

Altered Pain Processing in Veterans With Posttraumatic Stress Disorder

Elbert Geuze, PhD; Herman G. M. Westenberg, PhD; Anja Jochims, MS; Carien S. de Kloet, MD; Martin Bohus, MD; Eric Vermetten, MD, PhD; Christian Schmahl, MD

Context: Posttraumatic stress disorder (PTSD) is a chronic and debilitating anxiety disorder. Several brain areas related to pain processing are implicated in PTSD. To our knowledge, no functional imaging study has discussed whether patients with PTSD experience and process pain in a different way than control subjects.

Objective: To examine neural correlates of pain processing in patients with PTSD.

Design: The experimental procedure consisted of psychophysical assessment and neuroimaging with functional magnetic resonance imaging. Two conditions were assessed during functional magnetic resonance imaging in both experimental groups, one condition with administration of a fixed temperature of 43°C (fixed-temperature condition) and the other condition with an individual temperature for each subject but with a similar affective label equaling 40% of the subjective pain intensity (individual temperature condition).

Setting: Academic outpatient unit in a department of military psychiatry in collaboration with an imaging center at a psychiatric hospital.

Participants: Twelve male veterans with PTSD and 12 male veterans without PTSD were recruited and matched for age, region of deployment, and year of deployment.

Main Outcome Measures: Changes in functional magnetic resonance imaging blood oxygenation level–dependent response to heat stimuli, reflecting increased and decreased activity of brain areas involved in pain processing.

Results: Patients with PTSD rated temperatures in the fixed-temperature assessment as less painful compared with controls. In the fixed-temperature condition, patients with PTSD revealed increased activation in the left hippocampus and decreased activation in the bilateral ventrolateral prefrontal cortex and the right amygdala. In the individual temperature condition, patients with PTSD showed increased activation in the right putamen and bilateral insula, as well as decreased activity in the right precentral gyrus and the right amygdala.

Conclusions: These data provide evidence for reduced pain sensitivity in PTSD. The witnessed neural activation pattern is proposed to be related to altered pain processing in patients with PTSD.

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Author Affiliations: Department of Military Psychiatry, Central Military Hospital (Drs Geuze, de Kloet, and Vermetten), and Department of Psychiatry, Rudolf Magnus Institute of Neuroscience (Drs Geuze, Westenberg, and Vermetten), Utrecht, the Netherlands; and Department of Psychosomatic Medicine, Central Institute of Psychiatry, University of Heidelberg (Ms Jochims and Drs Bohus and Schmahl), Mannheim, Germany.

PAIN EXPERIENCE CONSISTS OF a sensory-discriminative, an affective, and a cognitive component, which are mediated by different parts of the central nervous system. From a neuroanatomical viewpoint, the sensory-discriminative pathway of pain is localized in the lateral nociceptive system (lateral thalamic nuclei and primary and secondary somatosensory cortex). The affective component of pain is anatomically connected with the medial nociceptive system (insula, medial thalamic nuclei, and anterior cingulate cortex [ACC]), whereas the cognitive component is localized in the prefrontal cortex (PFC).¹ Imaging studies²⁻⁸ using functional magnetic resonance imaging (fMRI) or positron

emission tomography have confirmed the ACC, PFC, limbic cortex, insular cortex, and somatosensory cortex as part of the neural circuitry of pain.

Posttraumatic stress disorder (PTSD) is an anxiety disorder that may occur in individuals exposed to a traumatic event and is characterized by chronic arousal, reexperience of the event, and avoidance of stimuli related to the event. Clinical studies⁹⁻¹¹ report that pain experience in persons with PTSD is significantly increased compared with control subjects and that chronic pain is a commonly reported symptom of patients with PTSD. However, previous empirical research also indicates that patients with PTSD report a decrease in pain intensity ratings after being exposed to traumatic reminders.¹²

This has been purported to be related to opioid-mediated stress-induced analgesia.¹³ Activation of the μ -opioid receptor system by endogenous opioid peptides is associated with reductions in sensory and affective ratings of pain experience.^{14,15}

Despite the increase in the numbers of neuroimaging studies of pain, no functional imaging study (to our knowledge) has explored neural correlates of pain processing in patients with PTSD. Recently, a functional neuroimaging study¹⁶ in borderline personality disorder (BPD), a related psychiatric condition, revealed an antinociceptive neural network that includes the right amygdala, rostral ACC, and PFC. The present study used the same design (fMRI in combination with painful tonic-heat stimuli) to compare the brain activity in patients with PTSD and in controls. We used fixed-temperature heat stimuli that were the same for all subjects and individual temperature heat stimuli that were adjusted for equal subjective pain in all subjects. We predicted that patients with PTSD would display altered activity in brain areas related to pain processing.

METHODS

SUBJECTS

Twelve male Dutch veterans with PTSD and 12 male Dutch veterans without PTSD were recruited. Patients with PTSD were recruited from the Department of Military Psychiatry, Central Military Hospital, Utrecht, the Netherlands. Control subjects were recruited via direct mail to veterans who were registered at the Veterans Institute, Doorn, the Netherlands. All participants were veterans who had served in United Nations peace-keeping missions in Lebanon, Cambodia, and Bosnia. Control veterans were matched to the patient group for age, handedness, year of deployment, and country of deployment.

Posttraumatic stress disorder was diagnosed using *DSM-IV* criteria and was confirmed using the Clinician-Administered PTSD Scale¹⁷ and by consensus with 3 clinicians (E.G., C.S.K., and E.V.). Only patients with Clinician-Administered PTSD Scale scores exceeding 50 were included in the study. Comorbid disorders were examined using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID).¹⁸ Control subjects were assessed using the SCID and the Clinician-Administered PTSD Scale. All control subjects fulfilled the *DSM-IV* criterion A1 (ie, they had all experienced a traumatic event). All subjects received a physical examination by a physician (C.S.K.). Subjects were excluded if they had claustrophobia, any clinical significant abnormality of a clinical laboratory test result, a history of psychiatric illness (controls only) or neurological dysfunction (all subjects), or a history of alcohol or other drug abuse (*DSM-IV* criteria) within 6 months before the study. None of the veterans included were physically injured at the time of deployment. All of the participants had been free of psychotropic and analgesic medication for 4 weeks before entering the study. Written informed consent was obtained from all subjects who participated in the study after receiving a complete written and verbal description of the study. This study was approved by the institutional review boards of the University Medical Centre of Utrecht and the Central Institute of Mental Health, Mannheim.

EXPERIMENTAL PROCEDURE

The experimental procedure followed a protocol first used by Schmahl et al.¹⁶ It consisted of a psychophysical assessment per-

formed before the imaging procedure, followed by a neuroimaging session.

Psychophysical Assessment

After a verbal introductory instruction phase, the subjective pain intensity of various painful stimuli was assessed using the Thermal Sensory Analyzer II (Medoc Advanced Medical Systems Ltd, Ramat Yishay, Israel), a device to induce thermal stimuli.¹⁹⁻²² Temperatures between 40°C and 48°C were applied in blocks of 30 seconds in length with 1-minute intervals on the dorsal right hand of each subject. These temperatures oscillated with an amplitude of 2°C to avoid adaptation. Five stimulus temperatures (40°C, 42°C, 44°C, 46°C, and 48°C) were applied consecutively in increasing and decreasing order. The full protocol consisted of 20 heat stimuli (5 stimuli and 4 repetitions). Subjective pain estimates were given by the participants immediately after the temperature blocks, using a numerical rating scale (NRS) ranging from 0 (no pain at all) to 100 (worst imaginable pain). These values were used to calculate the temperature equaling a subjective pain intensity of 40, using regression analysis.

Neuroimaging Using fMRI

The second part of the experiment was performed on a 1.5-T scanner (Magnetom Vision; Siemens Medical Solution, Erlangen, Germany). Functional data were assessed using a functional echo-planar imaging series (number of contiguous transverse sections, 25; section thickness, 5 mm; field of view, 220 × 220 mm²; matrix, 64 × 64 pixels; section acquisition time, 107 milliseconds; volume acquisition time, 2675 milliseconds; and repetition time, 4175 milliseconds). During acquisition of the functional data sets, 10 blocks of 30 seconds in length were applied with the temperature equaling the subjective pain intensity of 40 on the NRS (individual temperature) or with a fixed temperature of 43°C. Interspersed between these blocks were 1-minute intervals with a baseline temperature of 35°C. Subjects were asked for a pain rating on an NRS of 0 to 100 after the first poststimulation image and before the baseline image. Thermal stimuli were applied to the dorsal right hand using the Thermal Sensory Analyzer II with a thermode designed for use in the MR imaging room.

After the functional data were acquired, a high-resolution anatomical series using MP-RAGE (3-dimensional magnetization-prepared rapid acquisition gradient echo) with a voxel size of 1 × 1 × 1 mm³ was performed. This series was used as an individual template for coregistration of functional and anatomical data and for spatial standardization into the stereotactic system of Talairach and Tournoux.²³ Immediately before and after the fMRI data acquisition, a Dissociative State Questionnaire²⁴ was given to all participants. This questionnaire consists of 20 items measuring dissociation and 1 item measuring aversive inner tension.

DATA ANALYSIS

All the image data preparation and preprocessing steps, as well as the statistical analyses and the map volumetric projection, were performed using the cross-platform neuroimaging tool Brain Voyager QX 1.6 (Brain Innovation, Maastricht, the Netherlands). The first 2 images were excluded from the data analysis. Three-dimensional data preprocessing included section imaging time correction (using sinc interpolation), linear trend removal, temporal high-pass filtering to remove low-frequency nonlinear drifts of 3 cycles or fewer per time course, and 3-dimensional motion correction to detect and correct for small head movements by spatial alignment of all volumes to

Table 1. Subject Demographics and Psychometric Data*

Variable	Patients With PTSD (n = 12)	Control Subjects (n = 12)	P Value†
Age, y	34.50 ± 6.02	33.26 ± 4.24	.56
Year of deployment, 1980 to 2002	1994 ± 5.90	1994 ± 6.90	.88
Country of deployment			
Bosnia	8	8	
Lebanon	2	2	
Cambodia	1	1	
Afghanistan	1	1	
Edinburgh Handedness Inventory score	85 ± 29	88 ± 26	.83
Dissociative State Questionnaire score‡			
Before fMRI	10.58 ± 11.58	1.25 ± 2.98	<.05
After fMRI	14.08 ± 14.59	0.58 ± 1.44	<.001
Aversive inner tension score			
Before fMRI	2.42 ± 1.92	0.67 ± 0.88	<.05
After fMRI	1.92 ± 2.60	0.42 ± 1.16	.09

Abbreviations: fMRI, functional magnetic resonance imaging; PTSD, posttraumatic stress disorder.

*Data are given as mean ± SD unless otherwise indicated.

†Two-tailed *t* test.

‡Range, -100 (extreme left-handedness) to 100 (extreme right-handedness).

the first volume by rigid body transformations. Estimated translation and rotation parameters were inspected and never exceeded 3 mm. Coregistration of functional and 3-dimensional structural measurements was computed by relating T2-weighted images and the T1-weighted 3-dimensional MP-RAGE measurement, which yields a 4-dimensional functional data set. Structural 3-dimensional and functional 4-dimensional data sets were transformed into the standard space corresponding to the atlas of Talairach and Tournoux.²³

The stimulation protocol was convoluted using a hemodynamic response function to account for the expected delay and generic shape of the blood oxygenation level-dependent signal.²⁵ To correct for multiple comparisons, the false discovery rate (FDR) controlling procedure was applied on the resulting *P* values for all voxels. The value of *q* specifying the mean maximum FDR tolerated was set to 0.01. With this value, a single-voxel threshold is chosen by the FDR procedure that ensures that, from all voxels shown as active, only 1% or less are false-positive findings.^{26,27} Brain areas responding to the fixed and the individual temperature conditions were identified by the temperature-specific main effects in the general linear model (heat vs baseline) and were corrected for serial correlations.¹⁶ Voxel level and region of interest-level intergroup linear contrasts were computed using 2-tailed *t* tests. 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 sample size and the high variability of the population compared with the signal-to-noise ratio of the measurements, interindividual variance was not accounted for in the voxel-level group analysis, and all contrast maps were computed using a fixed-effects model.²⁸ To extend our inferences and results to the clinical population, significantly activated clusters of 200 voxels in the first-level intergroup voxel-level analysis were selected for a more sensitive second-level region of interest analysis using a random-effects model in the 2-sample *t* tests. Data are given as mean ± SD.

PSYCHOMETRIC DATA

Patients with PTSD and control veterans were matched for age (34.50 ± 6.02 and 33.26 ± 4.24 years, respectively) (**Table 1**). Patients with PTSD had significantly greater Clinician-Administered PTSD Scale, Hamilton Anxiety Rating Scale, and Hamilton Depression scores. According to the SCID, the PTSD group met lifetime (past) DSM-IV diagnostic criteria for major depressive disorder (n = 2), bipolar disorder (n = 2), alcohol abuse (n = 4), alcohol dependence (n = 2), substance abuse (n = 2), substance dependence (n = 1), and panic disorder without agoraphobia (n = 2). Only 1 subject with PTSD met current diagnostic criteria for panic disorder. Among the control subjects, the SCID did not reveal any current or lifetime psychiatric disorders. None of the subjects had a pain disorder or somatization disorder as determined by the SCID. In addition, none of the subjects reported the presence of current or chronic pain.

PSYCHOPHYSICS

When plotted in linear coordinates (**Figure 1A**), the mean ratings given were positively accelerating functions of heat temperature. Patients with PTSD rated the objectively equal temperatures as subjectively less painful. The fixed temperature of 43°C was rated as 10.5 ± 7.0 by patients with PTSD compared with 23.9 ± 12.7 by controls ($t_{22}=3.20$, $P<.005$; 2-tailed *t* test). Consequently, the temperature that corresponded to an NRS rating of 40 was 46.82°C ± 1.03°C for patients with PTSD compared with 45.35°C ± 1.73°C for controls ($t_{22}=2.53$, $P<.05$; 2-tailed *t* test). Patients with PTSD showed a significantly reduced offset of the stimulus-response function (ie, the stimulus-response function of the patients is shifted to the right with respect to the controls; *y*-intercept at the mean stimulus temperature of 44°C, 16.77 ± 10.07 in patients with PTSD and 32.06 ± 15.42 in controls; $t_{22}=2.87$, $P<.01$; 2-tailed *t* test). When plotted in log-log coordinates (**Figure 1B**), the functions were fit by linear regression lines. Correlation coefficients (Pearson product moment correlation *r*) computed for these regressions of mean ratings against stimulus temperatures revealed a significant effect of temperature on pain ratings in both groups ($r=0.832$, $P<.05$ in patients with PTSD; and $r=0.978$, $P<.01$ in controls). The linearity of these functions in double logarithmic coordinates indicates that the relationships between the scaling responses and stimulus temperature intensity (minus the baseline temperature of 34°C) can be described by power functions as follows: $f(x)=k(t-34)^x$, where *x* is the heat pain exponent; *k*, a constant; and *t*, the stimulus temperature in degrees Celsius.^{29,30} Heat pain exponents were obtained by computing the slope of the regression lines (in double logarithmic coordinates), and the values were not significantly different (4.03 ± 1.37 in patients with PTSD and 3.07 ± 0.92 in controls; $t_{22}=1.40$, $P>.05$). These exponents are similar to those found in other heat pain studies^{29,31} and indicate that the rate of change in the pain rating is not significantly different between the groups.

During imaging, the subjects were also asked to give pain ratings after each 30-second block. Again, the fixed temperature of 43°C during imaging was rated as 5.0 ± 5.5 on the NRS by patients with PTSD compared with 30.8 ± 20.9 by controls, which was significantly different ($t_{22}=4.13$, $P<.001$; 2-tailed t test). During fMRI, the pain intensity for the individual temperature was rated as 39.9 ± 19.6 by patients with PTSD and as 49.9 ± 18.1 by controls ($t_{22}=1.31$, $P>.05$, 2-tailed t test)

fMRI PSYCHOMETRICS

Patients with PTSD experienced significantly more aversive inner tension (2.4 ± 1.9 in patients vs 0.7 ± 0.9 in controls) before imaging ($t_{22}=2.86$, $P<.05$) (score range, 0-9). After imaging, aversive inner tension was not significantly different. Patients with PTSD experienced significantly more dissociative symptoms before fMRI (10.6 ± 11.6 in patients vs 1.3 ± 3.0 in controls; $t_{22}=2.70$, $P<.05$) and after fMRI (14.1 ± 14.6 in patients vs 0.6 ± 1.4 in controls; $t_{22}=3.19$, $P<.01$). However, the difference between levels of dissociative symptoms after fMRI compared with levels of dissociative symptoms before imaging was not significantly different between patients with PTSD (3.5 ± 16.9) and controls (-0.7 ± 1.6) ($t_{22}=0.85$, $P>.05$).

fMRI MAIN EFFECTS

In a first analysis step, activations for the main effects of the 2 conditions were investigated. Activations were thresholded at $q \leq 0.01$ (**Table 2**). In the patient group, solid activations were seen in the ACC, left claustrum, right putamen, left hippocampus, parietal cortex, medial PFC, dorsolateral PFC, and bilateral ventrolateral PFC in the fixed-temperature condition, as well as increased activity in the bilateral insular cortex, left and right superior temporal gyri, and a region of reduced activity in the right amygdala, bilateral precuneus, posterior cingulate cortex, and right somatosensory cortex. A similar pattern of activity was seen in the individual temperature condition. In the control group in the fixed-temperature condition, significant activations were seen in the ACC, left claustrum, right amygdala, insular cortex, parietal cortex, and bilateral PFC, as well as regions of signal decrease in the left amygdala, left precuneus, right precentral and postcentral gyri, and bilateral posterior cingulate cortex. In the individual temperature condition, this pattern of activity was more pronounced. In this condition, the right medial thalamus and the left putamen were also significantly activated in controls.

fMRI GROUP ANALYSIS

In the group comparison, patients with PTSD displayed altered activity in the insula, putamen, amygdala, hippocampus, precentral gyrus, and ventrolateral PFC (**Table 3**). In the fixed-temperature condition, patients with PTSD revealed more activity in the left hippocampus ($t<0$ in 2 patients and 9 controls; $t>0$ in 10 patients and 3 controls; t_{patients} , 2.08 ± 2.21 , and t_{controls} , -0.91 ± 1.78 ; random-effects analysis, $P<.001$)

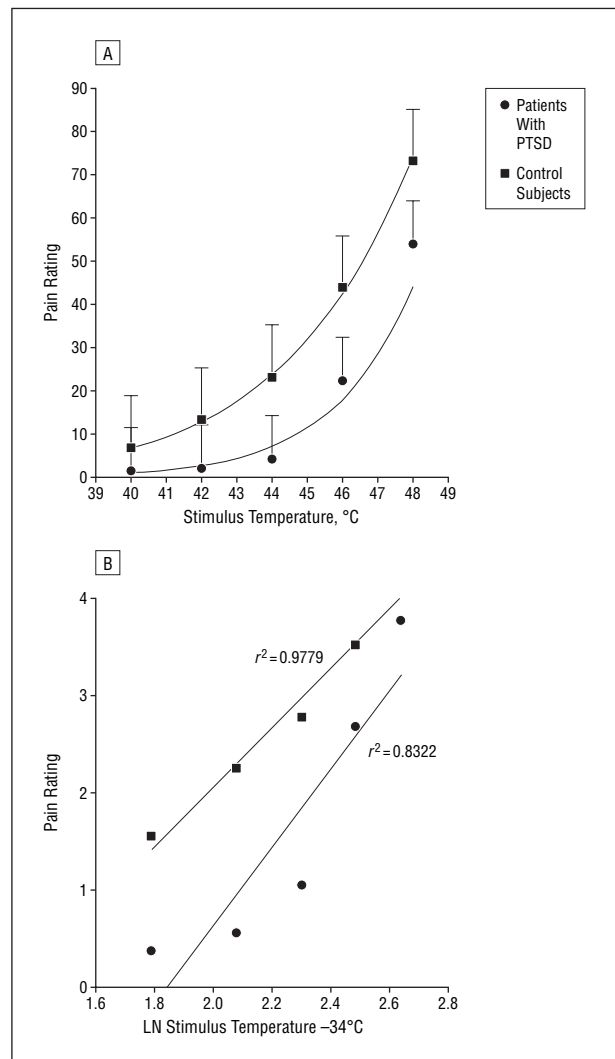


Figure 1. Temperature and mean perceived pain intensity (range, 0-100) in patients with posttraumatic stress disorder (PTSD) and control subjects. A, Stimulus temperature–numerical rating functions plotted in linear coordinates. Vertical bars indicate standard errors. B, Stimulus temperature–numerical rating functions plotted in log-log coordinates. The slopes of these lines and the power function exponents are 4.03 for patients with PTSD and 3.07 for controls. LN indicates natural log.

(**Figure 2A**). In addition, patients with PTSD displayed less activity in the bilateral ventrolateral PFC (*left ventrolateral PFC*: $t<0$ in 8 patients and 2 controls; $t>0$ in 4 patients and 10 controls; t_{patients} , -0.96 ± 2.25 , and t_{controls} , 1.76 ± 2.30 ; random-effects analysis, $P<.01$; and *right ventrolateral PFC*: $t<0$ in 8 patients and 2 controls; $t>0$ in 4 patients and 10 controls; t_{patients} , -0.71 ± 2.63 , and t_{controls} , 1.95 ± 1.99 ; random-effects analysis, $P<.01$) (**Figure 2B**). Compared with controls, patients with PTSD also displayed a signal decrease in the right amygdala ($t<0$ in 9 patients and 2 controls; $t>0$ in 3 patients and 10 controls; t_{patients} , -1.18 ± 1.81 , and t_{controls} , 0.83 ± 1.54 ; random-effects analysis, $P<.01$). In the individual temperature condition, patients with PTSD revealed more activity in the right putamen ($t<0$ in 1 patient and 5 controls; $t>0$ in 11 patients and 7 controls; t_{patients} , 2.33 ± 1.80 , and t_{controls} , -0.00 ± 2.29 ; random-effects analysis, $P<.01$). A similar pattern of more activity in patients with PTSD was

Table 2. Main Effects of the Fixed-Temperature Condition and the Individual Temperature Condition in Veterans With PTSD and in Control Veterans Without PTSD

Region	Fixed-Temperature Condition (43°C)								Individual Temperature Condition (NRS Score of 40)							
	Control Subjects				Patients With PTSD				Control Subjects				Patients With PTSD			
	x	y	z	z Score	x	y	z	z Score	x	y	z	z Score	x	y	z	z Score
Right anterior cingulate																
Peri	11	35	8	8.02	13	35	8	10.22	NA	NA	NA	NA	NA	NA	NA	NA
Mid	8	19	42	8.70	4	24	42	7.56	8	20	43	10.53	6	18	42	10.38
Left anterior cingulate																
Mid	-3	19	41	8.73	-6	24	43	8.12	-2	20	42	9.93	-6	14	42	10.26
Peri	-11	34	8	6.27	-11	36	9	10.26	NA	NA	NA	NA	NA	NA	NA	NA
Left posterior cingulate	-6	-46	17	-7.13	-1	-54	23	-7.72	-5	-52	17	-6.93	-2	-51	18	-7.15
Left cingulate gyrus	-3	-47	27	-5.17	-1	-44	27	-6.90	-6	-44	28	-5.10	-5	-44	28	-7.49
Precuneus																
Right	NA	NA	NA	NA	2	-48	31	-6.46	NA	NA	NA	NA	4	-48	31	-7.43
Left	-3	-47	32	-5.72	-3	-47	31	-6.73	-1	-53	31	-6.95	-9	-47	31	-7.52
Right posterior cingulate	3	-47	17	-7.02	4	-42	25	-6.90	7	-50	17	-5.25	1	-50	18	-7.15
Posterior parietal cortex																
Right	38	-54	35	7.27	41	-56	36	6.45	36	-53	35	8.41	38	-54	35	11.37
Left	-42	-48	40	5.93	-42	-50	39	5.78	-44	-47	36	6.63	-40	-55	35	9.19
Right precentral gyrus	45	-15	41	-8.92	NA	NA	NA	NA	47	-14	41	-6.31	NA	NA	NA	NA
Right postcentral gyrus	47	-16	44	-8.92	48	-17	44	-5.58	38	-21	47	-5.59	38	-23	47	-5.02
Right middle frontal gyrus																
BA9	46	13	28	7.49	39	35	19	8.91	42	14	34	8.48	47	13	28	12.52
BA6	NA	NA	NA	NA	NA	NA	NA	NA	29	46	0	6.33	NA	NA	NA	NA
Left middle frontal gyrus	-29	28	28	6.61	-35	23	28	7.06	-30	27	28	5.83	-29	30	28	6.95
Right inferior frontal gyrus	41	43	3	9.11	43	45	4	9.63	42	43	3	10.94	41	43	1	10.82
Right inferior frontal gyrus	49	15	3	8.73	34	26	1	7.10	49	13	3	10.03	49	14	4	11.25
Superior temporal gyrus																
Right	53	-1	5	6.07	52	-3	4	4.23	53	-3	5	7.35	53	-3	6	10.97
Left	NA	NA	NA	NA	-51	-6	5	6.08	-49	-2	6	7.06	-49	0	7	12.66
Left middle temporal gyrus	-48	-57	11	-7.47	-48	-66	11	-4.57	-47	-55	12	-8.11	NA	NA	NA	NA
Insula																
Left	-40	15	1	8.68	-30	21	9	5.65	-40	15	1	12.14	-40	13	1	10.90
Right	33	17	10	7.87	37	16	2	5.99	38	15	1	12.03	32	16	1	13.25
Medial thalamus																
Left	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-6	-15	0	6.63
Right	NA	NA	NA	NA	NA	NA	NA	NA	2	-15	-1	5.57	6	-15	1	5.04
Left claustrum	-29	16	4	7.90	-29	16	3	6.09	NA	NA	NA	NA	-28	15	3	10.73
Right amygdala	23	-8	-11	5.24	25	-11	-11	-3.80	NA	NA	NA	NA	25	-10	-15	-4.50
Left hippocampus	-29	-11	-19	-4.47	-25	-12	-19	7.41	NA	NA	NA	NA	-27	-16	-20	4.70
Putamen																
Left	NA	NA	NA	NA	NA	NA	NA	NA	-17	4	4	5.70	-17	4	5	7.45
Right	NA	NA	NA	NA	18	2	6	5.48	NA	NA	NA	NA	30	-8	-2	9.44

Abbreviations: BA, Brodmann area; NA, not activated; NRS, numerical rating scale; PTSD, posttraumatic stress disorder.

Table 3. Regions of Interest With Significant Group Differences for the 2 Conditions

Region	Fixed-Temperature Condition (43°C)				Individual Temperature Condition (NRS Score of 40)			
	x	y	z	z Score	x	y	z	z Score
Ventrolateral prefrontal cortex								
Right	31	40	4	-6.47	ND	ND	ND	ND
Left	-36	30	9	-6.69	ND	ND	ND	ND
Right precentral gyrus	ND	ND	ND	ND	52	-6	38	4.80
Anterior insula								
Right	ND	ND	ND	ND	30	16	13	5.37
Left	ND	ND	ND	ND	-35	19	13	5.07
Right putamen	ND	ND	ND	ND	30	-9	-2	5.74
Right amygdala	27	-8	-13	-4.91	23	-8	-14	-4.57
Left hippocampus	-28	-12	-19	7.39	ND	ND	ND	ND

Abbreviations: ND, not different; NRS, numerical rating scale.

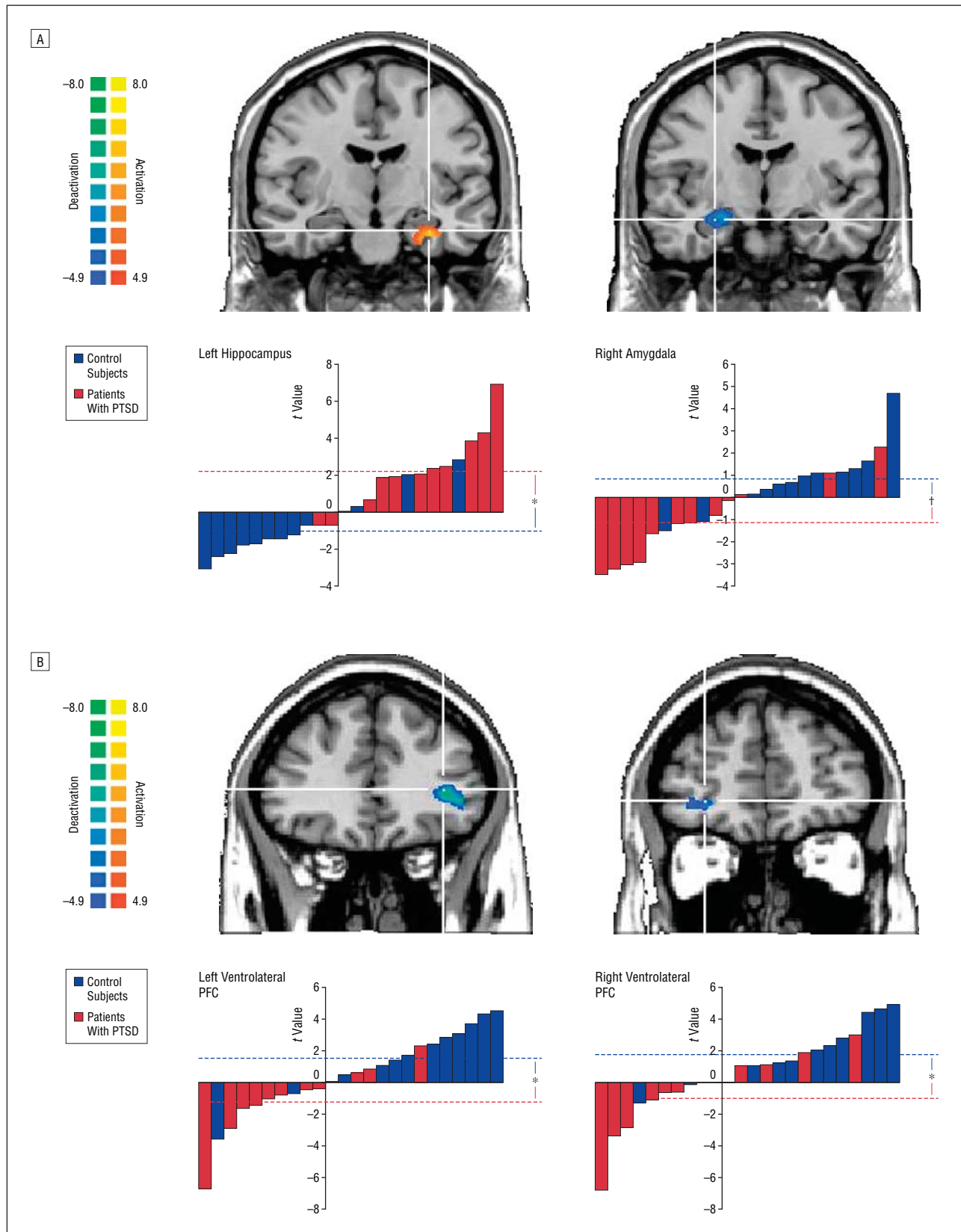


Figure 2. Group comparison of responses to fixed-temperature conditions. Brain activity for the fixed-temperature condition is shown in the left hippocampus and the right amygdala (A) and in the left ventrolateral prefrontal cortex (PFC) and the right ventrolateral PFC (B). Each upper row displays the group differences between patients with posttraumatic stress disorder (PTSD) and control subjects in coronal sections ($P < .001$; cluster corrected with a minimum cluster size of 200 voxels, whole-brain corrected). Each lower row displays the region of interest–based random-effects analysis, with individual t values sorted by height in patients with PTSD and controls. Positive values indicate that the condition-specific predictor explained a net signal increase from the mean signal during baseline, whereas negative values explain a net signal decrease. * $P < .01$, 2-tailed t test. † $P < .001$, 2-tailed t test.

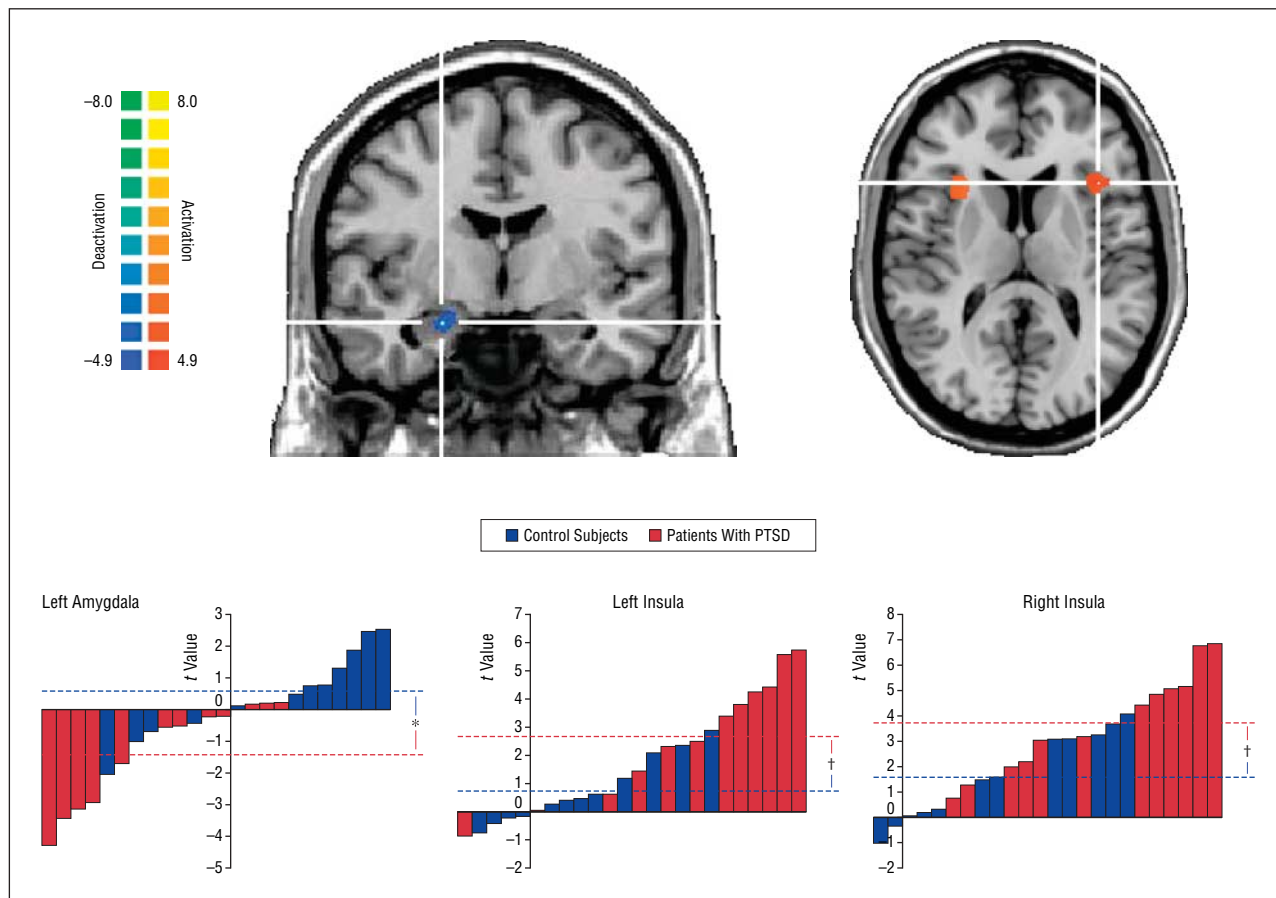


Figure 3. Group comparison of responses to individual temperature conditions. Brain activity for the fixed-temperature condition is shown in the right amygdala and the bilateral insula. The upper row displays the group differences between patients with posttraumatic stress disorder (PTSD) and control subjects in coronal and transverse sections (* $P < .001$; cluster corrected with a minimum cluster size of 200 voxels, whole-brain corrected). The lower row displays the region of interest–based random-effects analysis, with individual t values sorted by height in patients with PTSD and controls. Positive values indicate that the condition-specific predictor explained a net signal increase from the mean signal during baseline, whereas negative values explain a net signal decrease. † $P < .01$, 2-tailed t test.

found in the bilateral anterior insula (*left anterior insula*: $t < 0$ in 1 patient and 4 controls; $t > 0$ in 11 patients and 8 controls; $t_{\text{patients}}, 2.77 \pm 2.15$, and $t_{\text{controls}}, 0.72 \pm 1.17$; random-effects analysis, $P < .01$; and *right anterior insula*: $t < 0$ in 2 controls; $t > 0$ in all patients and 10 controls; $t_{\text{patients}}, 3.80 \pm 2.04$, and $t_{\text{controls}}, 1.62 \pm 1.76$; random-effects analysis, $P < .01$) (**Figure 3**). In the right precentral gyrus, patients with PTSD also displayed more activity ($t < 0$ in 2 patients and 7 controls; $t > 0$ in 10 patients and 5 controls; $t_{\text{patients}}, 1.40 \pm 1.47$, and $t_{\text{controls}}, -0.60 \pm 1.61$; random-effects analysis, $P < .01$). Patients with PTSD continued to display significantly less right amygdala activity in the individual temperature condition ($t < 0$ in 9 patients and 4 controls; $t > 0$ in 3 patients and 8 controls; $t_{\text{patients}}, -1.37 \pm 1.65$, and $t_{\text{controls}}, 0.51 \pm 1.42$; random-effects analysis, $P < .01$).

COMMENT

To our knowledge, this is the first fMRI study that investigates pain processing in patients with PTSD. Patients with PTSD showed a shifted stimulus response function to heat stimuli. Before fMRI, patients with PTSD already showed a significant reduction in pain sensitiv-

ity. During imaging, patients with PTSD rated a fixed temperature as significantly less painful than control veterans. This contrasts with previous reports of increased pain sensitivity and more subjective complaints in patients with PTSD.⁹⁻¹¹ In the fixed-temperature condition, patients with PTSD revealed increased activation in the left hippocampus and decreased activation in the bilateral ventrolateral PFC and the right amygdala compared with controls. During stimulation with an individually adjusted temperature, patients with PTSD showed increased activation in the right putamen and bilateral insula, as well as decreased activity in the right precentral gyrus and the right amygdala.

The reduced right amygdala activation is a prominent finding that was displayed by veterans with PTSD in the fixed-temperature and the individual temperature conditions. The amygdala integrates nociceptive information and plays a dual facilitatory and inhibitory role in the modulation of emotional pain behavior.³² The amygdala is an important brain structure involved in the processing of analgesia information and has been hypothesized to play a role in opioid antinociception.³³ Prolonging the anticipated duration of a nociceptive stimulus also results in deactivation of the amygdala and may

reflect cognitive modulation of the aversiveness of the heat stimulus.^{34,35} Reduced right amygdala activity was displayed by patients with BPD in an earlier study on neural correlates of pain processing in BPD by Schmahl et al.¹⁶ Both PTSD and BPD may be seen along a trauma spectrum perspective, because they show similar underlying etiology and several overlapping symptoms.³⁶ The symptoms of BPD and PTSD tap into neural circuitry involved in emotional regulation such as the amygdala, hippocampus, and orbitofrontal cortex.^{37,38} Although traumatic experience is involved in both disorders, BPD involves developmental or acquired brain dysfunction, possibly associated with early traumatic experience in most patients, whereas trauma usually occurs later in life in patients with PTSD (especially in veterans).³⁹

Negative blood oxygenation level-dependent responses should be interpreted with caution, as this may reflect a reduction or suppression of neuronal activity resulting in decreased cerebral blood flow^{40,41} or a hemodynamic effect in which blood is diverted or allocated to the most active areas, while adjacent areas reveal reduced blood flow.^{42,43} However, it was not likely in our study that this negative blood oxygenation level-dependent response was induced by a reallocation of blood flow from the posterior cingulate cortex or the amygdala to adjacent areas (there were no adjacent areas that exhibited a significantly increased cerebral blood flow); therefore, a reduction of neuronal activity in these areas (compared with baseline activity) is a more plausible explanation. Other studies^{16,44-46} found a decrease in these areas after application of noxious stimuli, and these signal decreases were not unexpected.

In the individual temperature condition, each subject received a stimulus that corresponded to a score of 40 on the NRS. In this condition, the affective value given to the stimulus was similar in both groups. Pain ratings that were taken during the imaging session for the individual condition were slightly higher than those before fMRI for patients with PTSD and controls. However, there were no significant differences between the affective ratings given by patients with PTSD compared with controls during fMRI, showing that both groups attributed the same affective label to stimuli in this condition. In the individual temperature condition, patients with PTSD revealed increased activity in the bilateral insula compared with controls. Activity of the insula in pain research is common and is usually related to discrimination of stimulus intensity and to emotional processing.⁴⁷⁻⁵¹ Bilateral anterior insular cortex activation is also related to cognitive evaluation of pain intensity.⁵² The observed increase in activity in patients is perhaps related to a similar mechanism.

We had expected that the rostral ACC, which plays an important role in affective pain processing,^{6,53} would be less active in the PTSD group because patients consistently rated the fixed temperature as less painful. However, it may be that we had insufficient power to differentiate between patients and controls in this area, because in both groups the ACC was highly active compared with baseline activity. Cognitive attention given to other stimuli (eg, other sounds in the MR imaging room) by patients with PTSD could lead to reduced pain perception, while ACC activity would still be present.⁶

In the fixed-temperature condition (43°C), veterans with PTSD displayed reduced activation in the bilateral ventrolateral PFC and the right amygdala, as well as increased activation in the hippocampus. Reduced activation of the ventrolateral PFC is consistent with previous functional imaging research that found decreased neural activity in the PFC of patients with PTSD.⁵⁴⁻⁶⁰ Activation of prefrontal regions is usually attributed to mediation of the cognitive dimension of pain processing associated with localization and encoding of the attended stimulus.^{47,53} Previous research indicates that the ventrolateral PFC is activated during cutaneous painful heat stimulation.⁶¹ The reduced activity in the ventrolateral PFC found in patients with PTSD may be related to the reduced cognitive pain processing during the fixed-temperature condition. However, the reduced activity of the ventrolateral PFC is observed in the context of reports of lower pain intensity by veterans with PTSD, which may also explain this finding.

In patients with PTSD, the hippocampus (which plays an important role in the regulation of the hypothalamo-pituitary-adrenal axis) is structurally and functionally abnormal. Patients have shown reduced hippocampal volume and have displayed altered activity in the hippocampal area in several paradigms.^{58,62-65} The hippocampal role in pain processing is usually attributed to the intensity of nociceptive stimulation.⁶ That patients with PTSD show a net signal increase in this area during the fixed-temperature condition cannot be related to stimulus intensity, as this was the same in both groups. Other hippocampal functions such as memory encoding, memory retrieval, novelty detection, or contextual conditioning are a more probable explanation for the increased activity observed in patients with PTSD. Glucocorticoid receptors in the hippocampus are activated by rising glucocorticoid levels during stress to mediate fast feedback inhibition of the hypothalamo-pituitary-adrenal axis. It is also plausible that the increased blood oxygenation level-dependent response in the left hippocampus (which extended into the parahippocampal gyrus) witnessed in our patients reflects this activity. The net signal decrease in the left hippocampus displayed by controls has been previously reported and is thought to pertain to the affective response to pain.^{46,53}

The fMRI results need to be interpreted in light of an altered stimulus response to heat stimuli. A mechanism that may be involved in this shift is stress-induced analgesia. Earlier studies^{12,13} demonstrate that patients with PTSD reveal opioid-mediated stress-induced analgesia after watching a stressful combat video. Activation of the μ -opioid receptor system by endogenous opioid peptides is associated with reductions in sensory and affective ratings of pain experience.^{14,15} High levels of opioid receptor binding are seen in the ACC, PFC, putamen, amygdala, caudate nucleus, and insular cortex.⁶⁶⁻⁶⁹ Several pain regions that showed an altered response in PTSD in our study, most notably the amygdala, insular cortex, and ventrolateral PFC, are involved in the endogenous opioid modulation of sensory and affective pain elements.^{14,15} In our study, patients with PTSD experienced significantly more aversive inner tension during the fMRI session than controls. However, whether the

stress of the psychophysical examination before fMRI and the stress experienced during fMRI was sufficient to induce opioid-mediated analgesia needs to be investigated.

The finding of a signal decrease in the precentral gyrus ipsilateral to the stimulus presentation in both groups is more difficult to interpret, although this phenomenon has been observed before.⁵³ It may be related to an inhibition of movement or to a contrast-enhancing mechanism such as anticipation or stimulus repetition.⁵³ In addition, both groups showed reduced activity in the precuneus and posterior cingulate cortex compared with baseline in both conditions.

The pain model used in this study is phasic thermal heat pain and may not necessarily be related to clinical pain conditions. Nevertheless, it is a useful probe for the examination of pain regulation mechanisms in PTSD. Future research should extend these findings to patients with PTSD related to trauma among civilians. The use of trauma controls in this study allows us to differentiate between these groups based on the presence and absence of PTSD only. The addition of a third control group consisting of healthy subjects who have not been subjected to trauma would allow us to observe differences in pain processing related to the effect of trauma or (former) occupation (all subjects were veterans). Although the number of subjects in this study was sufficient to permit random-effects analysis and to allow generalization of these results to the clinical population, future research should include more subjects to enable subgroup analyses.

To our knowledge, this is the first study to use fMRI to differentiate pain processing in patients with PTSD compared with trauma controls. Compared with controls, veterans with PTSD revealed an analgesic response when subjected to heat stimuli. Patients with PTSD showed altered pain processing in brain areas associated with affective and cognitive pain processing, such as the insula, hippocampus, amygdala, and ventrolateral PFC. We propose that the neural pattern with decreased activity in the right amygdala and the bilateral ventrolateral PFC reflects altered pain regulation mechanisms in patients with PTSD.

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Correspondence: Elbert Geuze, PhD, Department of Military Psychiatry T2, Central Military Hospital, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands (s.g.geuze@umcutrecht.nl).

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