

Training in Cognitive Reappraisal Normalizes Whole-Brain Indices of Emotion Regulation in Borderline Personality Disorder

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ABSTRACT

BACKGROUND: Borderline personality disorder (BPD) is the prototypical disorder of emotion dysregulation. We have previously shown that patients with BPD are impaired in their capacity to engage cognitive reappraisal, a frequently employed adaptive emotion regulation strategy.

METHODS: Here, we report on the efficacy of longitudinal training in cognitive reappraisal to enhance emotion regulation in patients with BPD. Specifically, the training targeted psychological distancing, a reappraisal tactic whereby negative stimuli are viewed dispassionately as though experienced by an objective, impartial observer. At each of 5 sessions over 2 weeks, 22 participants with BPD (14 female) and 22 healthy control participants (13 female) received training in psychological distancing and then completed a widely used picture-based reappraisal task. Self-reported negative affect ratings and functional magnetic resonance imaging data were acquired at the first and fifth sessions. In addition to behavioral analyses, we performed whole-brain pattern expression analyses using independently defined patterns for negative affect and cognitive reappraisal implementation for each session.

RESULTS: Patients with BPD showed a decrease in negative affect pattern expression following reappraisal training, reflecting a normalization in neural activity. However, they did not show significant change in behavioral self-reports.

CONCLUSIONS: To our knowledge, this study represents the first longitudinal functional magnetic resonance imaging examination of task-based cognitive reappraisal training. Using a brief, proof-of-concept design, the results suggest a potential role for reappraisal training in the treatment of patients with BPD.

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Emotion dysregulation or affective instability is a defining characteristic of borderline personality disorder (BPD) (1). In addition to emotion dysregulation, BPD is characterized by impaired interpersonal relationships, unstable identity, impulsivity, and self-destructiveness (1–3), symptoms that are also related to emotional dysregulation. This impaired ability to regulate emotional responses is of great clinical relevance because it negatively impacts social functioning and life satisfaction and is associated with the self-destructiveness and identity disturbances in patients with BPD (2,3). Thus, the enhancement of emotion regulation represents a promising intervention target for patients with BPD and other affectively-disordered populations (4–6).

Several cognitive behavioral psychotherapies for BPD, including dialectical behavior therapy (7), employ nonspecific emotion regulation skills training. While such treatments have shown efficacy, they are resource intensive and typically extend over many months. One study that documented

reduced amygdala responsiveness to emotionally arousing cues used 12 months of the combination of weekly individual dialectical behavior therapy, weekly skills training sessions, and telephone counseling (8). Little is known about the active ingredients of these treatments and their symptom and neural targets. Thus, the current study examined a specific, well-characterized, and highly adaptive emotion regulation strategy, cognitive reappraisal, and used neuroimaging as a sensitive indicator of change. This approach has the potential to contribute to the development of more efficient, accessible, and personalizable treatment methods.

We focus on cognitive reappraisal, an emotion regulation strategy that involves changing the meaning of an emotional stimulus in a way that alters its emotional impact (9,10). When employed to downregulate negative emotion, reappraisal has been shown to lead to reductions in self-reported negative affect in healthy individuals (9–11) as well as attenuated activity in brain regions associated with negative emotion reactivity,

including the amygdala, and increased activity in control regions such as the ventrolateral and dorsolateral prefrontal cortices (12–14). Increased prefrontal cortex activity, including in the ventrolateral and ventromedial prefrontal cortices, has been shown to predict attenuated amygdala activity (15,16). We have shown previously that when reappraising versus simply looking at negative pictures, patients with BPD did not show decreased amygdala activity or increased anterior cingulate activity as healthy volunteers did (17). This finding motivated our efforts to determine whether patients with BPD could enhance their reappraisal capability with training.

Recent work in social cognitive neuroscience has begun to extend beyond examination of individual brain regions and toward examination of whole-brain functional networks (18–20). This approach has the advantage of greatly limiting the multiple comparison problem in neuroimaging data analysis (i.e., among disparate regions of interest) as well as providing an independently defined and multivariate basis against which to test hypotheses concerning the engagement of particular psychological states. One such method of interrogating whole-brain networks, employed in the current study, involves assessing the correspondence (i.e., whole-brain correlation) between independently defined whole-brain patterns for particular psychological states (e.g., experiencing negative affect or implementing cognitive reappraisal) and functional magnetic resonance imaging (fMRI) contrast maps for comparisons of interest for individual participants (18,20). In the current study, we acquired and used whole-brain weighted pattern maps for both picture-induced negative affect (18) and reappraisal implementation (13).

Cognitive reappraisal can be operationalized via one or more regulatory tactics (21). Our examination of cognitive reappraisal focused on the reappraisal tactic known as psychological distancing, which involves appraising an emotional stimulus by adopting the perspective of an objective, impartial observer (10,11) and/or increasing the perceived spatial or temporal distance between oneself and the emotional stimulus (22,23), consistent with construal level theory (24). Distancing can be contrasted with other reappraisal tactics such as reinterpretation, which involves generating a stimulus-specific narrative characterizing how a particular situation is not as bad as it first seemed [for example (9,10)]. We have previously shown in healthy adults that a 4-session course of distancing training led to longitudinal reductions in self-reported negative affect and uniquely led to longitudinal attenuation of perceived stress in daily life in a pattern not observed in reinterpretation training (11). Thus, distancing represents a promising tactic for reappraisal training, particularly for populations of individuals who experience negative emotional stimuli as particularly arousing and overwhelming, as is the case in BPD.

Previous neuroimaging evidence has suggested that compared with healthy adults, patients with BPD show anomalous neural activity in reacting to emotional cues and when implementing emotion regulation via reappraisal. Two neuroimaging meta-analyses have provided evidence of amygdala hyperreactivity in patients with BPD compared with healthy control participants when reacting to negative emotional stimuli (25,26). Furthermore, 2 studies found that when invoking reappraisal by distancing, patients with BPD did not show decreased activity in regions of the salience network,

amygdala (17), and insula (27) compared with healthy control participants.

In the current study, consistent with previous work that has examined longitudinal reappraisal-by-distancing training behaviorally in healthy adults (5,11), we examined a relatively brief, 5-session reappraisal-by-distancing training paradigm in patients with BPD and healthy control participants. Our primary aims were to compare posttraining to pretraining behavioral effects and neural patterns related to emotion processing and regulation. We hypothesized that patients with BPD would show behavioral and neural evidence of elevated negative emotion reactivity and impaired emotion regulation at baseline compared to healthy control participants and that longitudinal reappraisal training would attenuate these group differences and show evidence of a normalized pattern in patients with BPD.

METHODS AND MATERIALS

Participants

We recruited 31 patients with BPD and 26 healthy control participants from outpatient clinics at the Mount Sinai Medical Center and the James J. Peters VA Medical Center in New York City, as well as from newspaper and online advertisements. All participants provided written informed consent after procedures were fully explained. Exclusions due to motion, signal quality, and related issues are detailed in the Supplement. In total, 9 patients with BPD and 4 healthy control participants were excluded, which yielded an analyzable total of 22 patients with BPD (mean age = 36.28 years; 14 female) and 22 healthy control participants (mean age = 32.91 years; 13 female). Among these participants, behavioral data were not retrievable for a total of 4 nonscanned intermediate training sessions from 4 participants. There were no significant age differences by group ($t_{42} = 1.13, p = .27$), and there were no significant differences in gender ratio ($\chi^2_{1,44} = 0.10, p = .76$). See Table S1 for demographic and clinical features of the groups.

Participants with BPD met DSM-IV criteria for BPD, including the affective instability criterion. Participants with BPD did not meet DSM-IV criteria for past or present bipolar I disorder, schizophrenia, schizoaffective disorder, avoidant personality disorder, posttraumatic stress disorder, substance dependence, or current major depression. All participants had to be psychotropic medication free for 2 weeks (6 weeks in the case of fluoxetine). Three patients with BPD were in psychotherapy at the time of participation. Healthy control participants did not meet DSM-IV criteria for any Axis I or Axis II disorders. Diagnostic assessments were obtained using the Structured Clinical Interview for DSM-IV-Patient Edition and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders. Our group has achieved an interrater reliability of 0.81 for diagnosing BPD.

Materials

Three hundred negative and 150 neutral pictures were shown in the emotion regulation task. An additional comparable 60 negative and 30 neutral pictures were used for a third, follow-up scan session, the results of which are beyond the scope of

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the current analyses; these additional pictures were part of the counterbalanced stimulus bank (see the [Supplement](#)). All pictures (negative and neutral) were social, depicting 2 or more people interacting. Importantly, all negative pictures contained themes specifically relevant to BPD, including interpersonal rejection, sadness, frustration, anger, and violence. Pictures were drawn from the International Affective Picture System (28), Empathy Picture System (29), and online image repositories and were rated using the Self-Assessment Manikin (30) for comparability (see the [Supplement](#)).

Task Design

During each of 5 sessions, spaced approximately 1 to 2 days apart (average time between sessions = 1.97 days), participants received reappraisal-by-distancing training and then completed a widely used picture-based reappraisal task (11,14,31).

Reappraisal Training. At the beginning of each session, participants first received training in psychological distancing via an approximately 15-minute one-on-one interaction with an experimenter during which a standardized set of instructions were given, consistent with procedures used in previous work (11,17); however, the instruction script was slightly modified from that used by Denny and Ochsner (11) to use language and examples that would be appropriate and well-suited to patients with BPD. Demand characteristics were minimized by never mentioning the term “training” to participants at any time during the experiment; participants were simply told that they were taking part in a multisession study involving fMRI scanning and the completion of a picture-based task.

During training, participants were told about the 2 types of instruction cues that they would see on a trial-by-trial basis: look and distance. For pictures preceded by a look cue, participants were instructed to simply look at and respond naturally to the picture. For pictures preceded by the distance cue, participants were instructed to view the picture with a detached, objective, impartial, and scientific mindset (10,31) and/or imagine that the pictured events happened far away or a long time ago (22–24).

Each day’s session began with 3 walk-through pictures that were presented for interactive training in the task, in parallel with procedures used previously (11). At each of the 5 sessions, 1 picture was used to illustrate the procedure for the look negative picture condition, and 2 pictures were used to provide practice for the distance negative condition. During this process, the participant was encouraged to voice aloud his/her thinking in carrying out the tasks to allow the

experimenter to model and shape the participant’s use of the distancing strategy. Walk-through pictures were unique for each of the 5 sessions and were counterbalanced across sessions. At session 1 only, participants then completed 9 fixed-pace practice trials that demonstrated the timing of the actual picture-based task described below. Afterward, at each of the 5 sessions, the participant completed the reappraisal task.

Reappraisal Task. The reappraisal task was very similar to one that has been described previously and used in numerous previous studies (11,14,17,31,32). The trial structure for the task is shown in [Figure 1](#). For each trial, a cue (either look or distance) was presented for 2 seconds followed by presentation of a neutral or negative picture for 10 seconds, during which time participants were instructed to implement the look or distance instruction; there was a rating period during which participants rated the current strength of their negative affect on a scale of 1 (least) to 5 (most) for 4 seconds and, finally, an intertrial fixation interval of either 3 or 5 seconds (average of 4 seconds).

Three different trial types were presented at each session: look neutral (i.e., look instruction paired with a neutral picture), look negative (i.e., look instruction paired with a negative picture), and reappraise negative (i.e., distance instruction paired with a negative picture). Ninety trials were presented per session with 30 trials each per trial type. These were presented across 3 task runs (with short breaks in between) comprising 10 trials of each trial type per run. Unique stimuli were presented on each trial at all 5 sessions. Picture sets were counterbalanced across sessions and trial types. Within runs, trials were presented in a randomized order.

Data Acquisition and Analysis

Self-Reported Negative Affect. At sessions 1 and 5, self-reported negative affect ratings were acquired using a 5-button response glove during fMRI scanning and recorded using E-Prime software (Psychology Software Tools, Inc.). At sessions 2, 3, and 4, self-reported negative affect ratings were acquired with participants seated at a computer running E-Prime software. Self-reported affect data were analyzed using a linear mixed model incorporating predictors for group (BPD and healthy control), session (1 through 5), and trial type (look neutral, look negative, reappraise negative) and their interactions, as well as a random intercept for each participant.

Functional Magnetic Resonance Imaging. fMRI data were acquired at sessions 1 and 5. Whole-brain fMRI data

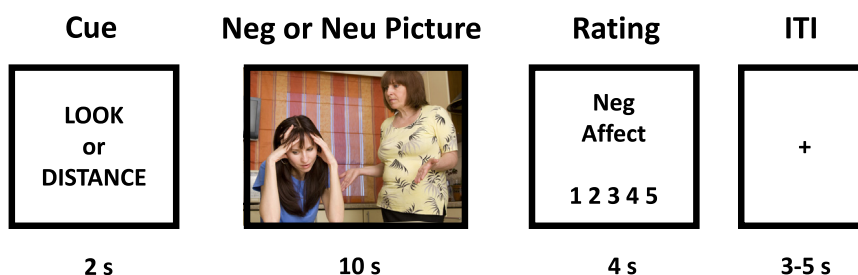


Figure 1. Trial structure. ITI, intertrial interval; Neg, negative; Neu, neutral.

were acquired using the same scanner for each participant, either a 3T Philips Achieva scanner (11 patients with BPD and 14 healthy control participants) or a 3T Siemens MAGNETOM Skyra scanner (11 patients with BPD and 8 healthy control participants). There were no significant differences in scanner allocation ratio by group ($\chi^2_{1,44} = 0.83, p = .36$). Acquisition and preprocessing information is provided in the [Supplement](#).

At sessions 1 and 5, for each participant, a random-effects general linear model was computed with regressors for fMRI responses to the cue (differentiated by 2 cues: look and distance), stimulus presentation (differentiated by the 3 trial types: look neutral, look negative, and reappraise negative), and rating period (undifferentiated by trial type). Additional details are provided in the [Supplement](#).

Pattern Expression Analyses. Task fMRI data were analyzed using the FMRIB Software Library to generate participant-specific, whole-brain contrast maps reflecting activity, relative to fixation baseline, during the stimulus presentation period separately for look neutral, look negative, and reappraise negative trials.

We procured whole-brain patterns derived from whole-brain cross-validated machine learning analyses for picture-induced negative emotion signature (PINES) (18) and a quantitative meta-analysis of reappraisal implementation (13) by contacting the authors of the respective studies. The PINES map included positive weights for regions including but not limited to the amygdala, dorsomedial prefrontal cortex, and posterior cingulate cortex (Figure 2A). The reappraisal implementation map from Buhle *et al.* (13) included the posterior dorsomedial prefrontal cortex, bilateral dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and posterior parietal lobe (Figure 2B).

For PINES correspondence score (PCS) calculation, we used the whole-brain unthresholded PINES pattern mask as shown in a representative sagittal view in Figure 2A. For reappraisal correspondence score (RCS) calculation, to reduce the influence of potentially noisy and spurious voxel data in each whole-brain pattern map, we applied a lower-bound threshold of $Z = 2$ [see (20)]. We estimated the correlation for each participant

between each whole-brain pattern during the reappraisal task (i.e., individual contrast maps for look neutral, look negative, and reappraise negative, each vs. fixation baseline) and the negative affect and reappraisal implementation pattern maps using AFNI's *3ddot* tool to assess the extent to which their brain activity during the reappraisal task engaged the reference whole-brain patterns (i.e., using *3ddot -doc* to compute the correlation coefficient for each participant). This resulted in 1 correlation coefficient per participant for each correspondence measure (i.e., PCS and RCS), respectively [for additional details, see (20)]. PCS and RCS values were analyzed using linear mixed models incorporating predictors for group (borderline and healthy control), session (1 and 5), and trial type (look neutral, look negative, reappraise negative) and their interactions, as well as a random intercept for each participant. Exploratory models including age and gender as covariates are provided in the [Supplement](#).

RESULTS

Self-Reported Negative Affect

Figure 3 shows negative affect self-reports by trial type and session for each group. As expected, at baseline, patients with BPD showed greater reactivity behaviorally to negative stimuli than healthy volunteers ($t_{42} = 2.04, p < .05$, 2-tailed) (Figure 3). When reappraising at baseline, however, the groups did not show a significant difference ($t_{42} = 1.04, p = .30$, 2-tailed) (Figure 3).

There was a significant effect of group ($F_{1,42} = 4.15, p < .05$), with patients with BPD reporting greater negative affect during the task on average. There was also a main effect of session ($F_{4,576} = 6.03, p < .001$), indicating a decreasing trend in self-reported negative affect over time overall. Furthermore, there was a main effect of trial type ($F_{2,576} = 618.71, p < .001$). An omnibus group \times trial type \times session interaction, including the look neutral trial type, was nonsignificant ($F_{8,576} = 0.69, p = .70$). A trend-level group \times trial type interaction was present ($F_{2,576} = 2.62, p = .07$). To examine comparisons of a priori interest, we conducted paired and independent sample *t* tests to assess change over time (i.e., session 5 vs. session 1) by

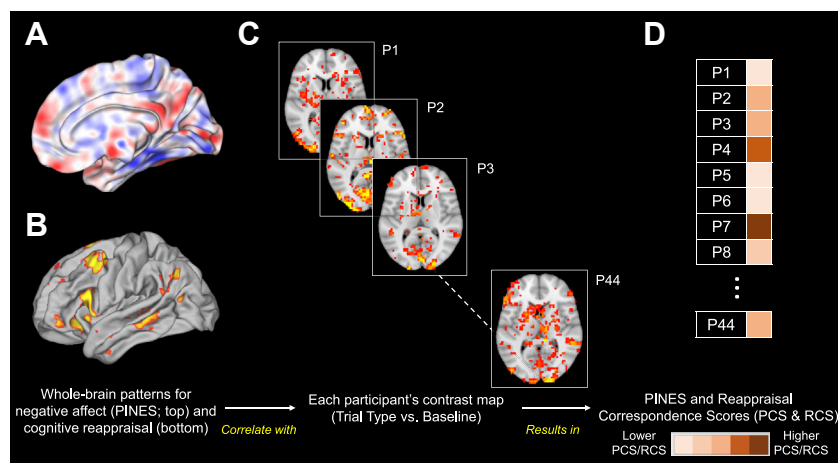


Figure 2. Overview of computations for picture-induced negative emotion signature (PINES) correspondence scores (PCS) and reappraisal correspondence scores (RCS). Whole-brain patterns for (A) negative affect from Chang *et al.* (PINES) (18) and (B) cognitive reappraisal from the meta-analysis of Buhle *et al.* (13) were (C) correlated with each participant's contrast map (trial type vs. baseline) to (D) produce 1 PCS and 1 RCS value per trial type per session per participant. P, pattern.

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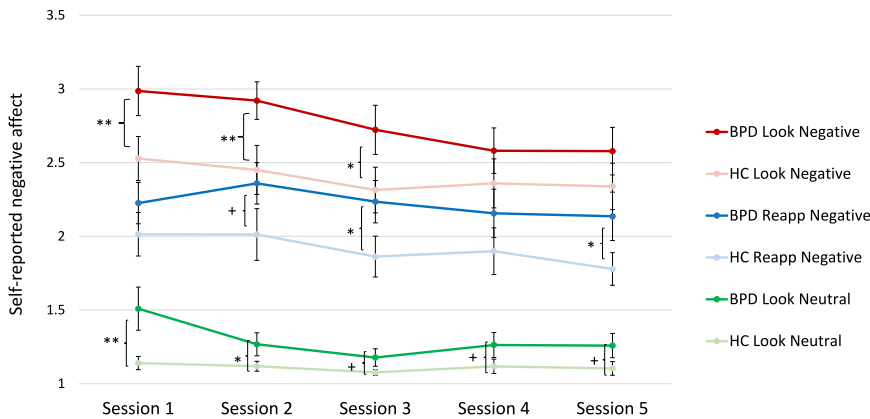


Figure 3. Change over time in negative affect reports by group, session, and trial type. **significant between-group difference, $p < .05$, 2-tailed; * $p < .05$, 1-tailed; + $p < .10$, 1-tailed. BPD, borderline personality disorder; HC, healthy control participant; Reapp, reappraise.

group and trial type. For look neutral trials, patients with BPD showed a marginal decrease over time in self-reported negative affect ($t_{21} = 1.85, p < .08$, 2-tailed) as did healthy control participants ($t_{21} = 2.07, p < .06$, 2-tailed). For look negative trials, patients with BPD showed a significant drop in self-reported negative affect over time, $t_{21} = 3.30, p = .003$, 2-tailed, while healthy control participants showed a trend-level drop in negative affect over time ($t_{21} = 1.81, p < .09$, 2-tailed). For reappraise negative trials, healthy control participants showed a significant drop in self-reported negative affect ($t_{21} = 2.39, p < .03$, 2-tailed) whereas patients with BPD exhibited no significant drop in self-reported negative affect ($t_{21} = 0.79, p = .44$, 2-tailed).

Pattern Expression Analyses

PINES Correspondence Score. Pattern expression analysis results using the independently defined pattern map for PINES (18) are shown in Figure 4. There was a main effect of session ($F_{1,210} = 13.72, p < .001$), indicating some global attenuation in PCS scores across both groups across sessions. There was also a main effect of trial type ($F_{2,210} = 79.95, p < .001$). When only negative picture trials across groups and sessions were examined, there was also a main effect of session ($F_{1,126} = 8.54, p = .004$). We examined these relationships further via planned t tests.

Following reappraisal training, patients with BPD showed a significant decrease in PCSs when reappraising negative pictures by distancing at session 5 compared with session 1 ($t_{21} = 1.88, p < .04$, 1-tailed); healthy control participants showed a weaker effect in the same direction for this comparison ($t_{21} = 1.36, p < .10$, 1-tailed). At session 1, healthy control participants showed a decrease in PCS when distancing compared with looking at negative pictures that did not reach significance ($t_{21} = 1.25, p = .11$, 1-tailed), whereas patients with BPD did not show a decrease in PCS at baseline when distancing compared with looking ($t_{21} = 0.67, p = .51$, 2-tailed). However, by session 5, after training, patients with BPD showed a pattern suggestive of that of healthy control participants in session 1, with attenuation of PCS when reappraising compared with looking ($t_{21} = 1.34, p < .10$, 1-tailed). In contrast, at session 5, healthy control participants did not show a significant decrease in reappraise negative versus look negative ($t_{21} = 1.24, p = .23$, 2-tailed).

Notably, for look negative trials, patients with BPD showed no significant habituation in PCS ($t_{21} = 0.60, p = .56$, 2-tailed), suggesting that PCS attenuation during reappraisal trials in patients with BPD was not simply the effect of time or retest exposure. Healthy control participants also showed no

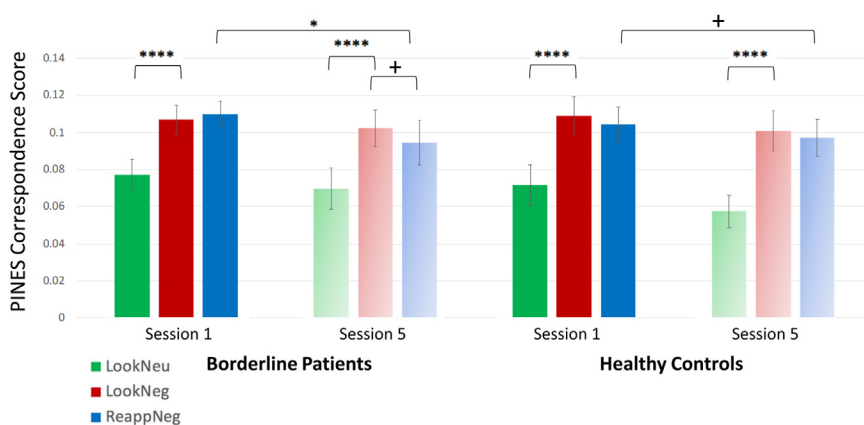


Figure 4. Picture-induced negative emotion signature (PINES) correspondence score change with training. **** $p < .001$, 2-tailed; * $p < .05$, 1-tailed; + $p < .10$, 1-tailed. Error bars reflect SEM. LookNeg, look negative; LookNeu, look neutral; ReappNeg, reappraise negative.

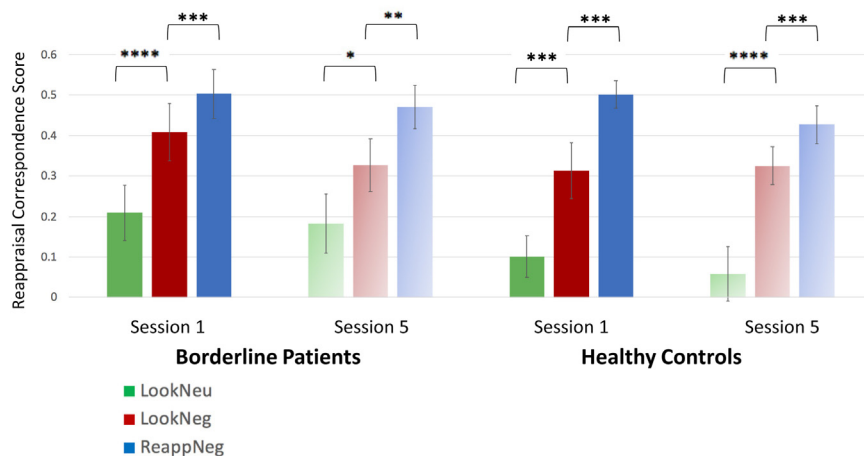


Figure 5. Reappraisal correspondence score change with training. **** $p < .001$, 2-tailed; *** $p < .01$, 2-tailed; ** $p < .05$, 2-tailed; * $p < .05$, 1-tailed. Error bars reflect SEM. LookNeg, look negative; LookNeu, look neutral; ReappNeg, reappraise negative.

significant attenuation in PCS for look negative trials over time ($t_{21} = 1.57$, $p = .13$, 2-tailed).

Reappraisal Implementation Network. RCSs derived from the pattern map for reappraisal implementation (13) are shown in Figure 5. There was a main effect of trial type ($F_{2,210} = 46.90$, $p < .001$) and a marginal effect of session ($F_{1,210} = 1.99$, $p = .16$). As expected, both patients with BPD and healthy control participants showed greater recruitment of the reappraisal implementation network during reappraise negative trials than during look negative trials at session 1 (patients with BPD: $t_{21} = 2.96$, $p < .01$, 2-tailed; healthy control participants: $t_{21} = 3.28$, $p < .01$, 2-tailed) and session 5 (patients with BPD: $t_{21} = 2.70$, $p = .01$, 2-tailed; healthy control participants: $t_{21} = 2.96$, $p < .01$, 2-tailed). There was no significant change over time in recruitment of the reappraisal network for reappraise negative trials in healthy control participants ($t_{21} = 1.28$, $p = .21$, 2-tailed) or patients with BPD ($t_{21} = 0.59$, $p = .56$, 2-tailed).

DISCUSSION

In this study, we examined whether longitudinal training in cognitive reappraisal by distancing would enhance emotion regulation in patients with BPD, who characteristically show significant emotion dysregulation. We examined the efficacy and neural correlates of a relatively brief, 5-session training paradigm in patients with BPD and healthy control participants. To our knowledge, these results represent the first longitudinal fMRI examination of task-based cognitive reappraisal training in any population. We predicted that patients with BPD would show behavioral and neural evidence of elevated negative emotion reactivity and impaired emotion regulation at baseline compared with healthy control participants and that longitudinal reappraisal training would attenuate these group differences and show evidence of a normalizing neural pattern in patients with BPD.

The neural findings were largely consistent with the hypothesized improvement in distancing-related downregulation of negative responses in patients with BPD who received training. As discussed below, patients with BPD showed a

reduction in a multivariate pattern of negative affect during reappraisal at session 5 after training compared with session 1, as reflected in the whole-brain neural signature of picture-induced negative affect.

For behavioral results, at baseline, patients with BPD showed elevated negative behavioral responses to negative images compared with healthy control participants, as expected. However, they did not show the expected reduced efficacy in distancing at baseline. This could be because self-reports are subject to demand effects or because of the small sample size.

Our primary analyses interrogated pattern correspondence of whole-brain functional networks rather than univariate brain activity (18,19). This approach allowed us to assess the full neural ensembles engaged in negative affect response and reappraisal implementation in an unbiased manner. It alleviated the multiple testing problem in brain imaging analysis and targeted our analyses to hypothesis-driven questions concerning engagement of and longitudinal change in multivariate neural patterns associated in previous work with PINES (18) as well as reappraisal implementation (13). Furthermore, using the pattern correspondence approach for PINES also permitted the contribution of negatively weighted regions (i.e., those predictive of experiencing less negative affect) including the bilateral parahippocampal gyrus, right superior temporal gyrus, left temporal parietal junction, right caudate, somatomotor cortex, and occipital cortex (18). The PINES pattern expression provides a more robust correspondence with a validated brain basis for negative affect than interrogation of discrete a priori- or a posteriori-defined regions of interest alone and thus may have greater sensitivity than a focus on individual regions of interest.

Implications for the Neural Mechanisms of Reappraisal Training via Distancing in Patients With BPD

Our findings suggest that it may be possible to train patients with BPD to enhance their utilization of cognitive reappraisal by distancing with a relatively time-limited intervention, as reflected in an improved ability to downregulate the brain ensemble that reacts to negative stimuli and in a response

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pattern more similar to that of healthy individuals. Interestingly, the training did not result in increased pattern expression of the reappraisal implementation network, which includes the bilateral dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, posterior dorsomedial prefrontal cortex, and posterior parietal cortex. This result suggests that with training, individuals with BPD may achieve downregulation of the PINES network through changes in bottom-up reactivity (33) or by engaging a different regulatory network than the one characteristically employed for reappraisal by healthy individuals.

Behaviorally, we did not observe significant attenuation of self-reported negative affect during reappraisal trials in patients with BPD following reappraisal training. While contrary to our hypothesis, it is consistent with recent work showing that behavioral effects may be limited or absent in short-duration cognitive control training interventions, whereas physiological effects may be more robust, less susceptible to demand effects, and potentially more reliable (34,35). Furthermore, a number of studies have demonstrated a disconnect between the reported experience of patients with BPD and their physiological responses (36–38).

Limitations and Future Directions

Limitations of the current study include the relatively short duration of reappraisal training, the lack of an independent training success measure, the absence of an association between self-reported affect and neural change over time, not being preregistered, and the modest sample size. The fMRI task used to measure the training effect was the task used in the training process, although with different images. While this permitted a focused neural assessment of the training, it limits the generalizability of the finding of successful reappraisal training to other reappraisal scenarios and to real-world situations. Future work should examine the extent to which training inside the lab translates to affective changes outside the lab, including decreased symptomatology and improved function in daily life. Future work should also examine the durability of reappraisal training effects in patients with BPD after the conclusion of active training.

Conclusions

In summary, the current work examined the efficacy and neural mechanisms of a novel, relatively brief emotion regulation training paradigm in patients with BPD to enhance an emotion regulation tactic that is highly adaptive and widely used by healthy individuals. While the findings must be interpreted with caution because of modest, but significant, statistical effects and the absence of some predicted behavioral findings, the significant decrease in the whole-brain pattern signature reflective of negative affect after reappraisal training calls for further investigation of distancing training as an approach to enhancing emotion regulation in patients with BPD.

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REFERENCES

- Carpenter RW, Trull TJ (2013): Components of emotion dysregulation in borderline personality disorder: A review. *Curr Psychiatry Rep* 15:335.
- Skodol AE, Gunderson JG, Pfohl B, Widiger TA, Livesley WJ, Siever LJ (2002): The borderline diagnosis I: Psychopathology, comorbidity, and personality structure. *Biol Psychiatry* 51:936–950.
- Koenigsberg HW, Harvey PD, Mitropoulou V, Schmeidler J, New AS, Goodman M, *et al.* (2002): Characterizing affective instability in borderline personality disorder. *Am J Psychiatry* 159:784–788.
- Berking M, Wupperman P, Reichardt A, Pejic T, Dippel A, Znoj H (2008): Emotion-regulation skills as a treatment target in psychotherapy. *Behav Res Ther* 46:1230–1237.
- Denny BT (2020): Getting better over time: A framework for examining the impact of emotion regulation training. *Emotion* 20:110–114.
- Cohen N, Ochsner KN (2018): From surviving to thriving in the face of threats: The emerging science of emotion regulation training. *Curr Opin Behav Sci* 24:143–155.
- Linehan MM (1993): *Cognitive-Behavioral Treatment of Borderline Personality Disorder*. New York: Guilford Press.
- Goodman M, Carpenter D, Tang CY, Goldstein KE, Avedon J, Fernandez N, *et al.* (2014): Dialectical behavior therapy alters emotion regulation and amygdala activity in patients with borderline personality disorder. *J Psychiatr Res* 57:108–116.
- Gross JJ (2015): Emotion regulation: Current status and future prospects. *Psychol Inq* 26:1–26.
- Gross JJ (1998): Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. *J Pers Soc Psychol* 74:224–237.
- Denny BT, Ochsner KN (2014): Behavioral effects of longitudinal training in cognitive reappraisal. *Emotion* 14:425–433.
- Ochsner KN, Silvers JA, Buhle JT (2012): Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci* 1251:E1–E24.
- Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, *et al.* (2014): Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cereb Cortex* 24:2981–2990.
- Ochsner KN, Bunge SA, Gross JJ, Gabrieli JDE (2002): Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci* 14:1215–1229.
- Urry HL, van Reekum CM, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, *et al.* (2006): Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and

- predict the diurnal pattern of cortisol secretion among older adults. *J Neurosci* 26:4415–4425.
16. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN (2008): Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* 59:1037–1050.
 17. Koenigsberg HW, Fan J, Ochsner KN, Liu X, Guise KG, Pizzarello S, *et al.* (2009): Neural correlates of the use of psychological distancing to regulate responses to negative social cues: A study of patients with borderline personality disorder. *Biol Psychiatry* 66:854–863.
 18. Chang LJ, Gianaros PJ, Manuck SB, Krishnan A, Wager TD (2015): A sensitive and specific neural signature for picture-induced negative affect. *PLoS Biol* 13:e1002180.
 19. Barrett LF, Satpute AB (2013): Large-scale brain networks in affective and social neuroscience: Towards an integrative functional architecture of the brain. *Curr Opin Neurobiol* 23:361–372.
 20. Shahane AD, Lopez RB, Denny BT (2019): Implicit reappraisal as an emotional buffer: Reappraisal-related neural activity moderates the relationship between inattention and perceived stress during exposure to negative stimuli. *Cogn Affect Behav Neurosci* 19:355–365.
 21. McRae K, Ciesielski B, Gross JJ (2012): Unpacking cognitive reappraisal: Goals, tactics, and outcomes. *Emotion* 12:250–255.
 22. Ayduk O, Kross E (2008): Enhancing the pace of recovery: Self-distanced analysis of negative experiences reduces blood pressure reactivity. *Psychol Sci* 19:229–231.
 23. Davis JI, Gross JJ, Ochsner KN (2011): Psychological distance and emotional experience: What you see is what you get. *Emotion* 11:438–444.
 24. Trope Y, Liberman N (2010): Construal-level theory of psychological distance. *Psychol Rev* 117:440–463.
 25. van Zutphen L, Siep N, Jacob GA, Goebel R, Amtz A (2015): Emotional sensitivity, emotion regulation and impulsivity in borderline personality disorder: A critical review of fMRI studies. *Neurosci Biobehav Rev* 51:64–76.
 26. Schulze L, Schmahl C, Niedtfeld I (2016): Neural correlates of disturbed emotion processing in borderline personality disorder: A multimodal meta-analysis. *Biol Psychiatry* 79:97–106.
 27. Schulze L, Domes G, Krüger A, Berger C, Fleischer M, Prehn K, *et al.* (2011): Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. *Biol Psychiatry* 69:564–573.
 28. Lang PJ, Greenwald MK, Bradley MM, Hamm AO (1993): Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiology* 30:261–273.
 29. Geday J, Gjedde A, Boldsen AS, Kupers R (2003): Emotional valence modulates activity in the posterior fusiform gyrus and inferior medial prefrontal cortex in social perception. *NeuroImage* 18:675–684.
 30. Bradley MM, Lang PJ (1994): Measuring emotion: The Self-Assessment Manikin and the semantic differential. *J Behav Ther Exp Psychiatry* 25:49–59.
 31. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, Gross JJ (2004): For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage* 23:483–499.
 32. McRae K, Hughes B, Chopra S, Gabrieli JD, Gross JJ, Ochsner KN (2010): The neural bases of distraction and reappraisal. *J Cogn Neurosci* 22:248–262.
 33. Denny BT, Inhoff MC, Zerubavel N, Davachi L, Ochsner KN (2015): Getting over it: Long-lasting effects of emotion regulation on amygdala response. *Psychol Sci* 26:1377–1388.
 34. Beauchamp KG, Kahn LE, Berkman ET (2016): Does inhibitory control training transfer?: Behavioral and neural effects on an untrained emotion regulation task. *Soc Cogn Affect Neurosci* 11:1374–1382.
 35. de Oliveira Rosa V, Rosa Franco A, Abrahão Salum Júnior G, Moreira-Maia CR, Wagner F, Simioni A, *et al.* (2020): Effects of computerized cognitive training as add-on treatment to stimulants in ADHD: A pilot fMRI study. *Brain Imaging Behav* 14:1933–1944.
 36. Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, *et al.* (2001): Evidence of abnormal amygdala functioning in borderline personality disorder: A functional MRI Study. *Biol Psychiatry* 50:292–298.
 37. Hazlett EA, Speiser LJ, Goodman M, Roy M, Carrizal M, Wynn JK, *et al.* (2007): Exaggerated affect-modulated startle during unpleasant stimuli in borderline personality disorder. *Biol Psychiatry* 62:250–255.
 38. Hazlett EA, Zhang J, New AS, Zelmanova Y, Goldstein KE, Haznedar MM, *et al.* (2012): Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. *Biol Psychiatry* 72:448–456.