Research Paper

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Deficits in pain perception in borderline personality disorder: results from the thermal grill illusion

Robin Bekrater-Bodmann[a,*], Boo Young Chung[a], Ingmarie Richter[a], Manon Wicking[a], Jens Foell[a,b], Falk Mancke[c], Christian Schmahl[d], Herta Flor[a]

Abstract

It is well documented that borderline personality disorder (BPD) is characterized by reduced pain sensitivity, which might be related to nonsuicidal self-injury and dissociative experiences in patients with BPD. However, it remains an open question whether this insensitivity relies at least partly on altered sensory integration or on an altered evaluation of pain or a combination of both. In this study, we used the thermal grill illusion (TGI), describing a painful sensation induced by the application of alternating cold and warm nonnoxious stimuli, in patients with either current or remitted BPD as well as matched healthy controls. Two additional conditions, applying warm or cold temperatures only, served as control. We further assessed thermal perception, discrimination, and pain thresholds. We found significantly reduced heat and cold pain thresholds for the current BPD group, as well as reduced cold pain thresholds for the remitted BPD group, as compared with the HC group. Current BPD patients perceived a less-intense TGI in terms of induced pain and unpleasantness, while their general ability to perceive this kind of illusion seemed to be unaffected. Thermal grill illusion magnitude was negatively correlated with dissociation and traumatization only in the current BPD patients. These results indicate that higher-order pain perception is altered in current BPD, which seems to normalize after remission. We discuss these findings against the background of neurophysiological evidence for the TGI in general and reduced pain sensitivity in BPD and suggest a relationship to alterations in *N*-methyl-*D*-aspartate neurotransmission.

Keywords: Borderline personality disorder, Thermal grill illusion, Pain, Dissociation, Traumatization, *N*-methyl-*D*-aspartate

1. Introduction

Borderline personality disorder (BPD) is characterized by disturbances in emotion regulation, social interaction, and self-image as well as impulsivity.[31] A special attribute of BPD is reduced pain sensitivity, which has repeatedly been reported in previous studies.[31,37,39,40,41] Patients with BPD displayed heightened pain thresholds to experimentally applied pain stimuli involving mechanical, chemical, electrical, and thermal stimulation,[30,33,39] which correlates with the level of state dissociation.[30] Previous results indicate that reduced pain sensitivity is associated with early traumatic experiences,[14] which are frequent in the history of patients with BPD. It is hypothesized that dissociation and reduced pain perception are mechanisms to cope with uncontrollable traumatic stress.[37] Furthermore, reduced pain sensitivity may be associated with BPD symptoms such as self-injurious behavior.[7,31] Borderline personality disorder shows relatively high remission rates,[50] but it is unclear which alterations are related to current BPD symptomatology, and which persist beyond remission.

From previous studies, it can be assumed that these perceptual alterations are related to changes in affective rather than sensory pain components.[10,40] Consistently, neuroimaging studies on pain processing in patients with BPD revealed altered activity in a frontolimbic network, including the amygdala, anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex, which has been associated with the cognitive and emotional evaluation of pain.[21,39] However, the induction of pain in previous studies always relied on nociceptive input, complicating the differentiation of peripheral and central alterations.

Thus, an experimental induction of pain by nonnociceptive input might provide important insights into physiological and psychological dimensions of pain processing in BPD. The thermal grill illusion (TGI)—first described by Thunberg[45]—offers such an opportunity for the induction of pain in the absence of nociceptive input. In this paradigm, simultaneous application of nonnoxious cold and warm temperatures to the skin induces an unpleasant, often painful sensation (eg, Refs. 11,12). Physiological experiments on TGI indicate that this kind of illusory pain is caused by central integration of thermoafferent signals,[11,25] and thus, this experiment can assess potential alterations in pain-related sensory integration. Illusory thermal pain evoked during the TGI is associated with activity in a pain processing network, including the thalamus, anterior insula,[28] and ACC.[12] Thus, although the

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[a] *Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany,* [b] *Department of Psychology, Florida State University, Tallahassee, FL, USA,* [c] *Department of General Psychiatry, Heidelberg University, Heidelberg, Germany,* [d] *Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany*

**Corresponding author. Address: Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Square J5, 68159 Mannheim, Germany. Tel.: +49-621-1703-6322; fax: +49-621-1703-6305. E-mail address: r.bekrater-bodmann@zi-mannheim.de (R. Bekrater-Bodmann).*

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TGI does not involve nociceptive input, it activates the nociceptive system at a higher central level of processing. The underlying processes have already been related to clinically altered pain processing,[44] highlighting the importance of sensory integration for pain perception.

We found no reference for previous use of the TGI in patients with BPD and we expected that TGI would yield a reduced pain perception in this patient group. We also expected higher thermal pain perception thresholds. Because there might be state and trait influences of BPD on pain perception, an additional sample of remitted BPD patients was recruited to differentiate between them. We expected a normalization of pain perception accompanied by remission of the disorder. Furthermore, we expected dissociation and traumatization to be negatively correlated with pain perception in patients with BPD.

2. Methods

2.1. Sample

Current and remitted BPD patients were recruited through online announcements, flyers, and from the pool of inpatients and outpatients of the Department of Psychosomatic Medicine and Psychotherapy at the Central Institute of Mental Health and of the Department of General Psychiatry at the University of Heidelberg. Fourteen healthy controls (HCs) were recruited through the local resident registration office, and eight were recruited from a database of persons who already participated in earlier experiments. While all of them underwent assessment for DSM-IV disorders (see next paragraph), the participants from earlier experiments did not complete the entire questionnaire battery (see section 2.6).

We included 29 participants with current BPD diagnosis (mean age = 27.55 years; SD = 7.12), 19 participants with BPD in remission (mean age = 30.89 years; SD = 6.11), and 22 HC (mean age = 28.95 years; SD = 8.13). All participants were female and there was no significant difference in age, $F_{2,67}$ = 1.24, P = 0.30. Sixty-eight participants were Caucasian, 1 African-Caucasian, and 1 Black Hispanic-Caucasian and all had been living in Germany at least since the age of 4 years. All but 2 left-handed and 2 ambidextrous participants in the remitted BPD group were right handed. The diagnosis of BPD according to the DSM-IV[1] was assessed with the International Personality Disorder Examination.[29] For the current BPD group, the patients had to fulfill 5 or more criteria, whereas patients were included into the remitted group when they fulfilled 3 or less criteria at the time of the investigation, but had fulfilled full BPD diagnostic criteria at an earlier time point. The inclusion criterion for remission time was at least 2 years. All diagnostic interviews were performed by experienced clinical psychologists or psychiatrists who were trained in conducting the interviews. Analyses of 3 diagnostic interviews taped on video indicated high interrater reliability with respect to both the number of BPD criteria (International Personality Disorder Examination[29]) and the dimensional score as assessed by the Zanarini Rating Scale[51] for DSM-IV borderline psychopathology with intraclass coefficients of 0.99 and 0.91, respectively.

All participants gave written informed consent before they were included in the study. We excluded participants with scars at the palmar side of their hands (due to self-injurious behavior or other reasons). Further exclusion criteria were a lifetime diagnosis of schizophrenia or bipolar I disorder, substance dependence within 2 years before study, current substance abuse, pregnancy, history of epilepsy, brain trauma, brain tumor, or other significant neurological or medical conditions. Psychotropic medication was also an exclusion criterion. Comorbid mental disorders are given in **Table 1**. The study was approved by the ethics review board of the Medical Faculty Mannheim, Heidelberg University and adhered to the Declaration of Helsinki.

2.2. The thermal grill

We used a TGI device in which the thermal stimuli were applied by eight borosilicate tubes (**Fig. 1**), which were heated or cooled by perfused water. The participant's hand rested on a versatile plastic bar unit (placed between the borosilicate tubes). Through a pneumatic control unit, 2 cuffs were alternately provided with compressed air with a predefined pressure (see Text, Supplemental Digital Content 1, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A117, which describes the technical details, and Figure, Supplemental Digital Content 2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A118, which shows the schematic setup as well as the components of the TGI device). In the off-block condition (no thermal stimulation), the lower cuff was filled with air, causing the plastic bars along with the resting hand to rise until no contact between the hand and the borosilicate tubes existed, while the upper cuff was emptied. In the on-block condition (thermal stimulation), the upper cuff was filled with compressed air, whereas the lower cuff was emptied, producing standardized contact between the hand and the borosilicate tubes.

Previous results indicated that the intensity of TGI depends on the magnitude of the temperature differential of cold and warm innocuous stimuli: a differential of 21°C to 25°C results in the highest frequency and highest ratings of pain for the TGI.[8] Since our material reduced the effective temperature compared with metallic tubes, we used temperatures (16°C and 40°C) close to pain threshold, but actually below the often reported thresholds for heat pain (about 45°C[2,8,20,26]) and cold pain (about 13°C[8,20]), excluding purposefully the nociceptive system. In a pilot study, we tested the device and found comparable results to previous metallic devices (see Text, Supplemental Digital Content 3, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A119, which describes the design and results of a study testing the TGI device).

2.3. Assessment of thermal perception and pain thresholds

We assessed perception and pain thresholds for the warm and cold domains by using a Thermal Sensory Analyzer (Medoc Ltd, Ramat Yishai, Israel). Thermal stimuli were applied through a thermode of 30 × 30 mm attached to the thenar eminence of the left hand. The temperature of the thermode either rose or fell at a rate of 1.2°C/s for cold and warm perceptions, and 3.0°C/s

Table 1
Comorbidities of the samples.

Comorbidities, n(%)	Current BPD (N = 29)	Remitted BPD (N = 19)	HC (N = 22)
Comorbid major depression	10 (34)	4 (21)	0 (0)
Major depression (remitted)	5 (17)	2 (11)	0 (0)
Comorbid posttraumatic stress disorder	4 (14)	1 (5)	0 (0)
Other acute comorbid disorder	12 (41)	4 (21)	0 (0)
More than 1 acute comorbid disorder	10 (34)	2 (11)	0 (0)

BPD, borderline personality disorder; HC, healthy control.

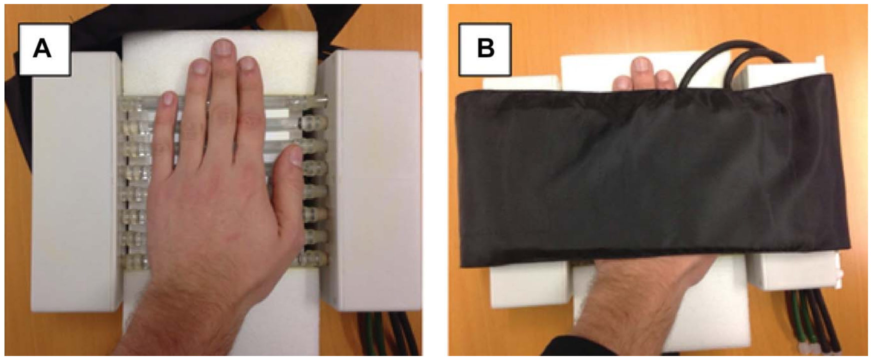

Figure 1. The thermal grill thermode. View from above on the assembled thermal grill device thermode ready for experimental use (A) with hand and without cuff, and (B) with hand and with cuff (experimental setup).

for cold and heat pain.[25,27] The subject signaled the onset of thermal perception or pain by pressing a switch, which then reversed the temperature change and returned the temperature of the thermode to 32˚C baseline. We always assessed threshold for the warm domain first, always starting with perception threshold assessment. For each threshold, we ran 5 trials; the first trial was used to familiarize with the task. The threshold value entering the analyses is the average of the remaining 4 trials each.

Furthermore, we assessed thermal discrimination thresholds using the method of Thermal Sensory Limen: after an initial phase of 20-second baseline temperature (32˚C), the participants had to indicate when they perceived a subjectively warm temperature by pressing a switch, whereupon the thermode changed to a temperature-reducing mode until the participant perceived a subjectively cold temperature. The temperature of the thermode either rose or fell at a rate of 1.2˚C/s. Thus, we assessed 10 thresholds for warmth and coldness. The first 2 trials each were used to familiarize the subject with this task, with the result that the discrimination thresholds were defined as the mean of the 8 remaining trials for warmth and coldness. Because of technical problems, three current BPD patients and 1 HC did not perform the discrimination task.

For reasons of safety, the thermode turned itself off when the temperature reached 52˚C or 0˚C, if a subject did not press the switch before then. Because of this safety measure, some pain thresholds might actually be higher than recorded when they exceeded the limits. This safety limit was reached in 7 current BPD patients, 3 remitted BPD patients, and 2 HC for the heat pain threshold assessment, and in 6 current BPD patients and 2 remitted BPD patients for the cold pain threshold assessment.

2.4. Thermal grill illusion induction

The thermal grill experiment was performed after the threshold assessment, with an intertrial interval of approximately 10 minutes. In this study, we implemented three conditions: the TGI condition (EXP, with an alternating pattern of 16˚C/40˚C) and 2 control conditions controlling for the cold and warm temperatures (the COLD condition with a pattern of 16˚C/16˚C and the WARM condition with a pattern of 40˚C/40˚C). The order of conditions was randomized. For each condition, the instruction for the participants was kept identical, communicating to the participants to keep their left, stimulated hand still and flat on the device and to not resist the passive movement performed by the pneumatic components. The participants were informed that innocuous temperatures would be applied in the coming trial, which may or may not induce discomfort or pain.

The participants had approximately 20 minutes to adapt to the thermal environment of the testing room (with a relatively constant temperature of 24.6˚C, SD = 2.2). We assessed hand temperature by measuring on the thenar eminence of the left hand. The mean hand temperature was 32.2˚C (SD = 2.1), and there were no hand temperature differences between the 3 groups, $F_{2,67}$ = 0.66, P = 0.52.

The participants' left hand was placed on the plastic resting bars so that the entire palm and the first phalanges of the fingers were located above the borosilicate tubes. The compressed air cuff was closed and the experimenter left the testing room, starting the presentation software controlling the pneumatic unit.

Each trial consisted of 3 on-blocks (hand pneumatically pressed against the borosilicate tubes) separated by 2 off-blocks (hand pneumatically elevated, not touching the borosilicate tubes), lasting for 20 seconds each. This duration allowed enough time for the passive hand lowering toward the borosilicate tubes (approximately 5 seconds) and a sufficiently long stimulation time of approximately 15 seconds. With a starting phase of 5 seconds off-block, 1 condition lasted for 105 seconds.

After each condition, the experimenter handed the response questionnaire to the participant, asking the items described below. To avoid inaccuracies in stimulus characteristics, as well as to ensure normalization of hand temperature and receptor function, we implemented an intertrial duration of at least 10 minutes. This time was used to let the participants complete several questionnaires assessing perceptual traits required for another study.

2.5. Response questionnaire

The response questionnaire asked for nonpainful and painful sensory and affective components of the TGI. After each condition, participants were asked to indicate unpleasantness and arousal pertaining to perceptions during the trial, using the self-assessment manikin scale (see Ref. 9; for more intuitive reading, the arousal scale was later inverted so that higher values represent both higher unpleasantness and higher arousal). The participants were asked to indicate the perception of 6 different qualities of pain: heat pain (hot pain, burning pain), cold pain (freezing pain, cold pain), and, as a control category, pain qualities that were not expected during this experiment (pulling pain, sharp pain). These items were taken from a previous study on pain qualities during the TGI.[3] Finally, the participants were asked to indicate the general intensity of pain perceived during the trial using a 100-mm visual analog scale (VAS) ranging from "no pain" to "worst pain imaginable."

2.6. Other psychometric instruments

The Fragebogen zu Dissoziativen Symptomen (FDS[15]) is the German adaptation of the Dissociative Experiences Scale by Bernstein-Carlson and Putnam.[5] This self-assessment instrument is a screening tool for detecting various dissociative phenomena in terms of a trait. Its use is recommended in the context of dimensional diagnosis of dissociative traits in several psychological and psychiatric disorders including BPD. We used the general sum score. One current BPD patient did not complete the FDS.

The Childhood Trauma Questionnaire (CTQ[4]; German version[48]) is a self-assessment instrument, which assesses different forms of abuse (emotional, physical, sexual) and neglect (emotional, physical) experiences in early life. Higher scores represent higher rates of abuse or neglect. In this study, we confine analysis to the abuse subscales because we had the expectation that abuse experiences are correlated to altered pain perception.[14] Two current BPD patients did not complete the CTQ.

Before each experimental TGI condition and thermal threshold assessment, the subjects had to complete the DSS-4 (see Ref. 43; short version of the dissociation tension scale[42]), reliably assessing state dissociation, even when used repeatedly during the course of an experiment. Seven HCs did not complete the DSS-4.

The questionnaires described above were usually given before the experiment, at the stage of the central diagnostic assessment. However, the 8 HC recruited from earlier experiments did not complete the questionnaires. In addition, missing trait assessment instruments (FDS, CTQ) of 1 current and 1 remitted BPD patient were completed after the assessment at home and mailed in (see section 2.7).

2.7. Statistical analyses

Because some of the thermal pain thresholds were expected to be cut due to safety reasons (see section 2.3), we decided to analyze these data nonparametrically. We performed Kruskal–Wallis tests for group differences and tested for which group caused the differences post hoc using Mann–Whitney tests. We provide the test statistics, the Bonferroni-corrected 2-tailed P value and r (applying the equation $r = Z/\sqrt{N}$) as a value for effect sizes. For the nonparametric tests, we used the Monte Carlo procedure (10,000 samples). Since no ceiling effect occurred for the thermal perception and discrimination thresholds, these data were analyzed using parametric 1-way analyses of variance. In case of significance, we applied Bonferroni-corrected post hoc tests to evaluate which group caused the difference.

The TGI data were analyzed using mixed-design analyses of variance, modeling the effects for group (current BPD, remitted BPD, HC) and condition (COLD, WARM, EXP). When Mauchly's test of sphericity was significant, degrees of freedom, F values, and P values were adjusted applying Greenhouse–Geisser correction. T tests were used for post hoc analyses. We provide the test statistics and the Bonferroni-corrected 2-tailed P value (for conditions or groups). Furthermore, we provide Cohen's d (calculated by using the mean and the SD) as a measure for effect size. In case of a significant Levene's test, the degrees of freedom, the t value, and the P values were adjusted. In each group, we tested whether a painful TGI percept was present. This was done by subtracting the linear combination of WARM and COLD from it and performing a 1-sample t test with a test value of 0. Besides the original values of the VAS pain ratings, we used the relative superadditive effect, which represents a standardized measure of the illusory percept (defined as [VAS EXP − VAS WARM − VAS COLD]/[VAS EXP + VAS WARM + VAS COLD]). Thus, the relative superadditive effect (ranging from −1 to +1) represents a TGI measure, which is adjusted for suggestibility and response biases by subtracting the responses of the control conditions from the response in the experimental condition, divided by the sum of all VAS responses. We further provide descriptive data for the quality of painful TGI sensations induced during the EXP condition to evaluate potential differences between current and remitted BPD patients and HC.

Finally, we performed correlational analyses between thermal pain thresholds, the relative superadditive TGI effect, unpleasantness related to the TGI percept, dissociation, and traumatic experiences, since (1) it has been shown that dissociative states reduce the perception of the TGI[19] and (2) there is evidence that reduced pain sensitivity might be a consequence of early traumatization.[14] These analyses were only performed in TGI responders (ie, subjects displaying a positive relative superadditive effect). Dependent on the involvement of parametrical or nonparametrical data, we used 1-tailed Pearson's or Spearman's correlations and provide the correlation coefficient (r or ρ, respectively) and P values. Because of multiple testing for identical hypotheses regarding a history of abuse (emotional, physical, sexual) and dissociation (state, trait), the P values were Bonferroni-corrected accordingly. To obtain a Bonferroni-corrected P value, we always multiplied the observed P value by the number of tests, meaning that the significance level is constantly at 0.05. Because only little variance was expected for HC in these clinical measures and we did not have complete data on all HC, we only performed correlational analyses for current and remitted BPD patients. Statistical analyses were performed with IBM SPSS Statistics (V20.0.0).

3. Results

3.1. Thermal perception, discrimination, and pain thresholds

There was no significant group difference for warm perception thresholds ($M_{currentBPD}$ = 34.49°C, SD = 1.52; $M_{remittedBPD}$ = 34.06°C, SD = 0.97; M_{HC} = 33.76°C, SD = 0.78; $F_{2,67}$ = 2.44, P = 0.10), but cold perception thresholds were significantly different ($M_{currentBPD}$ = 29.66°C, SD = 1.64; $M_{remittedBPD}$ = 30.22°C, SD = 0.93; M_{HC} = 30.64°C, SD = 0.58; $F_{2,67}$ = 4.16, P = 0.020). Post hoc tests revealed that the current BPD had significantly higher perception thresholds than the HC (P = 0.017).

There were no significant group differences for thermal discrimination thresholds, neither for the warm ($M_{currentBPD}$ = 35.64°C, SD = 1.92; $M_{remittedBPD}$ = 35.51°C, SD = 2.37; M_{HC} = 35.08°C, SD = 1.96; $F_{2,63}$ = 0.45, P = 0.64) nor the cold domain ($M_{currentBPD}$ = 29.37°C, SD = 2.01; $M_{remittedBPD}$ = 29.61°C, SD = 1.79; M_{HC} = 29.98°C, SD = 0.94; $F_{2,63}$ = 0.76, P = 0.47).

In contrast, we found a significant group difference for heat pain thresholds ($Mdn_{currentBPD}$ = 48.45°C, interquartile range (IQR) = 3.95; $Mdn_{remittedBPD}$ = 47.43°C, IQR = 8.23; Mdn_{HC} = 44.58°C, IQR = 4.56; H_2 = 9.17, P = 0.008) and cold pain thresholds ($Mdn_{currentBPD}$ = 6.53°C, IQR = 10.06; $Mdn_{remittedBPD}$ = 6.18°C, IQR = 11.20; Mdn_{HC} = 14.44°C, IQR = 9.97; H_2 = 11.43, P = 0.003). Post hoc tests revealed that the current BPD patients had significantly higher heat (U_{49} = 153.50, P = 0.003, r = 0.44) and cold pain thresholds than the HC (U_{49} = 154.00, P = 0.003, r = 0.44). In addition, the remitted BPD patients had significantly higher cold pain thresholds compared with the HC (U_{39} = 108.00, P = 0.021, r = 0.41). **Fig. 2** illustrates the group differences for the thermal pain thresholds.

3.2. Thermal grill illusion

3.2.1. Pain induced by the thermal grill illusion

The majority of participants in each group perceived the TGI (between 55% and 74%, **Table 2**). For the pain intensity ratings (**Table 2**), there was a significant main effect of condition ($F_{1.36,91.09}$ = 48.71, P < 0.001). Contrasts revealed that the ratings in the EXP condition were significantly higher compared with the COLD ($F_{1,67}$ = 57.61, P < 0.001) and the WARM condition ($F_{1,67}$ = 49.73, P < 0.001). Furthermore, we found a significant main effect of group ($F_{2,67}$ = 4.58, P = 0.014), which was driven by significantly less induced pain in the current BPD group compared with the HC group (P = 0.011). There was a significant condition × group interaction, $F_{2.72,91.09}$ = 3.39, P = 0.025. Compared with HC, we found a significantly reduced pain perception in the current BPD group only for the EXP condition ($t_{30.99}$ = 2.62, P = 0.040, d = 0.77). **Fig. 3A** illustrates the differences in VAS ratings. In each group, there was a significant TGI effect as indicated by an absolute superadditive effect >0 (t values ranged from 2.61 to 3.82; P values ranged from 0.008 to < 0.001, 1-tailed). The groups differed significantly in this absolute measure ($F_{2,69}$ = 3.84, P = 0.026), which was driven by a significantly higher effect in the remitted BPD patients compared with the current BPD patients (P = 0.022). There was a similar, but nonsignificant difference between remitted BPD patients and HCs. However, there was no significant group difference related to the relative superadditive TGI effect (given in **Table 2**) in the responder subgroups, $F_{2,41}$ = 0.88, P = 0.42.

3.2.2. Quality of pain during the thermal grill illusion

Across the entire sample, most of the participants described the painful sensation during the EXP condition as "burning" (45%-53%) or "hot" (59%-74%), that is, the majority of subjects (who reported at least one of these 2 qualities) perceived a heat pain quality (current BPD: 62%, remitted BPD: 79%, HC: 68%). Only a minority of participants perceived "cold" and/or "freezing" pain (current BPD: 20%, remitted BPD: 26%, HC: 22%). About 1 of 5 subjects perceived both heat and cold pain (current BPD: 20%, remitted BPD: 21%, HC: 18%). About 40% of participants described the pain as "sharp" (current BPD: 35%, remitted BPD: 47%, HC: 46%), and 5% to 24% as "pulling." There were no obvious group differences related to the quality of perceived pain.

3.2.3. Unpleasantness and arousal during the thermal grill illusion

For the unpleasantness ratings, we found a significant main effect of condition ($F_{2,132}$ = 37.34, P < 0.001) and group ($F_{2,66}$ = 7.66, P = 0.001). Contrasts revealed that the experiences in the EXP condition were evaluated significantly more unpleasant than in the COLD condition ($F_{1,66}$ = 8.40, P = 0.005) and the WARM condition ($F_{1,66}$ = 90.04, P < 0.001). Post hoc tests showed that only the current BPD patients experienced significantly less unpleasantness compared with the HC (P = 0.001). By comparing the ratings between these 2 groups in the individual conditions, we found significantly lower unpleasantness ratings in the current BPD group for both the EXP ($t_{48.71}$ = 3.73, P = 0.001, d = 1.03) and the COLD condition (t_{48} = 2.88, P = 0.018, d = 0.82). **Fig. 3B** illustrates the findings related to the unpleasantness ratings.

For arousal, there was a significant main effect of condition ($F_{2,132}$ = 41.77, P < 0.001) and group ($F_{2,66}$ = 7.63, P = 0.001). Contrasts revealed that the EXP condition induced significantly higher arousal than the COLD condition ($F_{1,66}$ = 29.75, P = 0.001) and the WARM condition ($F_{1,66}$ = 88.72, P < 0.001). Post hoc tests revealed that the current BPD patients experienced significantly less arousal compared with the HC (P = 0.002) and also the remitted BPD group reported less arousal compared with the HC (P = 0.007). However, this seemed to be a general effect since HC and current BPD only differed in the COLD condition ($t_{30.59}$ = 3.25, P = 0.008, d = 0.97), and HC and remitted BPD patients differed in the COLD (t_{38} = 3.19, P = 0.009, d = 1.02) and the WARM condition (t_{39} = 2.56, P = 0.044, d = 0.81). There were no significant differences for the relevant TGI EXP condition.

In the remitted BPD group and the HC, there was a significant positive correlation between TGI VAS intensity and unpleasantness ratings (remitted BPD: r_{17} = 0.62, P = 0.002; HC: r_{20} = 0.61, P = 0.001) and TGI VAS intensity and arousal ratings (remitted BPD: r_{17} = 0.63, P = 0.002; HC: r_{20} = 0.39, P = 0.036). There was no significant association in the current BPD group (unpleasantness: r_{27} = 0.28, P = 0.07; arousal: r_{27} = 0.05, P = 0.40; all P values 1-tailed).

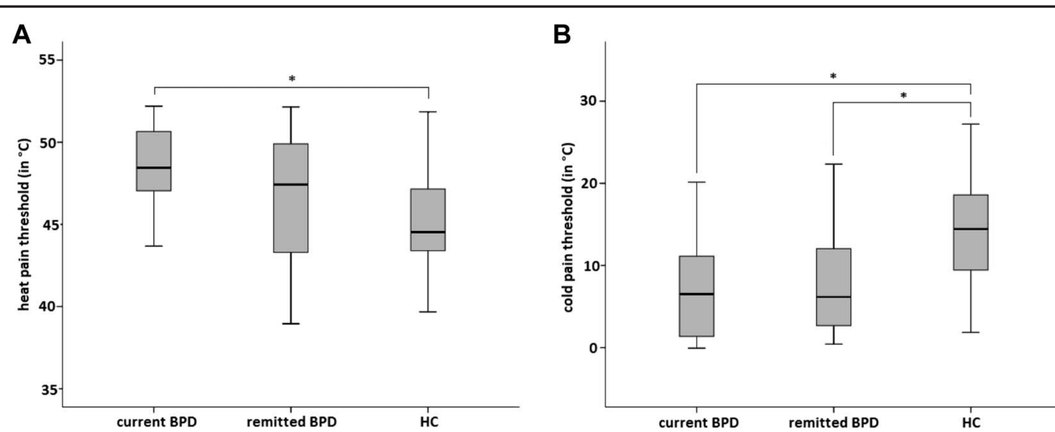

Figure 2. Pain thresholds of the samples. Heat pain (A) and cold pain thresholds (B) for patients with current borderline personality disorder (BPD), with remitted BPD, and healthy controls (HCs). *P < 0.05.

Table 2

Main measures in the TGI experiment (separately for the EXP condition, and both control conditions [WARM and COLD]) for current BPD patients, remitted BPD patients, and HCs.

Condition	Measure	Mean (SD)		
		Current BPD	Remitted BPD	HC
EXP	Response rate* (%)	55	74	55
	Pain VAS	12.76 (15.86)	29.05 (28.38)	30.27 (28.14)
	Relative superadditive effect†	0.75 (0.33)	0.79 (0.32)	0.62 (0.36)
	Unpleasantness	3.55 (2.40)	5.38 (2.58)	5.68 (1.67)
	Arousal	3.60 (2.08)	3.86 (2.01)	5.00 (1.93)
WARM	Pain VAS	1.00 (3.34)	0.84 (2.12)	7.00 (13.28)
	Unpleasantness	2.00 (1.65)	1.95 (1.20)	2.68 (1.84)
	Arousal	1.86 (1.41)	1.71 (1.23)	2.86 (1.64)
COLD	Pain VAS	4.55 (9.93)	3.58 (5.15)	9.77 (14.15)
	Unpleasantness	3.14 (1.92)	3.86 (2.08)	4.71 (1.90)‡
	Arousal	2.34 (1.26)	2.05 (1.47)	4.00 (2.07)‡

* Positive relative superadditive TGI effect.

† In responders.

‡ n = 1 missing data.

BPD, borderline personality disorder; EXP, experimental; HC, healthy control; TGI, thermal grill illusion; VAS, visual analog scale.

3.2.4. Correlations of pain measures and dissociation as well as abuse experiences

3.2.4.1. Dissociation

In TGI-responsive patients with current BPD, we found a significant negative correlation between the relative superadditive TGI effect and state dissociation (Pearson's $r_{14} = -0.54$, $P = 0.032$; **Fig. 4A**) and a nonsignificant relationship in the same direction for trait dissociation ($r_{13} = -0.36$, $P = 0.19$). In remitted BPD patients, we did not find such significant relationships (both $P \geq 0.28$). Thermal grill illusion unpleasantness ratings did not significantly correlate with trait and state dissociation (all $P \geq 0.62$, in both groups).

In patients with current BPD, there was no significant relationship between thermal pain thresholds and state dissociation (heat pain threshold: Spearman's $\rho_{26} = -0.10$, $P = 0.60$; cold pain threshold: $\rho_{26} = 0.36$, $P = 0.06$) or trait dissociation (heat pain threshold: $\rho_{26} = 0.06$, $P = 0.76$; cold pain threshold: $\rho_{26} = -0.08$, $P = 0.68$). In remitted BPD patients, there were also no significant relationships (all $P \geq 0.07$).

3.2.4.2. Experiences of abuse

In TGI-responsive patients with current BPD, correlation analyses between the relative superadditive effect and different types of abuse experiences revealed a significant negative relationship for physical abuse (Pearson's $r_{12} = -0.62$, $P = 0.026$; **Fig. 4B**) and a nonsignificant relationship in the same direction for sexual abuse ($r_{12} = -0.44$, $P = 0.17$). There was no significant relationship for emotional abuse ($r_{12} = -0.18$, $P = 0.80$). In remitted BPD patients, we did not find such significant relationships (all $P \geq 0.70$). Thermal grill illusion unpleasantness ratings did not significantly correlate with experiences of abuse (all $P \geq 0.12$, in both groups).

For the thermal pain thresholds in current BPD patients, significant correlations were only found for experiences of sexual abuse and heat pain threshold ($\rho_{25} = 0.53$, $P = 0.006$), with only

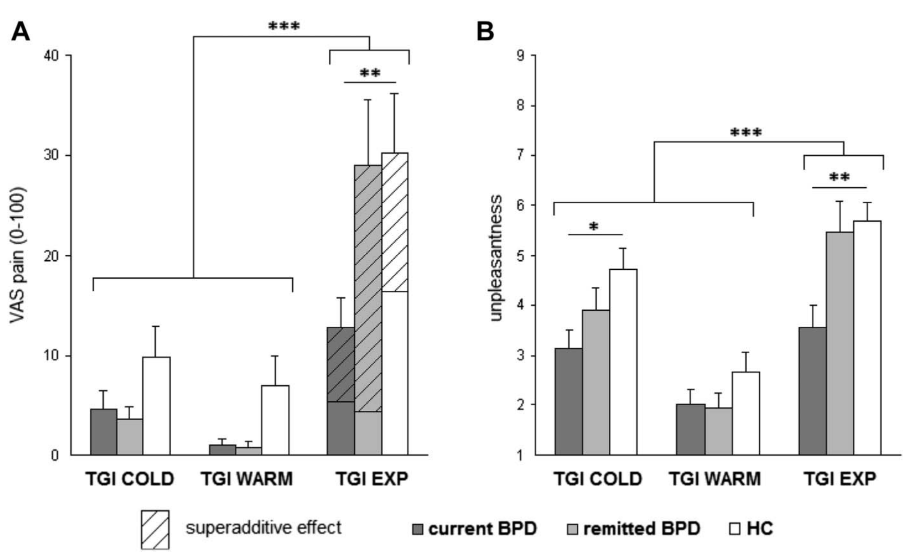

Figure 3. Main results for the thermal grill illusion (TGI) for the WARM and COLD condition as well as the experimental (EXP) condition. Given are the mean ratings for pain using a visual analog scale, VAS (A), unpleasantness (B), for current borderline personality disorder (BPD) patients, remitted BPD patients, and healthy controls (HCs). Error bars indicate the standard error of the mean. $^{**}P < 0.01$; $^{***}P < 0.001$.

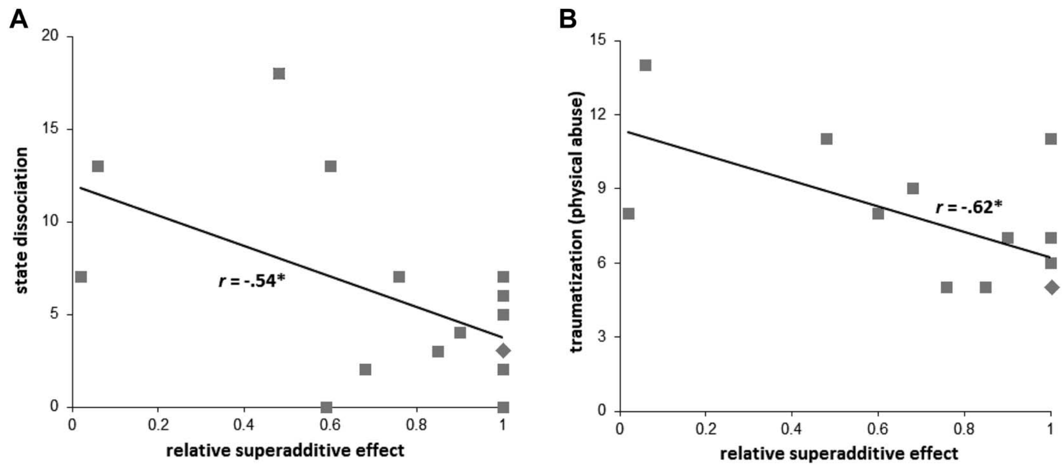

Figure 4. Correlation between thermal grill illusion (TGI) and dissociation and experiences of abuse. Scatter plot for relationships between the relative superadditive TGI effect and (A) state dissociation or (B) traumatization (physical abuse) in current borderline personality disorder patients who responded to TGI. A rhombus represents 3 (A) or 2 (B) individuals sharing the same data point. $^*P < 0.05$.

a trend for cold pain threshold ($\rho_{25} = -0.36$, $P = 0.10$). All other correlations between pain thresholds and abuse are $P \geq 0.74$. In remitted BPD patients, there was a similar pattern of relationship between a history of sexual abuse and thermal pain (heat pain threshold: $\rho_{17} = 0.67$, $P = 0.002$; cold pain threshold: $\rho_{17} = -0.38$, $P = 0.17$).

4. Discussion

In our study, we replicated the well-documented reduced pain sensitivity in BPD.[30,31,33,37,39] This was true for both heat and cold pain thresholds. Furthermore, we showed that remitted BPD patients displayed normalized heat pain thresholds similar to those of the HC, but still elevated cold pain thresholds. These results may highlight that altered heat pain sensitivity in BPD is a variable related to the manifestation of current disorder rather than a trait variable.

By using our TGI device, we induced vivid pain in the absence of nociceptive input in the majority of HC, with similar percentages as well as intensity and unpleasantness ratings as reported in the literature (eg, Refs. 8,18–20,28). In both TGI pain intensity and unpleasantness, current, but not remitted, BPD showed significantly reduced ratings compared with HC. A post hoc power analysis on pain, unpleasantness, and arousal for group and condition revealed a power of 0.8 and higher, suggesting that the power was high enough to explore the TGI effects.

The participants reported primarily a painful heat sensation induced by the TGI device. Since TGI sensations specifically exclude nociceptive input, our results indicate that the central processing of pain and its evaluation are altered in patients with current BPD. The absence of significant group differences in warm perception and thermal discrimination thresholds suggests that general sensory-discriminative properties are unaffected.[40] Furthermore, cold perception thresholds were elevated in the current BPD group, suggesting that this may not be uniform across modalities and the reasons for this have to be further explored. However, the presence of current BPD did not prevent the induction in the TGI in general. This conclusion is driven by a comparable number of TGI responders in each group, a significant TGI effect also in the BPD group, and that each group reported similar pain qualities. These results indicate that although current BPD patients can integrate intramodal input in the TGI experiment, comparable with HC, the strength of the perception seems to be reduced. Interestingly, remitted BPD patients seemed to perceive a stronger TGI compared with current BPD patients and HC, which might reflect a compensatory effect in pain perception accompanied by remission of the disorder. Only in the current BPD group, we found no significant positive correlation between induced TGI pain intensity and unpleasantness ratings, indicating altered sensory-discriminative and affective-motivational pain processing.[13,17,35,36] This finding might help to understand problematic behavior in BPD, such as self-injurious behavior: if the sensory component of pain perception is uncoupled from aversive evaluation, the inhibition threshold to perform such a behavior might be reduced. This post hoc result should be further explored in prospective studies.

We found a significant negative relationship between state dissociation and the magnitude of the TGI in responsive current BPD patients. Trait dissociation showed a trend for a relationship in the same direction. Furthermore, we found significantly less TGI perceptions in persons with more physical abuse and a trend in the same direction for sexual abuse only in current BPD. Considering the small number of participants included in these analyses, even the trends reported so far might be clinically relevant. For the thermal pain thresholds, we observed that higher thresholds were significantly related to a more extensive history of sexual abuse in current and in remitted BPD patients.

What may be the underlying mechanisms responsible for these effects? Both, the relationship between pain perception and dissociation as well as experiences of abuse might relate to alterations in neurotransmission in BPD. Kern et al.[19] showed that ketamine, an *N*-methyl-*D*-aspartate (NMDA) receptor antagonist inducing dissociation,[23,34] significantly reduced TGI perceptions in healthy participants, but did not influence thermal pain thresholds. Our results might relate to this finding: while we observed a negative relationship between dissociation and TGI intensity, there was no such association for thermal pain thresholds, suggesting that dissociation might specifically influence pain-related sensory integration. A role of the NMDA neurotransmission, which might explain both, dissociation and altered pain perception in BPD, has previously been proposed,[16] but supporting evidence is still lacking. However, it has been shown that early-life stress affect NMDA-modulated neuroplasticity,[38,46] which might contribute to altered pain perception in adulthood.[14] In animal studies, NMDA receptor antagonists have been shown to attenuate the activity of neurons involved in pain perception in the ACC.[49] Activity alterations in this area are associated with antinociception in BPD.[39] In posttraumatic stress disorder, a mental disorder that is accompanied by dissociative states similar to BPD, script-driven imagery-induced dissociation is associated with altered activity in ACC,[24] which is also true when painful stimulation is applied.[32] Furthermore, patients with BPD who experienced interpersonal trauma show diminished functional connectivity between the ACC and frontal areas,[22] which might be related to the trauma-associated reduced pain sensitivity previously reported.[14] Because the ACC is involved in the TGI,[12] these alterations might reflect the neurophysiological correlate of the findings presented in this study.

Furthermore, it has been shown that the TGI activates a cortical network, involving frontal and parietal areas, as well as the thalamus and the insula.[28] The involvement of the thalamus and the insula in the TGI underlines the importance of the affective-motivational pathway of pain[47] in this kind of perception, especially since activity in the insula is correlated with TGI unpleasantness ratings[28] as well as dissociation in patients with BPD,[32] indicating a functional relationship between dissociation and neural activity in brain regions involved in the processing of pain in BPD. However, since we did not find significant correlations between dissociation or experiences of abuse and unpleasantness ratings for the TGI percept, the underlying processes might be rather complex. Additional investigation of the neural correlates of pain perception and TGI sensations in BPD is needed due to the perceptual disturbances unique to the disorder. Since there is a lack of evidence related to neurophysiological correlates of remission of BPD, one can only speculate how this might change neural functioning. However, it might be that remission of the disorder is accompanied by neuroplastic changes, probably normalizing distorted neural processes.

This study has several limitations. The different methods of sample recruitment might have skewed the results, and the after-the-fact assessment of 2 psychometric data sets might have violated standardization. However, since both the psychometric instruments as well as the diagnostic interviews have good reliability and validity, the potential influences are expected to be rather small.

Thermal threshold assessment seems to be problematic in mental disorders accompanied by reduced pain perception due to limitations in the intensity of the stimulation that can be applied. About 1 of four current BPD patients may have higher heat pain thresholds than the safety limit. Thus, the actual thresholds might in fact lead to an underestimation of the differences between patients with BPD and HC.

One might assume that the selected temperatures for the TGI are too close to the mean pain threshold reported in the literature; however, as we described, the actual temperatures applied to the participant's hand are not that intense (difference to the chosen temperatures of up to 6°C toward moderate levels), due to the use of the poorly conducting borosilicate (see Text, Supplemental Digital Content 1, which describes the physical properties of our TGI device). Thus, it is unlikely that any of the participants received nociceptor-activating thermal stimulation. However, since we further assessed TGI percepts only subjectively, prospective studies should use the TGI and relate it to central nervous system responses to confirm altered pain processing due to the integration of nonnociceptive input in BPD. Given the homogeneity of the sample, future studies also have to test the generalizability of the results.

Finally, we did not adjust the temperature differential in the TGI experimental condition for individual pain thresholds (cf. Ref. 6). We did not adjust for mainly 2 reasons: first, since especially current BPD patients were expected to display elevated thermal pain thresholds, we were apprehensive of the (actually occurring) ceiling effects due to the shut-off of the thermode. In these subjects, a meaningful adjustment of temperatures is not possible. Second, an adjustment might eliminate the advantages of the TGI, namely the induction of pain without nociceptive involvement. Since there is no evidence that the function of the nociceptive system is altered in BPD per se, an adjustment of temperatures would potentially involve the nociceptive system by entering the thermal border which activates the thermal nociceptors. Furthermore, the finding that HC and remitted BPD patients did not significantly differ in their ratings of pain intensity and perceived valence suggests that the reported findings represent reduced higher-order pain processing in current BPD. Nevertheless, prospective studies could replicate our findings with adjusted temperatures.

In conclusion, our findings support the presence of reduced pain perception in current BPD, even in the absence of nociceptive input. Remission of BPD normalizes pain processing. Our results point to a dysfunctional coping strategy, involving the attenuation of acute pain perception in more traumatized BPD patients, modulated by dissociation. Alterations in NMDA neurotransmission might at least partly relate to these effects.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendices. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A117, http://links.lww.com/PAIN/A118, http://links.lww.com/PAIN/A119.

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