

Neural Correlates of Antinociception in Borderline Personality Disorder

Christian Schmahl, MD; Martin Bohus, MD; Fabrizio Esposito, PhD; Rolf-Detlef Treede, MD; Francesco Di Salle, MD; Wolfgang Greffrath, MD; Petra Ludaescher, MS; Anja Jochims, MS; Klaus Lieb, MD; Klaus Scheffler, PhD; Juergen Hennig, PhD; Erich Seifritz, MD

Context: A characteristic feature of borderline personality disorder (BPD) is self-injurious behavior in conjunction with stress-induced reduction of pain perception. Reduced pain sensitivity has been experimentally confirmed in patients with BPD, but the neural correlates of antinociceptive mechanisms in BPD are unknown. We predicted that heat stimuli in patients with BPD would activate brain areas concerned with cognitive and emotional evaluation of pain.

Objective: To assess the psychophysical properties and neural correlates of altered pain processing in patients with BPD.

Design: Case-control study.

Setting: A university hospital.

Participants: Twelve women with BPD and self-injurious behavior and 12 age-matched control subjects.

Interventions: Psychophysical assessment and blood oxygen level–dependent functional magnetic resonance imaging during heat stimulation with fixed-temperature heat

stimuli and individual-temperature stimuli adjusted for equal subjective pain in all the participants.

Main Outcome Measure: Blood oxygen level–dependent functional magnetic resonance imaging signal changes during heat pain stimulation.

Results: Patients with BPD had higher pain thresholds and smaller overall volumes of activity than controls in response to identical heat stimuli. When the stimulus temperature was individually adjusted for equal subjective pain level, overall volumes of activity were similar, although regional patterns differed significantly. Patient response was greater in the dorsolateral prefrontal cortex and smaller in the posterior parietal cortex. Pain also produced neural deactivation in the perigenual anterior cingulate gyrus and the amygdala in patients with BPD.

Conclusion: The interaction between increased pain-induced response in the dorsolateral prefrontal cortex and deactivation in the anterior cingulate and the amygdala is associated with an antinociceptive mechanism in patients with BPD.

Arch Gen Psychiatry. 2006;63:659-667

BORDERLINE PERSONALITY DISORDER (BPD) is characterized by affective and cognitive dysregulation and a high prevalence of traumatic stress.¹ Patients with BPD frequently experience stress-induced aversive states of reduced pain perception and dissociation, which are often relieved by self-injurious behavior.¹ Experimental studies²⁻⁴ confirm reduced pain sensitivity in patients with BPD under nonstress and stress conditions. In general, reduced pain sensitivity under conditions of high stress can be central for adaptation and survival.^{5,6} In patients with BPD, however, this mechanism may become part of the disorder.

Pain perception has been found to consist of 2 central components. First, a sensory-discriminative component is nec-

essary for stimulus localization, intensity, and quality discrimination. Second, an affective-motivational component is responsible for negative hedonic evaluation of pain sensations and for emotional and behavioral reactions related to pain perception.⁷ Two anatomically distinct pathways can be distinguished according to their projections through thalamic nuclei⁸: (1) a sensory-discriminative “lateral” pathway projecting from the lateral thalamic nuclei to the primary and secondary somatosensory cortices and (2) an affective-motivational “medial” pathway projecting from the medial thalamic nuclei to the insula and cingulate cortex. In healthy individuals, painful heat stimuli can activate lateral and medial pathways, and several neuroimaging investigations⁹⁻¹² have demonstrated an

Author Affiliations are listed at the end of this article.

Table 1. Demographic and Psychometric Data

	Patients With BPD (n = 12)	Controls (n = 12)
Age, mean ± SD, y	28.67 ± 5.88	27.67 ± 6.83*
BDI score, mean ± SD	23.06 ± 10.04	0.27 ± 0.65†
DSS score, mean ± SD	3.27 ± 2.76	1.44 ± 1.74*
Axis I comorbidity (current [lifetime] No.)	Major depressive disorder (1 [11]) Dysthymia (2 [2]) Panic disorder without agoraphobia (3 [3]) Panic disorder with agoraphobia (1 [2]) Agoraphobia without panic disorder (1 [1]) Posttraumatic stress disorder (5 [8]) Social phobia (3 [6]) Body dysmorphic disorder (1 [1]) Anorexia nervosa (1 [4]) Bulimia nervosa (0 [5]) Sedative dependence (0 [1]) Opioid dependence (0 [1]) Polydrug dependence (0 [1]) Obsessive-compulsive disorder (1 [2]) Delusional disorder (0 [1])	Social phobia (1 [1])
Axis II comorbidity (No.)	Schizoid PD (1) Paranoid PD (1) Obsessive-compulsive PD (3) Avoidant PD (4)	None

Abbreviations: BDI, Beck Depression Inventory; BPD, borderline personality disorder; DSS, Dissociative States Scale; PD, personality disorder.

*Not statistically significant.

† $P < .001$ using a 2-tailed t test.

important role of the anterior cingulate cortex (ACC) in affective pain components. Painful stimuli also engage areas in the dorsolateral prefrontal cortex (DLPFC),¹³ which is thought to be involved in pain control.

A previous study⁴ using laser-evoked pain provided evidence that reduced pain sensitivity in patients with BPD is not associated with sensory-discriminative or attentional factors. Thus, it can be assumed that disturbed affective pain components or disturbed pain control mechanisms underlie reduced pain perception in patients with BPD. However, the neurobiologic correlates of these antinociceptive mechanisms are unknown. Herein, we used functional magnetic resonance imaging (fMRI) and painful heat stimuli (applied to the right hand) to examine the patterns of brain activity in patients with BPD and in control subjects. To match the stimuli in terms of individual subjective pain sensitivity and physical temperature, we used fixed-temperature heat stimuli, which were the same for all the participants, and individual-temperature stimuli, which were adjusted for equal subjective pain in all the participants. We focused on the temporal profile of neural response to tonic pain stimuli because cognitive and emotional neural circuits seem to exhibit patterns of responding that are temporally dissociable in humans.¹⁴ This study investigated the psychophysical properties and neural correlates of pain processing in patients with BPD. We predicted that heat stimuli in patients with BPD would produce dissociable neural responses in brain areas concerned with cognitive (prefrontal regions) and emotional (ACC and amygdala) evaluation of pain.

METHODS

PARTICIPANTS

Twelve women with BPD and 12 healthy age-matched women were included. Axis I and II diagnoses were assessed by a trained psychologist (P. L. and A. J.) using the *Structured Clinical Interview for DSM-IV Axis I Disorders*¹⁵ and the *International Personality Disorder Examination*,¹⁶ respectively. All the patients reported self-injurious behavior (cutting, burning, etc), which included partial or complete absence of pain. Painfulness of the last self-injurious act was assessed by patients on a scale from 0 to 100 (0=no pain at all and 100=worst imaginable pain), with a mean±SD score of 21.75±26.12 (range, 0-70). Demographic and psychometric data are given in **Table 1**.

All the participants were free of major medical illness on the basis of history, physical examination, and laboratory testing and were not abusing alcohol or other substances within 6 months of the study. Participants also were free of psychotropic medications for at least 4 weeks before the beginning of the study. Exclusion criteria consisted of serious medical or neurologic illness, organic mental disorders or lifetime psychotic disorders, retained metal, a history of head trauma, loss of consciousness, cerebral infectious disease, and dyslexia. In addition, controls were excluded if they had a lifetime diagnosis of BPD as assessed by the *International Personality Disorder Examination* or a current axis I diagnosis as assessed by the *Structured Clinical Interview for DSM-IV Axis I Disorders*. (One control participant fulfilled the criteria for social phobia but did not differ in any other psychometric characteristics from the remaining controls and thus was not excluded from further analysis.) After receiving a thorough explanation of the study, participants provided written informed consent for participa-

tion. The study was approved by the ethics committee of the University of Freiburg Medical School.

PSYCHOPHYSICAL EXPERIMENT

Heat stimuli were delivered to the back of the right hand using a thermode (3 × 3 cm) controlled by a quantitative sensory tester (TSA-II; Medoc Advanced Medical Systems, Ramat Yishai, Israel). This device is built for use in the MRI environment using nonmagnetic materials.

Immediately before the fMRI sessions, sensitivity to tonic heat stimuli was tested in each participant outside the MRI room. The heat stimuli consisted of temperatures of 40°C to 48°C (rising and falling rates: 2°C per second), oscillating with an amplitude of 2°C to avoid adaptation. Stimuli were applied in blocks of 30 seconds, alternating with 60-second blocks of neutral temperature (35°C; baseline condition). Immediately after the blocks, participants were instructed to rate their average level of pain across the 30 seconds using a numeric rating scale (NRS) ranging from 0 (no pain at all) to 100 (worst imaginable pain).

Five different stimulus temperatures (40°C, 42°C, 44°C, 46°C, and 48°C) were applied repeatedly in increasing and decreasing order. Thus, the full protocol consisted of 20 heat stimuli (5 temperatures and 4 repetitions). In some cases, the full protocol was not completed because the participant either abandoned a trial or had an NRS rating of 80 or higher for a previous stimulus. Pain intensity values were used to calculate the temperature matching a subjective NRS pain intensity rating of 40, individually, using regression analysis. Psychometric functions were constructed by fitting the cumulative frequency of painful ratings (ie, NRS rating >0) at the 5 temperatures tested using the Boltzman equation. The pain threshold was defined as the center of the sigmoidal function corresponding to the stimulus temperature that produced painful sensations in 50% of the trials. For linear regression analysis, ratings at missing temperatures were approximated up to a maximum rating of 100 using individual regression equations. When a participant abandoned a trial owing to intolerable pain, this and all the following stimuli at the same temperature were set to 100. Because 40°C was below the pain threshold in BPD, ratings for this heat level were not included in regression analysis to avoid a floor effect.

FUNCTIONAL IMAGING

The first 7 matched pairs of patients and controls were measured using a 1.5-T scanner equipped with a Sonata gradient system and a circularly polarized head coil, and the second set of 5 matched pairs of patients and controls were measured using a 1.5-T scanner equipped with a Vision gradient system and a circularly polarized head coil (Siemens Medical Solution, Erlangen, Germany). For whole-brain structural volumes, we used a T1-weighted, 3-dimensional, magnetization-prepared, rapid-acquisition, gradient echo sequence with a voxel size of 1 mm³ in all the participants. The blood oxygen level-dependent (BOLD) signal was acquired using gradient-recalled echoplanar imaging (identical parameters for both scanner systems: number of contiguous transversal sections, 25; position, covering all but the apical 20 mm of the brain; section thickness, 5 mm; echo time, 60 milliseconds; flip angle, 60°; matrix, 64 × 64 pixels; and volume repetition time, 4175 milliseconds). However, for technical reasons, the Sonata and Vision systems differed in their fields of view (180 × 180 and 220 × 220 mm²), volume acquisition times (2675 and 2600 milliseconds), and silent periods between images (1500 and 1575 milliseconds). The silent periods interspersed between volumes were used to ask the participants for pain intensity evaluation

after the first poststimulation volume and to obtain their rating after the subsequent volume. During acquisition of the functional data, 10 stimulation blocks lasting 30 seconds each were applied. Five blocks consisted of a fixed temperature (43°C), and 5 blocks consisted of the individual temperature adjusted to correspond with a subjective NRS pain intensity rating of 40. Again, temperatures oscillated with an amplitude of 2°C. Stimulation blocks were interrupted by 60-second intervals of neutral temperature (35°C). At the end of each 30-second block of heat stimulation, participants were asked to rate their average pain intensity for the block using the NRS. Mean scores were calculated for the 5 blocks with the fixed temperature and for the 5 blocks with the individually adjusted temperature.

IMAGE ANALYSIS

After discarding the first 4 frames, images were corrected for section acquisition time, warped into standard space, resampled into 3-mm isotropic voxels, corrected for head motion and slow frequency drifts, and smoothed using an 8-mm full-width at half-maximum gaussian kernel (BrainVoyager QX 1.4; Brain Innovation B.V., Maastricht, the Netherlands). The variance of all image time series was explained voxelwise according to a general linear model¹⁷ parametric estimate. Findings from the study by Becerra and colleagues¹⁴ suggest that the pain-induced brain response is segregated into 2 temporal components with different brain activity patterns. Accordingly, we based our analyses on early and late components of activity. We modeled the hemodynamic response function assuming 2 conceptually separate phases of BOLD response to pain: early and late. The 2 phases represent a stringent and reasonable model for the responses and were previously worked out in the context of pain stimulation by Becerra et al.¹⁴ After convolution with a double-gamma kernel, the early and late phases, together with their first-order derivatives, were used as regressors for the general linear model analyses.¹⁸ Cortical areas responding to the fixed and individual temperatures were identified by the temperature-specific main effects in the general linear model (heat vs baseline) of the time series in each image voxel.¹⁹ A correction for serial correlations was performed using a fit-refit procedure: after a first general linear model fit, a 1-lag autoregressive model was estimated for the residual term and eliminated before the second general linear model fit (refit). Voxel-level and region of interest-level intra-group and intergroup linear contrasts were computed using 1- and 2-tailed *t* tests, respectively.

The statistical maps resulting from voxel-level analyses were thresholded after a whole-brain correction for multiple comparisons at a voxel level ($P < .05$) using either the Bonferroni criterion or the gaussian field theory,^{20,21} with cluster-level significance at $P < .001$. To preserve the maximal specificity of the analysis and limit the number of fMRI findings, we used the Bonferroni correction criterion wherever possible, switching to the gaussian field theory only to enhance the visibility of clusters that otherwise would have been too tiny at the visual inspection. Three-dimensional statistical maps were overlaid on the Talairach-transformed Montreal Neurological Institute T1-weighted brain template (<http://www.bic.mni.mcgill.ca>).

Because of the small sample size and the relatively high variability of the population compared with the single-voxel signal-to-noise ratio of the measurements, interindividual variance was not accounted for in voxel-level group analysis, and all contrast maps were computed using a fixed-effects model.²² To extend our inferences and results from the studied sample to the clinical population and to rule out that the outcome could be driven by a few individuals in the samples, regionally averaged individual time series were analyzed in all clusters detected in the first-level intergroup voxel-based analysis and sub-

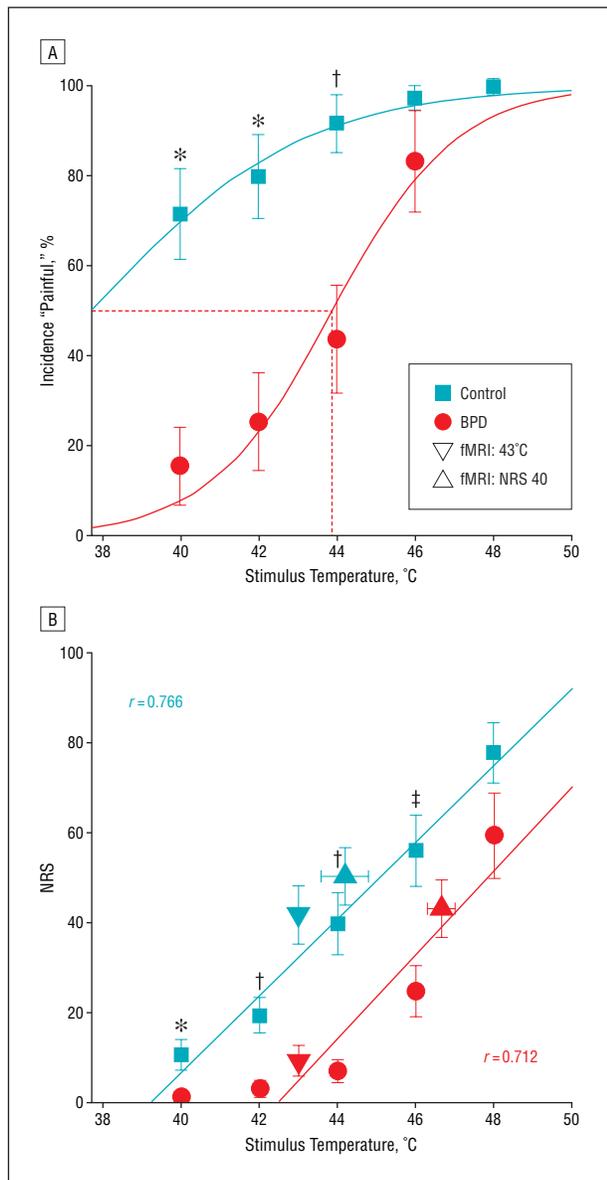


Figure 1. Heat pain in response to tonic thermal stimulation is significantly reduced in borderline personality disorder (BPD). A, Mean cumulative frequencies of painful sensations induced by different stimulus temperatures applied for 30 seconds in patients with BPD and controls display a rightward shift in patients with BPD. Dotted lines indicate the pain threshold; *, $P < .001$ using a 2-tailed t test; and †, $P < .01$ using a 2-tailed t test. B, Correlation between temperature and perceived pain intensity in patients and controls. Data are given as mean perceived pain intensities (0–100 points) from the psychophysical experiment. fMRI indicates numeric rating scale pain intensity ratings during functional magnetic resonance imaging at the 2 conditions; NRS 40, numeric rating scale pain intensity rating of 40; and error bars, SEM. *, $P < .05$ using a 2-tailed t test; †, $P < .001$ using a 2-tailed t test; and ‡, $P < .01$ using a 2-tailed t test.

mitted to a second-level region of interest–based analysis in which a random-effects model was used in the 2-sample t tests.

RESULTS

PSYCHOPHYSICS

Using an NRS with a range of 0 (no pain at all) to 100 (worst imaginable pain), we found that patients with BPD

had lower pain sensitivity to tonic heat than controls (mean \pm SEM pain threshold, center of Boltzman fit, $43.9^\circ\text{C} \pm 0.35^\circ\text{C}$ vs $37.7^\circ\text{C} \pm 0.60^\circ\text{C}$; $P < .001$) (**Figure 1A**). However, all the participants could discriminate between different pain intensities (range of individual Pearson $r = 0.637\text{--}0.991$; $P < .05$ for each). Linear regression analysis revealed a highly significant effect of temperature on pain ratings in both groups ($r = 0.71$, $n = 48$ [4 temperatures \times 12 patients] and $r = 0.77$, $n = 60$ [5 temperatures \times 12 controls]; $P < .001$) and a reduced offset of the stimulus-response function in patients (mean \pm SEM y-intercept at the mean stimulus temperature of 44°C , 14.1 ± 3.3 in patients vs 40.6 ± 2.7 in controls; $P < .001$, 2-tailed t test) (**Figure 1B**). Analyses also revealed no differences in mean \pm SEM slope (9.3 ± 1.4 per degree Celsius vs 8.6 ± 0.9 per degree Celsius; $P = .63$) or correlation coefficients ($r = 0.93 \pm 0.03$ vs $r = 0.91 \pm 0.02$; $P = .51$) between patients and controls. In conclusion, there was a downward shift of the stimulus-response function in patients by approximately 30 points on the NRS. A similar difference was found during fMRI with 43°C (mean \pm SEM NRS rating, 9.2 ± 3.4 in patients vs 41.8 ± 6.7 in controls; $P < .001$). The mean \pm SEM temperature causing perceived pain intensity of NRS 40 was found to be $46.7^\circ\text{C} \pm 0.4^\circ\text{C}$ for patients and $44.2^\circ\text{C} \pm 0.6^\circ\text{C}$ for controls ($P < .005$). During fMRI, mean \pm SEM pain intensity for the individually adjusted stimulus temperatures was 43.1 ± 6.4 for patients and 50.3 ± 6.4 for controls ($P = .44$) (**Figure 1B**), neither of which differed from an individual NRS rating of 40 ($P = .64$ and $.14$).

FUNCTIONAL IMAGING

Main Effects

The fMRI experiment revealed a consistent pattern of regional signal increases in both groups and both temperature conditions (**Figure 2** and **Table 2**). However, for the fixed-temperature condition of 43°C , z scores and volumes of significant signal increase were smaller in the BPD group as an objective correlate of the lower pain rating. For temperatures individually adjusted for equal subjective pain, overall volumes of activated regions were similar for both groups, consistent with the similar pain ratings.

In patients and controls, we found a consistent pattern of activation by heat stimuli (**Table 2**), with activity in the lateral pain system occurring for both temperature conditions. The primary somatosensory cortex was activated during the late phase in patients (individual temperature condition) and controls (fixed-temperature condition). In addition, patients and controls revealed bilateral activation for both temperature conditions in the secondary somatosensory cortex. The posterior parietal cortex (PPC) also showed bilateral activation for all conditions. In the medial pain system, the medial thalamus was activated bilaterally in patients and contralaterally in controls. We found activation in a larger area in the midcingulate, extending into the supplementary motor area. The anterior insula and anterior putamen were bilaterally activated for both conditions and groups. In the DLPFC, there was an extensive activation pattern, but this pattern differed between patients and controls. In ad-

dition to activation in the midcingulate, significant decreases in the BOLD signal were found in the perigenual ACC and the amygdala for the individual temperature condition in the patient group during the late phase of the stimulation period.

Group Differences

Contrasting brain activity between patients and controls, we found differences in the activity of the DLPFC, PPC, ACC, and amygdala (**Table 3**). In response to the fixed-temperature heat stimulus, patients had significantly lower activity in the right PPC during the early phase of the stimulation period but not during the late phase. The individually matched temperatures were more sensitive to revealing different patterns of cortical processing in controls vs patients. In the early phase, there was more activity in the left DLPFC in the patient group than in the control group ($t < 0$ in 3 patients and 8 controls; $t > 0$ in 9 patients and 4 controls; mean \pm SD t_{patients} , 0.97 ± 1.23 , and t_{controls} , -1.02 ± 1.89 ; random-effects analysis, $P = .006$) (**Figure 3A**). An opposite pattern of less activity in patients compared with controls was detected in the right PPC ($t < 0$ in 7 patients and 0 controls; $t > 0$ in 5 patients and 12 controls; mean \pm SD t_{patients} , 0.26 ± 1.62 , and t_{controls} , 2.08 ± 1.35 ; random-effects analysis, $P = .007$) (**Figure 3B**). In the late phase, there was also less activity in the perigenual part of the ACC in patients compared with controls ($t < 0$ in 10 patients and 4 controls; $t > 0$ in 2 patients and 8 controls; mean \pm SD t_{patients} , -1.70 ± 1.79 , and t_{controls} , 0.76 ± 1.81 ; random-effects analysis, $P = .003$) (**Figure 3C**). A similar pattern of less activity in patients during pain stimulation was found in the left temporal pole and the right amygdala ($t < 0$ in 10 patients and 6 controls; $t > 0$ in 2 patients and 6 controls; mean \pm SD t_{patients} , -1.93 ± 1.91 , and t_{controls} , 0.63 ± 1.64 ; random-effects analysis, $P = .002$) (**Figure 3D**). Although possible bias of the scanner was a priori unlikely because the patients and controls were assigned to the 2 systems as matched pairs, we performed a 2-factorial analysis of variance with the factors group and scanner to quantitatively exclude possible scanner effects on group differences. No significant interactions were found in any of the regions described in **Figure 3**.

COMMENT

Patients with BPD in the present study displayed a significant reduction in pain sensation and a dissociable neural response in brain areas concerned with cognitive and emotional evaluation of pain. The first finding is consistent with previous studies.²⁻⁴ Heat stimuli with a fixed temperature of 43°C were perceived as less painful by patients with BPD compared with controls. Possibly related to that, the overall volume of activated brain regions was smaller in patients compared with controls when stimulated with 43°C. Both groups revealed a consistent pattern of activation in the lateral (primary and secondary somatosensory cortices) and medial (medial thalamus, anterior insula, and ACC) pain pathways. For individually adjusted temperature, the overall volume of

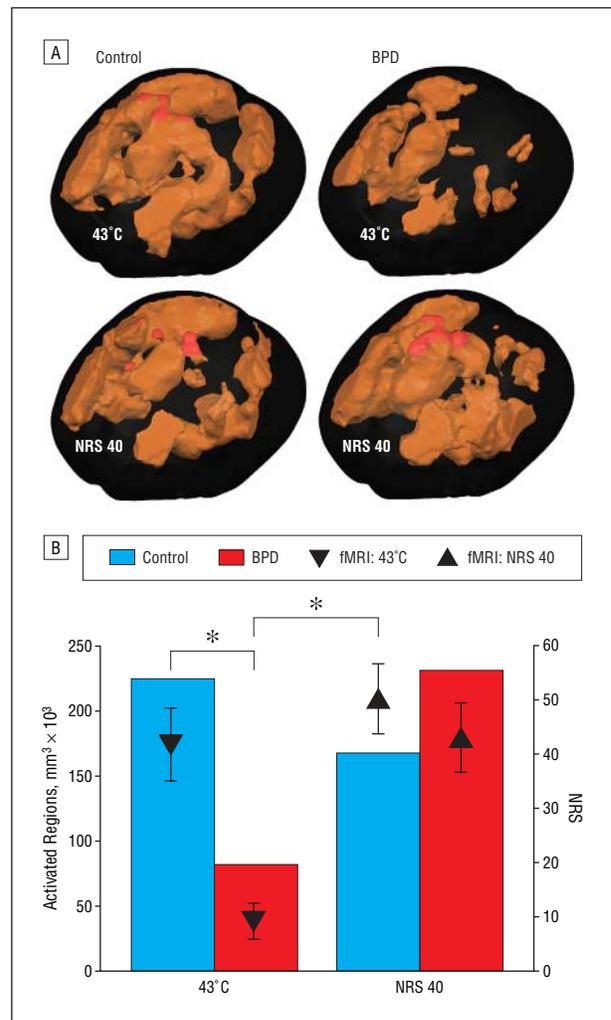


Figure 2. Volumes of brain regions activated by thermal stimuli correspond to subjectively induced pain intensity. A, Glass brain views for the 4 conditions ($P < .05$; whole-brain corrected). B, Overall mean volumes of the activated regions for patients with borderline personality disorder (BPD) and controls and for a fixed stimulus temperature of 43°C and individually adjusted temperatures to a numeric rating scale pain intensity rating of 40 (NRS 40). The respective mean \pm SEM pain ratings during the functional magnetic resonance imaging (fMRI) sessions are given by triangles. Error bars indicate SEM; *, $P < .001$ using a 2-tailed t test.

activated regions was in a comparable range. However, the pattern of activation was significantly different in several brain regions, thus providing a possible circuit of pathologically reduced pain perception. Patients had significantly lower activity in the parietal cortex and greater activity in the left DLPFC compared with controls. In addition, patients showed neural deactivation during pain perception in the perigenual portion of the ACC and in the right amygdala, whereas controls did not.

Previous brain imaging studies^{9-12,23} have revealed a brain network underlying pain processing in humans. This distributed network can be separated into (1) areas concerned mainly with sensory-discriminative processes and (2) areas concerned mainly with affective-motivational pain processes. This distinction converges with findings obtained in animal models; however, the affective-motivational and cognitive-evaluative pain processing circuits have not been as extensively investigated as have the sen-

Table 2. Main Effects of Temperature Stimulation in Control Subjects and Patients With BPD

Region	Fixed Temperature (43°C)								Individual Temperature (NRS 40)							
	Controls				Patients With BPD				Controls				Patients With BPD			
	x	y	z	z Score	x	y	z	z Score	x	y	z	z Score	x	y	z	z Score
Left medial thalamus	-6	-16	1	8.1	-6	-16	1	5.27	NA	NA	NA	NA	-6	-16	1	8.61
Right medial thalamus	NA	NA	NA	NA	9	-13	1	5.23	NA	NA	NA	NA	6	-16	1	7.79
Left M I	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-42	-16	49	5.64
MCC/SMA	-3	5	49	13.2	0	5	52	9.14	-3	5	49	11.28	1	7	49	12.92
Left S II	-51	-22	17	8.64	-42	-22	11	6.58	-50	-25	16	9.49	-45	-19	13	11.48
Right S II	55	-22	25	7.52	51	-13	14	7.28	54	-22	25	8.85	48	-10	9	10.99
Left anterior insula	-33	14	10	10.19	-30	14	10	6.67	-30	15	10	10.06	-36	14	7	10.23
Left anterior putamen	-12	5	12	9.23	-18	8	4	7.03	-20	5	6	6.78	-24	-1	4	7
Right anterior putamen	18	8	4	8.6	18	5	7	8.12	21	8	4	7.52	18	5	8	8.27
Right anterior insula	33	17	13	11.5	30	14	9	7.56	33	15	10	9.94	33	13	7	13.08
Left PPC	-36	-52	37	10.07	-45	-40	37	5.87	-39	-43	37	8.54	-33	-64	34	8.54
Right PPC	49	-40	40	10.07	44	-49	37	7.84	31	-58	37	9.2	42	-49	34	9.3
Right superior parietal sulcus	NA	NA	NA	NA	NA	NA	NA	NA	12	-65	37	9.95	NA	NA	NA	NA
Left DLPFC	NA	NA	NA	NA	-54	5	28	6.39	-45	-4	28	9.11	-49	-1	22	9.49
Right DLPFC	42	-1	28	9.99	42	-1	31	7.4	48	2	19	9.68	39	-1	26	9.47
Left inferior frontal sulcus	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-39	26	32	8.41
Right inferior frontal sulcus	NA	NA	NA	NA	38	21	22	8.04	NA	NA	NA	NA	33	26	31	10.96
Left superior frontal sulcus	-36	38	25	11.03	-30	50	26	7.64	-33	44	19	8.34	NA	NA	NA	NA
Right superior frontal sulcus	36	29	34	12.03	38	41	25	7.78	39	47	19	11.23	NA	NA	NA	NA

Abbreviations: DLPFC, dorsolateral prefrontal cortex; MCC/SMA, midcingulate cortex/supplementary motor area; M I, primary motor cortex; NA, not activated; NRS 40, numeric rating scale pain intensity rating of 40; PPC, posterior parietal cortex; S II, secondary somatosensory cortex.

Table 3. Regions With Significant Group Differences for Different Phases and Conditions

Region	Fixed Temperature (43°C); Early Phase				NRS 40, Early Phase				NRS 40, Late Phase			
	x	y	z	z Score	x	y	z	z Score	x	y	z	z Score
Left DLPFC	ND	ND	ND	ND	-48	-26	20	5.09	ND	ND	ND	ND
Right PPC	12	-66	43	-4.90	15	-65	37	-4.90	ND	ND	ND	ND
Perigenual ACC	ND	ND	ND	ND	ND	ND	ND	ND	-1	25	1	-6.14
Right amygdala	ND	ND	ND	ND	ND	ND	ND	ND	24	-1	25	-6.63
Left temporal pole	ND	ND	ND	ND	ND	ND	ND	ND	-26	9	-29	-5.76

Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; ND, no difference; NRS 40, numeric rating scale pain intensity rating of 40; PPC, posterior parietal cortex.

sory-discriminative circuits.⁸ The “classic pain circuit,” the main elements of which include the primary and secondary somatosensory cortices, insula, thalamus, and basal ganglia,^{12,14,24} may be sufficient to explain normal pain processing. We found pain-induced activity in these regions in controls and patients with BPD. Also, the reduced pain sensitivity in patients with BPD is not accounted for by general impairment of the sensory-discriminative component of pain, hyperactive descending inhibition, or attention deficit during noxious stimulation.⁴

The most striking difference between patients and controls was present in the perigenual part of the ACC, which interacts with various aspects of pain processing. The anterior cingulate is a large area that can be divided into the perigenual ACC, anterior midcingulate, and posterior midcingulate.²⁵ In addition to its role in the evaluation of pain intensity,²⁶ the anterior midcingulate is in-

involved in the affective evaluation of pain.¹⁰ The expectancy of pain seems to involve more rostral parts of the cingulate cortex.^{27,28} The perigenual ACC, in conjunction with other prefrontal and posterior parietal areas, has been suggested to participate in an attentional network of pain processing,^{29,30} but its specific role remains unclear. Becerra and coworkers¹⁴ described an increase in the BOLD signal in the perigenual ACC mainly during the late phase of a tonic 30-second pain stimulation. In the present study, we found an inverse response to pain in patients that was characterized by an extended decrease in the BOLD signal during the late phase of pain stimulation.

Note that BOLD signal decreases need to be interpreted with caution because they could represent vascular stealing effects related to perfusion reserve reallocation phenomena, resulting from neural activation in nearby areas. However, in the entire brain, and specifi-

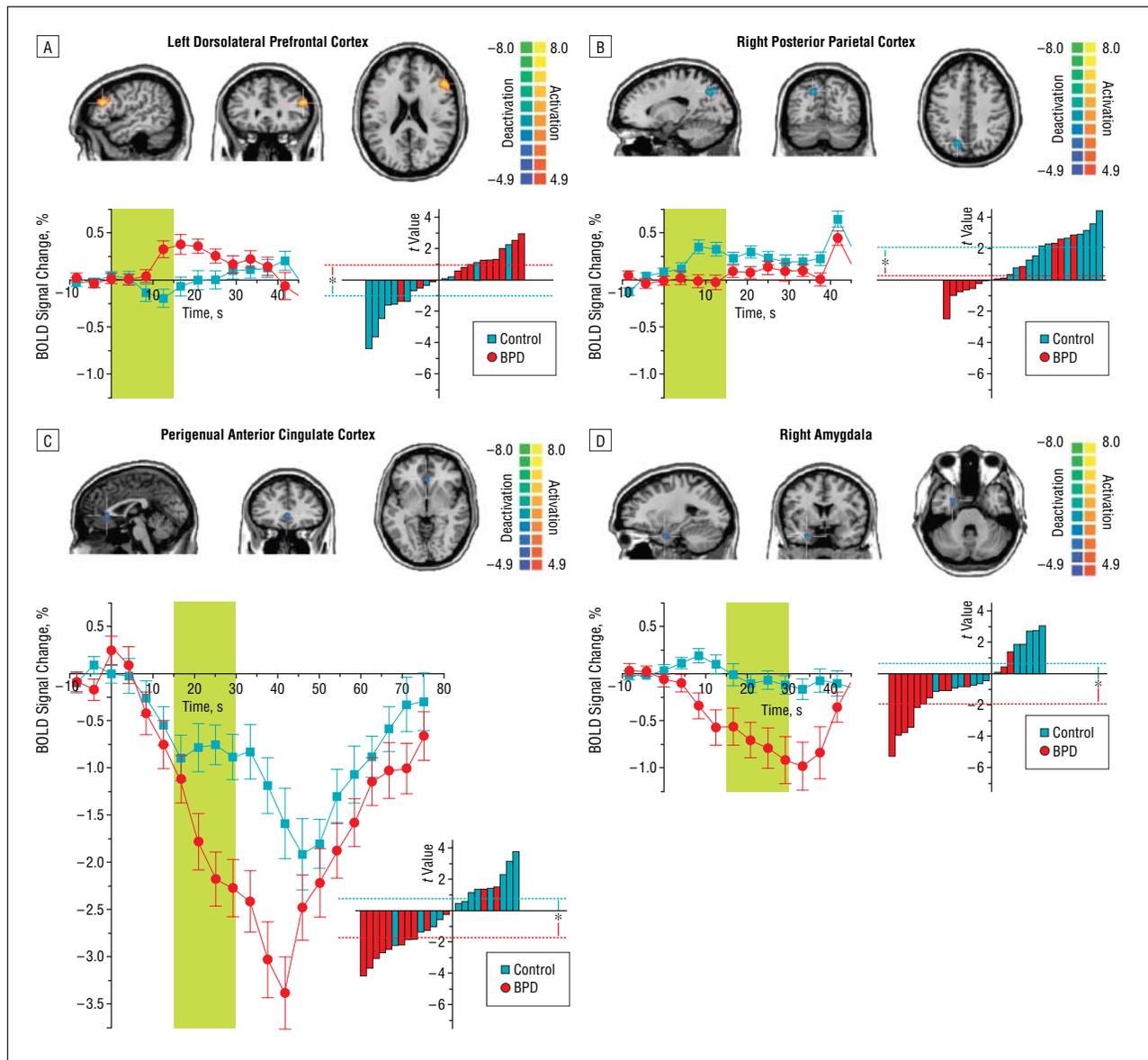


Figure 3. Group comparison of responses to a temperature individually adjusted to produce equally perceived pain intensity. Brain activity during individually adjusted painful heat stimulation differed between patients with borderline personality disorder (BPD) and controls during the early-stimulation phase in the left dorsolateral prefrontal cortex (A) and the right posterior parietal cortex (B). In the late phase of individually adjusted heat pain, intergroup differences in brain activity were seen in the perigenual part of the anterior cingulate cortex (C) and in the right amygdala (D). Each upper row displays the group differences in sagittal (left), coronal (middle), and transversal (right) sections ($P < .001$; cluster corrected with a minimum cluster size of 82 mm^3 , whole-brain height corrected). In each lower row, time courses of the mean blood oxygen level–dependent (BOLD) signal changes for the BPD and control groups are given on the left side; the respective time phase is marked by the green background. Each right side displays the region of interest–based random-effects analysis, with individual t values sorted by height in the 12 patients with BPD and the 12 controls. Positive values indicate that the phase-specific predictor explained a net individual signal increase from the mean signal during the corresponding coded phase, whereas negative values explain a net signal decrease. The reported BOLD signal changes are averaged with respect to the onset of the pain stimulation, without distinction of possible multiple phases of the responses. Group means are indicated by dashed red and blue lines for BPD and control, respectively. Error bars indicate SEM; *, $P < .01$ using a 2-tailed t test.

cally in nearby areas, we did not find increased BOLD signals accounting for vascular stealing, which suggests an actual reduction in neural activity.³¹ Another possible source of the observed group difference is that higher temperatures in the BPD group were necessary to achieve the same subjective intensity ratings as the control group. However, this explanation is unlikely because a correlation analysis between individual temperatures and BOLD signal change in the anterior cingulate revealed no significant association in the patients and a positive correlation in the controls (ie, less negative signal change with

increasing temperatures). In addition, stimulus intensity should affect earlier neural processes in regions such as the thalamus and the somatosensory cortex, which was not observed in the present study.

An additional question arising from our findings concerns the starting point of the reduction in neural activity in the amygdala and ACC in patients with BPD. For example, if patients with BPD had increased neural tone in these areas before stimulation, pain may have returned exaggerated neural activity to normal values. Evidence suggests that neural deactivation in the peri-

genual anterior cingulate may be related to gating processes that suppress less relevant sensory information to optimize the cognitive and emotional resources necessary for goal-directed behaviors³² or anticipated emotional states.³³ As such, our findings converge with the role of the anterior cingulate as a central relay station that integrates emotional and cognitive processes.³⁴

Deactivation in the ACC in patients with BPD was associated with greater activation in response to pain in the DLPFC. Although this interpretation is speculative, one study¹³ indicated that the DLPFC participates in a pain control network that regulates corticosubcortical and corticocortical loops by inhibiting ascending pathways through the ACC. This study found an inverse correlation between the subjective unpleasantness and the perceived intensity of a heat stimulus and activation of the DLPFC. It is possible that this brain area is activated in patients with BPD at higher temperatures. In turn, this activation may inhibit activity in the somatosensory cortex and the anterior cingulate. A limitation of the present study is that education and intelligence were not controlled for. These parameters are important in the evaluation of cognitive control mechanisms.

Our patients with BPD clearly demonstrated effective mechanisms of antinociception. This finding is consistent with other studies on conditions characterized by hyperalgesia. These studies^{35,36} found an opposite pattern of increased activity in the ACC and decreased activity in the DLPFC. Deactivation of the ACC was also associated with deactivation in the amygdala. Apart from its role in emotional evaluation of sensory information,³⁷ the amygdala has been implicated in the processing of analgesia information: it may contribute to antinociception through emotional factors (eg, fear) and by mediating opioid antinociception.³⁸ Limbic deactivation has been found to correlate with the degree of coping in aversive situations in general³³; in relation to pain, amygdala deactivation was found when the anticipated duration of a painful stimulus was increased, suggesting a possible cognitive modulation of pain aversiveness.³⁹ During the visual presentation of aversive visual stimuli, the amygdala seems to be hyperactive in patients with BPD compared with controls.⁴⁰ Thus, in view of these findings, self-inflicted pain may function to normalize neural activity in specific brain regions involved in emotional and cognitive processing. Alternatively, repeated self-injury could lead to an adaptation of pain thresholds and pain processing reflected in the current findings of elevated pain thresholds and disturbed prefrontal and limbic pain processing. A possible way to further elucidate this question is to combine the analysis of genetic predisposition (eg, genes related to pain perception) with neuroimaging during paradigms that lead to either sensitization or habituation in healthy individuals.

During stimulation with 43°C, a large area in the PPC was found to be activated in controls but not in patients with BPD. Animal studies have revealed reduced pain sensitivity after PPC lesions,⁴¹ and the PPC also has been shown to play an important role in somatosensory attention in humans.⁴² Reduced activity in this area may, therefore, correlate to the neglect of painful stimuli by patients with BPD.

The fMRI data were acquired using 2 different Siemens 1.5-T scanners. To address this potential method-

ological problem on the study design level, matched patient-control pairs were assigned to the scanners in an attempt to minimize a priori possible scanner effects on the group differences. To formally exclude such bias, we performed a 2-factorial analysis of variance, which did not yield interaction effects between group and scanner in any of the regions with a significant group effect.

These data suggest that the interaction of increased pain-induced response in the DLPFC and deactivation in the anterior cingulate and the amygdala represents a neuroanatomical correlate of an antinociceptive mechanism. In patients with BPD, this mechanism may modulate pain circuits, primarily through down-regulation of the emotional components of pain, as demonstrated in patients who repetitively seek painful experiences.

Submitted for Publication: March 11, 2005; final revision received November 23, 2005; accepted December 1, 2005.

Author Affiliations: Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany (Drs Schmahl and Bohus and Mss Ludaescher and Jochims); Department of Psychiatry and Psychotherapy, University of Freiburg Medical School, Freiburg, Germany (Dr Lieb); Department of Neurological Sciences, University of Naples "Federico II," Naples, Italy (Dr Esposito); Institute of Physiology und Pathophysiology, Johannes-Gutenberg-University, Mainz, Germany (Drs Treede and Greffrath); Department of Neurological Sciences, University of Pisa, Pisa, Italy (Dr Di Salle); Department of Radiological Research—Medical Physics, University of Freiburg (Drs Scheffler and Hennig); MR-Physics, Department of Medical Radiology, University Hospital, Basel, Switzerland (Dr Scheffler); University Hospital of Psychiatry Bern, Bern, Switzerland (Dr Seifritz); and Department of Psychiatry, University of Basel, Basel, Switzerland (Dr Seifritz).

Correspondence: Christian Schmahl, MD, Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, J 5, D-68159 Mannheim, Germany (christian.schmahl@zi-mannheim.de).

Author Contributions: Drs Schmahl, Bohus, Esposito, Treede, Di Salle and Greffrath contributed equally to this work.

Funding/Support: This study was supported by the Borderline Personality Disorder Research Foundation (Drs Schmahl and Bohus), grants Tr 236/11-3 and 13-3 from the German Research Foundation (Dr Treede), and grant PP00B-103012 from the Swiss National Science Foundation (Dr Seifritz).

REFERENCES

1. Lieb K, Zanarini MC, Schmahl C, Linehan M, Bohus M. Borderline personality disorder. *Lancet*. 2004;364:453-461.
2. Russ MJ, Roth SD, Lerman A, Kakuma T, Harrison K, Shindeldecker RD, Hull JW, Mattis S. Pain perception in self-injurious patients with borderline personality disorder. *Biol Psychiatry*. 1992;32:501-511.
3. Bohus M, Limberger MF, Ebner UW, Glocker FX, Schwarz B, Wernz M, Lieb K. Pain perception during self-reported distress and calmness in patients with borderline personality disorder and self-mutilating behavior. *Psychiatry Res*. 2000; 95:251-260.
4. Schmahl C, Greffrath W, Baumgaertner U, Schlereth T, Magerl W, Philipsen A,

- Lieb K, Bohus M, Treede R-D. Differential nociceptive deficit in patients with borderline personality disorder and self-injurious behavior: laser-evoked potentials, spatial discrimination of noxious stimuli, and pain ratings. *Pain*. 2004; 110:470-479.
5. Millan MJ. Descending control of pain. *Prog Neurobiol*. 2002;66:355-474.
 6. Mayer EA, Fanselow MS. Dissecting the components of the central response to stress. *Nat Neurosci*. 2003;6:1011-1012.
 7. Melzack R, Casey KL. *The Skin Senses*. Sensory, motivational, and central control determinants of pain: a new conceptual model. In: Kenshalo DR, ed. Springfield, Ill: Charles C Thomas; 1968:423-443.
 8. Treede RD, Kenshalo DR, Gracely RH, Jones AKP. The cortical representation of pain. *Pain*. 1999;79:105-111.
 9. Davis KD. The neural circuitry of pain as explored with functional MRI. *Neurol Res*. 2000;22:313-317.
 10. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science*. 1997; 277:968-971.
 11. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science*. 2000;288:1769-1772.
 12. Derbyshire SW, Whalley MG, Stenger VA, Oakley DA. Cerebral activation during hypnotically induced and imagined pain. *Neuroimage*. 2004;23:392-401.
 13. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain*. 2003;126:1079-1091.
 14. Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D. Reward circuitry activation by noxious thermal stimuli. *Neuron*. 2001;32:927-946.
 15. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders: Patient Edition (SCID-I/P)*. New York, NY: American Psychiatric Press; 1995.
 16. Loranger AW. *International Personality Disorder Examination (IPDE): DSM-IV and ICD-10 Modules*. Odessa, Fla: Psychological Assessment Resources; 1999.
 17. Friston KJ, Frith CD, Frackowiak RS, Turner R. Characterizing dynamic brain responses with fMRI: a multivariate approach. *Neuroimage*. 1995;2:166-172.
 18. Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-related fMRI: characterizing differential responses. *Neuroimage*. 1998;7:30-40.
 19. Friston K, Holmes A, Worsley K, Poline J, Frith C, Frackowiak R. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp*. 1995;2:189-210.
 20. Worsley KJ, Marrett S, Neelin P, Vandall AC, Friston KJ, Evans AC. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp*. 1996;4:58-73.
 21. Worsley KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F, Evans AC. A general statistical analysis for fMRI data. *Neuroimage*. 2002;15:1-15.
 22. Friston KJ, Holmes AP, Worsley KJ. How many subjects constitute a study? *Neuroimage*. 1999;10:1-5.
 23. Hofbauer RK, Rainville P, Duncan GH, Bushnell MC. Cortical representation of the sensory dimension of pain. *J Neurophysiol*. 2001;86:402-411.
 24. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. *Pain*. 1995;60:3-38.
 25. Vogt BA, Berger GR, Derbyshire SWG. Structural and functional dichotomy of human midcingulate cortex. *Eur J Neurosci*. 2003;18:3134-3144.
 26. Buchel C, Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C. Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance study. *J Neurosci*. 2002;22:970-976.
 27. Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN. Dissociating pain from its anticipation in the human brain. *Science*. 1999;284: 1979-1981.
 28. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science*. 2004;303:1162-1167.
 29. Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenex F, Mauguiere F, Michel D, Laurent B. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. *Brain*. 1999;122:1765-1779.
 30. Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. *Brain*. 2002;125: 310-319.
 31. Harel N, Lee SP, Nagaoka T, Kim DS, Kim SG. Origin of negative blood oxygenation level-dependent fMRI signals. *J Cereb Blood Flow Metab*. 2002;22:908-917.
 32. Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci*. 2001;2:685-694.
 33. Simpson JR Jr, Drevets WC, Snyder AZ, Gusnard DA, Raichle ME. Emotion-induced changes in human medial prefrontal cortex, II: during anticipatory anxiety. *Proc Natl Acad Sci U S A*. 2001;98:688-693.
 34. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci*. 2000;4:215-222.
 35. Derbyshire SWG, Jones AK, Devani P, Friston KJ, Feinmann C, Harris M, Pearce S, Watson JD, Frackowiak RS. Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography. *J Neurol Neurosurg Psychiatry*. 1994;57:1166-1172.
 36. Jones AKP, Derbyshire SWG. Reduced cortical responses to noxious heat in patients with rheumatoid arthritis. *Ann Rheum Dis*. 1997;56:601-607.
 37. LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci*. 2000;23:155-184.
 38. Manning BH. A lateralized deficit in morphine antinociception after unilateral inactivation of the central amygdala. *J Neurosci*. 1998;18:9453-9470.
 39. Petrovic P, Carlsson K, Peterson KM, Hansson P, Ingvar M. Context-dependent deactivation of the amygdala during pain. *J Cogn Neurosci*. 2004;16:1289-1301.
 40. Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, Thron A, Sass H. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biol Psychiatry*. 2001;50:292-298.
 41. Dong WK, Hayashi T, Roberts VJ, Fusco BM, Chudler EH. Behavioral outcome of posterior parietal cortex injury in the monkey. *Pain*. 1996;64:579-587.
 42. Binkofski F, Kunesch E, Classen J, Seitz RJ, Freund HJ. Tactile ataxia: unimodal apraxic disorder of tactile object exploration associated with parietal lobe lesions. *Brain*. 2001;124:132-144.