Neural Correlates of the Use of Psychological Distancing to Regulate Responses to Negative Social Cues: A Study of Patients with Borderline Personality Disorder

Harold W. Koenigsberg, Jin Fan, Kevin N. Ochsner, Xun Liu, Kevin G. Guise, Scott Pizzarello, Christine Dorantes, Stephanie Guerreri, Lucia Tecuta, Marianne Goodman, Antonia New, and Larry J. Siever

Background: Emotional instability is a defining feature of borderline personality disorder (BPD); yet, little is understood about its underlying neural correlates. One possible contributing factor to emotional instability is a failure to adequately employ adaptive cognitive regulatory strategies such as psychological distancing.

Methods: To determine whether there are differences in neural dynamics underlying this control strategy between BPD patients and healthy control (HC) subjects, blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging signals were acquired as 18 BPD and 16 HC subjects distanced from or simply looked at pictures depicting social interactions. Contrasts in signal between distance and look conditions were compared between groups.

Results: Borderline personality disorder patients showed a different pattern of activation compared with HC subjects when looking at negative versus neutral pictures. When distancing versus looking at negative pictures, both groups showed decreased negative affect ratings and increased activation of the dorsolateral prefrontal cortex, areas near/along the intraparietal sulcus (IPS), ventrolateral prefrontal cortex, and posterior cingulate/precuneus regions. However, the BPD group showed less BOLD signal change in dorsal anterior cingulate cortex and IPS, less deactivation in the amygdala, and greater activation in the superior temporal sulcus and superior frontal gyrus.

Conclusions: Borderline personality disorder and HC subjects display different neural dynamics while passively viewing social emotional stimuli. In addition, BPD patients do not engage the cognitive control regions to the extent that HCs do when employing a distancing strategy to regulate emotional reactions, which may be a factor contributing to the affective instability of BPD.

Key Words: Cognitive reappraisal, emotion, emotion regulation, fMRI, psychological distancing, social cognitive neuroscience

Emotional instability, one of the most prominent features of borderline personality disorder (BPD), occurs especially in reaction to negative social experiences (1–3) and is linked to many of its most maladaptive symptoms and interpersonal disturbances (4,5), including suicidality, extreme anger, identity disturbance, and chronic emptiness (6). Despite its centrality to borderline pathology, the neural mechanisms underlying this instability remain poorly understood (7). Given the difficulty that BPD patients have in modulating their emotional reactions (4), it is plausible that their affective instability derives, in part, from a dysfunction in the neural mechanisms underlying emotion regulation (8–10).

One of the most commonly employed, flexible, and adaptive methods for regulating emotion is cognitive reappraisal, which involves reinterpreting the meaning of an emotional stimulus in ways that alter one's emotional response to it (11–13). Neuroimaging studies have shown that in healthy individuals cognitive reappraisal activates prefrontal and cingulate systems implicated in cognitive control processes and modulates systems involved in emotional responding, such as the amygdala (14–21). To date, no studies have examined the neural correlates of emotion regulation by cognitive reappraisal in BPD. Extant data do, however, suggest that there may be dysfunction in neural systems implicated in passive emotional responding (22–25) and in impulse control (26–30) in BPD, as well as decreased structural volumes in BPD patients in the anterior cingulate cortex (ACC), orbital frontal cortex, amygdala, and parietal regions (31–35).

Against this backdrop, we aimed to better understand sources of emotional dysregulation in BPD by comparing the neural correlates of the passive processing of social emotional cues and of cognitive reappraisal of these cues in BPD and healthy control (HC) subjects. There are two main kinds of cognitive reappraisal strategies, known as reinterpretation and distancing (14,36–38). The former entails reinterpreting stimuli in a less disturbing manner, whereas distancing entails viewing stimuli from the perspective of a detached and objective observer. We focused on the distancing strategy because borderline patients have particular difficulty navigating between overintense involvement and remoteness in interpersonal situations (3,39) and therefore it seemed likely to differentiate between BPD patients and HC subjects. Our paradigm was adapted from those used previously (14). We asked BPD and HC participants to either look at negative social images and let themselves respond naturally (the look baseline condition) or to distance themselves from them

From the Department of Psychiatry (HWK, JF, XL, KGG, CD, SG, LT, MG, AN, LJS), Mount Sinai School of Medicine, New York; The Mental Health Patient Care Center (HWK, MG, LJS), James J. Peters Veterans Affairs Medical Center, Bronx; and Department of Psychology (KNO), Columbia University, New York, New York; and the Department of Psychology (SP), Florida State University, Tallahassee, Florida.

Address correspondence to Harold W. Koenigsberg, M.D., Mount Sinai School of Medicine, James J. Peters VA Medical Center, 130 West Kingsbridge Road, 116A, Bronx, NY 10468; E-mail: HWarrenK@nyc.rr.com.

Received Oct 28, 2008; revised Jun 1, 2009; accepted Jun 10, 2009.

0006-3223/09/$36.00
doi:10.1016/j.biopsych.2009.06.010

Published by Elsevier Inc on behalf of Society of Biological Psychiatry

(the distance reappraisal condition). Motivated by prior work, we hypothesized that BPD patients might exhibit abnormal activation in prefrontal, anterior cingulate, temporal, and parietal regions previously implicated in reappraisal in general and distancing in particular, in combination with a relative failure to decrease amygdala activation.

Methods and Materials

Subjects

Subjects were 18 BPD patients (mean age 32.6 ± 10.4 years; 10 female patients) and 16 HC volunteers (mean age 31.8 ± 7.7 years; 9 female volunteers) recruited from outpatient clinics at the Mount Sinai Medical Center and the James J. Peters Veterans Affairs (VA) Medical Center in New York City and advertisements in local newspapers and local postings. Borderline personality disorder subjects met DSM-IV criteria for BPD and had prominent affective instability as indicated by the presence of three of four DSM-IV criteria associated with affective instability, i.e., 1) affective instability due to a marked reactivity of mood, 2) chronic feelings of emptiness, 3) unstable and intense interpersonal relationships, and 4) identity disturbance.

Exclusion criteria applied to the BPD group were present or past bipolar I disorder, schizophrenia, schizoaffective disorder, substance dependence, organic mental syndromes, or substance abuse disorder within the previous 6 months. Healthy control subjects were excluded if they met criteria for any current or past DSM-IV Axis I or Axis II disorder or had first-degree relatives with an Axis I disorder. Histories of significant head trauma, central nervous system (CNS) neurological disease, or significant medical illness were exclusion criteria for all subjects. Subjects were free of psychotropic medication for at least 2 weeks (6 weeks in the case of fluoxetine) before the scan. Subjects with any contraindications to functional magnetic resonance imaging (fMRI) scanning, pregnant women, and those with current active suicidal ideation were excluded. All subjects provided written informed consent.

Diagnostic assessment was obtained using the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P) for Axis I (40) and the Structured Interview for DSM-IV Personality (SIDP-IV) for Axis II diagnoses (41). In previous studies, we have documented an interrater reliability kappa = .81 for diagnosing BPD (42).

Affective instability was assessed with the Affective Lability Scale (ALS) (43), a self-report instrument shown to correlate with clinician-rated affective instability in patients with BPD (42). Depression was rated with the 21-item Hamilton Depression Rating Scale (HAM-D) (44), state and trait anxiety with the Spielberger Trait Anxiety Inventory (STAI) (45), impulsivity with the Barratt Impulsivity Scale-II (BIS-II) (46), anger with the Spielberger State Trait Anger Expression Inventory (STAXI) (47), and handedness with the Edinburgh Handedness Inventory.

Subject Characteristics. The BPD and HC groups did not differ in age, sex, or handedness (Table 1). As expected, the BPD patients scored higher (Table 1) in depression (HAM-D), affective lability (ALS), impulsiveness (BIS-II), and state and trait anger (STAXI). They scored lower in state anxiety (STAI-State) and did not differ in trait anxiety (STAI-Trait). None of the BPD patients met criteria for current major depressive disorder, two had generalized anxiety disorder, and two met criteria for current posttraumatic stress disorder (PTSD). As is typical of clinical samples of BPD patients, a history of depression or anxiety disorders was common, with 12 patients reporting prior major depression. One patient had past panic disorder, two had past generalized anxiety disorder, seven had past PTSD, and two had a past eating disorder. Axis II comorbidity was present, as is typical in BPD samples (Table S1 in Supplement 1).

Table 1. Sample Characteristics

	BPD $n = 18$	HC $n = 16$	Statistic
Age (SD)	32.6 ± 10.4	31.8 ± 7.7	$t(32) = .27$ (ns)
Sex	10 female	9 female	$\chi^2 = .002$ (ns)
Handedness	17 R; 1 L	14 R; 1 L; 1 M	$\chi^2 = 1.177$ (ns)
ALS Total	94.9 ± 23.7	20.3 ± 16.0	$t(31) = 10.4^a$
HAM-D	11.6 ± 4.3	1.9 ± 1.7	$t(28) = 7.4^a$
BIS-II	77.9 ± 8.7	51.1 ± 9.7	$t(30) = 8.2^a$
STAI–Trait	47.9 ± 1.6	45.3 ± 2.9	$t(30) = 1.4$
STAI–State	42.8 ± 6.7	47.6 ± 3.5	$t(30) = 2.4^a$
STAXI–Trait	24.8 ± 5.9	14.8 ± 4.5	$t(30) = 5.3^a$
STAXI–State	12.8 ± 4.3	10.1 ± .4	$t(30) = 2.3^a$

ALS, Affective Lability Scale; BIS-II, Barratt Impulsiveness Scale, version II; BPD, borderline personality disorder; HAM-D, Hamilton Depression Scale (21 Item); HC, healthy control; L, left; M, mixed handedness; R, right; STAI, Spielberger State and Trait Anxiety Inventory; STAXI, Spielberger State and Trait Anger Inventory.

$^a p < .05$.

Materials

Stimuli for the reappraisal task were pictures depicting aversive (negative) and neutral interpersonal situations from the International Affective Picture System (IAPS) (48). Since BPD patients are particularly emotionally responsive to interpersonal cues (2) and social and nonsocial emotions are processed differently in the brain (49–52), we chose to restrict our stimuli to social cues, specifically excluding nonsocial IAPS pictures that have been intermixed with social stimuli in prior reappraisal studies. Selected negative interpersonal scenes included pictures of people in situations depicting loss or grief, abuse, or physical threat. Neutral images depicted persons engaged in work or hobbies or attending public events. For the two instructional conditions described below, we selected two sets of negative images that were matched for valence [mean valence norm ratings 2.3 and 2.4, respectively, where 1 = most negative and 9 = most positive; $t(45) = .95$, ns] and two sets of neutral images also matched for valence [mean ratings 5.2 in each set; $t(47) = .49$, ns]. Images were also matched for arousal rating between conditions. Negative images were more arousing than neutral images [mean scores 6.1 and 5.7, respectively, for negative images, $t(45) = 1.30$, ns; and 3.8 and 3.5 for neutral images, $t(47) = 1.22$, ns, where 1 = least arousing and 9 = most arousing].

Experimental Design

Task Design. The task consisted of 96 trials divided into 4 blocks of 24 trials each. The trial structure and timings are presented in Figure 1. In each block, the order of trials (negative-distance, negative-look, neutral-distance, neutral-look) was pseudorandom and this order was used for all subjects.

Training Procedures. Training of the subjects in the reappraisal by distancing technique included initial instruction followed by practice as the investigator observed and shaped their technique, following the method of Ochsner *et al.* (14). Participants were specifically instructed not to look away from the images or to close their eyes. Once they had mastered the technique to the satisfaction of the investigator, they practiced it on a laptop computer for 20 trials, using the same protocol and

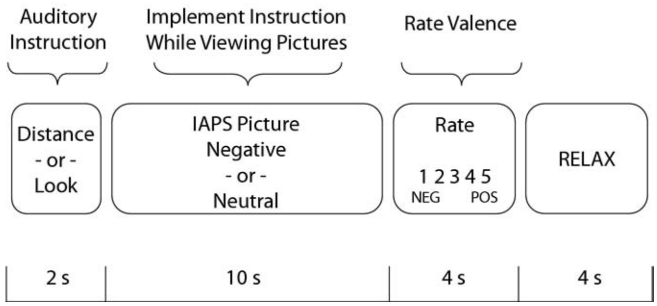

Figure 1. Schematic depiction of a single trial in the imaging paradigm. Each 20-sec trial consisted of a 2-sec (maintain or suppress) presented over earphones, a 10-sec presentation of an IAPS picture (negative or neutral), a 4-sec rating period, and a 4-sec interstimulus interval (relax). During the rating period, subjects indicated their emotional reaction to the picture after carrying out the instruction (using a 5-button hand pad; 1 = very negative to 5 = very positive). Ninety-six trials were presented in 4 blocks of 24 trials each. Each block contained six trials of each of the four conditions in the 2 × 2 design (picture valence × instruction) presented in pseudorandom order. IAPS, International Affective Picture System.

timings that would be used during the scan but different IAPS pictures. They were instructed to apply the distancing technique in response to the auditory instruction "suppress" and to look while responding naturally and not diminishing their emotional reaction when they heard a "maintain" instruction.

Image Acquisition and Analysis

As subjects performed the reappraisal task (Figure 1), blood oxygenation level-dependent (BOLD) images were obtained using a Siemens 3.0 T Allegra scanner (Siemans Medical Solutions USA, Malvern, Pennsylvania) with a gradient-echo echo-planar imaging (GE-EPI) sequence using the following protocol: 42 axial slices, 2.5 mm thick, skip = .825 mm, repetition time (TR) = 3 sec, echo time (TE) = 27 msec, flip angle = 84°, field of view (FOV) = 210 mm, matrix = 64 × 64. For anatomical localization, a high-resolution T2-weighted anatomical scan was acquired on an axial plane parallel to anterior commissure-posterior commissure (AC-PC) line with a turbo spin-echo pulse sequence.

Preprocessing and statistical analyses were carried out using SPM2 (Wellcome Department of Cognitive Neurology, London, England) standard workflow: motion correction of echo-planar images (EPIs) with realignment, co-registration of EPIs onto corresponding subjects' high-resolution T2 scan, normalization to a standard template (Montreal Neurological Institute), and spatial smoothing with a Gaussian kernel (full-width at half maximum [FWHM] = 8 mm). General linear modeling (GLM) for each participant used the default statistical parametric mapping (SPM) basis function convolved with regressors of interest (53). The linear combination of seven regressors was used to model the hemodynamic response (instruction cue: look or distance, as an event; picture viewing: negative-look, negative-distance, neutral-look, neutral-distance, as epochs; valence rating, as an event). Contrast images for all participants were entered into second-level random-effects group conjunction and contrast analyses as implemented in SPM2. The voxel level significance was set to $p < .01$ and the minimum cluster extent threshold was set to $k = 85$ to correct for multiple comparisons to reach a corrected $p < .05$ as decided by a Monte Carlo simulation. Anatomic regions were identified using the anatomical automatic labeling algorithm (54). A conjunction analysis was carried out using the method of Friston *et al.* (55), which tests the global null using the minimum t statistic with a global false-positive rate of .01 for the height threshold. This conjunction analysis makes the inference that the consistent effects are significant but not that the significant effects are consistent (55).

Results

Behavioral Results

In postscan debriefing, subjects reported that they implemented the distancing strategy as instructed and did not close their eyes or look away from the images during either the distancing or look conditions. Self-report affect ratings during the scan (Figure 2) demonstrated an overall image type (negative vs. neutral) × instruction (look vs. distance) interaction, as well as

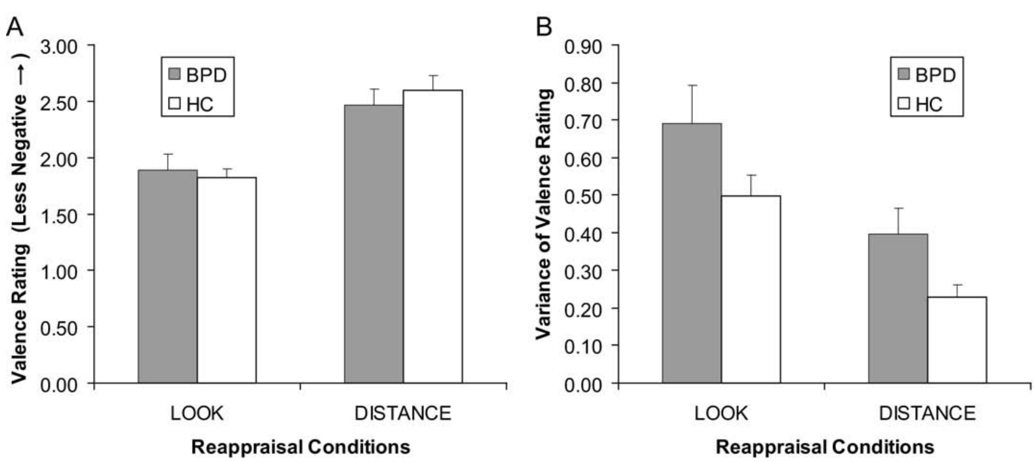

Figure 2. (A) Subjective ratings of valence of negative IAPS pictures following the look and distance instructions. There is an image type (negative vs. neutral) × instruction (look vs. distance) interaction: $F(1,31) = 69.63$, $p < .001$. Main effects for image type and instruction are also significant: $F(1,31) = 102.40$, $p < .01$, and $F(1,31) = 15.00$, $p < .01$, respectively. Interactions with diagnosis were not significant: image type × diagnosis: $F(1,31) = .48$, ns; instruction × diagnosis: $F(1,31) = 1.83$, ns; image type × instruction × diagnosis: $F(1,31) = .08$, ns. There was no main effect of diagnosis [$F(1,31) = .36$, ns]. **(B)** Within-subject variance in valence ratings for negative IAPS pictures. There is a significant main effect of group [$F(1,31) = 5.83$, $p = .02$] and of instruction [$F(1,31) = 69.85$, $p < .001$] but not of image type [$F(1,31) = .66$, ns]. There were no significant group × instruction × image type [$F(1,31) = .02$, ns], group × image type [$F(1,31) = .04$, ns], or group × instruction interactions [$F(1,31) = .20$, ns]. BPD, borderline personality disorder; HC, healthy control; IAPS, International Affective Picture System.

Table 2. Activation Foci that Differed Between the Groups When Looking at Negative Versus Neutral IAPS Pictures

		MNI Coordinates			
Region	k	x	y		*Z* S
Healthy Control Subjects > Borderline Patients					
R fusiform (BA 18)	96	26	−80	−2	3.10
L lingual gyrus (BA 19)	105	−26	−64	−8	3.06
L inferior temporal gyrus (BA 20)	114	−58	−24	−16	2.88
R fusiform (BA 20)	121	40	−16	−22	3.48
L frontal inferior gyrus (BA 45)	159	−50	28	16	3.72
R superior medial frontal gyrus (BA 9)	281	10	44	36	3.47
L superior frontal gyrus (BA 9)	92	−18	54	28	3.17
Borderline Patients > Healthy Control Subjects					
L cerebellum	106	−4	−68	−18	3.68
R superior temporal gyrus (BA 48)	208	56	−34	22	3.18
Posterior cingulate (BA 23)	1679	4	−20	46	3.83
Anterior cingulate (BA 32)	439	0	8	46	3.76

Notes: k = cluster size in 2 × 2 mm × 2 mm voxels. $p < .01$, minimum cluster size, k = 85.
BA, Brodmann area; IAPS, International Affective Picture System; L, left; MNI, Montreal Neurological Institute; R, right.

main effects for image type and instruction. Interactions with diagnosis were not significant (for statistical test results, see Figure 2). There was no main effect of diagnosis. Planned comparisons revealed that for negative pictures BPD and HC subjects reported less negative affect (i.e., higher scores) following distancing as compared with looking [BPD: look = 1.91, distance = 2.52, $t(14) = 3.60$, $p < .01$; HC: look = 1.82, distance = 2.59, $t(14) = 5.73$, $p < .01$]. For neutral pictures, affect ratings were close to the neutral value of 3.0 in both the look and distance conditions, although they were slightly higher in the look condition [BPD: look = 3.39, distance = 3.11, $t(15) = 3.86$, $p < .01$; HC: look = 3.20, distance = 3.07, $t(14) = 1.99$, $p < .01$].

We examined the variance in valence ratings, averaging over groups the within-subject variance for each image type and reappraisal condition, as an index of affective instability. There was a significant main effect of group with the BPD patients showing a greater variance in valence rating (BPD: .53 ± .42 vs. HC: .36 ± .28) and a main effect of condition in which there was less variance in the distance compared with look conditions (Figure 2). There was no main effect of image type and no group by condition by image type, group by image type, or group by condition interactions (for statistical tests, see Figure 2). Post hoc tests showed that when distancing from negative pictures BPD patients had a greater variance in valence ratings than HC subjects [BPD: .40 ± .29 vs. HC: .23 ± .14; $t(31) = 2.05$, $p = .05$].

Imaging Results

We first compared the activation between groups in the look condition when viewing negative compared with neutral pictures. The BPD patients showed greater right superior temporal, anterior, and posterior cingulate and left cerebellar activation than the HC subjects, while the HC subjects showed greater activation in the fusiform gyrus and prefrontal regions (Table 2).

Imaging findings for the negative pictures are the focus of this article because our hypotheses address differences in the neural dynamics of BPD and HC subjects when attempting to down-regulate negative emotion.[1] For each group separately, we identified regions that were activated when viewing negative pictures in the distance > look and look > distance contrasts (Table S3 in Supplement 1). We then compared and contrasted the two groups to identify regions that were commonly or differentially activated by BPD and HC subjects when distancing versus looking.

Commonly Activated Regions. The conjunction analysis revealed that for the distance > look contrast both BPD patients and HC subjects together engaged the dorsolateral prefrontal cortex (DLPFC), right and left lateral and ventrolateral prefrontal cortex (right and left middle and superior frontal gyri [Brodmann area (BA) 10, BA 8]), extensive regions bordering the intraparietal sulci (IPS) bilaterally, right posterior cingulate cortex (PCC) extending into the precuneus, right parahippocampal gyrus, right insula, and the left superior temporal gyrus. In the look > distance contrast, both groups showed extensive activation in the cuneus, left inferior parietal lobule, and activation of the right postcentral gyrus and left supplementary motor area (Figure 3, Table 3).

Differentially Activated Regions. To identify differences in patterns of neural activation between BPD patients and HC subjects when viewing negative pictures in the distancing versus looking contrast, we constructed SPM interaction maps of the double differences in BOLD activation: BPD (distance − look) − HC (distance − look) and the reverse (Figures 4, 5, and 6; Table 4). The graphs in Figures 4, 5, and 6 depict the change in activation from baseline (beta weights) to the look or distance conditions for the volumes of interest.

For the distancing minus looking contrast, HC subjects demonstrated greater activation than BPD patients in the dorsal anterior cingulate cortex (dACC) (BA 32), bilateral IPS region, right middle occipital gyrus, and right fusiform gyrus. To separate the effects of group and instruction condition upon activation in the dACC and IPS—two regions related to control—we examined the regression weights (betas) quantifying signal change for each group in each condition over all voxels in a 6-mm radius sphere centered on the local maximum for the above contrast in each region. In both dACC and IPS, HC subjects activated more strongly (relative to baseline) in the distance condition compared with the look condition, while the BPD patients showed less activation (Figure 4A and 4B). For these volumes of interest, the

[1]For completeness, we have provided in Table S2 in Supplement 1 activation foci contrasting BPD and HC subjects when attempting to distance from neutral pictures, showing greater engagement of the insula and superior/middle frontal gyri bilaterally in BPD compared with HC subjects.

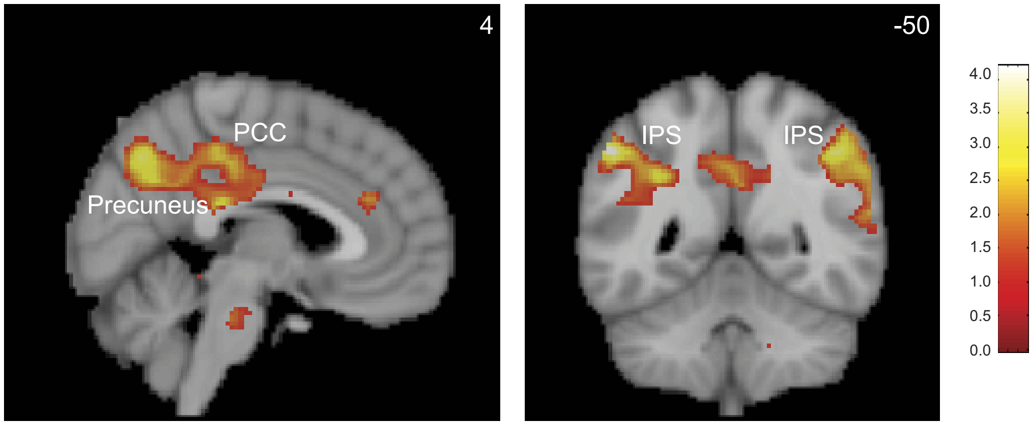

Figure 3. Regions of common activation in both BPD and HC subjects when distancing versus looking at negative pictures. BOLD signals are displayed overlaid on the Montreal Neurological Institute SPM canonical anatomic template. The display threshold is $p < .01$. The color bar indicates t values. BOLD, blood oxygenation level-dependent; BPD, borderline personality disorder; HC, healthy control; IPS, intraparietal sulcus; PCC, posterior cingulate gyrus; SPM, statistical parametric mapping.

group × condition interactions were significant and post hoc look versus distance comparisons for each group were significant except for the HC subjects in the IPS [dACC: group × condition: $F(1,32) = 10.68$, $p = .003$; post hoc HC $F(1,15) = 5.85$, $p = .03$; BPD $F(1,17) = 4.84$, $p = .04$; and for the IPS: group × condition $F(1,32) = 9.34$, $p = .005$; post hoc HC $F(1,15) = 1.97$, ns; BPD $F(1,17) = 8.79$, $p = .009$]. In the look condition, there was no difference in activation between groups [post hoc $F(1,32) = .201$, ns, and $F(1,32) = .091$, ns, for IPS and dACC, respectively).

Borderline personality disorder subjects showed greater distance versus look activation than the HC subjects in various regions, including the superior temporal sulcus (STS), right superior frontal gyrus (BA 8), and right amygdala (Figure 5, Table 4). The extracted beta weights for the volume of interest (Figure 5) indicate that relative to baseline HC subjects showed less activation in the amygdala when distancing compared with looking [post hoc $F(1,15) = 4.41$, $p = .05$], while the reverse was true for BPD patients [post hoc $F(1,17) = 6.01$, $p = .03$]. In the look condition, BPD patients showed less amygdala activation relative to their baseline than the HC subjects [post hoc: $F(1,32) = 8.78$, $p = .006$]. For both the STS and right superior frontal gyrus (SFG) (Figure 6), the extracted beta weights for the volumes of interest showed group × condition effects [STS: $F(1,32) = 14.59$, $p = .0006$; SFG: $F(1,32) = 9.00$, $p = .005$]. In both regions, the BPD patients showed greater activation in the distance compared with look condition [post hoc STS: $F(1,32) = 22.12$, $p = .00005$; SFG: $F(1,32) = 14.73$, $p = .0006$], while there was little difference between conditions for the HC subjects [STS: $F(1,32) = .67$, ns; SFG: $F(1,32) = .25$, ns].

We repeated the analysis excluding BPD subjects with histories of PTSD and confirmed that the significant group differences in the distance versus look contrast described above remained for the regions described above: the dACC, IPS, right STS, right superior frontal gyrus, and right amygdala.

Table 3. Conjunctive Activation by Both Groups When Distancing Versus Looking at Negative IAPS Pictures

			MNI Coordinates			
Region	BA	k	x			Z
Distance > Look						
L inferior parietal lobule	40	1538	−54	−50	46	5.61
R inferior parietal lobule	40	3131	46	−52	46	5.30
R precuneus	7	3254	6	−66	44	4.89
L superior temporal gyrus	42	275	−62	−38	14	3.69
R parahippocampal gyrus	28	122	18	−6	−24	3.42
R middle frontal gyrus	10	1314	38	56	4	4.72
R superior frontal gyrus	8	93	26	20	60	3.87
L superior frontal gyrus	10	283	−18	58	10	3.51
R middle frontal gyrus	9	100	44	12	50	3.44
L middle frontal gyrus	8	241	−30	28	52	3.38
R insula	48	87	34	−16	18	3.32
Look > Distance						
R cuneus	17	8,081	14	−96	14	6.53
L inferior parietal lobule	7	2056	−28	−48	54	4.52
L supplementary motor area	6	159	−4	−6	54	3.53
R postcentral gyrus	3	285	58	−10	32	3.51

Notes: k = cluster size in 2 × 2 × 2 mm voxels. $p < .01$, minimum = 85.

BA, Brodmann area; IAPS, International Affective Picture System; L, left; MNI, Montreal Neurological Institute; R, right.

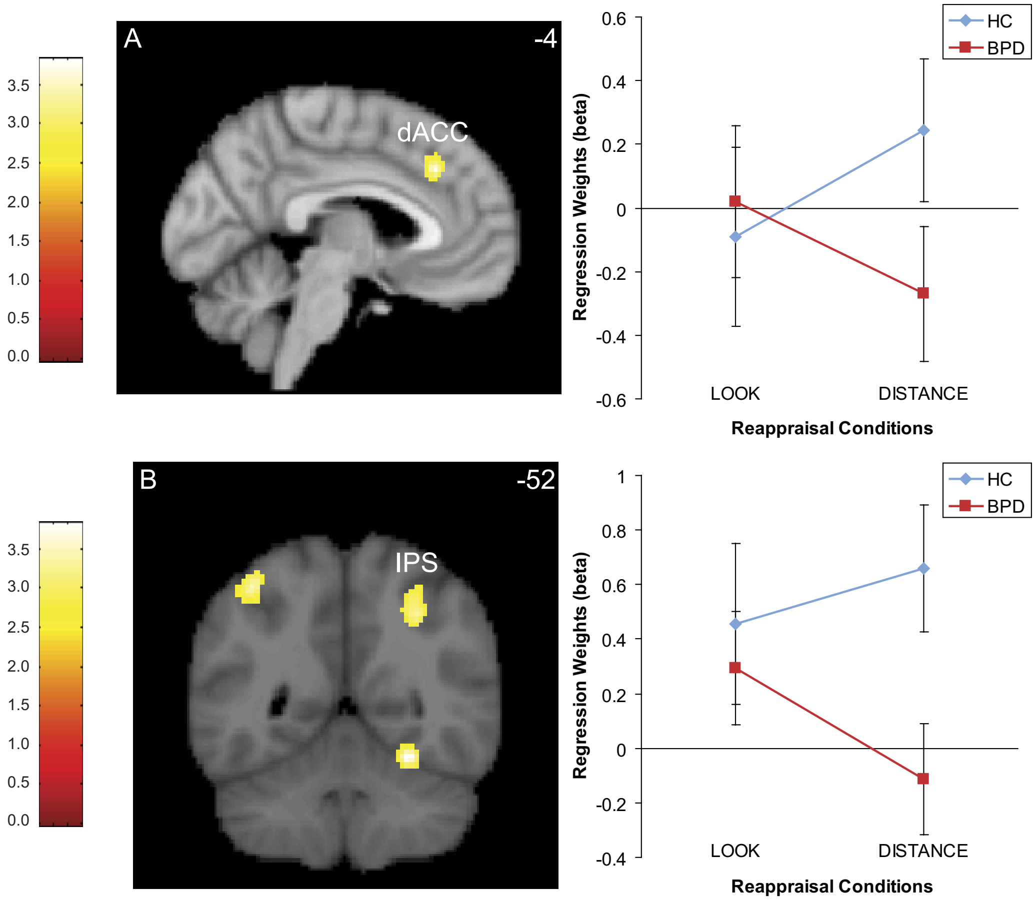

Figure 4. (A) Sagittal section illustrating foci of increased BOLD activation in healthy control subjects relative to borderline patients when carrying out the distance versus look instruction to negative IAPS pictures and plot of regression weights in dorsal ACC for healthy control (HC) subjects and borderline patients (BPD) when carrying out the look and distance instructions. **(B)** Coronal section illustrating regions of increased activation in healthy control subjects relative to borderline patients and plot of regression weights for each group in right intraparietal sulcus region. BOLD signals are displayed overlaid on the Montreal Neurological Institute SPM canonical anatomic template. The display threshold is $p < .01$. The color bar indicates t values. ACC, anterior cingulate cortex; BOLD, blood oxygenation level-dependent; dACC, dorsal anterior cingulate cortex; IAPS, International Affective Picture System; SPM, statistical parametric mapping.

Discussion

The purpose of the current study was to further understanding of affective instability in BPD by determining whether the neural bases of one kind of reappraisal—known as distancing—were disturbed in BPD.

Behavioral Observations

As expected, subjects reported less negative affect after distancing as compared with just looking at negative images, but not neutral images. Interestingly, these affect ratings did not differentiate the groups, which runs counter to the expectation that BPD patients would respond more intensely than HC subjects to negative images and would downregulate these responses less effectively. It is consistent, however, with prior reports of no differences between BPD patients and HC subjects in their self-reported affective responses to IAPS pictures despite differences in neural activation (24). One possible explanation is that subjective ratings reflect momentary intensity rather than the chronic instability of affective experience that characterizes BPD (7). This fits with the finding that BPD and non-BPD personality disorder patients differ in ratings of affective instability but not subjective affective intensity (42). In fact, examining the variance in valence ratings as an index of affective instability, we found a higher variance in BPD patients than HC subjects when distancing from negative pictures. Another possibility consistent with our finding and that of Herpertz *et al.* (24) is that in BPD patients there is a disconnect between the subjective experience of emotion and the physiological emotional response.

Neural Dynamics of Passive Looking

When looking at negative social emotional images compared with neutral images, borderline patients showed a different pattern of neural activation compared with healthy volunteers, indicating that borderline patients process emotional images differently than control subjects. The BPD patients showed greater activation in the superior temporal gyrus, posterior cingulate, anterior cingulate, and cerebellum than the HC subjects. We did not find the increased amygdala and fusiform activity reported by Herpertz *et al.* (24). This difference may be due to the fact that we employed exclusively social emotional pictures in both the negative and neutral conditions, whereas in the Herpertz *et al.* (24) study, faces appeared in the negative but not in the neutral pictures, which were all inanimate objects. Since faces are strong activators of the amygdala and fusiform,

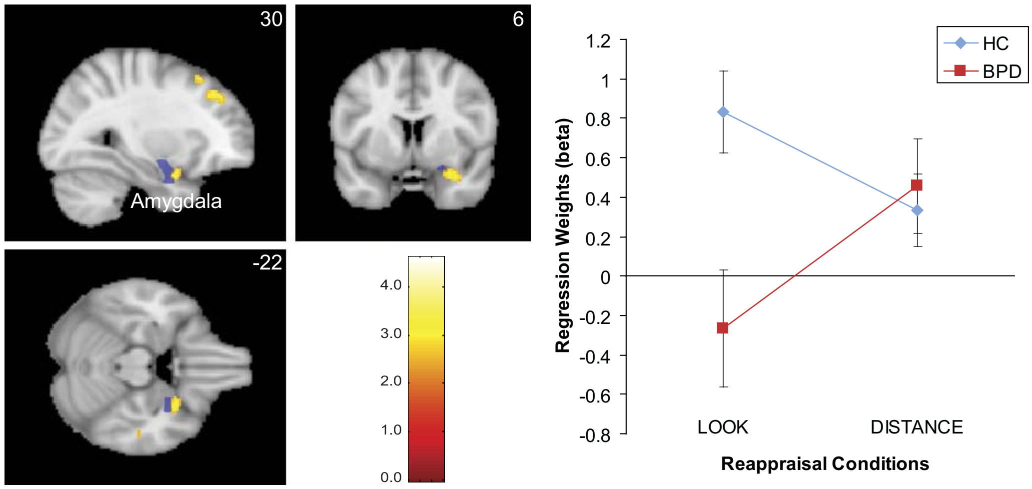

Figure 5. Coronal, sagittal, and horizontal sections illustrating greater activation in the amygdala of BPD patients compared with healthy control subjects when distancing and plot of regression weights for each group in right amygdala. The BOLD signal appears in yellow and the anatomic locus of the amygdala is shown in blue. BOLD signals are displayed overlaid on the Montreal Neurological Institute SPM canonical anatomic template. The display threshold is $p <$ .01. The color bar indicates *t* values. BOLD, blood oxygenation level-dependent; BPD, borderline personality disorder; HC, healthy control; SPM, statistical parametric mapping.

we would expect greater activation when the effect of faces is not subtracted out in the contrast.

Neural Dynamics of Reappraisal By Distancing

Common Features in Borderline Patients and Healthy Control Subjects. Borderline patients activated many of the same networks as healthy control subjects during distancing, including networks implicated in executive function, goal maintenance, and the representation of social intentions (the DLPFC) (56); top-down control of attention allocation (the DLPFC/IPS network) (57–59); and self-other perspective taking (the precuneus/PCC) (60–66). Notably, DLPFC and IPS (67), but not precuneus/PCC, activity has been reported in prior work on reappraisal (for reviews, see [11,15]), possibly because this region is activated only in response to distancing from social cues, which have not been examined specifically until now. The look versus distance contrast identified primary visual regions whose activity diminished during reappraisal. This finding is consistent with prior reports (e.g., Ochsner *et al.* [16]) and the idea that distancing involves an inward focus of attention.

Differences between Borderline Patients and Healthy Control Subjects. Beyond the above commonalities, BPD patients showed a distinctly different pattern of activation compared with HC subjects in a set of regions related to control and emotional responding. Specifically, during distancing compared with looking, BPD patients showed less activation relative to baseline in the dACC and IPS and greater activation in the right superior frontal gyrus (BA 8) and STS, whereas HC subjects showed the reverse. Both groups showed comparable activation in the look condition. Unlike HC subjects, BPD patients increased amygdala activation relative to baseline during distancing compared with looking (Figure 5). In addition, during look trials, BPD patients showed less activation than HC subjects relative to their respec-

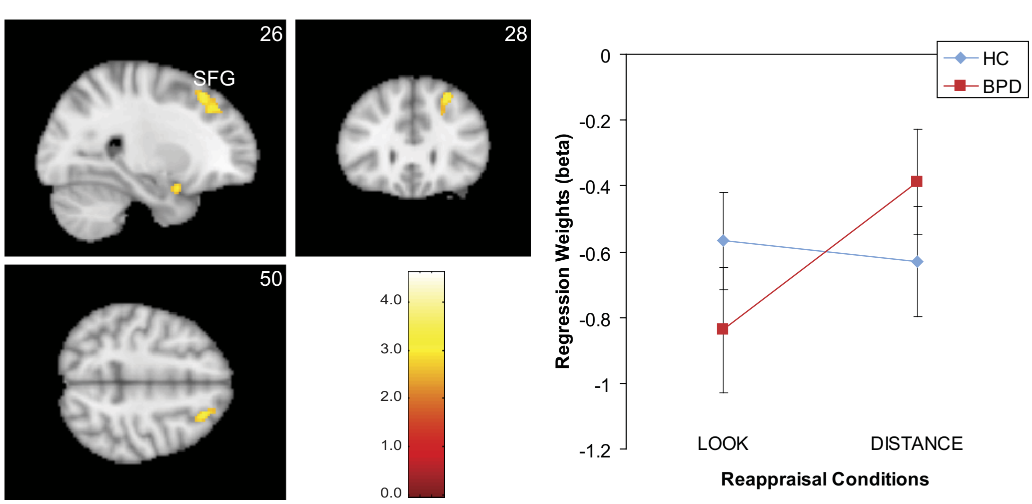

Figure 6. Coronal, sagittal, and horizontal sections illustrating greater activation in the superior frontal gyrus (SFG) of BPD patients compared with healthy control subjects when distancing and plot of regression weights for each group in right SFG. BOLD signals are displayed overlaid on the Montreal Neurological Institute SPM canonical anatomic template. The display threshold is $p <$ .01. The color bar indicates *t* values. BOLD, blood oxygenation level-dependent; BPD, borderline personality disorder; HC, healthy control; SPM, statistical parametric mapping.

Table 4. Activation Foci that Differed Between the Groups When Distancing Versus Looking at Negative IAPS Pictures

Region	BA	k	MNI Coordinates			*Z*
			x			
Healthy Control Subjects > Borderline Patients						
R middle occipital gyrus	19	107	40	−76	4	3.06
R middle occipital gyrus	19	266	30	−70	20	3.20
R fusiform gyrus	37	149	28	−54	−16	3.44
R inferior/superior parietal lobule	7	175	30	−52	44	3.01
L inferior parietal lobule	40	173	−40	−50	54	3.29
L anterior cingulate gyrus	32	128	−4	30	36	3.34
Borderline Patients > Healthy Control Subjects						
R superior temporal gyrus	41	113	42	−20	6	4.01
R middle/superior temporal gyrus	21/22	427	50	−18	14	3.64
R amygdala		89	30	6	−22	2.96
R superior frontal gyrus	8	307	26	28	50	3.14

Notes: k = cluster size in $2 \times 2 \times 2$ mm voxels. $p < .01$, minimum = 85.
BA, Brodmann area; IAPS, International Affective Picture System; L, left; MNI, Montreal Neurological Institute; R, right.

tive baselines. A possible explanation for these paradoxical differences in the look condition is that at baseline, BPD patients had higher levels of amygdala activation than HC subjects and their activation decreased as they focused on the task of looking at pictures, while for the HC subjects, activation increased from a low baseline when they looked at the pictures. The decrease in activation in the HC subjects in the distancing condition is consistent with a downregulation of the amygdala when distancing. What remains unclear is what accounts for the increased amygdala activation in BPD patients during distancing.

The regions showing differential activation between BPD and HC subjects have been implicated in various control and affective functions relevant to BPD. Theories of cognitive control postulate the dACC and DLPFC work hand-in-hand to signal the need for control and to implement control processes, respectively (68–70). The IPS has been implicated in top-down attentional control (57–59) and the STS has been implicated in representing social cues of the intentions of others (52,71–75).

Our finding of differences in neural activation between borderline patients and healthy control subjects during reappraisal by distancing must be considered in the context of our finding of differences in activation in the passive viewing condition as well. Thus, we cannot rule out the possibility that the different activation patterns in the reappraisal condition arise from a more general difference in overall emotion processing and not from differences in the mechanism of reappraisal per se. Nevertheless, our findings allow us to reject the null hypothesis that in explicit emotion regulation BPD patients and HC subjects do not differ in neural activation. Moreover, with respect to the IPS and dACC, the BPD versus HC differences during reappraisal do not appear to be a consequence of differences in passive emotion processing, since activation (regression weights) in the look condition did not differ between the groups.

Limitations of the Present Study

Although this study is the first to our knowledge to examine the neural dynamics of cognitive reappraisal in borderline patients, it is important to acknowledge its limitations as well. As in other studies of cognitive reappraisal, we relied upon subjects' reports that they carried out the task as directed. The lack of a psychophysiological measure indexing the reappraisal task is a limitation of this study and future studies should make an effort to monitor reappraisal processes within the scanner. Self-reports of affective response may be influenced by demand. Redirection of eye gaze away from emotionally charged regions in the pictures could play a role in downregulation of the emotional response and is associated with differences in BOLD signal when reappraising versus looking (76). Eye gaze is regulated by both bottom-up and top-down control networks (77) and may be an intervening mechanism in reappraisal implemented differently in BPD patients and HC subjects. While the present study could not determine the extent to which eye gaze redirection was employed to downregulate emotion in each group, it demonstrates clear differences in the neural dynamics of distancing in BPD patients versus healthy volunteers. We cannot eliminate the possibility that contrary to our instructions some subjects closed their eyes or looked away from the pictures.

We cannot exclude the possibility that group differences could be explained by socioeconomic or cognitive differences. The BPD group was heterogeneous in terms of comorbidity and prior psychiatric history and further studies are called for to replicate these findings in more homogeneous samples. While group differences in depression as measured by the HAM-D were present, no correlations between HAM-D score and activation were detected.

Implications for Borderline Pathology and Directions for Future Research

The finding that borderline patients do not downregulate amygdala activity as healthy control subjects do and do not recruit the networks that healthy subjects employ in cognitive reappraisal by distancing suggests that BPD patients may be impaired in their ability to cognitively regulate their emotions, an impairment which may in turn contribute to the affective instability of borderline patients. To reduce task heterogeneity, the present study examined the single strategy of distancing, selected as one likely to distinguish BPD from HC subjects. Future studies should examine other commonly employed reappraisal strategies such as reinterpretation and response-focused strategies (12,14). Further studies are called for to replicate and to extend the findings of this study to other psychopathological groups, to help determine whether the results reported here are specific to borderline pathology.

This work was supported in part by grants from the National Institute of Mental Health (RO1 MH077813, Principal Investiga-

tor: HWK; MH076137, Principal Investigator: KNO) and from the National Center for Research Resources, National Institutes of Health for the Mount Sinai General Clinical Research Center (5MO1 RR00071).

The authors reported no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

1. Stiglmayr CE, Grathwol T, Linehan MM, Ihorst G, Fahrenberg J, Bohus M (2005): Aversive tension in patients with borderline personality disorder: A computer-based controlled field study. *Acta Psychiatr Scand* 111: 372–379.
2. Gunderson JG (2007): Disturbed relationships as a phenotype for borderline personality disorder. *Am J Psychiatry* 164:1637–1640.
3. Gunderson JG, Lyons-Ruth K (2008): BPD's interpersonal hypersensitivity phenotype: A gene-environment-developmental model. *J Pers Disord* 22:22–41.
4. Linehan M (1993): *Cognitive-Behavioral Treatment of Borderline Personality Disorder*. New York: Guilford Publications.
5. Stone M (1988): Toward a psychobiological theory of personality disorder. *J Trauma Dissociation* 1:2–15.
6. Koenigsberg HW, Harvey PD, Mitropoulou V, New AS, Goodman M, Silverman J, *et al.* (2001): Are the interpersonal and identity disturbances in the borderline personality disorder criteria linked to the traits of affective instability and impulsivity? *J Pers Disord* 15:358–370.
7. Rosenthal MZ, Gratz KL, Kosson DS, Cheavens JS, Lejuez CW, Lynch TR (2008): Borderline personality disorder and emotional responding: A review of the research literature. *Clin Psychol Rev* 28:75–91.
8. Phillips ML, Drevets WC, Rauch SL, Lane R (2003): Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry* 54:504–514.
9. Phillips ML, Drevets WC, Rauch SL, Lane R (2003): Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry* 54:515–528.
10. Ochsner KN (2008): The social-emotional processing stream: Five core constructs and their translational potential for schizophrenia and beyond. *Biol Psychiatry* 64:48–61.
11. Ochsner KN, Gross JJ (2008): Cognitive emotion regulation: Insights from social cognitive and affective neuroscience. *Curr Dir Psychol Sci* 17:153–158.
12. Gross JJ (2002): Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology* 39:281–291.
13. Gross JJ, John OP (2003): Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *J Pers Soc Psychol* 85:348–362.
14. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, *et al.* (2004): For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23:483–499.
15. Ochsner KN, Gross JJ (2005): The cognitive control of emotion. *Trends Cogn Sci* 9:242–249.
16. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD (2002): Rethinking feelings: An FMRI study of the cognitive regulation of emotion. *J Cogn Neurosci* 14:1215–1229.
17. Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME (2005): Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. *Biol Psychiatry* 57:210–219.
18. 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.
19. Kim SH, Hamann S (2007): Neural correlates of positive and negative emotion regulation. *J Cogn Neurosci* 19:776–798.
20. Beauregard M, Levesque J, Bourgouin P (2001): Neural correlates of conscious self-regulation of emotion. *J Neurosci* 21:RC165.
21. Levesque J, Eugene F, Joanette Y, Paquette V, Mensour B, Beaudoin G, *et al.* (2003): Neural circuitry underlying voluntary suppression of sadness. *Biol Psychiatry* 53:502–510.
22. Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, *et al.* (2003): Amygdala hyperreactivity in borderline personality disorder: Implications for emotional dysregulation. *Biol Psychiatry* 54: 1284–1293.
23. Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ (2007): Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: An event-related fMRI study. *Psychiatry Res* 155:231–243.
24. 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.
25. Koenigsberg H, Siever L, Lee H, Pizzarello S, New A, Goodman M, *et al.* (2009): Neural correlates of emotion processing in borderline personality disorder. *Psychiatry Res* 172:192–199.
26. Soloff PH, Meltzer CC, Becker C, Greer PJ, Kelly TM, Constantine D (2003): Impulsivity and prefrontal hypometabolism in borderline personality disorder. *Psychiatry Res* 123:153–163.
27. Soloff PH, Meltzer CC, Becker C, Greer PJ, Constantine D (2005): Gender differences in a fenfluramine-activated FDG PET study of borderline personality disorder. *Psychiatry Res* 138:183–195.
28. New AS, Buchsbaum MS, Hazlett EA, Goodman M, Koenigsberg HW, Lo J, *et al.* (2004): Fluoxetine increases relative metabolic rate in prefrontal cortex in impulsive aggression. *Psychopharmacology (Berl)* 176:451–458.
29. Silbersweig D, Clarkin JF, Goldstein M, Kernberg OF, Tuescher O, Levy KN, *et al.* (2007): Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. *Am J Psychiatry* 164:1832–1841.
30. New AS, Hazlett EA, Buchsbaum MS, Goodman M, Mitelman SA, Newmark R, *et al.* (2007): Amygdala-prefrontal disconnection in borderline personality disorder. *Neuropsychopharmacology* 32:1629–1640.
31. Tebartz van Elst L, Hesslinger B, Thiel T, Geiger E, Haegele K, Lemieux L, *et al.* (2003): Frontolimbic brain abnormalities in patients with borderline personality disorder: A volumetric magnetic resonance imaging study. *Biol Psychiatry* 54:163–171.
32. Hazlett EA, New AS, Newmark R, Haznedar MM, Lo JN, Speiser LJ, *et al.* (2005): Reduced anterior and posterior cingulate gray matter in borderline personality disorder. *Biol Psychiatry* 58:614–623.
33. Irle E, Lange C, Sachsse U (2005): Reduced size and abnormal asymmetry of parietal cortex in women with borderline personality disorder. *Biol Psychiatry* 57:173–182.
34. Rusch N, van Elst LT, Ludaescher P, Wilke M, Huppertz HJ, Thiel T, *et al.* (2003): A voxel-based morphometric MRI study in female patients with borderline personality disorder. *Neuroimage* 20:385–392.
35. Schmahl CG, Vermetten E, Elzinga BM, Douglas Bremner J (2003): Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Res* 122:193–198.
36. Olsson A, Ochsner KN (2008): The role of social cognition in emotion. *Trends Cogn Sci* 12:65–71.
37. Kalisch R, Wiech K, Critchley HD, Seymour B, O'Doherty JP, Oakley DA, *et al.* (2005): Anxiety reduction through detachment: Subjective, physiological, and neural effects. *J Cogn Neurosci* 17:874–883.
38. Kross E, Ayduk O (2008): Facilitating adaptive emotional analysis: Distinguishing distanced-analysis of depressive experiences from immersed-analysis and distraction. *Pers Soc Psychol Bull* 34:924–938.
39. Gunderson JG (1996): The borderline patient's intolerance of aloneness: Insecure attachments and therapist availability. *Am J Psychiatry* 153: 752–758.
40. First M, Spitzer R, Gibbon M (1996): *Structured Clinical Interview for DSM-IV Axis I Disorders*. New York: New York State Psychiatric Institute.
41. First M, Gibbon M, Spitzer R (1996): *Structured Clinical Interview for DSM-IV Personality Disorders (SCIP-II)*. Washington, DC: American Psychiatric Publishing.
42. 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.
43. Harvey PD, Greenberg BR, Serper MR (1989): The affective lability scales: Development, reliability, and validity. *J Clin Psychol* 45:786–793.
44. Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.
45. Spielberger C (1983): *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

46. Patton J, Stanford M, Barratt E (1995): Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol* 51:768–774.
47. Spielberger C (1991): *State-Trait Anger Expression Inventory: Professional Manual*. Odessa, FL: Psychological Assessment Resources.
48. Lang PJ, Bradley MM, Cuthbert BN (2001): *International Affective Pictures System (IAPS): Technical Manual and Affective Ratings*. Gainesville, FL: NIMH Center for the Study of Emotion and Attention.
49. van den Bos W, McClure SM, Harris LT, Fiske ST, Cohen JD (2007): Dissociating affective evaluation and social cognitive processes in the ventral medial prefrontal cortex. *Cogn Affect Behav Neurosci* 7:337–346.
50. Britton JC, Phan KL, Taylor SF, Welsh RC, Berridge KC, Liberzon I (2006): Neural correlates of social and nonsocial emotions: An fMRI study. *Neuroimage* 31:397–409.
51. Harris LT, McClure SM, van den Bos W, Cohen JD, Fiske ST (2007): Regions of the MPFC differentially tuned to social and nonsocial affective evaluation. *Cogn Affect Behav Neurosci* 7:309–316.
52. Lestou V, Pollick FE, Kourtzi Z (2008): Neural substrates for action understanding at different description levels in the human brain. *J Cogn Neurosci* 20:324–341.
53. Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998): Event-related fMRI: Characterizing differential responses. *Neuroimage* 7:30–40.
54. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, *et al.* (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15:273–289.
55. Friston KJ, Penny WD, Glaser DE (2005): Conjunction revisited. *Neuroimage* 25:661–667.
56. Weissman DH, Perkins AS, Woldorff MG (2008): Cognitive control in social situations: A role for the dorsolateral prefrontal cortex. *Neuroimage* 40:955–962.
57. Hopfinger JB, Buonocore MH, Mangun GR (2000): The neural mechanisms of top-down attentional control. *Nat Neurosci* 3:284–291.
58. Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL (2000): Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nat Neurosci* 3:292–297.
59. Pessoa L, Kastner S, Ungerleider LG (2002): Attentional control of the processing of neural and emotional stimuli. *Brain Res Cogn Brain Res* 15:31–45.
60. Schilbach L, Wohlschlaeger AM, Kraemer NC, Newen A, Shah NJ, Fink GR, *et al.* (2006): Being with virtual others: Neural correlates of social interaction. *Neuropsychologia* 44:718–730.
61. Binder JR, Frost JA, Hammeke TA, Bellgowan PS, Rao SM, Cox RW (1999): Conceptual processing during the conscious resting state. A functional MRI study. *J Cogn Neurosci* 11:80–95.
62. Kjaer TW, Nowak M, Lou HC (2002): Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. *Neuroimage* 17:1080–1086.
63. Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF (2002): Finding the self? An event-related fMRI study. *J Cogn Neurosci* 14:785–794.
64. Ochsner KN, Beer JS, Robertson ER, Cooper JC, Gabrieli JD, Kihsltrom JF, *et al.* (2005): The neural correlates of direct and reflected self-knowledge. *Neuroimage* 28:797–814.
65. Vogt BA (2005): Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci* 6:533–544.
66. Fossati P, Hevenor SJ, Graham SJ, Grady C, Keightley ML, Craik F, *et al.* (2003): In search of the emotional self: An fMRI study using positive and negative emotional words. *Am J Psychiatry* 160:1938–1945.
67. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN (2008): Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* 59:1037–1050.
68. Mohanty A, Engels AS, Herrington JD, Heller W, Ho MH, Banich MT, *et al.* (2007): Differential engagement of anterior cingulate cortex subdivisions for cognitive and emotional function. *Psychophysiology* 44:343–351.
69. Botvinick MM, Cohen JD, Carter CS (2004): Conflict monitoring and anterior cingulate cortex: An update. *Trends Cogn Sci* 8:539–546.
70. Kerns JG, Cohen JD, MacDonald AW 3rd, Cho RY, Stenger VA, Carter CS (2004): Anterior cingulate conflict monitoring and adjustments in control. *Science* 303:1023–1026.
71. Allison T, Puce A, McCarthy G (2000): Social perception from visual cues: Role of the STS region. *Trends Cogn Sci* 4:267–278.
72. Frith U, Frith CD (2003): Development and neurophysiology of mentalizing. *Philos Trans R Soc Lond B Biol Sci* 358:459–473.
73. Gallagher HL, Happe F, Brunswick N, Fletcher PC, Frith U, Frith CD (2000): Reading the mind in cartoons and stories: An fMRI study of "theory of mind" in verbal and nonverbal tasks. *Neuropsychologia* 38:11–21.
74. Kourtzi Z, Kanwisher N (2000): Activation in human MT/MST by static images with implied motion. *J Cogn Neurosci* 12:48–55.
75. Pelphrey KA, Viola RJ, McCarthy G (2004): When strangers pass: Processing of mutual and averted social gaze in the superior temporal sulcus. *Psychol Sci* 15:598–603.
76. van Reekum CM, Johnstone T, Urry HL, Thurow ME, Schaefer HS, Alexander AL, *et al.* (2007): Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect. *Neuroimage* 36:1041–1055.
77. McDowell JE, Dyckman KA, Austin BP, Clementz BA (2008): Neurophysiology and neuroanatomy of reflexive and volitional saccades: Evidence from studies of humans. *Brain Cogn* 68:255–270.