ARCHIVAL REPORT

Neuronal Correlates of Cognitive Reappraisal in Borderline Patients with Affective Instability

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Background: Borderline personality disorder has been characterized by enhanced emotional reactivity and deficient emotion regulation in behavioral and functional imaging studies. We aimed to validate patients' difficulties in the cognitive regulation of negative emotions and investigated if emotion regulation deficits are restricted to the decrease of negative emotions. A cognitive reappraisal paradigm was used and hence a regulation strategy that is typically applied in cognitive-behavioral therapy.

Methods: Fifteen unmedicated female borderline patients with affective instability and 15 healthy female control subjects underwent functional magnetic resonance imaging during a delayed reappraisal paradigm. Hemodynamic responses were measured in response to aversive pictures in an initial viewing phase and a subsequent reappraisal phase with three different conditions: decreasing, increasing, and maintaining the initial emotional reaction.

Results: Patients demonstrated enhanced activation of left amygdala and right insula during the initial viewing of aversive stimuli. During attempting to decrease the initial emotional reaction, patients showed attenuated activation of the left orbitofrontal cortex and increased activation of the bilateral insula. The attempt to increase negative emotions resulted in enhanced activity in amygdala and insula, whereas no group differences were found.

Conclusions: The results point to the role of two distinguishable processes of emotional difficulties in borderline personality disorder: enhanced emotional reactivity as well as deficits of voluntarily decreasing aversive emotions by means of cognitive reappraisal. The results suggest the neuronal substrate of deficits in explicit emotion regulation in the orbitofrontal cortex, which is in line with previous findings of a dysfunctional prefrontal network in borderline personality disorder.

Key Words: Borderline personality disorder, emotion, emotion regulation, fMRI, orbitofrontal cortex, reappraisal

Borderline personality disorder (BPD) is characterized by a pervasive pattern of emotional instability and impaired impulse control, resulting in unstable interpersonal relations. Affective instability is the most frequent and stable criterion of borderline patients (1–6), playing a pivotal role in treatment approaches (4) and understanding of self-injurious behavior (7).

Emotional responding has been conceptualized as a product of rapidly occurring initial emotional reactivity and cognitive processes of emotion regulation, including reappraisal (8). Cognitive reappraisal results in changes in self-reported emotional experience and modified physiological responses, e.g., startle amplitude and skin conductance (9,10). Functional magnetic resonance imaging (fMRI) studies demonstrated associations of cognitive reappraisal of aversive stimuli with activity in the dorsolateral prefrontal cortex, orbitofrontal, and anterior cingulate cortex (9,11,12). Critically, these studies showed that the activity of the amygdala and insula, a region broadly involved in emotion processing and the representation of visceral states with connections to orbitofrontal structures, can be altered according to the regulatory goal (9,11–13). Another study reported an association between attenuated functional coupling of prefrontal and limbic areas during emotion regulation and dysfunctional diurnal regulation of cortisol secretion, emphasizing the significance of emotion regulation for adapting to stress in everyday life (14). Research reporting alterations in the neural circuitry underlying the regulation of negative emotions in patients with major depressive disorder (e.g., [13]) highlights the potential significance of these alterations for the development of mental disorders characterized by deficient regulation of negative affect.

Previous work hypothesized particularly two parts of emotional difficulties—emotional reactivity and cognitive control—in borderline patients. For instance, studies based on two-dimensional models of adult social attachment (15) found elevated scores in borderline patients on attachment anxiety, which reflects extreme emotional reactivity, and attachment avoidance (16). Attachment avoidance in borderline patients was furthermore correlated with executive functioning and cognitive control (17). Congruently, two-dimensional models of temperament report high negative affectivity and low effortful control in borderline personality disorder (18), related to marked deficits in conflict resolution (19). In addition, borderline patients are highly vigilant for negative stimuli (20), especially if associated with negative schema-related cues (21), and show prolonged emotional responses (22). Borderline patients' performance during negative priming, directed forgetting, and a linguistic go/no-go task indicates attenuated inhibition of negative emotional stimuli (23,24), possibly a crucial part of emotion dysregulation, which could interfere with social-cognitive abilities (25).

So far, fMRI studies have highlighted enhanced amygdala activity in response to aversive scenes and facial expressions in borderline patients (26–28). Additionally, borderline patients show dysfunctional anterior insula activity in the context of cooperation and social norm violation (29) and enhanced insula activity in response to unresolved aversive life events (30). Attenuated activation in the

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Received Jun 12, 2010; revised Sep 27, 2010; accepted Oct 21, 2010.

0006-3223/$36.00
doi:10.1016/j.biopsych.2010.10.025

rostral cingulum (31) and orbitofrontal cortex (24) was found for tasks requiring implicit regulation of negative emotions (e.g., suppressing emotional content in a cognitive discrimination task), suggesting deficient prefrontal inhibitory control over the amygdala. A positron emission tomography study demonstrated reduced coupling of orbitofrontal and amygdala metabolism (32). In a recently published study, Koenigsberg *et al.* (33) were able to show that patients with borderline personality disorder had difficulties engaging prefrontal areas, namely the dorsolateral and ventrolateral prefrontal cortex, when employing psychological distancing to regulate negative emotions. These difficulties in emotion regulation possibly underlie the use of self-injurious behavior in the majority of patients with borderline personality disorder, as painful sensory stimulation was found to reduce neural activity in emotion processing areas (34) and to decrease negative emotional arousal (35).

Altogether, there is substantial evidence for functional changes in the neural networks underlying emotional reactivity and emotion regulation in borderline personality disorder. We conducted an fMRI study, allowing an explicit differentiation of the spontaneous reactivity to an emotional stimulus and modulation of this response by cognitive reappraisal—in the sense of reinterpretation (9,10). Borderline patients were expected to demonstrate enhanced activity of the amygdala and insula during the initial response. Additionally, we hypothesized that patients would show reduced activity in parts of the orbitofrontal and rostral anterior cingulate cortex during the attempt to downregulate emotional responses to negative stimuli, along with less efficient attenuation of limbic activity. Furthermore, the consequences of upregulating negative affect were explored to gain initial data, if borderline patients' deficits in emotion regulation are exclusively restricted to the decrease of negative affect.

Methods and Materials

Participants

The study included 16 women with borderline personality disorder recruited from a specialized psychotherapeutic inpatient treatment facility (with planned patient admission) and 16 healthy control subjects. To avoid gender influences in affective responding and emotion regulation, only women were investigated (36). Healthy control subjects had been free of psychotropic medication, patients for at least 2 weeks. All participants were right-handed, had an intelligence quotient above 80, and did not report any nonmagnetic resonance imaging (MRI)-compatible condition. We excluded one patient due to scanning artifacts and one control subject with amygdala activity more than three standard deviations from the mean to negative pictures in the initial phase, resulting in two groups of 15 subjects.

Borderline patients underwent diagnostic screening with the Structured Clinical Interview for DSM-IV and the International Personality Disorder Examination; regarding homogeneity and validity of the borderline group, only patients meeting the criteria of affective instability were included. All structured interviews were conducted by a trained and clinically experienced diagnostician (M.F.). Patients were excluded if they had lifetime comorbid diagnoses of primary organic, psychotic, or bipolar disorder or a current major depressive episode. Comorbid Axis I diagnoses (lifetime) were posttraumatic stress disorder (PTSD) ($n = 7$), alcohol abuse ($n = 2$), substance abuse ($n = 2$), panic disorder with agoraphobia ($n = 1$), and dysthymia ($n = 1$). Current comorbid Axis I diagnoses were obsessive-compulsive disorder ($n = 1$), agoraphobia without panic disorder ($n = 1$), bulimia nervosa ($n = 1$), dissociative disorder ($n = 1$), dysthymia ($n = 1$), alcohol abuse ($n = 1$), and substance abuse ($n = 1$).

Control subjects were recruited via advertisement and had no diagnosis of neurological or psychiatric disorder. Demographic and psychometric data are presented in Table 1.

This study was approved by the Institutional Review Board of the Medical Faculty of the University of Rostock and subjects provided written informed consent.

Experimental Design

We used an established reappraisal paradigm to distinguish processes of emotional reactivity and cognitive reappraisal (9,10), comprising a 3-second initial viewing phase, a 1-second instruction phase, and an 8-second regulation phase, with participants cognitively modulating the personal relevance of the pictured events (12).

The initial phase began with a picture appearing on the screen. Participants were requested to view and understand the content of the picture and let their emotional reaction occur. Adjacently, we presented a single-word instruction in the center of the screen and asked participants to MAINTAIN, INCREASE, or DECREASE their initial emotion. Subjects were asked to INCREASE their emotional response by imagining that they or a close relative were involved in the depicted situation and to DECREASE by imagining that the situation was not real or that they were a detached observer. MAINTAIN trials required the participants to view the pictures attentively without trying to alter the affective reaction. All participants were trained to ensure correct and confident use of the reappraisal strategies and completed a practice session. The experimenter corrected the participants, if there was any indication that the participant used different strategies. Subjects were further instructed to look directly at the picture and not to avert their gaze.

The stimulus set comprised 72 negative (e.g., scenes of threat and suffering; excluding pictures of sexual violence) and 24 neutral (e.g., urban and working scenes) pictures selected from the International Affective Picture System (IAPS) set (37) and supplemented by similar pictures, thereby making the complexity of the stimuli comparable between valence categories. Negative pictures were randomly assigned to the regulation conditions, while neutral pictures were exclusively presented with the instruction MAINTAIN. There were four runs. Each run contained six trials of each of the four conditions.

All participants provided postscan ratings of valence and arousal of the pictures on a scale from 1 to 9 and assessed their success in following the regulation instruction. On the day of diagnostic session, all but five control subjects completed questionnaires on childhood traumatization (Childhood Trauma Questionnaire [38]) and severity of borderline symptomatology (Borderline Symptom List [39]).

Magnetic Resonance Imaging

Imaging data were acquired using a 1.5 T scanner (Magnetom Avanto, Siemens, Erlangen, Germany) equipped with a standard head coil. Visual stimuli were presented via a pair of stereoscopic MRI compliant goggles (VisuaStim, Resonance Technology, Los Angeles, California). Functional images were obtained by a T2*-weighted echo-planar imaging sequence (repetition time = 2550, echo time = 40, flip angle = 90°, field of view = 192, matrix = 64 × 64). Each volume comprised 34 interleaved measured axial slices (thickness = 3 mm, gap = 1 mm). Data were recorded in four runs of 192 volumes (490 sec). Finally, a structural scan in sagittal plane was acquired, using a high-resolution T1-weighted sequence (magnetization-prepared rapid acquisition with gradient echo, repetition time = 1160, echo time = 4.17, flip angle = 15°, field of view = 256, matrix = 256 × 256) recording 160 slices (thickness = 1 mm, no gap).

Table 1. Descriptive Statistics for Demographic and Psychometric Variables, as Well as Valence and Arousal Ratings of the Presented Pictures Across Groups

	HC ($n = 15$)		BPD ($n = 15$)			
	M	SD	M	SD	*T*	*p*
Demographic Data						
Age	24.53	2.85	27.60	7.85	−1.42	.166
IQ	117.79	14.96	107.60	20.19	1.45	.158
Psychometric Data						
BSL	49.60	16.04	183.87	53.64	−9.10	< .001
CTQ	31.09	10.67	62.83	17.65	−5.16	< .001
Regulation Performance						
Decrease	6.09	1.51	5.67	1.80	1.09	.288
Increase	7.18	1.89	6.33	2.02	.63	.532
Ratings						
Valence						
Neutral	6.52	1.33	6.22	1.01		
Negative	3.06	.57	2.82	.59		
Maintain	3.05	.62	2.87	.60		
Decrease	3.14	.56	2.91	.60		
Increase	2.99	.59	2.67	.68		
Ratings						
Arousal						
Neutral	1.37	.38	1.60	.76		
Negative	5.78	1.37	5.69	1.61		
Maintain	5.62	1.43	5.69	1.53		
Decrease	5.58	1.63	5.66	1.56		
Increase	5.79	1.70	6.05	1.33		

BSL, Borderline Symptom List; BPD, borderline personality disorder; CTQ, Childhood Trauma Questionnaire; HC, healthy control subjects; IQ, intelligence quotient.

Image Analysis

The MRI data processing was conducted with the Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, United Kingdom). The functional images of each participant were slice-time corrected, realigned, and unwarped. Afterward, the functional scans were co-registered to the individual anatomical images, spatially normalized to Montreal Neurological Institute space, resampled with a voxel size of $2 \times 2 \times 2$ mm^3, and smoothed by a three-dimensional Gaussian kernel (full width at half maximum 8 mm).

A first-level analysis was computed at the single subject level. For each of the four (neutral-maintain, negative-decrease, negative-increase, negative-maintain) experimental conditions, two regressors were modeled using a convolution of the hemodynamic response function with boxcar functions of 3 seconds for the initial and 8 seconds for the regulation phase. All main effects, except for a regressor modeling the onset of the instruction on the screen, were entered into group analyses.

At the group level, we employed a random effects factorial design to account for intersubject variance and allow population-based inferences (40). Main effects of conditions are corrected for family-wise errors ($p < .05$). For group by condition interactions, only clusters >10 voxels meeting a threshold of at least $p < .001$ (uncorrected) for whole-brain analyses are reported. For the initial phase, we compared the effects of picture valence (negative and neutral), and for the regulation phase, we compared the regulation—decrease, increase—with the maintenance of the elicited negative emotion. This analysis procedure was also used for calculation of within-group contrasts (Supplement 1). Coordinates of significant activations are reported in Montreal Neurological Institute space. Further analyses were conducted to characterize the nature of whole-brain interactions and within the regions of interest (amygdala). Regions were defined by the Automated Anatomical Labeling software (41). The extraction and calculation of the percentage signal change was conducted with the RFXPlot toolbox (42). Correlation analyses were performed using the mean percent signal change of an anatomical region or functional derived sphere and the questionnaire scores.

Results

Ratings of Valence, Arousal, and Regulation Performance

Negative pictures were rated as less positive [$F(1,28) = 267.18$; $p < .001$] and more arousing [$F(1,28) = 253.90$; $p < .001$] than neutral pictures. Borderline patients rated pictures as neither more negative or arousing in general [valence: $F(1,28) = 1.02$; $p = .321$; arousal: $F(1,28) = .25$; $p = .622$] nor in the context of a certain picture category [valence: $F(1,28) = .01$; $p = .908$; arousal: $F(1,28) = .07$; $p = .792$].

Reappraisal modulated ratings of negative pictures in the total group [valence: $F(2,56) = 5.07$; $p = .009$; arousal: $F(1.52.42.50) = 4.30$; $p = .029$, Greenhouse-Geisser]. Again, ratings revealed neither general group differences [valence: $F(1,28) = 1.36$; $p = .253$; arousal: $F(1,28) = .03$; $p = .872$] nor interactions with a particular regulation condition [valence: $F(2,56) = .67$; $p = .517$; arousal: $F(1.52.42.50) = 1.10$; $p = .328$, Greenhouse-Geisser].

We also analyzed the within-subject variance of the ratings, previously proposed to reflect affective instability (33). In borderline patients, ratings of negative stimuli varied more strongly than neutral pictures [valence: $F(1,28) = 3.96$, $p = .056$, arousal: $F(1,28) = 4.53$, $p = .042$], and they showed, in general, greater variance in valence ratings than healthy control subjects [valence: $F(1,28) = 5.51$, $p = .026$; arousal: $F(1,28) = 2.10$, $p = .159$]. Borderline patients showed also greater variance in valence ratings across reappraisal conditions [valence: $F(1,28) = 12.63$, $p = .001$, arousal: $F(1,28) = 1.84$, $p = .186$].

Brain Activity in the Initial Viewing Phase

In the initial viewing phase, we found enhanced left amygdala activity to negative compared with neutral pictures for the whole group (Table 2). Furthermore, there was enhanced activation of clusters in the bilateral middle temporal and supramarginal gyrus, right inferior and superior parietal gyrus, as well as the left fusiform gyrus, right thalamus, right posterior cingulate gyrus, and thalamus. The right inferior temporal gyrus, right superior frontal gyrus—medial and inferior frontal gyrus—triangular were also stronger activated during the presentation of negative pictures.

Using a more sensitive approach, we also found enhanced activation in the right amygdala (22,−4, −12; $Z = 4.60$; $p < .001$[small volume corrected]).

Regarding group differences in the processing of emotional pictures (control subjects$^{\text{negative} > \text{neutral}} >$ patients$^{\text{negative} > \text{neutral}}$), we found significant clusters in the right insula, the bilateral temporal gyrus, and in right superior frontal gyrus—dorsolateral and bilateral medial cingulate gyrus. In addition, significant interactions of valence and group were found in the right caudate nucleus, right inferior frontal gyrus, bilateral parietal re-

Table 2. Significant Clusters of Neural Activation Associated with the Processing of Aversive Pictures During the Initial Viewing Phase

Region		BA	Coordinates x	y	z	Size	*Z*
Contrast: Negative > Neutral Pictures[a]							
Middle temporal gyrus	R	37	52	−64	−2	2710	> 8
Inferior temporal gyrus	R	—	42	−52	−14	LM	> 8
Inferior temporal gyrus	R	—	44	−44	−18	LM	> 8
Middle temporal gyrus	L	39	−52	−66	8	330	> 8
Fusiform gyrus	L	37	−44	−46	−20	330	> 8
Inferior parietal gyrus	R	7	28	−54	54	356	6.52
Superior parietal gyrus	R	5	38	−48	62	LM	5.53
Thalamus	R	—	10	−20	−12	28	6.09
Supramarginal gyrus	L	40	−62	−26	34	75	5.89
Supramarginal gyrus	R	2	66	−20	30	97	5.68
Postcentral gyrus	R	2	52	−20	32	LM	5.51
Cerebellum	R	—	16	−70	−26	41	5.60
Inferior parietal gyrus	L	40	−42	−42	52	42	5.50
Postcentral gyrus	R	—	30	−36	40	18	5.48
Posterior cingulate gyrus	R	31	−2	−48	28	33	5.46
Superior frontal gyrus, medial	R	9	6	56	30	73	5.44
Superior frontal gyrus, medial	R	9	8	56	38	LM	5.11
Superior occipital gyrus	R	19	26	−80	38	19	5.13
Inferior parietal gyrus	L	40	−42	−32	40	7	5.03
Inferior frontal gyrus, triangular	R	46	44	20	26	9	4.96
Amygdala	L	—	−22	−2	−14	6	4.94
Caudate nucleus	R	—	8	2	−2	5	4.92
Contrast: HC$^{\text{negative} > \text{neutral}} >$ BPD$^{\text{negative} > \text{neutral}}$ [b]							
Insula	R	—	38	−10	−8	195	4.44
Insula	R	13	44	−8	−2	LM	4.32
Caudate nucleus	R	—	22	−2	30	44	3.98
Inferior frontal gyrus, opercular	R	—	30	2	28	LM	3.52
Precentral gyrus	R	6	26	−16	68	54	3.96
Middle temporal gyrus	L	22	−50	−24	0	27	3.91
Cerebellum	R	—	4	−64	−40	27	3.79
Medial cingulate gyrus	R	24	2	0	30	21	3.70
Superior temporal gyrus	R	22	56	−14	−8	20	3.69
Middle temporal gyrus	L	22	−54	−42	6	47	3.63
Angular gyrus	L	—	−42	−58	34	73	3.62
Inferior parietal gyrus	L	—	−50	−52	36	LM	3.41
Middle temporal gyrus	R	20	48	−6	−26	17	3.55
Superior frontal gyrus, dorsolateral	R	8	24	16	50	20	3.54
Medial cingulate gyrus	L	24	−6	−20	44	22	3.51
Middle temporal gyrus	R	38	46	4	−26	14	3.49
Postcentral gyrus	L	5	−24	−42	66	10	3.46
Inferior parietal gyrus	R	40	36	−40	52	13	3.44
Superior temporal gyrus	R	40	58	−46	22	11	3.42
Middle temporal gyrus	L	39	−50	−56	22	11	3.40
Contrast: BPD$^{\text{negative} > \text{neutral}} >$ HC$^{\text{negative} > \text{neutral}}$ [b]							
No suprathreshold voxels							

BA, Brodmann area; BPD, borderline personality disorder; FWE, family-wise error; HC, healthy control subjects; L, left hemisphere; LM, Local maximum; R, right hemisphere.

[a] Cluster with $p < .05$ (FWE corrected) and extent threshold of at least five voxels.

[b] Cluster with $p < .001$ (uncorrected) and an extent threshold of at least 10.

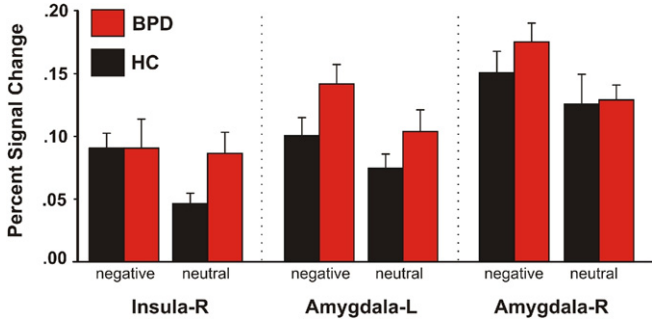

Figure 1. Effects of stimuli valence regarding neuronal activity of the amygdala and insula in the initial viewing phase. The mean percent signal change was calculated using anatomical regions of interest for the amygdala and a 3 mm sphere centered on the coordinate (38,−10,−8) derived from the whole-brain analysis. Borderline personality disorder patients showed enhanced activation for neutral pictures, as stated by an interaction of valence and group in the right insula [$F(1,28) = 5.42$, $p = .027$]. We observed further a trend for enhanced responding to neutral and negative pictures in the left amygdala within the borderline personality disorder group [$F(1,28) = 3.62$, $p = .067$]. The bars depict the percentage signal change + SEM. BPD, borderline personality disorder; HC, healthy control subjects; L, left; R, right.

gions, and the right cerebellum (for a more detailed presentation, see Table 2).

To further characterize the interaction of the right insula (Figure 1), we performed additional analyses of the percentage signal change. Insular activity was generally enhanced for negative stimuli [$F(1,28) = 8.03$, $p = .008$], and in accordance with the whole-brain analysis, we found an association between picture valence and group [$F(1,28) = 5.42$, $p = .027$], with single comparisons showing enhanced insula activation for neutral pictures in the patients group [$t(28) = -2.07$, $p = .047$].

Subsequently, the percentage signal change of the amygdala was calculated using anatomical regions (Figure 1). The two-way analysis of variance revealed enhanced amygdala activity to negative pictures [left amygdala: $F(1,28) = 9.98$, $p = .004$; right amygdala: $F(1,28) = 8.77$, $p = .006$] and a trend for stronger left amygdala activation in the patient group regardless of picture valence [left amygdala: $F(1,28) = 3.62$, $p = .067$; right amygdala: $F(1,28) = .42$, $p = .520$].

Modulation of Brain Activity During the Regulation Phase

Searching for areas activated during downregulation (DECREASE > MAINTAIN negative), whole-brain analysis of the complete group revealed enhanced activations in the bilateral orbitofrontal, left dorsolateral, and medial prefrontal cortex and a cluster comprising the supplementary motor area (Figure 2). Beyond that, we found significant clusters in the left precentral and middle frontal gyrus, as well as the left inferior frontal and supramarginal gyrus. The upregulation (INCREASE > MAINTAIN negative) was among others accompanied by enhanced activation in the left orbitofrontal and anterior cingulate cortex, the bilateral insula, and again a cluster comprising the supplementary motor area (for a more detailed presentation, see Table 3).

We conducted regions-of-interest analyses of the bilateral amygdala to show effects of reappraisal in the complete group. Increasing the initial response resulted in enhanced activity of the right amygdala [$t(29) = 2.08$, $p = .047$], whereas we found no activation differences in the bilateral amygdala regarding downregulation. Insular findings were clearer in this respect. As mentioned above, we found increased activation during upregulation in the bilateral insula and also decreased activation associated with the attempt to dampen the initial response.

To reveal brain areas that were recruited to a lesser extent in the patient group during the downregulation of emotions, we calculated the whole-brain contrast control subjects$^{\text{decrease} > \text{maintain}}$ > patients$^{\text{decrease} > \text{maintain}}$ (Table 4) and found significant clusters in the right pallidum, the left orbitofrontal cortex, and middle frontal gyrus, as well as the right superior temporal gyrus, left precuneus, and left middle temporal gyrus. Further analysis revealed that patients recruited the orbitofrontal cortex (Figure 3) to a lesser extent during downregulation compared with control subjects [$t(28) = 2.21$, $p = .035$].

The reverse contrast (patients$^{\text{decrease} > \text{maintain}}$ > control subjects$^{\text{decrease} > \text{maintain}}$) showed enhanced activation in the bilateral insula and precentral and medial cingulate gyrus. Clusters in the

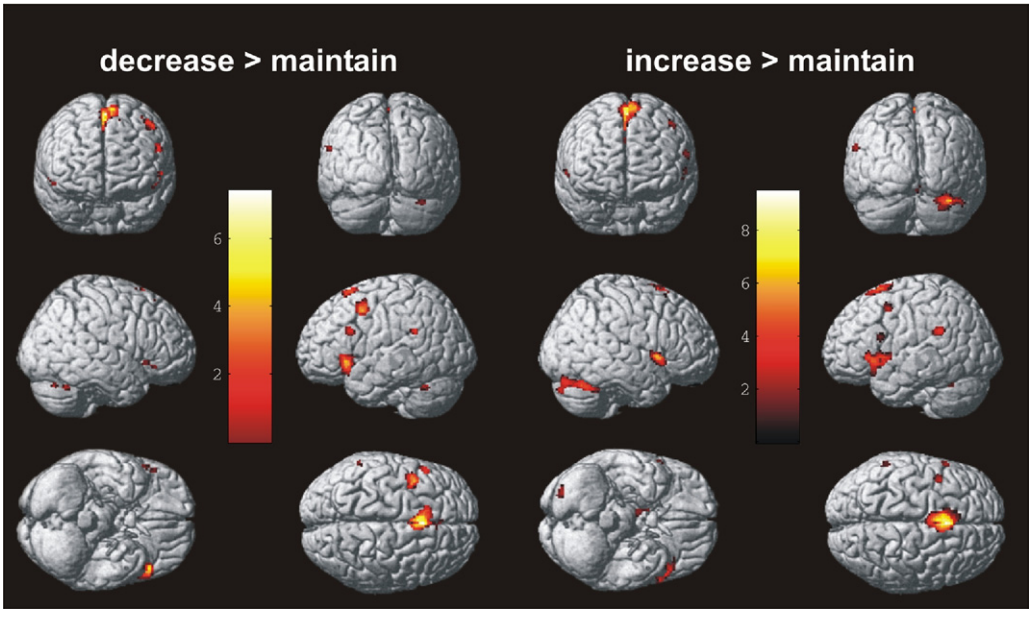

Figure 2. Whole group analyses. Brain areas associated with the DECREASE and INCREASE of emotional responses compared with MAINTAIN. Statistical parametric maps are plotted with a threshold of .05 (family-wise error corrected) and an extent cluster threshold of 10 voxels.

Table 3. Significant Clusters of Neural Activation Associated with the Regulation of Negative Emotions

Region		BA	Coordinates x	y	z	Size	*Z*
Contrast: Decrease > Maintain Emotions							
Inferior frontal gyrus, orbital	L	47	−52	20	−6	257	6.93
SMA	L	8	−2	14	56	577	6.73
SMA	L	6	−8	20	64	LM	6.23
SMA	L	32	−2	22	44	LM	5.65
Precentral gyrus	L	6	−44	8	48	194	6.55
Precentral gyrus	L	—	−34	8	42	LM	5.36
Middle frontal gyrus	L	6	−34	4	54	LM	5.10
Cerebellum	L	—	−34	−56	−30	48	6.13
Inferior frontal gyrus, triangular	L	9	−52	20	26	52	5.81
Supramarginal gyrus	L	33	−58	−46	26	32	5.45
Cerebellum	R	—	36	−56	−30	24	5.42
Cerebellum	R	—	36	−68	−28	22	5.37
Superior frontal gyrus, dorsolateral	L	32	−14	22	46	25	5.34
Inferior frontal g gyrus orbital	R	—	50	30	−10	11	5.20
Superior frontal gyrus, medial	L	32	−2	36	32	11	5.12
Inferior frontal gyrus, orbital	R	47	56	20	−4	21	5.11
Contrast: Maintain > Decrease Emotions							
No suprathreshold voxels							
Contrast: Increase > Maintain Emotions							
Inferior frontal gyrus, triangular	L	47	−52	16	−4	485	> 8
Insula	L	13	−40	6	2	LM	6.47
Inferior frontal gyrus, triangular	L	47	−38	26	0	LM	6.13
SMA		6	0	10	62	1384	7.71
Medial cingulate gyrus	R	32	2	16	40	LM	6.78
SMA	L	6	−6	22	66	LM	6.51
Supramarginal gyrus	L	40	−54	−44	26	99	6.62
Insula	R	13	46	14	−2	213	6.37
Rolandic operculum	R	22	56	12	0	LM	6.00
Cerebellum	R	—	34	−54	−30	530	6.31
Cerebellum	R	—	30	−76	−24	LM	6.28
Cerebellum	R	—	40	−62	−28	LM	6.24
Anterior cingulate gyrus		—	0	4	20	97	5.92
Hippocampus	R	—	10	−8	−12	50	5.73
Pallidum	R	—	14	2	−6	LM	5.18
Precentral gyrus	L	—	−44	8	48	44	5.73
Inferior frontal gyrus, opercular	L	44	−60	14	18	21	5.61
Thalamus	L	—	−4	−30	6	135	5.54
Cerebellum		—	0	−38	0	LM	5.39
Posterior cingulate gyrus	L	—	−10	−36	10	LM	5.32
No ROI		—	0	20	10	17	5.44
Hippocampus	R	—	30	−42	4	26	5.40
Cerebellum	L	—	−32	−56	−28	16	5.38
Contrast: Maintain > Increase Emotions							
Inferior temporal gyrus	R	21	62	−44	−14	44	5.49
Superior parietal gyrus	R	40	40	−48	56	63	5.46
Postcentral gyrus	R	2	44	−34	58	27	5.19

Cluster with $p < .05$ (FWE corrected) and extent threshold of at least 10 voxels.
BA, Brodmann area; FWE, family-wise error; L, left hemisphere; LM, local maximum; R, right hemisphere; ROI, region of interest; SMA, supplementary motor area.

insula were of further interest, as interactions may have been triggered by group differences related to the attempt to decrease the initial emotional response (Figure 3). Healthy control subjects demonstrated a decrease in activity of the bilateral insula [$t(14) = -3.04$, $p = .009$], whereas borderline patients showed no significant change in insula activity when attempting to decrease their emotions [$t(14) = 1.63$, $p = .125$]. Compared with healthy control subjects, borderline patients showed consequently enhanced activity in the bilateral insula during the decrease condition [$t(28) = -2.76$, $p = .010$].

Finally, we analyzed both groups regarding differences in the increase of initial affect (Table 4). The contrast control subjects$^{\text{increase > maintain}}$ > patients$^{\text{increase > maintain}}$ showed interactions in the right inferior frontal gyrus (opercular part), bilateral thalamus, right precuneus, and left medial cingulate gyrus. The reverse contrast, patients$^{\text{increase > maintain}}$ > control subjects$^{\text{increase > maintain}}$, showed interactions in the left inferior parietal gyrus, left inferior temporal gyrus, left middle occipital gyrus, and left postcentral gyrus. No group differences were found in the bilateral amygdala.

Table 4. Significant Group Effects Regarding the Neural Correlates Associated with the Regulation of Negative Emotions

Region		BA	Coordinates			Size	*Z*
			x	y	z		
Contrast: $HC^{decrease > maintain} > BPD^{decrease > maintain}$							
Pallidum	R	—	24	0	−2	33	4.14
Inferior frontal gyrus, orbital	L	47	−48	28	−6	43	3.82
Superior temporal gyrus	R	40	50	−54	22	37	3.68
Middle frontal gyrus	L	8	−36	16	52	25	3.59
Precuneus	L	7	−2	−74	38	19	3.48
Middle temporal gyrus	L	—	−50	−46	−2	15	3.42
Contrast: $BPD^{decrease > maintain} > HC^{decrease > maintain}$							
Insula	L	—	−28	−12	16	44	4.27
Medial cingulate gyrus	L	31	−18	−38	−40	28	4.09
Precentral gyrus	R	6	30	−16	68	24	4.01
Insula	R	13	34	−24	20	28	3.83
Cerebellum	L	—	−4	−78	−28	23	3.78
Precentral gyrus	L	6	−28	−22	72	18	3.73
Medial cingulate gyrus	R	32	16	10	42	17	3.52
Contrast: $HC^{increase > maintain} > BPD^{increase > maintain}$							
Inferior frontal gyrus, opercular	R	13	38	12	10	25	3.80
Precuneus	R	7	2	−76	46	42	3.69
Medial cingulate gyrus	L	24	−8	−10	32	10	3.65
Thalamus	R	—	18	−32	2	16	3.57
Thalamus	L	—	−10	−28	−2	11	3.47
Contrast: $BPD^{increase > maintain} > HC^{increase > maintain}$							
Inferior parietal gyrus	L	40	−50	−28	50	38	3.77
Postcentral gyrus	L	40	−52	−36	56	LM	3.58
Middle occipital gyrus	L	—	−28	−74	2	17	3.74
Inferior temporal gyrus	L	20	−44	−6	−30	12	3.47

Cluster with $p < .001$ and an extent threshold of 10.
BA, Brodmann area; BPD, borderline personality disorder; HC, healthy control subjects; L, left hemisphere; LM, local maximum; R, right hemisphere.

An additional analysis of variance with age and intelligence as covariates was calculated. The results replicated the reported findings and illustrated group differences to be independent from these two demographic variables. Self-reported borderline symptoms and childhood traumatization in borderline patients did not significantly correlate with neural activity in amygdala, insula, or orbitofrontal cortex.

Despite the rather small sample size, borderline patients with and without PTSD were compared to test for influences of this frequent comorbid disorder on a liberal significance level of $p < .1$. Borderline patients with PTSD showed an actual increase in insular activity related to the attempt to decrease their emotional response compared with borderline patients without PTSD [$F(1,13) = 6.640$, $p = .023$].

Discussion

We provide evidence for enhanced blood oxygenation level-dependent activity in emotion processing areas and difficulties in the cognitive reappraisal of negative emotions in female patients with borderline personality disorder, using a well-established approach to investigate the neural basis of emotion regulation (9,10). First, we found enhanced activity in the right insula to neutral pictures and a trend for enhanced reactivity of the left amygdala independent of picture category during the initial viewing phase. Second, patients showed decreased activity in the left orbitofrontal cortex and increased activation of the bilateral insula when attempting to downregulate their negative emotional responses. Interestingly, deficits in emotion regulation might be exclusively restricted to the decrease of negative affect, as we found no significant differences in regions associated with emotion processing or regulation during the attempt to increase elicited negative emotions.

Enhanced activation of insula and amygdala regions in the initial viewing phase nicely complements previous findings on emotional hyperactivity in borderline patients (26–28,35). Stronger activation of the amygdala and insula was found in response to negative and neutral social scenes, adding further support to the model of emotional hyperactivity in borderline patients. However, we found no group differences in valence or arousal ratings of the presented stimuli. Similar valence and arousal ratings of IAPS stimuli were reported previously ([27,33,35,43,44], but see [45]). This might be at least partially due to significantly greater intraindividual variability in ratings provided by borderline patients. Nonetheless, there might be a dissociation of neural responses and ratings of social stimuli in borderline patients. On the one hand, patients report high levels of alexithymia (46) and might have difficulties to accurately label and communicate their emotional reactions (4). On the other hand, fMRI studies with IAPS stimuli consistently reported greater activity in emotion processing areas in borderline patients (27,33,35,44) with our finding of higher amygdalar and insular activities in BPD patients in response to neutral social scenes being consistent with previous studies using either IAPS pictures (35) or facial stimuli (26). Therefore, our findings may suggest that hyperreactivity is not only related to negative stimuli but also holds for neutral pictures—probably due to the primarily social contents of the selected pictures. Enhanced limbic activity to neutral stimuli raises the issue of the role of anticipation and emotional reactivity in borderline patients. Anticipating negative events leads to enhanced activation of emotion processing areas, as was recently demonstrated in patients with unipolar depression (47). As we pre-

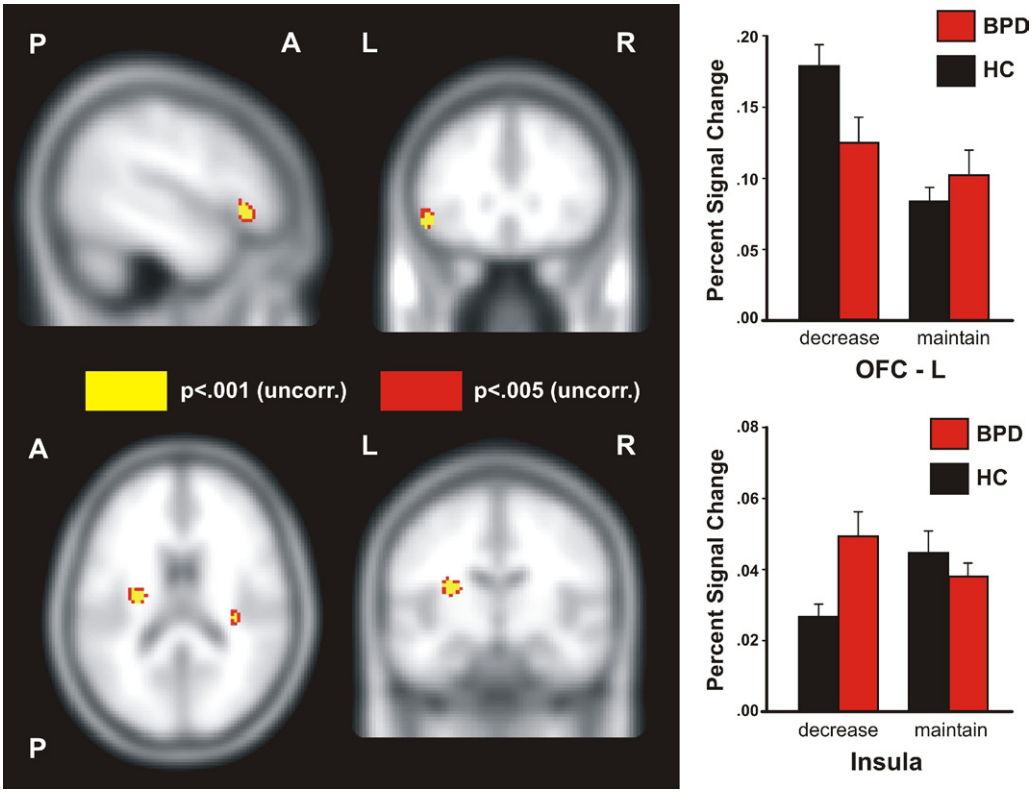

Figure 3. The left orbitofrontal cortex (−48,28,−6) demonstrated enhanced activity during the decrease of the initial emotional response for the healthy control compared with the borderline personality disorder group [$t(28) = 2.21$, $p = .035$], accompanied by dampened activation of the bilateral insula in the healthy control group [$t(14) = -3.04$, $p = .009$] but not for borderline personality disorder patients [$t(14) = 1.63$, $p = 125$]. The bars depict the mean percent signal change of a 3 mm sphere + SEM. A, anterior; BPD, borderline personality disorder; HC, healthy control subjects; L, left; OFC, orbitofrontal cortex; P, posterior; R, right.

sented mainly negative pictures, our design might have led BPD patients to more strongly expect the appearance of negative pictures, resulting in enhanced activation of the insula and amygdala to neutral stimuli. Stronger anticipation of negative events fits with typical cognitions in borderline patients in terms of seeing the world and others as dangerous (48) and with research demonstrating a negativity bias in the perception of facial emotions and the evaluation of others (25,49).

Analysis of the regulatory phase in the total sample replicated previous findings implicating orbitofrontal, dorsolateral, and medial prefrontal structures and the anterior cingulate cortex in the cognitive reappraisal of negative emotions (9,11–14). Neural activity of the insula was modulated in accordance with the regulatory goal. Amygdala activity differed significantly when participants were asked to increase their emotional state. Regarding the borderline group, our study presents first evidence for difficulties in voluntary effortful downregulation of negative emotions, as demonstrated by reduced activations of the left orbitofrontal cortex and enhanced bilateral insula activity. So far, studies in borderline patients investigating emotions focused on limbic structures, although insular structures are consistently implicated in emotion processing (for discussion, see [50]) and were shown to exhibit functional alterations in borderline patients (29,30,35). Future studies should combine fMRI with autonomic monitoring during emotional processing to shed light on states of bodily experience and highly aversive experienced tension often reported by borderline patients (51). It might be speculated that prolonged emotional arousal, a characteristic of borderline patients (22), reflects a failure to decrease insular activity as effectively as healthy volunteers.

Several fMRI studies in BPD provided indications for deficits in implicit emotion regulation in the context of negative emotions, reporting functional changes in the orbitofrontal and anterior cingulate cortex (24,28,31). A recent study by Silbersweig *et al.* (24) found decreased activity in orbitofrontal and anterior cingulate cortex in borderline patients when performing an emotional go/no-go task. Successful reappraisal of negative emotions was shown to be mediated by a distributed frontal cortical network, including the orbitofrontal cortex (52), thought to play a particular role in altering and updating the context-sensitive motivational relevance of stimuli (12,53). Its deficient functioning during explicit and implicit processes of emotion regulation may enhance our understanding of the underlying nature of affect dysregulation in borderline personality disorder, at least in female subjects.

Although all patients fulfilled the criterion of affective instability, there was a considerable range in the self-reported ability to regulate emotions in patients and also healthy control subjects. Across the whole sample, self-reported difficulties in emotion regulation were correlated with activity in the orbitofrontal cortex ($R = -.43$, $p = .010$) and the insula ($R = .61$, $p = .001$) during cognitive reappraisal (Figure 4).

Although these results need further investigation, they might suggest a dimensional approach to provide important information in addition to recent categorical approaches. Furthermore, it might be assumed that this range might reflect varying experience in psychotherapy within the patient group, affecting the ability and capacity to regulate emotions, as learning of cognitive emotion regulation skills is an important module of current treatment approaches. The presented results, though correlational, might pro-

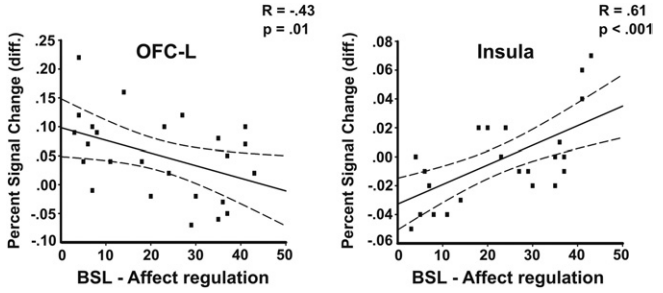

Figure 4. Correlation between self-reported deficits in emotion regulation (as measured by the subscale affect regulation of the Borderline Symptom List) and the differential percent signal change (DECREASE − MAINTAIN) in the left orbitofrontal cortex and the bilateral insula (note that two subjects overlap). BSL, Borderline Symptom List; diff., differential; L, left; OFC, orbitofrontal cortex.

vide a promising start to assess the neuronal effects of specific treatment modules and their influence on emotion regulation abilities, especially considering reports of functional changes during dialectic-behavioral therapy (54).

Most importantly, future research needs to more thoroughly address the specificity of functional findings in borderline patients by adding a psychopathological control group. This is of particular interest in emotion regulation, as deficits in this domain are postulated for a number of clinical disorders (55). For example, compared with control subjects, the functional connectivity between the ventrolateral and ventromedial prefrontal cortex and the amygdala is diminished in patients with major depressions who attempt to regulate their emotions (13). In addition, future studies should control for possible differences in cognitive effort across reappraisal conditions and between groups (56).

To summarize, the results replicate findings of abnormal emotional processing in borderline personality disorder with enhanced amygdala and insula activity to neutral and negative pictures. Critically, we provide evidence for difficulties in the cognitive reappraisal of aversive stimuli in female borderline patients, which are associated with attenuated orbitofrontal activity along with enhanced bilateral insula activity.

The preparation of the manuscript was supported by the German Research Foundation (DFG He 2660/7-1). *Dr. Shulze is currently affiliated with the Department of Educational Sciences and Psychology, Freie Universität Berlin, Germany; and the Department of Psychiatry, Charité Campus Benjamin Franklin, Germany.*

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

Supplementary material cited in this article is available online.

1. Linehan MM (1995): *Understanding Borderline Personality Disorder*. New York: Guilford Publications.
2. Trull TJ, Solhan MB, Tragesser SL, Jahng S, Wood PK, Piasecki TM, Watson D (2008): Affective instability: Measuring a core feature of borderline personality disorder with ecological momentary assessment. *J Abnorm Psychol* 117:647–661.
3. McGlashan TH, Grilo CM, Sanislow CA, Ralevski E, Morey LC, Gunderson JG, *et al.* (2005): Two-year prevalence and stability of individual DSM-IV criteria for schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders: Toward a hybrid model of axis II disorders. *Am J Psychiatry* 162:883–889.
4. Linehan MM (1993): *Cognitive-Behavioral Treatment for Borderline Personality Disorder*. New York: Guilford Publications.
5. Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M (2004): Borderline personality disorder. *Lancet* 364:453–461.
6. Glenn CR, Klonsky ED (2009): Emotion dysregulation as a core feature of borderline personality disorder. *J Pers Disord* 23:20–28.
7. Niedtfeld I, Schmahl C (2009): Emotion regulation and pain in borderline personality disorder. *Curr Psychiatry Rev* 5:48–54.
8. Gross JJ (2002): Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology* 39:281–291.
9. Eippert F, Veit R, Weiskopf N, Erb M, Birbaumer N, Anders S (2007): Regulation of emotional responses elicited by threat-related stimuli. *Hum Brain Mapp* 28:409–423.
10. Jackson DC, Malmstadt JR, Larson CL, Davidson RJ (2000): Suppression and enhancement of emotional responses to unpleasant pictures. *Psychophysiology* 37:515–522.
11. 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.
12. 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.
13. Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ (2007): Failure to regulate: Counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J Neurosci* 27:8877–8884.
14. 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.
15. Brennan KA, Shaver PR (1998): Attachment styles and personality disorders: Their connections to each other and to parental divorce, parental death, and perceptions of parental caregiving. *J Pers* 66:835–878.
16. Minzenberg MJ, Poole JH, Vinogradov S (2006): Adult social attachment disturbance is related to childhood maltreatment and current symptoms in borderline personality disorder. *J Nerv Ment Dis* 194:341–348.
17. Minzenberg MJ, Poole JH, Vinogradov S (2008): A neurocognitive model of borderline personality disorder: Effects of childhood sexual abuse and relationship to adult social attachment disturbance. *Dev Psychopathol* 20:341–368.
18. Posner MI, Rothbart MK, Vizueta N, Thomas KM, Levy KN, Fossella J, *et al.* (2003): An approach to the psychobiology of personality disorders. *Dev Psychopathol* 15:1093–1106.
19. Posner MI, Rothbart MK, Vizueta N, Levy KN, Evans DE, Thomas KM, Clarkin JF (2002): Attentional mechanisms of borderline personality disorder. *Proc Natl Acad Sci U S A* 99:16366–16370.
20. Herpertz SC, Gretzer A, Steinmeyer EM, Muehlbauer V, Schuerkens A, Sass H (1997): Affective instability and impulsivity in personality disorder. Results of an experimental study. *J Affect Disord* 44:31–37.
21. Sieswerda S, Arntz A, Mertens I, Vertommen S (2007): Hypervigilance in patients with borderline personality disorder: Specificity, automaticity, and predictors. *Behav Res Ther* 45:1011–1024.
22. 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.
23. Domes G, Winter B, Schnell K, Vohs K, Fast K, Herpertz SC (2006): The influence of emotions on inhibitory functioning in borderline personality disorder. *Psychol Med* 36:1163–1172.
24. 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.
25. Domes G, Schulze L, Herpertz SC (2009): Emotion recognition in borderline personality disorder—a review of the literature. *J Pers Disord* 23:6–19.
26. 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.
27. 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.

28. 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.
29. King-Casas B, Sharp C, Lomax-Bream L, Lohrenz T, Fonagy P, Montague PR (2008): The rupture and repair of cooperation in borderline personality disorder. *Science* 321:806–810.
30. Driessen M, Wingenfeld K, Rullkoetter N, Mensebach C, Woermann FG, Mertens M, Beblo T (2009): One-year functional magnetic resonance imaging follow-up study of neural activation during the recall of unresolved negative life events in borderline personality disorder. *Psychol Med* 39:507–516.
31. Wingenfeld K, Rullkoetter N, Mensebach C, Beblo T, Mertens M, Kreisel S, *et al.* (2009): Neural correlates of the individual emotional Stroop in borderline personality disorder. *Psychoneuroendocrinology* 34:571–586.
32. 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.
33. 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.
34. Schmahl C, Bohus M, Esposito F, Treede RD, Di Salle F, Greffrath W, *et al.* (2006): Neural correlates of antinociception in borderline personality disorder. *Arch Gen Psychiatry* 63:659–667.
35. Niedtfeld I, Schulze L, Kirsch P, Herpertz SC, Bohus M, Schmahl C (2010): Affect regulation and pain in borderline personality disorder: A possible link to the understanding of self-injury. *Biol Psychiatry* 68:383–391.
36. Domes G, Schulze L, Bottger M, Grossmann A, Hauenstein K, Wirtz PH, *et al.* (2010): The neural correlates of sex differences in emotional reactivity and emotion regulation. *Hum Brain Mapp* 31:758–769.
37. Lang PJ, Bradley MM, Cuthbert BN (1999): *International Affective Picture System (IAPS): Instruction Manual and Affective Ratings*. Gainesville, FL: Center for Research in Psychophysiology, University of Florida.
38. Bernstein DP, Fink L (1998): *Childhood Trauma Questionnaire: A Retrospective Self-Report Manual*. San Antonio, TX: Psychological Corporation.
39. Bohus M, Limberger MF, Frank U, Chapman AL, Kuhler T, Stieglitz RD (2007): Psychometric properties of the borderline symptom list (BSL). *Psychopathology* 40:126–132.
40. Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996): A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* 4:58–73.
41. 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.
42. Glascher J (2009): Visualization of group inference data in functional neuroimaging. *Neuroinformatics* 7:73–82.
43. Herpertz SC, Kunert HJ, Schwenger UB, Sass H (1999): Affective responsiveness in borderline personality disorder: A psychophysiological approach. *Am J Psychiatry* 156:1550–1556.
44. Koenigsberg HW, Siever LJ, Lee H, Pizzarello S, New AS, Goodman M, *et al.* (2009): Neural correlates of emotion processing in borderline personality disorder. *Psychiatry Res* 172:192–199.
45. Marissen MA, Meuleman L, Franken IH (2010): Altered emotional information processing in borderline personality disorder: An electrophysiological study. *Psychiatry Res* 181:226–232.
46. Guttman H, Laporte L (2002): Alexithymia, empathy, and psychological symptoms in a family context. *Compr Psychiatry* 43:448–455.
47. Abler B, Erk S, Herwig U, Walter H (2007): Anticipation of aversive stimuli activates extended amygdala in unipolar depression. *J Psychiatr Res* 41:511–522.
48. Pretzer J (1990): Borderline personality disorder. In: Beck TA, Freemann A, editors. *Cognitive Therapy of Personality Disorders*. New York: Guilford Publications.
49. Arntz A, Veen G (2001): Evaluations of others by borderline patients. *J Nerv Ment Dis* 189:513–521.
50. Phan KL, Wager TD, Taylor SF, Liberzon I (2004): Functional neuroimaging studies of human emotions. *CNS Spectr* 9:258–266.
51. Critchley HD (2009): Psychophysiology of neural, cognitive and affective integration: fMRI and autonomic indicants. *Int J Psychophysiol* 73:88–94.
52. Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan KL (2007): Amygdala-frontal connectivity during emotion regulation. *Soc Cogn Affect Neurosci* 2:303–312.
53. Rolls ET (2000): The orbitofrontal cortex and reward. *Cereb Cortex* 10: 284–294.
54. Schnell K, Herpertz SC (2007): Effects of dialectic-behavioral-therapy on the neural correlates of affective hyperarousal in borderline personality disorder. *J Psychiatr Res* 41:837–847.
55. Gross JJ, Levenson RW (1997): Hiding feelings: The acute effects of inhibiting negative and positive emotion. *J Abnorm Psychol* 106:95–103.
56. 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.