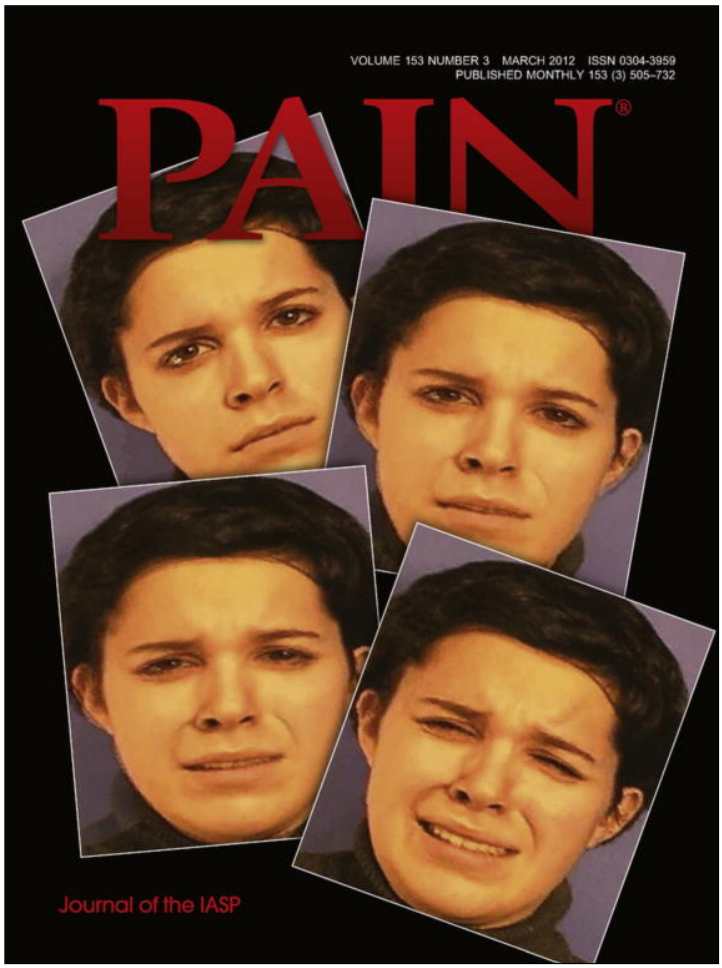

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Persistent antinociception through repeated self-injury in patients with borderline personality disorder

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ABSTRACT

Patients with borderline personality disorder, mostly female, exhibit severe autoaggressive behavior, namely an intentionally performed, nonsuicidal self-injury and severe blunting of pain perception, the mechanism of which is hitherto not understood. Because the nociceptive system displays a high degree of plasticity, the aim of this study was to analyze the relationship of pain perception to self-injurious behavior. Pain perception of mechanical and chemical noxious stimuli was studied by quantitative sensory testing in 22 patients (15 female, 7 male) with borderline personality disorder (BPD) according to DSM-IV and 22 age- and gender-matched controls. BPD patients exhibited a significantly higher pain threshold to pinprick stimuli (2.7 times higher than healthy control subjects), and significantly lower pain ratings to mechanical (pinprick, −28%) and chemical (capsaicin, −38%) stimulation. Capsaicin-induced pain decayed significantly faster in BPD patients (τ = 49 seconds) than in controls (τ = 76 seconds). These alterations of pain perception were generally present in the female, but not in the male subgroup of BPD patients. Analysis of pain intensity vs unpleasantness suggested that primarily the unpleasantness aspect of the pain experience was reduced. Blunting of pain sensation was significantly predicted by the recency of self-injurious behavior (multiple r = 0.58). In line with recent data, we suggest an excess of endogenous antinociception in BPD patients resulting from self-inflicted multiple injuries. This exaggerated pain control is conceived to operate via an uncoupling of the evaluative or emotional–affective from the sensory-discriminative dimension of pain.

1. Introduction

Patients with borderline personality disorder (BPD), a psychiatric disorder with a prevalence of 1.3% in general western populations and a preponderance in females [79], have a profound deficit in affective and cognitive self-regulation [46]. One characteristic feature is an autoaggressive behavior by intentionally performed, nonsuicidal self-injury occurring in 70% to 80% of patients [14]. Self-injurious behavior (SIB) is initiated to terminate states of negative affect or highly aversive inner tension, and SIB improves mood [16,20,33,66].

Importantly, the majority of BPD patients with SIB claim that their self-injury is not painful [43]. Likewise, BPD patients also display a relative insensitivity to experimental pain, namely to cold and heat pain, aggravated by acute stress exposure [8,66,71]. Painful stimulation improved the dysphoric mood in those BPD patients who did not perceive pain during self-injury, but not in those who felt pain or in healthy subjects [66]. Discontinuation of SIB partly reversed the suppression of pain sensitivity in BPD patients [48,49].

Specific testing of the pain pathways using laser-evoked potentials (LEPs) [80] confirmed reduced heat pain sensitivity but normal activation of ascending tracts in BPD patients up to primary (SI) and secondary (SII) somatosensory cortices and midcingulate cortex (MCC) (normal LEP latency and amplitude) [71]. This study also found normal spatial discrimination of painful stimuli and normal attentional modulation of pain and of LEPs [71] interpreted as evidence of undisturbed transmission of nociceptive input to the cortex. Functional magnetic resonance imaging, however, revealed that there was an overall reduction of brain activation in BPD patients [72]. At equally perceived pain intensity, however, overall

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activation was similar, but the pattern of activation differed across brain areas. Enhanced activation of the dorsolateral prefrontal cortex suggested exaggerated intracortical pain control [47] also suggested previously for diminished pain sensitivity in other psychiatric disorders [15,17].

Pain sensitivity is not a uniform trait, and different pain modalities rely on different genetic background [41,54,57,75] and are thus largely uncorrelated [29,58]. Previous studies in BPD patients assessed only cold and heat pain, the only pain modalities that are substantially correlated. We used more specific stimulation methods (capsaicin injection and pin prick) testing 2 well-characterized, independent nociceptive pathways (TRPV1-positive vs TRPV1-negative input) that can be differentiated by sensory testing in animals and humans. Capsaicin specifically activates TRPV1 receptors expressed in peptidergic polymodal nociceptors (TRPV1+, mostly C-fibers), also expressing μ-opioid receptors. Pin prick stimulation, which is a model of cutting injury [22] specifically excites capsaicin-insensitive (TRPV1−) Adelta-nociceptors, molecularly defined by mTOR/rapamycin-sensitive peripheral translation and expression of parathyroid hormone 2 and δ-opioid receptors. These nociceptive pathways have distinct functional roles in nociceptive processing [12,25,35,51–53,69,92].

In the present study, we examined the following questions: (1) Is pain sensitivity lowered across different pain modalities, targeted by probing 2 functionally unrelated nociceptive pathways by pin prick (TRPV1−) and capsaicin injection (TRPV1+)? (2) Is pain sensitivity related to severity of BPD, operationalized as scores in 3 instruments for BPD assessment and recency of SIB? (3) As a secondary aim, we probed possible gender differences by including a small subgroup of male BPD patients.

2. Methods

2.1. Participants

Twenty-two patients with BPD (15 female, 7 male; mean age ± SD: 29 ± 7 years) were studied (Table 1). Because little is known about pain processing in male BPD patients, we did not exclude male patients from the study sample. At the time of investigation, the majority of BPD patients (20/22) were inpatients at the Department of Psychiatry; 2 patients were former inpatients. The majority of BPD patients (n = 19) used 1 or more drugs at the time of investigation, usually selective reuptake inhibitors for serotonin and/or noradrenalin (n = 16), sometimes combined with tricyclic antidepressants and/or other open channel blockers (n = 7), α2-receptor antagonists (n = 3), or neuroleptics (n = 7). All drug treatments were stable regimens also present at the day of testing except for benzodiazepines, which were discontinued 3 days before testing. Compliance with drug treatment was verified by direct observation in the inpatients (20/22 BPD patients).

Twenty-two healthy control subjects (15 female, 7 male; mean age ± SD: 29 ± 7 years) were matched to the patients for age, gender, handedness, and social status. Healthy controls were recruited from hospital staff, by word of mouth, and via flyers/noteboard ads solely by the search criteria of a given age and gender (e.g., by posting a note that we needed a healthy 34-year-old male participant). They were at no time informed about the aims or hypotheses of the study. Healthy controls underwent the same testing procedures as BPD patients (detailed in the next sections). None of the healthy control subjects had previously participated in other experiments using the described methods. The experimental protocol was approved by the local ethics committee. All subjects and patients gave written informed consent before the experiments.

2.2. Diagnostic procedures

All patients and control subjects were thoroughly assessed by clinically experienced interviewers using the DSM-IV criteria for BPD according to the appropriate segment of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) [21]. The absence of axis I psychiatric disease was assessed by anamnestic interview and patient records, but we did not use more formal structured and validated assessment for axis I. In addition, the following psychometric assessments were performed (Table 2):

- Diagnostic Interview for Borderlines—Revised Version (DIB-R) [89]. The DIB-R consists of 4 dimensions (affect, cognition, impulse control, interpersonal functioning). Reliability of the DIB-R revealed excellent kappa values, namely 0.84 and 0.97 for inter-rater reliabilities at baseline and follow-up, 0.97 for test–retest reliability, and 0.96 for longitudinal reliability (among 3 generations of raters); intraclass correlations were 0.85 to 0.94 for DIB-R BPD diagnosis [91].
- Borderline Personality Inventory (BPI) [44]. The BPI consists of 4 subscales (identity diffusion, fear of nearness, primitive defense mechanisms, lack of adequate reality check). Psychometric properties of the BPI were tested in several studies. Outcome was independent of gender and age. Internal consistency and test–retest reliability were satisfactory (Cronbach's α = 0.68–091, test–retest r = 0.73–0.88); sensitivity of the BPI was 0.85 to 0.89, and specificity 0.78 to 0.89 [45].
- von Zerssen Mood Scale (Befindlichkeitsskala BfS [84]). The BfS scale consists of 28 bipolar adjective pairs rated on a VAS. The Bfs and its parallel form BfS' have split-half and

Table 1
Characteristics of study subjects and effect sizes.

Characteristic	Control subjects	BPD patients	Effect size (Cohen's d)	*P* value[a]
Gender	15 female, 7 male	15 female, 7 male		1.00
Age	29.4 ± 7.3	29.5 ± 7.4		.97
Educational status (1/2/3/4/5)[b]	−/3/1/16/1	3/−/9/8/2		.09
Job status (0/1/2)[c]	−/17/5	5/5/12		.20
Marital status (0/1/?)[d]	18/2/2	17/3/2		.60
SCID II scores	0.29 ± 0.56	6.86 ± 1.17	7.147	<.001
DIB-R scores	0.0 ± 0.0	8.35 ± 0.81	14.806	<.001
BPI-53 scores	1.90 ± 1.77 (7.5 percentile)	27.09 ± 6.11 (86.3 percentile)	5.614	<.001
Von Zerssen Mood Score	11.41 ± 8.47 (49.7 percentile)	29.41 ± 11.57 (87.3 percentile)	1.776	<.001

Data are mean ± SD. Positive values for effect sizes denote expression in BPD patients being stronger than in healthy controls.
[a] All comparisons by whole sample *t* test, except for educational, job, and marital status, which were by Mann–Whitney *U* test.
[b] 1 = secondary school; 2 = secondary school, plus apprenticeship; 3 = high school (w/o diploma); 4 = high school diploma/undergraduate; 5 = university degree.
[c] 1 = unemployed; 2 = in training/student; 3 = on the job.
[d] 0 = not married; 1 = married; ? = marital status not stated.

Table 2
Psychometric measure scores and effect sizes in study subjects.

	Female BPD patients (n = 15)	Male BPD patients (n = 7)	Effect size (Cohen's d)	*P* value[a]
SCID-II for DSM-IV				
Borderline personality disorder (D-score)	23.93 ± 0.43	23.86 ± 0.67	0.040	.49
Avoidant personality disorder	2.47 ± 0.29	2.00 ± 0.65	0.324	.53
Dependent personality disorder	2.20 ± 0.42	2.43 ± 0.69	0.132	.78
Obsessive–compulsive personality disorder	1.93 ± 0.30	1.43 ± 0.30	0.503	.25
Passive–aggressive personality disorder	1.87 ± 0.31	2.14 ± 0.34	−0.254	.56
Depressive personality disorder	3.60 ± 0.24	3.43 ± 0.43	0.164	.73
Paranoid personality disorder	2.00 ± 0.34	1.43 ± 0.37	0.490	.27
Schizotypical personality disorder	1.20 ± 0.31	1.43 ± 0.37	−0.021	.64
Schizoid personality disorder	1.73 ± 0.33	1.14 ± 0.40	0.503	.28
Histrionic personality disorder	0.87 ± 0.27	0.71 ± 0.18	0.197	.65
Narcissistic personality disorder	1.07 ± 0.27	1.43 ± 0.57	−0.277	.58
Antisocial personality disorder	0.73 ± 0.21	2.43 ± 0.43	−1.715	<.01
Diagnostic Interview (DIB-R)	8.46 ± 0.23	8.14 ± 0.26	0.402	.39
Affect	9.23 ± 0.26	8.57 ± 0.37	0.664	.18
Cognition	2.85 ± 0.23	2.71 ± 0.42	0.138	.79
Impulse control	6.08 ± 0.36	5.68 ± 0.34	0.341	.67
Interpersonal functioning	10.08 ± 0.77	8.00 ± 0.53	0.894	<.05
Borderline Personality Inventory (BPI)	28.20 ± 1.56	24.71 ± 2.25	0.581	.23
Identity diffusion	8.00 ± 0.45	4.57 ± 0.65	1.960	<.001
Fear of nearness	5.07 ± 0.46	4.71 ± 0.87	0.175	.73
Primitive defense mechanisms	5.13 ± 0.58	3.71 ± 0.64	0.713	.12
Lack of adequate reality check	1.40 ± 0.40	1.14 ± 0.55	0.173	.71
Von Zerssen Mood Score	29.13 ± 2.67	30.00 ± 5.57	−0.068	.89
Self-injurious behavior (SIB)				
Duration SIB (years)	15.4 ± 2.9	8.6 ± 2.0	0.774	.14
Recency of SIB (log10 days^{-1}) (→ mean time since last SIB)	−1.006 ± 0.242 (→10 days)	−2.142 ± 0.523 (→137 days)	0.961	.05
Pain/No pain on SIB	4 vs 11	4 vs 3		.17

Data are mean ± SEM. Positive values for effect sizes denote expression in female BPD patients being larger than in male BPD patients.
[a] All comparisons by whole-sample *t* test, except Pain/No pain on SIB by χ^2 test.

test–retest reliabilities >0.95 in patients and healthy controls. External validity as tested against single visual analogue scale (VAS), Hamilton Depression Scale, or experienced clinical observer is 0.90, 0.85, and 0.85, respectively [85].

Exclusion criteria were lifetime diagnosis of schizophrenia, bipolar I disorder, current substance abuse, major depression, or severe anorexia and any other axis I comorbidity as assessed by anamnestic interview. However, no further formal structured validated assessment for DSM axis-I-related psychiatric disease (e.g., by SCID-I) was made. Neither patients nor control subjects had a history of neurological disease as assessed by anamnestic interview and patient records.

2.3. Self-injurious behavior

The history of self-injurious behavior (SIB) was primarily assessed as the time elapsed since last SIB in all patients to a precision of 1 day. This information was obtained by open anamnestic interview (all done by coauthor D.B.) and relies on self-report. However, because all BPD patients were inpatients at the time of investigation, we verified this by visual inspection and double-checked by consulting records kept at the psychiatric ward, although this was possible only for recent SIBs (dating back up to approximately 1 month). However, this included the majority of BPD patients (16/22). For reported self-injury that dated back more than 1 month (6/22), we could only confirm that there was no visible evidence for a more recent SIB. Because of large variations over several orders of magnitude, these times were transformed into log10-values and the log10-values of the reciprocal of time since the last SIB was defined as recency of SIB [log10 (1/time since last SIB) days^{-1}]. Frequency of self-injurious behaviors (e.g., cutting, burning, head banging, etc.) could be assessed in only 11 patients and ranged from episodic single SIB up to 8 times per month within recent months (mean: 3 times per month). Patients were further subdivided according to whether they reported a subjectively complete or near complete analgesia (n = 14) or the presence of pain perception (n = 8) during SIB. Further, patients were stratified according to whether they reported pain to the test stimuli and/or exhibited an out-of-range pain threshold (i.e. pain thresholds could not be formally tested since the necessary stimulus forces exceeded the range of pain stimuli used for the examination).

2.4. Pain testing

Pain sensitivity of 2 nonoverlapping channels of the nociceptive system was tested.

2.4.1. Testing of TRPV1-negative pathway

A set of 7 punctate probes (forces of 8, 16, 32, 64, 128, 256, and 512 mN, applied 5 times at random series within 3-cm-diameter areas in both ventral forearms) were used to test mechanical pain perception. The punctate probes were cylindrical stainless steel wires (0.25-mm-diameter tip) mounted on plastic/metal rods that moved freely within a wider hand-held tube. These pinprick stimulators activate preferentially nociceptive primary afferents [24]. Psychophysical evidence in humans suggests that the pain to pin prick stimuli is elicited by action potentials mainly conveyed by a highly specific class of high threshold Aδ-mechano-nociceptors [51,92]. Subjects rated the magnitude of pain to mechanical test stimuli on a numerical rating scale (NRS) ranging from 0 = "non-painful" to 10 = "most intense pain imaginable." Care was taken to test in skin areas that did not have acute or scarified marks related to previous SIB.

2.4.2. Testing of TRPV1-positive pathway

Capsaicin (40 μg in 12.5 μL) was injected intradermally into the nondominant mid-ventral forearm. Pain to capsaicin was rated on a 10-cm visual analogue scale every 10 seconds for the first

minute, then every 30 seconds until the sensation had fully ceased. In addition, after the capsaicin-induced pain had faded, subjects were asked to rate the intensity and unpleasantness on separate visual analogue scales labeled "no pain" at the lower end and "maximal pain" and "maximal unpleasantness," respectively, at the upper end.

Testing was performed in the following fixed order: (1) BfS mood scale; (2) pin prick pain testing (rating of every single 1-second stimulus; 35 stimuli total); and (3) intradermal capsaicin injection (followed by continuous rating for 5 minutes; then global ratings of pain intensity and unpleasantness).

The order of pain testing could not be reversed, because capsaicin injection has the potential to modify pain sensitivity in 2 different ways. It is a very strong pain stimulus (average pain ratings >70/100) and will induce a strong local hyperalgesia over a larger skin area (secondary hyperalgesia lasting many hours). Also, it mimics a very strong injury-related noxious impact and may thus alter general pain sensitivity (whole body) by inducing endogenous antinociception (diffuse noxious inhibitory control [DNIC]). Thus, testing pin prick after capsaicin may confound the subject's/patient's acute response to challenge ("state") with his baseline pain sensitivity ("trait"). This may be especially critical in BPD patients.

2.5. Data evaluation and statistics

Psychometric functions for pinprick stimuli were constructed to estimate the population pain threshold to pinprick stimuli. Differences between BPD patients and control subjects were evaluated by comparison of the interpolated 50% incidence values. In addition, the pain threshold to pinpricks was estimated individually for every subject. When the pricking pain threshold was not reached, i.e., pain incidence was <50% at the upper limit of 512 mN, the next higher level above the stimulus range (1024 mN) was used as a conservative surrogate estimate. Pricking pain thresholds were $\log_2$ transformed (following the factor of 2 progression in stimulus force) to achieve secondary normal distribution. Differences of pinprick pain thresholds were evaluated by 2-way analysis of variance (ANOVA) with the main effects: group (BPD patients vs healthy controls) and gender.

According to Stevens' power law and experience in several earlier studies [50,92], pain ratings to pinprick stimuli were transformed into decadic logarithmic values to achieve secondary normal distribution. To avoid loss of zero values, a small constant (0.1) was added before transformation to all ratings (detailed in Magerl et al. [50]).

Capsaicin-induced pain ratings were compared for every time point between BPD patients and control subjects using a mixed model 2-way ANOVA with the main effects: group (BPD vs healthy controls) and time after injection. In addition, as a global parameter of capsaicin-induced pain the mean across ratings over the first 2 minutes after injection was used. Differences of capsaicin-related estimates of pain intensity and unpleasantness were evaluated by a mixed model 2-way ANOVA with the main effects: group (BPD vs healthy controls) and intensity vs unpleasantness. Significance of differences was tested by post hoc least significant differences test.

Forward stepwise multiple regression analysis was used to investigate the relationship of pricking pain, capsaicin-induced pain, psychometric scores, and SIB. To allow direct comparison of the different pain measures (mechanical pain threshold [MPT], mechanical pain rating [MPS], capsaicin-induced pain rating [CPS]), raw data were transformed into units of standard normal distribution (z values) weighted by the mean and standard deviation of the control subjects according to the formula: $z_i = (x_i - \text{mean}_{\text{controls}})/\text{SD}_{\text{controls}}$. These z values were analyzed by a mixed model 2-way ANOVA with the main effects: group (4 levels: SIB severity groups 1, 2, and 3 and control subjects) and pain measure (3 levels: MPT, MPS, and CPS). Homogeneity of variance (homoscedasticity) was confirmed using the Bartlett χ^2 test. Significance of differences was tested by post hoc least significant differences test. Correction for multiple comparisons was not done. For comparison of BPD patients and healthy controls, as well as for comparing female and male BPD patients, effects sizes were calculated as Cohen's d = (mean BPD − mean controls)/pooled standard deviation or as (mean female BPD − mean male BPD)/pooled standard deviation.

Demographic and psychometric data are shown as mean ± SD, experimental data are expressed as mean ± SEM. Throughout analyses, P values <.05 were considered statistically significant.

3. Results

3.1. Patients and healthy control subjects

Psychometric evaluation confirmed that all 22 patients fulfilled the diagnostic criteria for borderline personality disorder in the SCID-II and DIB-R, and were found highly abnormal in the BPI, whereas all 22 control subjects were devoid of DSM axis II-related symptoms (SCID-II D-score: 6.86 ± 1.17 vs 0.29 ± 0.56), specific borderline-related symptoms (DIB-R: 8.35 ± 0.81 vs 0.0 ± 0.0) and scored perfectly normal in the BPI (27.09 ± 6.11 vs 1.90 ± 1.77, $P < .001$, each; all effect sizes very large with $d > 5.6$) (Table 1). Moreover, patients with BPD exhibited a pronounced dysphoric mood as judged immediately before the experiments by the von Zerssen BfS mood scale. Mood scores deviated significantly from both population reference data and from the control subjects ($P < .001$; effect size very large with $d = 1.776$) (Table 1). There were no significant global differences in the psychometric measures (SCID-II D-score, DIB-R, BPI, BfS mood scale) between female and male patients (effect sizes small to medium size for DIB-R and BPI, and almost zero for SCID-II D-score, all $P > 0.20$ [but see subscale differences in Table 2 and section below on differences in pain sensitivity between male and female BPD patients]).

3.2. Pain thresholds to stimulation of the TRPV1-negative pathway (pin prick)

Patients and healthy control subjects were assessed for pain sensitivity using pin prick pain testing. Both groups exhibited proper sigmoid psychometric functions for pain reports, depending on stimulus force. However, the incidence of pain reports in BPD patients was significantly lower at any force (Yates corrected χ^2: at least $P < .05$; typically $P < .001$). The population pain threshold at 50% pain incidence as interpolated from the psychometric function was 74% higher in BPD patients (148 mN) than in control subjects (85 mN; Fig. 1A).

Also, when individual pain thresholds were estimated for all participants, pain thresholds in BPD patients (148 mN; $\log_2$ force = 7.206 ± 0.368) were significantly higher than in control subjects (54 mN; $\log_2$ force = 5.748 ± 0.381, $P < .01$; Fig. 1B; large effect size with $d = 0.829$). The difference may likely be even higher, because in 7 of 22 BPD patients, hit rates never met the 50% incidence criterion. Thus, pain thresholds in these patients could not be adequately estimated, as the necessary stimuli exceeded the range of forces used. These threshold values were replaced by the next higher stimulus level and likely underestimated to an unknown extent.

3.3. Pain sensitivity to stimulation of the TRPV1-positive pathway (capsaicin injection)

The intradermal injection of the TRPV1-receptor agonist capsaicin was typically experienced as a very intense burning pain, giving maximal pain

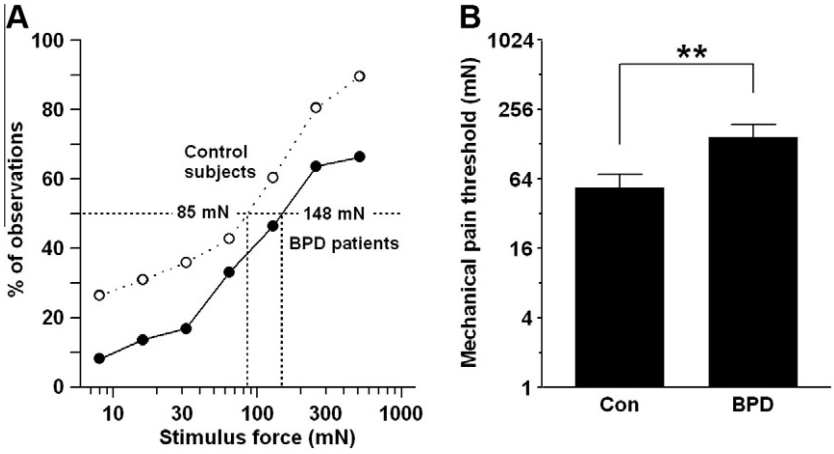

Fig. 1. Mechanical pain thresholds to punctate stimuli (pin pricks) in BPD patients and healthy control subjects. (A) Psychometric functions for pain depending on stimulus force. Both groups display proper sigmoid probability curves for pain detection as a function of the applied force of pin pricks. The population function for healthy controls (open circle, broken line) intersects with the 50% incidence level at 85 mN (population threshold). The population function for BPD patients (filled circle, solid line) is shifted rightward in parallel towards higher forces intersecting at 148 mN. (B) Mean and SEM of individual pain thresholds to pin prick stimulation. Mean threshold in BPD patients (BPD: 148 mN) was significantly higher than in healthy controls (Con: 54 mN). Note the logarithmic scaling of stimulus forces. $^{**}P < .01$.

ratings immediately upon injection and decaying in a mono-exponential fashion over the next couple of minutes (Fig. 2A). Analysis of variance revealed a significant effect of group (BPD vs healthy controls, $F_{1,42} = 4.97$; $P < .05$), of time after injection ($F_{4,168} = 175.42$; $P < .001$), and a significant group × time interaction ($F_{4,168} = 3.13$; $P < .05$). Peak pain ratings were not different upon injection and amounted to 76.7% of VAS in healthy controls and 70.7% of VAS in BPD patients ($P = .43$). However, pain ratings in BPD patients dropped significantly faster than in healthy control subjects (time constants: 49 seconds, $\log_{10}$ time constant = 1.668 ± 0.064 vs 76 seconds, $\log_{10}$ time constant = 1.883 ± 0.057; $P < .05$; very large effect size with $d = 1.715$). Thus, rating of capsaicin-evoked pain in BPD patients were significantly lower from 20 seconds after injection for the first 3 minutes (at least $P < .05$), but significance of differences vanished, when pain ratings dropped low. On, average pain ratings were 38% lower in BPD patients compared with healthy controls, with a maximal reduction of >50% during minutes 2 to 4.

Post hoc analysis of global ratings of pain intensity and pain unpleasantness revealed that there were no differences in rating of pain intensity (72.0 vs 74.8% VAS, $P = .50$) but significantly lower ratings of unpleasantness (64.6 vs 78.4% VAS, $P < .01$; Fig. 2B). There were no significant differences between patients with or without self-reported pain upon self-injurious behavior ($P > .30$).

3.4. Differences in pain sensitivity between male and female BPD patients

There were no gross differences in psychometric assessments between male and female patients, nor in control subjects (SCID-II D-score, DIB-R, BPI, BfS mood scale, all $P > .20$). However, some subtle gender differences for BPD patients were found on subscales (Table 2). Namely, male BPD patients scored significantly higher on the antisocial personality disorder subscale of the SCID-II (2.43 ± 0.43 vs 0.73 ± 0.21, $P < .01$; very large effect size with $d = -1.715$) and they exhibited significantly lower scores on the interpersonal functioning subscale of the DIB-R (10.08 ± 0.77 vs 8.00 ± 0.53, $P < .05$). Moreover, male BPD patients ranked significantly lower on the identity diffusion subscale of the BPI (4.57 ± 0.65 vs 8.00 ± 0.45, $P < .001$; very large effect size with $d = 1.960$). Also, SIB had occurred significantly more recently in female than in male BPD patients ($P < .05$).

There were significant differences of pain responses between female BPD patients and female healthy controls, but not male BPD patients and male healthy controls, regarding pain thresholds and pain ratings to pin prick stimuli and capsaicin injection (Fig. 3). Analysis of variance on pricking pain thresholds in both forearms revealed a significant group main effect for pricking pain thresholds (BPD vs

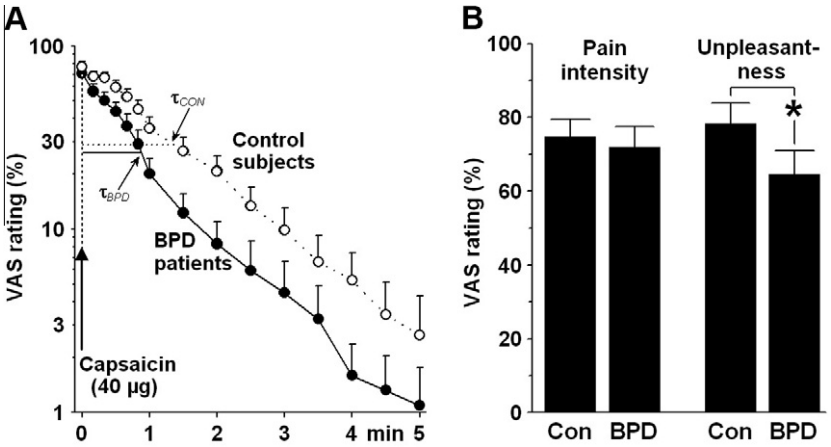

Fig. 2. Pain sensitivity to chemical stimulation of the skin by intradermal injection of capsaicin in BPD patients and healthy control subjects. (A) Time course of pain sensation elicited by capsaicin injection. Maximal pain occurs immediately upon injection and decays mono-exponentially within minutes. (Note the logarithmic scaling of pain ratings!) Pain decayed significantly faster in BPD patients (filled circles, solid line) than in healthy control subjects (open circles, broken line). (B) Bar graphs comparing perceived pain intensity and pain unpleasantness of capsaicin-induced pain. Patients and controls subjects displayed a similar magnitude of rating for pain intensity, but a significantly lower rating of pain unpleasantness. $^{*}P < .05$.

healthy controls, $F_{2,39} = 4.26$; $P < .05$). Differential responses of female and male patients or controls were distributed over both, gender main effect ($F_{2,39} = 2.04$; $P = .14$) and group × gender interaction ($F_{2,39} = 3.15$; $P = .054$). Post hoc contrasts revealed that pain thresholds in female patients were 4 times higher than in female controls (219 mN, $\log_2$ force = 7.780 ± 0.369 vs 54 mN, $\log_2$ force = 5.762 ± 0.434; $P < .005$; very large effect size with $d = 1.556$). In contrast, male patients and male controls exhibited similar pain thresholds (63 vs 53 mN, $P = .80$) that were also very similar to female control subjects (Fig. 3A). A similar reduction in pain sensitivity was found for pain ratings to pin prick stimuli in females, although only as a trend towards statistical significance (−41%, $P = .07$), but not in males (+8%, $P = .87$, Fig. 3B). Likewise, the magnitude of capsaicin-induced burning pain was significantly lower only in female patients as compared with female controls (−45%; average ratings: 13.6 ± 2.7 vs 24.9 ± 4.3; $P < .05$; large effect size with $d = 0.812$), but no difference was found between male patients and male control subjects (14.0 ± 2.6 vs 15.9 ± 2.8; $P = 0.62$; small effect size $d = 0.266$; Fig. 3C). Moreover, capsaicin-induced burning pain decayed significantly faster in female patients than in female control subjects (time constants: 46 seconds, $\log_{10}$ time constant = 1.658 ± 0.079 vs 85 s, $\log_{10}$ time constant = 1.928 ± 0.082; $P < .05$; large effect size with $d = 1.019$), but no such difference was seen in males (56 vs 61 s, $P = 0.50$). Thus, consistently female BPD patients exhibited a profound lack of pain sensitivity compared to female control subjects, whereas in all pain measures, male BPD patients did not differ from male controls.

3.5. Loss of pain sensitivity was related to self-injurious behavior but not to psychometric measures of BPD

Differences between female and male BPD patients related to SIB were found in the time since last self-injury (137 days in male patients, but only 10 days in female patients, $P < .05$; Table 2). Patients, who did report not to perceive pain at self-injury had an almost 3-fold longer history of self-injury than patients who did (17.3 ± 2.9 vs 6.2 ± 2.2 years, $P < 0.01$; large effect size with r = 1.240). Although not statistically significant, there was a trend towards longer SIB history in female than male BPD patients (15.4 ± 2.9 vs 8.6 ± 2.0 years; large effect size with $d = 0.774$) and a higher proportion without (self-reported) pain upon SIB (11/15 female = 73% vs 3/7 male = 43%).

Recency of SIB was significantly correlated to the global BPI-score (r = 0.48, $P < .05$), but no significant correlation was found to global DIB-R score (r = 0.27, $P = .25$) or the D-score of SCID-II (r = 0.17, $P = .46$). Pain thresholds to pin prick stimulation exhibited no correlation to psychometric measures (ranging from r = 0.01−0.12 for SCID-II D-score, DIB-R, BPI, BfS mood scale, all $P > .60$). In contrast, there was a significant correlation between the recency of SIB and pin prick pain threshold (r = 0.47, $P < .05$ explaining 22% of variance; Fig. 4A). Entering also capsaicin-induced pain ratings into a multiple regression function revealed that both mechanical pain threshold and capsaicin-induced pain were significantly correlated with the recency of SIB (multiple regression r = 0.58, $P < .05$ explaining 34% of variance; partial correlation coefficients were r = 0.49 and −0.44, respectively, $P < .05$ for each).

Grouping patients according to this criterion disclosed that patients whose last self-injury was >1 year before sensory examination exhibited normal pricking pain thresholds (43 mN; $\log_2$ force = 5.432 ± 0.493, n = 5, $P = .55$; small effect size $d = -0.213$). In contrast, in patients with relatively recent self-injury (on average ~1 month since last self-injury) had much higher pain threshold (145 mN; $\log_2$ force = 7.179 ± 0.826, n = 9, $P < .05$; medium to large effect size with $d = 0.661$). Pain thresholds in patients who frequently injured themselves (approximately 3–4 times per week) and in whom SIB had occurred very recently (average time since last self-injury: 1.5 days) were even higher (326 mN; $\log_2$ force = 8.346 ± 0.858, n = 8, $P < .001$; large effect size with $d = 1.217$; Fig. 4B).

Analysis of the suprathreshold pain measures (MPS, CPS) also revealed similar SIB-dependent losses of pain sensitivity. A 2-way ANOVA on normalized (z-transformed) data revealed a significant group effect ($F_{3,40} = 3.98$; $P < .05$ comparing SIB severity groups 1, 2, and 3 and control subjects), but no difference between pain measures ($F_{2,80} = 0.57$; $P = .31$ comparing MPT, MPS, and CPS) and no interaction between group and pain measures ($F_{6,80} = 0.57$; $P < .75$). Thus, losses of pain sensitivity as stratified by SIB severity occurred to a similar extent in all pain measures. Overall, patients in the frequent SIB subgroup were significantly less pain sensitive than control subjects ($P < .005$), and also less sensitive than the rare SIB subgroup ($P < .05$, post hoc least significant differences test). The same differences were also found to be significant in all 3 pain measures, when tested separately (at least $P < .05$; Fig. 5).

In contrast, the reflex erythema (flare) that developed around the capsaicin injection site (a measure of the integrity of nociceptive primary afferent nerve fibers) had the same extension in subjects and BPD patients (radius of erythema: 47 ± 2 vs 45 ± 2 mm, $P < .30$; effect size $d = -0.213$) suggesting the absence of peripheral nerve fiber damage.

3.6. Potential drug effects on loss of pain sensitivity

The majority of BPD patients (n = 19) used 1 drug or more at the time of investigation, usually selective reuptake inhibitors for serotonin and/or noradrenalin (n = 16), sometimes in combination with tricyclic antidepressants and/or other open channel blockers (n = 7), tetracyclic antidepressants (α_2-receptor antagonists, n = 3), or neuroleptics (n = 7). However, pain ratings did not differ between patients without any drugs or among the different drug groups (all

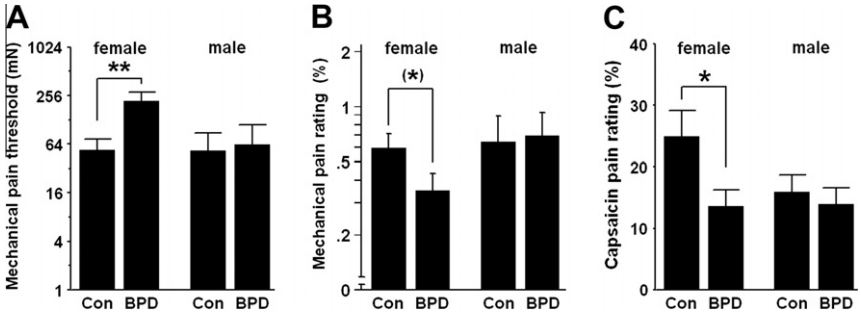

Fig. 3. Gender-related differences in pain sensitivity to mechanical and chemical stimulation of the skin in BPD patients and healthy control subjects. Female, but not male, BPD patients were significantly less pain sensitive than their conspecific gender controls. They displayed significantly higher mechanical pain thresholds (A), a trend towards lower pain ratings to mechanical stimulation (B), and a significantly lower pain rating to chemical stimulation by capsaicin (C). $^{(*)}P = .07$; $^{*}P < .05$; $^{**}P < .01$.

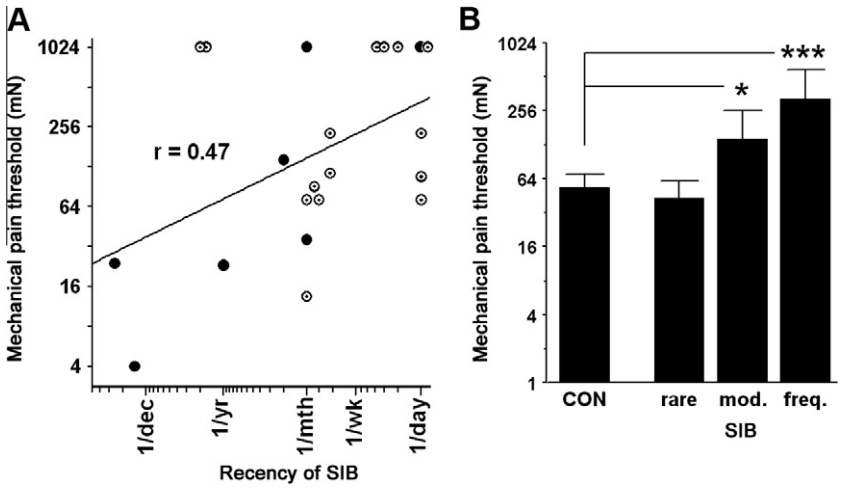

Fig. 4. Pain thresholds to punctate mechanical stimuli (pin prick) were related to self-injurious behavior. (A) Pricking pain threshold in BPD patients was significantly correlated (r = 0.47, $P < 0.05$) to the recency of SIB (log instantaneous frequency, i.e. the log of the inverse of time since last SIB). Open circle with dot indicates female BPD patients; filled circle indicates male BPD patients. (B) BPD Patients with rare SIB (>1 year since last SIB) did not deviate from the control group, while BPD patients with moderately frequent (approximately once per month) or very frequent SIB (daily to weekly) exhibited significantly enhanced mechanical pain thresholds to pin prick stimuli. $^{*}P < .05$; $^{***}P < .001$.

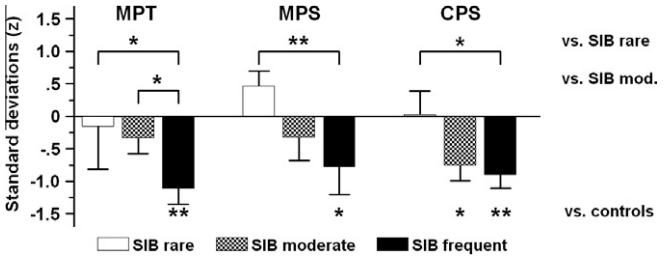

Fig. 5. All measures of pain sensitivity (MPT, MPS, CPS) in BPD patients were related to self-injurious behavior (analysis on z-transformed, i.e. standard normalized data). BPD patients with rare SIB (>1 year since last SIB, open bars, n = 5) never deviated significantly from the control group. In contrast, BPD patients with very frequent SIB (daily to weekly, filled bars, n = 8) exhibited significantly enhanced mechanical pain thresholds to pin prick stimuli compared to the control group and the group of BPD patients with rare SIB. In some measures also the moderate frequency SIB group (shaded bars, n = 9) deviated significantly from very frequent injurers (for MPT) or from the control group (for CPS). CPS = chemical pain sensation (VAS pain rating to intradermal capsaicin injection); MPS = mechanical pain sensation (NRS pain rating to pin prick stimuli); MPT = mechanical pain threshold. $^{*}P < .05$; $^{**}P < .01$.

$P > .30$). Specifically, BPD patients receiving drugs with potential analgesic properties, such as open channel blockers (including tricyclic antidepressants) or noradrenalin reuptake inhibitors did not differ from patients with nontricyclic antidepressant (either alone or pooled together), or no antidepressants (all $P > .60$). Furthermore, patients using reuptake inhibitors with selective or additional noradrenalin reuptake inhibition did not differ from those using selective serotonin reuptake inhibitors ($P > .60$).

4. Discussion

Borderline personality disorder is characterized by instability in affect regulation, impulse control, interpersonal relationships, and self-image, making these patients frequent users of mental health resources. One characteristic clinical sign is repeated self-injury, a nonsuicidal autoaggression that terminates states of negative affect or inner tension [16,20,33,66]. Many patients claim that self-injury causes little pain or is even completely painless [43].

4.1. Sensory channels

We found a consistent reduction of pain sensitivity in 2 functionally distinct pain modalities, mechanically-induced (pin prick) and chemically induced pain (capsaicin). Capsaicin acts on the specific membrane-bound receptor TRPV1 [11] mostly located on unmyelinated C-nociceptors and elicits burning pain. This nociceptor subsystem regulates the gain of other nociceptive inputs controlling excitability and receptive field size of spinal and cortical nociceptive neurons [10,82]. The sensors for pin prick stimuli are Aδ-mechanonociceptors lacking the TRPV1 receptor [51], with excellent spatial discrimination [70] and high relevance for protective guarding and withdrawal behavior [81,92]. Pain suppression was similar in both nociceptive channels, and similar to previous data for cold and heat pain [56,66,71,72]. We conclude that pain suppression in BPD is generalized and independent of nociceptive modality.

4.2. Endogenous pain control systems

Pain suppression in BPD is nonselectively generalized across all pain modalities despite their molecular diversity, making peripheral factors unlikely. A candidate for generalized pain suppression is enhanced endogenous pain control. BPD may be considered a stress-related disorder with increased cortisol release, or adaptation syndrome resulting from sustained stress as shown by reduced responsiveness in the dexamethasone suppression test [46]. Stress also precipitates dissociative states and aversive arousal leading to SIB and enhanced pain suppression [8]. Peak dissociation coincides with SIB, and pain thresholds correlate significantly with dissociation or aversive arousal [37,48,49].

The 2 major stress-related endogenous relief systems, namely, the endogenous opioid and cannabinoid systems act as powerful pain control systems [3,34,55,83,87,88]. Enkephalin was increased in plasma and CSF of BPD patients, but also in other psychiatric illness [15,17]. The opioid antagonists naltrexone and naloxone reduced analgesia in BPD, however, placebo was equally effective [7,60,67], not supporting a specific opioid involvement. Collectively, acutely activated endogenous pain control is consistent with our finding that pain upon capsaicin injection was similar to that in control subjects for the first few seconds but decayed significantly faster, suggesting a more efficient activation in BPD patients.

4.3. Possible role of exaggerated prefrontal pain control in BPD

Enhanced blood-oxygen-level dependence (BOLD) functional magnetic resonance imaging responses (activation) in the left dorsolateral prefrontal cortex (left dlPFC) [72], a brain region associated with sensory decisions [31,32,86], were associated with functional inhibition in the early phase of painful heat, together with suppression of a significant BOLD response in the posterior parietal cortex (PPC), a region functionally related to in-depth somatosensory signal processing. Interestingly, after a delay, a significantly reduced BOLD response (deactivation) prevailed in the amygdala and perigenual ACC, areas functionally related to affective pain processing [61–63] (reviewed by Apkarian et al. [1]). DlPFC activation was negatively correlated with the cluster of all other cortical pain-related areas, and it interrupted functional connectivity in the nociceptive network (positron emission tomography data in Lorenz et al. [47]).

The ACC, a brain region with high opioid receptor density in humans [2] plays a crucial role in emotion. Functional or structural deficits result in severe alterations of social behavior in animals and humans [6,26]. A major part of this control is exerted via the μ-opioid receptor system [94], which also controls the emotional–affective dimension of pain, as ACC μ-opioid receptor activation was negatively correlated with pain affect in a human PET study [93], and a behavioral animal model of pain affect [40]. Focusing on pain unpleasantness increases activity in the ACC and amygdala [39]. Our finding of a selective suppression of the unpleasantness component of a lasting pain stimulus in BPD patients (capsaicin) parallels previous findings [72] that the ACC and amygdala were significantly deactivated in later stages of tonic heat stimuli.

4.4. Evidence for malfunction of pain-related brain areas in BPD patients

The prefrontal cortex forms a higher-level control over ACC and midbrain areas controlling pain [27,28]. Up- and down-regulation of emotions by reappraisal strategies up- and down-regulate activity of dlPFC and amygdala [19]. Mood disorders, particularly dysphoria and depressive disorders associated with BPD [76,90], point to regulation deficits of the prefrontal cortex. BPD patients who did not perceive pain during SIB were significantly more stoic in a pain discrimination task than were patients who did experience pain [38,68]. Several studies have reported specific volume reductions for BPD patients in frontal/prefrontal brain areas, namely in the left orbitofrontal cortex, amygdala, and the midcingulate cortex (Brodmann area 24) [30,65,77]. BPD patients present with neurological "soft signs" of brain dysfunction to complex integrative tasks rarely found in normal subjects, suggesting nonfocal central nervous system failure in BPD [18]. Collectively, neurological and imaging studies point to abnormal frontolimbic neurocircuitry (reviewed in Brendel et al. [9]).

4.5. Gender, self-injurious behavior, and psychometric measures

Although patient numbers were small and thus are to be interpreted cautiously, the data from this study suggests some gender differences, namely, SIB being rare and pain suppression less present in male BPD patients. Comorbidities are frequent in BPD, and gender differences in pain sensitivity may be caused by differences in these comorbidities (e.g., depression), as other psychiatric disorders also exhibit reduced pain sensitivity [42]. Although there are generally more similarities than differences in male and female BPD patients, some gender specificities exist. Male patients more frequently show substance abuse, schizotypic, narcissistic, and antisocial personality disorders, whereas female patients display posttraumatic stress disorder, eating disorder, or borderline identity disturbance [36]. Some of the typical differences listed above were also present in our patient sample, namely antisocial personality and lower social functioning in males and stronger identity disturbances in females.

Based on these subtle differences in personality, we propose a model that links gender differences in SIB and pain disturbance, and integrates recent findings in BPD and current theories of central pain processing. The most striking difference was the absence of pain suppression in male patients and the fact that male patients exhibited very little SIB, supporting that pain suppression was related to SIB in line with the frequent finding that loss of pain is more severe in patients with vs without SIB [49]. When present, SIB in BPD patients is usually severe, and severe injuries alter the balance of facilitating and inhibiting pain subsystems and the net result is activation of endogenous antinociception. Recently, loss of pain has been related to duration of SIB in patients with eating disorders exhibiting SIB [13]. However, the fact BPD pain suppression in our data was still related to the most recent SIB suggests that a major part lies in the recent history of SIB.

Importantly, the nociceptive system also controls the extension of somatosensory maps in animals [10] and contributes to maintenance of the body image in humans [23,59,73,74]. The knock down of nociceptive sensitivity by SIB-induced antinociception may further contribute to identity diffusion, leading into a vicious cycle perpetuating SIB. Also, a note of caution is in order regarding analgesic treatment of BPD patients, which may trigger SIB [78]. Female patients may be more prone to building the analgesia-like disturbance of pain by synergy of their social role, gender-specific behavioral deficits, and self-directed aggression. Male BPD patients may be partially "protected" from SIB by virtue of their stronger inclination to direct bodily aggression against others, rather than against themselves, and escape this sequel.

We propose that analgesia-like loss of pain sensitivity is not a sign of BPD psychopathology per se (and thus no correlation was seen to psychometric measures of BPD), but rather a use-dependent functional rearrangement of brain areas involved in pain processing that may not be not specific for BPD. Because already single strongly painful stimuli can result in alterations of functional connectivity in the pain network owing to the engagement of endogenous pain control [47], we suggest that BPD-related SIB shifts the pain control set point, which is not specific to the psychopathology of BPD but is characterized by exaggerated pain control uncoupling emotional–affective or evaluative and sensory-discriminative dimensions of pain. Lasting loss of pain sensitivity elicited by sustained and frequent heat pain was not mediated by endogenous opioids, and returned to normal at 1-year follow-up [4,5,64].

4.6. Technical considerations and limitations

In this study, patient numbers were small, especially the male subsample; thus gender differences should be interpreted cautiously. However, effect sizes of differences were large when these differences were statistically significant, and elsewhere were very small, and thus the lack or presence of differences was not due to lack of power. More data on male BPD are urgently needed, to evaluate possible gender impact. Correlation of analgesia to recency of SIB should also be confirmed in larger samples. To reduce the impact of comorbidities, we attempted to exclude patients with DSM axis I comorbidity from the study by clinical assessment, but the absence of psychometrically validated axis I assessments is a limitation of this study. Likewise, the fact that diagnoses were not confirmed by independent evaluation of video-taped diagnostic interviews may be regarded as a shortcoming.

4.7. Summary and conclusions

Reduced pain sensitivity in BPD involves 2 distinct nociceptive sensory channels (TRPV1+ and TRPV1− afferents), suggesting that it is generalized and independent of nociceptive modality. Correlation of hypoalgesia with recency of SIB, but not psychometric scales, suggests that hypoalgesia may result from a learning process caused by repeated self-injury. Thus, BPD may be a model disease pinpointing the capacity of plasticity in endogenous pain control.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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