equipment, but we can social distance by communicating over HIPAA-Compliant Zoom in separate rooms.

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