BJPsych | The British Journal of Psychiatry (2015)
207, 165–172. doi: 10.1192/bjp.bp.114.153379

Incision and stress regulation in borderline personality disorder: neurobiological mechanisms of self-injurious behaviour

Sarah Reitz,* Rosemarie Kluetsch,* Inga Niedtfeld, Teresa Knorz, Stefanie Lis, Christian Paret, Peter Kirsch, Andreas Meyer-Lindenberg, Rolf-Detlef Treede, Ulf Baumgärtner, Martin Bohus and Christian Schmahl

Background
Patients with borderline personality disorder frequently show non-suicidal self-injury (NSSI). In these patients, NSSI often serves to reduce high levels of stress.

Aims
Investigation of neurobiological mechanisms of NSSI in borderline personality disorder

Method
In total, 21 women with borderline personality disorder and 17 healthy controls underwent a stress induction, followed by either an incision into the forearm or a sham treatment. Afterwards participants underwent resting-state functional magnetic resonance imaging while aversive tension, heart rate and heart rate variability were assessed.

Results
We found a significant influence of incision on subjective and objective stress levels with a stronger decrease of aversive tension in the borderline personality disorder group following incision than sham. Amygdala activity decreased more and functional connectivity with superior frontal gyrus normalised after incision in the borderline personality disorder group.

Conclusions
Decreased stress levels and amygdala activity after incision support the assumption of an influence of NSSI on emotion regulation in individuals with borderline personality disorder and aids in understanding why these patients use self-inflicted pain to reduce inner tension.

Declaration of interest
A.M.-L. has received fees for consultancy from AstraZeneca, Bristol Myers Squibb, Defined Health, Desitin Arzneimittel, Elsevier, F. Hoffmann-La Roche, Gerson Lehrman Group, Lundbeck, Outcome Europe Sárl, Outcome Sciences, Pricespective, Roche Pharma, Servier International and Thieme Verlag; for lectures, including travel fees from Abbott, Alexza Pharmaceuticals, AstraZeneca, Aula Médica Congresos, BASF, Groupo Ferrer International, Janssen-Cilag, Lilly Deutschland, LVR Klinikum Düsseldorf, Pfizer Pharma and Servier Deutschland; and also grants from the Hans-Jörg Weitbrecht Award and ECNP Neuropsychopharmacology Award. C.S. has received fees for lectures, including travel fees, from Pfizer Germany. R.-D.T. has received fees for consultancy from Astellas, AstraZeneca, Boehringer Ingelheim, Galderma, Glaxo Smith Kline, Grünenthal, Lilly, Merz, Merck-Sharpe & Dohme, Pfizer, Sanofi and Schwarz-Pharma/UCB; and for lectures from Astellas, AWD, Boehringer Ingelheim, Dr Kade, Nycomed, Grünenthal, Lilly, Mundipharma, Pfizer and Schwarz-Pharma/UCB; and also grants from Dr Kade, Boehringer Ingelheim, Astellas and AbbVie.

Non-suicidal self-injury (NSSI) is a widespread phenomenon with a prevalence of 18% in adolescents.[1] NSSI, predominantly skin-cutting, is also seen in 69–90% of female patients with borderline personality disorder,[2] where it is closely related to emotion dysregulation.[2,3] Since the primary motive for NSSI in people with borderline personality disorder is to downregulate aversive tension,[4] self-injurious behaviour can be conceptualised as a dysfunctional emotion regulation attempt[5] and may be maintained by negative reinforcement.[6,7] Aberrant impulse control, another symptom of borderline personality disorder, could be a critical factor as well, so one might suggest that NSSI is frequently driven by poor inhibitory control and disproportionate responses to stressors.[8] However, experimental evidence for this assumption is sparse. Strongly connected to NSSI are findings in people with borderline personality disorder showing reduced sensitivity to pain.[9,10] This hyposensitivity is further increased under stress.[11,12] Research has found that painful stimulation is related to a deactivation of the perigenual anterior cingulate cortex as well as the amygdala,[13] a region with increased activity during the presentation of emotionally aversive pictures in patients with borderline personality disorder compared with healthy controls.[14–16] Simultaneously, painful stimulation led to increased activation of the dorsolateral prefrontal cortex in participants with borderline personality disorder.[13] These findings led to the hypothesis that a potential neural mechanism behind NSSI in borderline personality disorder is a pain-mediated downregulation of elevated limbic activity by prefrontal cortex. This was supported in recent studies from our group, demonstrating that thermal stimuli led to a decrease in limbic activation induced by negative pictures in patients with borderline personality disorder[17] and, more specifically, that painful stimulation enabled amygdala–prefrontal coupling.[18] It was argued that this pattern of neural activation mirrors dysfunctional emotion regulation by means of an attentional shift, i.e. painful stimulation may serve to direct attention away from the emotional contents.[19]

Previous studies on pain processing in borderline personality disorder have used different types of non-damaging nociceptive thermal stimuli, such as heat, cold or laser-evoked pain.[11,20] However, most patients use methods of NSSI that lead to skin lesions, by means of cutting or burning.[4,5] This is important because different neural processes are activated by mechanical compared with thermal nociceptive stimuli, suggesting that different stimuli may also lead to different brain responses.[21] Therefore, one could argue that skin lesions in particular have an important role within the mechanisms of NSSI. A pain model that takes the aspect of the skin lesion into account is the

*These authors contributed equally to this work.

https://doi.org/10.1192/bjp.bp.114.153379 Published online by Cambridge University Press

incision–pain model,[22] where a 4 mm long incision with a scalpel is applied to the volar forearm. This model has been found acceptable by several ethics committees, because (a) pain levels are moderate, (b) bleeding is minimal and usually stops by itself and (c) healing is rapid and without visible scars.[22–24] Pogatzky-Zahn *et al*[23] investigated 44 right-handed male healthy volunteers with a functional magnetic resonance imaging (fMRI) block design. Fourteen out of 44 experienced a sham condition (pressing the handle bar of the scalpel on the skin of the right volar forearm), 30 underwent the incision procedure (as explained for our study). Dependent on painfulness, a 'high-sensitivity' and a 'low-sensitivity-subgroup' were analysed separately. In the latter, similar to our present borderline personality disorder sample and our earlier findings,[13] a deactivation of the left amygdala after incision could be shown, whereas the high-sensitivity subgroup showed an activation of the amygdala. In a pilot study[24] we confirmed the feasibility of the incision model and tested whether tissue damage reduces stress in patients with borderline personality disorder. The incision was applied after a stress induction[25] and resulted in a short-term increase in aversive tension in the healthy control group in contrast to a decrease in tension and heart rate in the borderline personality disorder group. In the present study, we aimed to investigate neural mechanisms of NSSI-associated tissue damage in borderline personality disorder by transferring the established incision paradigm into the fMRI environment. Specifically, we compared the effects of incision *v.* sham treatment following a stress induction while participants were undergoing fMRI. We hypothesised that subjective and objective stress responses would show a stronger decrease in the borderline personality disorder group compared with the healthy control group after incision, whereas in the sham condition, we expected the healthy control group to show a stronger decrease in stress measures (i.e. functional stress regulation) than the borderline personality disorder group. Furthermore, we hypothesised that incision after stress would lead to altered connectivity between the amygdala and prefrontal brain regions in the borderline personality disorder group. Given previous findings pointing to the relevance of the amygdala and its interaction with prefrontal areas in the context of stress regulation, we decided to focus on this brain region as a seed region of a functional connectivity analysis of the stress regulation phase after incision. On the basis of previous work, we also hypothesised that inhibitory coupling (i.e. negative connectivity between prefrontal and limbic regions) would be present in people with borderline personality disorder under the incision condition only, whereas it should be present in the healthy control group in the sham condition.

Method

Participants

Twenty-one female patients with borderline personality disorder and current NSSI (borderline personality disorder group) and 17 female healthy controls without any NSSI events in their history (control group) participated in this study. Both groups did not differ significantly in age (borderline personality disorder group: 25.95 (s.d. = 6.92), control group: 26.88 (s.d. = 8.29), $t_{(36)} = 0.38$, $P = 0.71$) or in educational background ($Z = 0.81$, $P = 0.53$). For demographic characteristics see Table 1. Patients met DSM-IV[26] criteria for borderline personality disorder according to the International Personality Disorder Examination (IPDE).[27] Axis I comorbidity was assessed by the Structured Clinical Interview for Axis I disorders (SCID-I).[28] Both interviews were administered by trained clinical psychologists. Interrater reliability for borderline personality disorder was kappa (κ) = 0.69 for the SCID-I (primary diagnosis) and $\kappa = 0.77$ for the IPDE. Exclusion criteria comprised a current episode of major depression, a lifetime diagnosis of schizophrenia, bipolar disorder, acute suicidal tendencies, major medical or neurological illness and psychotropic medication within the 4 weeks prior to the investigation. We only included patients who had shown NSSI at least once in the 6 months prior to study, as assessed with the structured self-rating Questionnaire for Non-Suicidal Self-Injury,[4] and who did not express a request for treatment. This questionnaire assesses frequency, motives and methods of self-injurious behaviour without the intent to die, preferred methods, as well as intensity and medical treatment of wounds. A total of 71% endorsed cutting as their preferred NSSI method. NSSI was mainly used to reduce aversive inner tension (57%) and negative emotions (21%). The healthy controls were excluded if they had any Axis I or Axis II lifetime morbidity or a history of NSSI.

Participants were given a written as well as a verbal explanation of the task. Remaining questions were answered, and after that all participants gave written informed consent. No participant withdrew consent during the course of the investigation. The

Table 1 Demographics and comorbidities

	Borderline personality disorder group ($n = 21$)	Control group ($n = 17$)
Age, years:[a] mean (s.d.)	25.95 (6.92)	26.88 (8.29)
Current body mass index, kg/m^2: mean (s.d.)	23.50 (6.29)	22.80 (4.83)
Educational background, *n* (%)		
Without graduation (0 years)	1 (4.76)	0 (0)
⩽9 years of school education	4 (19.05)	0 (0)
10 years of school education	3 (14.29)	2 (11.76)
⩾12 years of school education	13 (61.90)	15 (88.24)
Professional position, *n* (%)		
In education	7 (33.33)	12 (70.59)
Employed	6 (28.57)	3 (17.65)
Unemployed	8 (38.10)	2 (11.76)
Psychiatric comorbidities, *n* (%)		
Major depressive disorder, current	0 (0)	0 (0)
Major depressive disorder, lifetime	16 (76.19)	0 (0)
Dysthymia	2 (9.52)	0 (0)
Substance misuse, lifetime	5 (23.81)	0 (0)
Substance dependence, lifetime	5 (23.81)	0 (0)
Panic disorder, current	2 (9.52)	0 (0)
Panic disorder, lifetime	2 (9.52)	0 (0)
Agoraphobia, current	1 (4.76)	0 (0)
Social phobia, current	4 (19.05)	0 (0)
Social phobia, lifetime	2 (9.52)	0 (0)
Specific phobia, current	1 (4.76)	0 (0)
Obsessive–compulsive disorder, current	1 (4.76)	0 (0)
Obsessive–compulsive disorder, lifetime	2 (9.52)	0 (0)
Post-traumatic stress disorder, current	7 (33.33)	0 (0)
Post-traumatic stress disorder, lifetime	7 (33.33)	0 (0)
Anorexia nervosa, current	2 (9.52)	0 (0)
Anorexia nervosa, lifetime	4 (19.05)	0 (0)
Bulimia nervosa, current	2 (9.52)	0 (0)
Bulimia nervosa, lifetime	2 (9.52)	0 (0)
Eating disorder, not otherwise specified	2 (9.52)	0 (0)
Number of psychiatric comorbidities, *n* (%)		
0	6 (28.57)	17 (100)
1	5 (23.81)	0 (0)
2	1 (4.76)	0 (0)
3	3 (14.29)	0 (0)
4	0 (0)	0 (0)
5	2 (9.52)	0 (0)
Unknown	4 (19.05)	0 (0)

a. The borderline personality disorder group did not differ significantly from the control group in age ($t_{(36)} = 0.38$, $P = 0.71$).

https://doi.org/10.1192/bjp.bp.114.153379 Published online by Cambridge University Press

study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Medical Faculty Mannheim/University of Heidelberg (application no. 2008-234N-MA).

Stimulus material and procedure

Participants were investigated twice on two consecutive days. During fMRI, stress was induced in the first 21 min using the Montreal Imaging Stress Task (MIST),[25] which combines arithmetic with an algorithm causing disappointment. Both difficulty and time limit are manipulated to simulate poor performance (45–50% performance range). During the stress task, we employed a block design with three 7 min sessions of image acquisition.

After stress induction and disinfection with 70% alcohol, incision/sham was conducted according to the standardised incision protocol.[22,23] With a sterile ceramic scalpel, a small 4 mm long and 5–7 mm deep incision through the skin, fascia, and muscle of the anterior aspect of the volar forearm was conducted by one of the authors (T.K.). Painfulness of this procedure is comparable with a venipuncture and incision was well tolerated by all participants. In all participants, bleeding stopped spontaneously within 1 min. For the sham condition, the participants' skin was touched with the blunt end of the scalpel without cutting. On both days in permutated order, participants were not told which treatment they would receive. They were told the incision could happen once or on both days of the experiment. After incision/sham, participants underwent three 7 min blocks of resting-state fMRI, during which they were asked to relax and look at a fixation cross. Figure 1 shows an overview of the study design.

Subjective and objective assessment of stress levels

Participants rated their level of aversive tension at five time points, namely baseline, after stress induction and sessions 1 to 3 (7, 14 and 21 min post incision/sham, respectively) with a Self-Assessment Manikin (SAM)[29] on a visual analogue scale ranging from 1 (none) to 9 (extreme). Heart rate was calculated based on the analysis of the systolic peaks of the oximetry signal measured by finger mounted pulse oximetry. Heart rate was expressed as the number of beats per min and averaged for the rest and stress conditions of the MIST as well as the three time periods after incision/sham corresponding to the time intervals for which aversive tension was rated. Additionally, heart rate variability (HRV) was calculated non-parametrically with the HRV triangular index (HRV index; see Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[30]), and log-transformed because of violations of the normality assumption. Reliable HRV scores can be calculated based upon pulse oximetry data,[31] although compared with electrocardiogram data the derived parameter estimates have a lower precision because of a rather low sampling rate. As a result of technical problems and artefacts, heart rate and HRV data of four participants in the borderline personality disorder group and six in the control group had to be excluded from the analyses.

MRI acquisition

All imaging data were acquired using a 3-Tesla MRI scanner (TRIO, Siemens Medical Systems, Erlangen, Germany) equipped with a 32-channel head coil. In addition to a high resolution T_1-weighted structural scan, we acquired T_2*-weighted echo planar images with blood oxygenation level-dependent contrast (BOLD, repetition time (TR) = 2 s, echo time (TE) = 30 ms, 192 mm field of view, 64 × 64 matrix, 36 slices, 3 mm slice thickness, 3 mm slice gap; flip angle, 80°). As a result of technical problems or movement, we had to exclude two participants in the borderline personality disorder group and one in the control group. Imaging data were preprocessed using SPM 8 (www.fil.ion.ucl.ac.uk/spm, Wellcome Trust Centre for Neuroimaging, University College London, London, UK) according to standard procedures. The fMRI images pertaining to the three post-stress/incision/sham runs were further subjected to detrending using the REST toolbox version 1.7 (www.restfmri.net, Hangzhou Normal University, Zhejiang, China) in order to remove linear drifts.

Statistical analysis

Analysis of subjective and objective stress responses

To verify the effectiveness of the experimental stress induction through the MIST procedure, we computed a repeated measures analysis of variance (rm-ANOVA) for condition (incision, sham) and time (baseline, stress). Aversive tension, heart rate and HRV were analysed using a rm-ANOVA with the between-subjects factor group (borderline personality disorder, control) and the within-subjects factors condition and time. We included data for four time points: after stress induction, 7, 14 and 21 min after incision/sham. In case of significant effects, *post hoc* tests were computed, and effect sizes (Cohen's *d*) were reported. According to Cohen,[32] $d = 0.2$ reflects a small effect, $d = 0.5$ a medium and $d = 0.8$ a large effect size. All statistical analyses were carried out with SPSS for Windows (20.0.0).

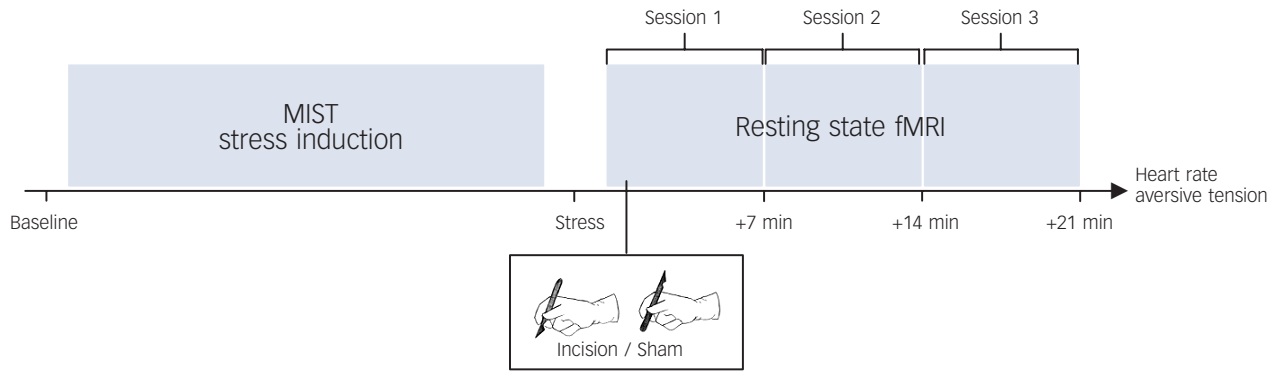

Fig. 1 Study design.

Following a stress induction (Montreal Imaging Stress Task, MIST) either an incision or a sham treatment was conducted, followed by three sessions of resting-state functional magnetic resonance imaging (fMRI). Heart rate and aversive tension were assessed throughout the experiment.

https://doi.org/10.1192/bjp.bp.114.153379 Published online by Cambridge University Press

MRI image analysis

In order to investigate functional connectivity post incision/sham, we extracted each participant's BOLD signal time courses from the three post-stress/incision/sham runs using in-house MATLAB code. For subsequent connectivity analyses, we extracted BOLD time signal from detrended data; for regression analyses of amygdala activity, we extracted BOLD time signal from non-detrended data. In both cases, bilateral amygdala was selected as a seed region and identified in each data-set using an anatomical mask defined by automated anatomical labeling (AAL) software (Groupe d'Imagerie Neuro-fonctionelle, Bordeaux Cedex, France).[33]

First, to analyse changes in amygdala activity over time, regression analyses of the extracted BOLD time signal were computed for each person using simple linear regression (ordinary least squares) in MATLAB, and the resulting regression coefficient (gradient) for each person was entered into subsequent statistical analyses. For connectivity analyses, the resulting time courses were entered as regressors of interest into first-level analyses in SPM 8 to identify regions showing a time course correlated with amygdala activity. The first-level analyses also included eight regressors of no interest comprising the six movement parameters as well as regressors for white matter and cerebrospinal fluid. For each participant, we computed separate first-level analyses for each of the three post-stress sessions. The resulting contrast images were then subjected to a full factorial second-level analysis with the between-subjects factor group (borderline personality disorder, control group) and the within-subjects factors condition (sham, incision) and time (session 1–3 after stress).

To reduce the possibility of type I errors, we combined a statistical threshold of $P<0.001$ with the cluster extent correction procedure implemented in SPM 8, which computes the number of expected voxels per cluster according to random field theory.[34] Based on this correction procedure, the minimum cluster size for the factorial analysis was determined to be 27 adjacent voxels. We focused on regions showing a group × condition interaction, i.e. effects that were stable over the post-stress course of the experiment.

Results

Effects of condition and stress induction on aversive tension and heart rate

Stress induction was successful in all participants, i.e. a $2\times2\times2$ rm-ANOVA for the time points 'baseline' and 'stress' revealed an increase in aversive tension after the stress induction ($F_{(1,36)}=69.9$, $P<0.001$, $f^2=1.39$, Fig. 2(a)). A main effect of group ($F_{(1,36)}=16.07$, $P<0.001$, $f^2=0.67$) confirmed higher aversive tension in the borderline personality disorder group compared with the control group. There was no interaction effect time × group ($F_{(1,36)}=046$, $P=0.500$, $f^2=0.11$). Heart rate increased with the induction of stress (main effect of time ($F_{(1,26)}=59.02$, $P<0.001$, $f^2=1.51$; Fig. 2(b)), but the data revealed neither a main effect of group ($F_{(1,26)}=2.40$, $P=0.133$, $f^2=0.30$) nor an interaction effect of timegroup ($F_{(1,26)}=0.04$, $P=0.843$, $f^2=0.04$). The HRV index showed a decrease during the stress induction ($F_{(1,26)}=15.27$, $P=0.001$, $f^2=0.77$; Fig. 2(c)). The rm-ANOVA for HRV index further revealed a significant interaction effect time × group ($F_{(1,26)}=4.23$, $P=0.05$, $f^2=0.40$) but no significant main effect of group ($F_{(1,26)}=0.33$, $P=0.572$). For none of the aforementioned parameters was a main or interaction effect regarding condition (sham/incision) observed, implying a successful stress induction independent of the day or condition of the investigation.

Effects of incision on aversive tension and heart rate

In order to test the immediate effects of the incision, we computed a $2\times2\times2$ rm-ANOVA, including condition (sham/incision), group (control/borderline personality disorder), and the two time points 'stress' and 'session 1'. For aversive tension, we found a significant condition × time × group interaction ($F_{(1,36)}=16.28$, $P<0.001$, $f^2=0.67$; Fig. 2(a)) with the borderline personality disorder group revealing a stronger decrease after incision compared with the control group ($t_{(36)}=2.19$, $P<0.05$, $d=0.71$). In contrast, the control group showed a stronger decrease after sham treatment

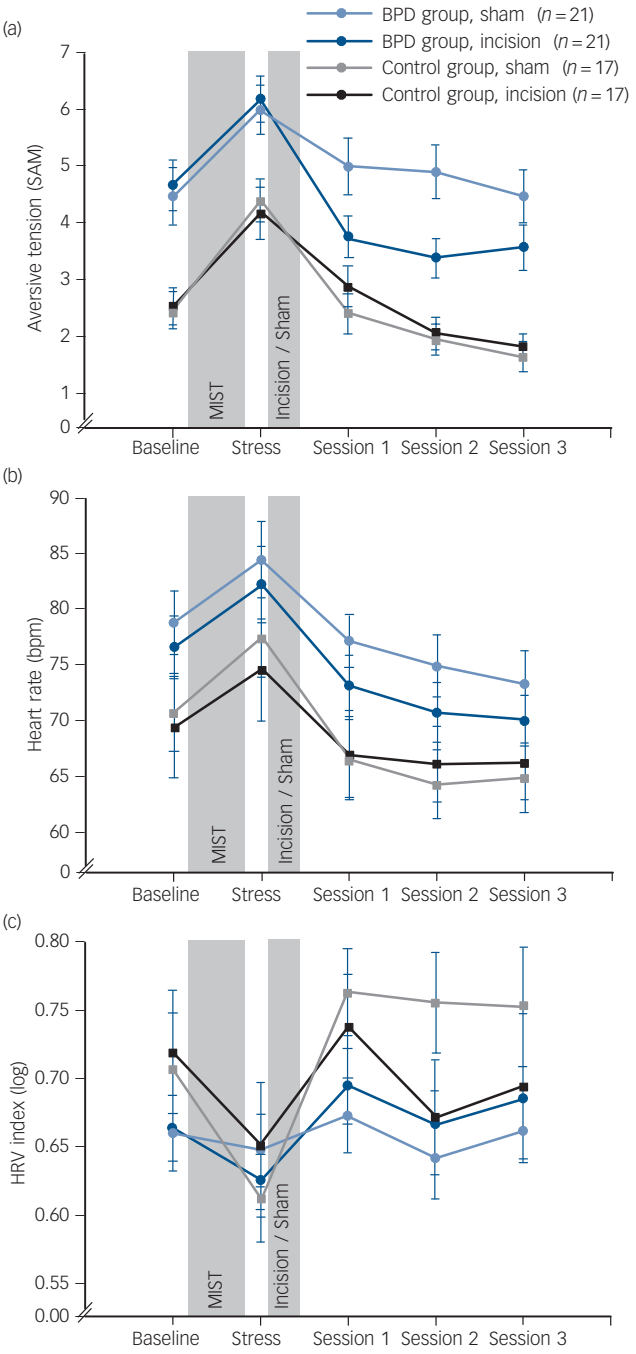

Fig. 2 Stress levels.

(a) Ratings of aversive tension for five time points (baseline, stress and sessions 1–3), two conditions and two groups; (b) and (c) show heart rate values and heart rate variability, respectively, for the same time points, conditions and groups. Grey shaded areas mark the time when the Montreal Imaging Stress Task (MIST) and incision or sham treatment were conducted. Error bars reflect standard errors. SAM, Self-Assessment Manikin; BPD, borderline personality disorder; BPM, beats per minute.

https://doi.org/10.1192/bjp.bp.114.153379 Published online by Cambridge University Press

compared with the borderline personality disorder group ($t_{(36)} = 2.17$, $P < 0.05$, $d = 0.72$). For heart rate, no immediate effect of incision could be confirmed statistically (condition × time × group: $F_{(1,26)} = 2.55$, $P = 0.123$; incision: $t_{(26)} = 0.53$, $P = 0.603$; sham: $t_{(26)} = 1.40$, $P = 0.173$; Fig. 2(b)). However, the analysis of HRV showed a condition × time × group interaction ($F_{(1,26)} = 5.07$, $P < 0.05$, $f^2 = 0.44$), with a stronger increase in the HRV index in the control group after sham treatment compared with the borderline personality disorder group ($t_{(26)} = 3.27$, $P < 0.01$, $d = 1.27$). Contrarily, no significant group difference could be found regarding HRV for the effects of incision ($t_{(26)} = 0.51$, $P = 0.612$; Fig. 2(c)).

In order to test the intermediate effects of the incision, we computed 4 × 2 × 2 rm-ANOVAs with the four time points after the stress induction. We found an interaction of condition × time × group ($F_{(2.32,83.43)} = 5.95$, $P < 0.01$, $f^2 = 0.41$) and condition × group ($F_{(1,36)} = 6.01$, $P < 0.05$, $f^2 = 0.41$) for aversive tension (Fig. 2(a)). After the stress induction, in particular during the first two sessions of resting state fMRI, those in the borderline personality disorder group stayed at a lower level of aversive tension after incision compared with sham (session 1: $t_{(20)} = 3.13$, $P < 0.01$, $d = 0.60$); session 2: $t_{(20)} = 4.64$, $P < 0.001$, $d = 0.77$). The analysis of heart rate (Fig. 2(b)) showed a trend effect of condition × time × group ($F_{(2.19,56.88)} = 2.49$, $P = 0.087$, $f^2 = 0.31$). Analogous to aversive tension, heart rate remained higher following the stress induction after sham compared with incision in the borderline personality disorder group. This effect was confirmed statistically for session 2 ($t_{(16)} = 2.74$, $P < 0.05$, $d = 0.37$), and found as a trend for session 1 ($t_{(16)} = 2.07$, $P = 0.055$, $d = 0.38$) and session 3 ($t_{(16)} = 2.02$, $P = 0.061$, $d = 0.30$). HRV again revealed a condition × time × group effect ($F_{(1.83,47.49)} = 3.64$, $P < 0.05$, $f^2 = 0.37$; Fig. 2c). Specifically, the control group showed a higher value on the HRV index in session 2 after sham compared with incision ($t_{(10)} = 2.51$, $P \leqslant 0.05$, $d = 0.64$).

Effects of incision on amygdala BOLD time series

In order to analyse bilateral amygdala activity over time, we computed a 2 × 2 ANOVA with the regression coefficient for amygdala activity in the resting-state session after the stress induction of each person as dependent variable and the factors group and condition as independent variable. This resulted in a main effect for group ($F_{(1,66)} = 6.73$, $P < 0.05$, $f^2 = 0.09$), showing that amygdala activity decreased more in the borderline personality disorder group than in the control group. More specifically, we found that regression coefficients were positive for the control group (mean = 0.014, s.d. = 0.029), pointing to an increase over time. In the borderline personality disorder group, regression coefficients were negative (mean = −0.015, s.d. = 0.059), pointing to an overall decrease of amygdala activity ($T_{(68)} = 2.581$, $P = 0.012$) (Fig. 3(b)).

Effects of incision on functional connectivity

The seed-based correlation analysis of fMRI data with the bilateral amygdala revealed a group × condition interaction effect in Brodmann area 8/superior frontal gyrus (Montreal Neurological Institute (MNI) coordinates 2, 24, 56; $P < 0.001$, $k = 34$, $Z = 3.50$, Fig. 3(a)). *Post hoc* *t*-tests showed a significant difference of amygdala functional connectivity in this region between the borderline personality disorder and control groups following incision ($t_{(33)} = 3.57$, $P < 0.001$, $d = 1.22$). Additional *post hoc* tests comparing amygdala superior frontal gyrus connectivity between the sham and incision condition in each group separately revealed a significant difference between conditions for the control group ($t_{(15)} = 2.77$, $P < 0.05$, $d = 0.99$) and a statistical trend for the

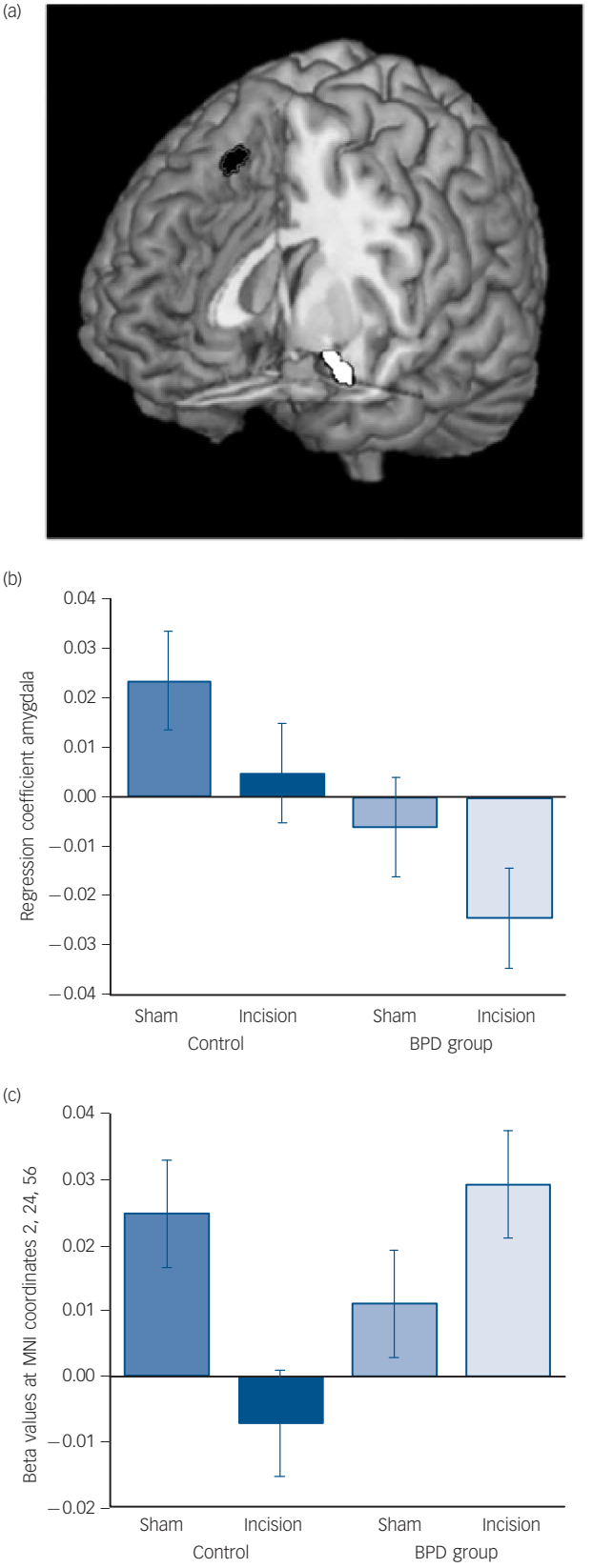

Fig. 3 Amygdala activity and connectivity analysis.

(a) Shows a cluster within the amygdala (white) that was used as a seed region in our functional connectivity analysis as well as a cluster in the superior frontal gyrus/Brodmann area 8 (black). (b) Depicts regression coefficients for amygdala activity after incision or sham treatment with positive values standing for an increase and negative values for a decrease over time. As depicted in (c) functional connectivity between these two brain regions was higher in the control group following sham treatment, whereas the borderline personality disorder (BPD) group showed higher connectivity after incision compared with sham. Error bars reflect standard errors. MNI, Montreal Neurological Institute.

https://doi.org/10.1192/bjp.bp.114.153379 Published online by Cambridge University Press

borderline personality disorder group ($t_{(18)} = 2.03$, $P = 0.057$, $d = 0.70$; Fig. 3(c)). Particularly, the control group showed reduced connectivity in response to incision compared with sham, whereas connectivity of amygdala with superior frontal gyrus was increased in the borderline personality disorder group after incision compared with sham. In order to ascertain that this effect was not caused by a difference in the amount of head motion,[35] we additionally performed a $3 \times 2 \times 2$ rm-ANOVA for realignment parameters. This revealed no significant group × condition interactions (translation: $P = 0.557$; rotation: $P = 0.481$). For complete data of amygdala connectivity see Table 2.

Discussion

Main findings

This is the first study to explore the effects of incision-induced pain and/or skin lesions on neural stress regulation in patients with borderline personality disorder. Our findings revealed a stress-reducing effect of tissue damage that affects subjective experience, psychophysiological functioning and cerebral processing (i.e. amygdala activity and connectivity) after stress selectively in the borderline personality disorder group. This offers a deeper understanding of the mechanisms underlying NSSI in people with borderline personality disorder.

Analysing subjective tension ratings, heart rate data and amygdala activity, we have replicated and extended our previous findings of decreased stress levels in people with borderline personality disorder in response to tissue damage.[24] Given that subjective tension associated with an increased reactivity to stress is one of the most aversive feelings for those with borderline personality disorder,[4] our findings support the notion that tissue damage has a soothing effect for these individuals. Lower levels on the HRV index in the borderline personality disorder group are consistent with the suggestion that reduced HRV indices may be linked to dysregulated affective styles.[36] In general, HRV is influenced by the interaction of sympathetic and parasympathetic outputs of the central autonomic nervous system (ANS), with high HRV indicating a healthy and adaptive organism.[37] Changes in ANS tone are found in different mental disorders, for example in patients with depression.[38] An increase in the range of HRV is related to a more vagally influenced heart rate (corresponding to an increased HRV index), whereas a decrease is related to a more sympathetically influenced heart rate (corresponding to a lower HRV index) and an increased risk of cardiac morbidity.[38] Because it has been suggested that psychological distress in borderline personality disorder is related to an inability to regulate intense physiological arousal,[39] we interpret our finding of reduced HRV in the borderline personality disorder group in terms of revealing a higher sympathetic tone and reduced resources for stress adaptation.

By simulating NSSI with an experimental pain model involving mild skin lesions, a higher ecological validity should be achieved, thereby enhancing our understanding of the psychological and neural processes underlying self-injury. Furthermore, we used a powerful method of stress induction, resulting in high and sustained aversive tension. We found that amygdala activity, which has been repeatedly found to be elevated in patients with borderline personality disorder,[40] decreased over time in the borderline personality disorder group, which was most pronounced after incision. Furthermore, we conducted an analysis of functional connectivity during the resting-state period following incision/sham. Here, the borderline personality disorder group showed a medium-sized effect (albeit only resulting in a statistical trend) for enhanced coupling between the amygdala and superior frontal gyrus (Brodmann area 8) following incision compared with sham. The opposite pattern was observed in the control group. This is in line with previous findings[13,18] and provides further evidence for the conceptualisation of NSSI as a dysfunctional attempt to cope with dysregulated affect.

Other groups also investigated the intermediate influence of stress on resting-state functional connectivity of the amygdala in the recovery phase after stress.[41] They found a coupling between amygdala and prefrontal regions and interpreted this finding in terms of a downregulation of emotional states and an adaptive recovery from stress. In our study, functional connectivity between amygdala and superior frontal gyrus was enhanced in the borderline personality disorder group in the incision condition compared with sham, whereas control group showed modulatory coupling only for the sham condition. Given these similarities, we speculate that healthy people's 'normal' connectivity between the amygdala and superior frontal gyrus is disturbed by incision. In contrast, we conclude that in individuals with borderline personality disorder the downregulation of emotional states and a recovery from stress are promoted by incision. In accordance with this view, it has previously been shown that prefrontal regions modulate emotional responses via functional coupling to limbic regions like the amygdala.[42] Activation in the superior frontal gyrus, or rather Brodmann area 8, has also repeatedly been observed during attentional distraction.[43,44] Therefore, our current findings may represent an enhanced prefrontal–limbic interaction through pain, which may have acted as an attentional distractor.[18]

Table 2 Full factorial analysis of seed-based connectivity with the bilateral amygdala

Brodmann area	Automated anatomical labelling	Cluster extent/number of voxels, *k*	*P* (family-wise error)	*P* (uncorrected)	Z-score	Montreal Neurological Institute coordinates		
Main effect: group								
13	Superior temporal gyrus	44	0.222	<0.001	4.150	−42	0	−12
	Midbrain	135	0.272	<0.001	4.085	0	−20	0
34	Parahippocampal gyrus	28	0.394	<0.001	3.957	30	6	−18
Interaction effect								
Time × condition								
Putamen	Lentiform nucleus	86	0.108	<0.001	4.385	−28	−18	6
Caudate body	Caudate	29	0.496	<0.001	3.903	20	12	20
7	Superior parietal lobule	25	0.875	<0.001	3.563	22	−58	64
Group × condition								
8	Superior frontal gyrus	34	0.894	<0.001	3.495	2	24	56
Time × group × condition								
Caudate tail	Caudate	36	0.290	<0.001	4.098	−30	−36	12
37	Middle occipital gyrus	28	0.922	<0.001	3.496	46	−68	−12

a. Results are significant at $P < 0.001$.

https://doi.org/10.1192/bjp.bp.114.153379 Published online by Cambridge University Press

Strengths and limitations

This study established the incision model in an fMRI environment and thereby links the elucidation of clinically relevant mechanisms with alterations in neuronal systems involved in NSSI in patients with borderline personality disorder. However, several important limitations must be kept in mind when interpreting our results. First, we did not use a conventional fMRI design, which is why we cannot draw inferences regarding brain activation patterns in response to a task/intervention, but only regarding brain activity over time and connectivity regarding resting state after stress. This approach was deemed necessary because incision treatment can only be applied once for ethical reasons. Second, aiming at a replication and extension of our prior results[24] to brain activity, we used a similar study design. As a consequence, we analysed resting-state connectivity after stress with a focus on intermediate (10–20 min) effects. Thus, one could argue that we cannot infer direct effects of incision on stress, which is only possible when combining both experimental factors at the same time. Although the analysis of seed-voxel connectivity is an adequate method to detect connections between brain areas, it is based on correlations, and causal interpretations should be treated with caution. However, our conclusions are based on combined observations regarding decreased amygdala activity and enhanced connectivity in participants with borderline personality disorder after incision, allowing for a more complex interpretation than connectivity analyses alone. Nevertheless, future studies should test explicit models of the assumed interactions, for example by dynamic causal modelling.

Third, our method does not enable us to differentiate neuronal traits underlying NSSI from changes in neuronal connectivity. Therefore, our results may also be traced back to previously existing traits, such as impulsivity. Besides, although we provided a more realistic model of NSSI than earlier studies, we cannot disentangle the effects of painful stimulation and tissue damage. Further studies should focus on this differentiation as well as the difference between an injury applied by an investigator and a self-inflicted injury.[45] One might assume that self-inflicted pain implicates cognitive appraisal processes that, in turn, have an impact on actual pain processing. Fourth, although our sample size is appropriate to detect large interaction effects between condition and group, the statistical power was insufficient to detect medium effect sizes ($1-\beta = 0.96$ and 0.65, respectively). Especially with regard to our connectivity analyses, this could be an explanation why we found only a statistical trend in the borderline personality disorder group (with $1-\beta = 0.82$), although this was related to a medium sized effect. Because we investigated only female participants, our results cannot be generalised to men with borderline personality disorder. Likewise, given that we excluded patients with borderline personality disorder taking medication, our findings pertain to a 'borderline personality disorder subgroup' and cannot be generalised to the average patient with borderline personality disorder. Interrater reliabilities for SCID-I and IPDE were relatively low. Finally, it has to be mentioned that NSSI not only occurs in people with borderline personality disorder, but also in depression and post-traumatic stress disorder.[46] Therefore, an important question for future studies is whether patients with other psychiatric disorders and who self-harm differ from those with borderline personality disorder.

Implications

Taken together, we found higher levels of inner tension and lower parasympathetic tone in patients with borderline personality disorder than in healthy controls. An experimental skin lesion normalised these symptoms and increased the connectivity between the amygdala and medial prefrontal brain regions. This was paralleled by decreased amygdala activity in people with borderline personality disorder in response to incision after a stress induction. Thus, we were able to confirm and extend previous findings on the important role of pain in emotion regulation in borderline personality disorder. Our data lend support to the assumption that NSSI may help to normalise disturbed emotion regulation circuits in borderline personality disorder and thus elucidate why these patients use NSSI to reduce high levels of stress.

Sarah Reitz, MD, **Rosemarie Kluetsch**, **Inga Niedtfeld**, PhD, **Teresa Knorz**, MD, **Stefanie Lis**, PhD, Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health Mannheim, Medical Faculty Mannheim/Heidelberg University, Mannheim; **Christian Paret**, Department Neuroimaging, Central Institute of Mental Health Mannheim, Medical Faculty Mannheim/Heidelberg University, Mannheim; **Peter Kirsch**, PhD, Department of Clinical Psychology, Central Institute of Mental Health Mannheim, Medical Faculty Mannheim/Heidelberg University, Mannheim; **Andreas Meyer-Lindenberg**, MD, Department of Psychiatry and Psychotherapy, Central Institute of Mental Health Mannheim, Medical Faculty Mannheim/Heidelberg University, Mannheim; **Rolf-Detlef Treede**, MD, **Ulf Baumgärtner**, MD, Department of Neurophysiology, Center for Biomedicine and Medical Technology, Medical Faculty Mannheim/Heidelberg University, Mannheim; **Martin Bohus**, MD, **Christian Schmahl**, MD, Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health Mannheim, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany

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

First received 25 Jun 2014, final revision 27 Oct 2014, accepted 2 Nov 2014

Funding

The study was supported by the Deutsche Forschungsgemeinschaft (KFO 256).

Acknowledgements

The authors would like to thank Jens Pruessner for providing the Montreal Imaging Stress Task as well as Martin Jungkunz and Lars Schulze for their help with the figures.

References

1 Muehlenkamp JJ, Claes L, Havertape L, Plener PL. International prevalence of adolescent non-suicidal self-injury and deliberate self-harm. *Child Adolesc Psychiatry Ment Health* 2012; **6**: 10.

2 Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G, Weinberg I, Gunderson JG. The 10-year course of physically self-destructive acts reported by borderline patients and axis II comparison subjects. *Acta Psychiatr Scand* 2008; **117**: 177–84.

3 Skodol AE, Gunderson JG, Pfohl B, Widiger TA, Livesley WJ, Siever LJ. The borderline diagnosis I: psychopathology comorbidity, and personaltity structure. *Biol Psychiatry* 2002; **51**: 936–50.

4 Kleindienst N, Bohus M, Ludaescher P, Limberger MF, Kuenkele K, Ebner-Priemer UW, et al. Motives for nonsuicidal self-injury among women with borderline personality disorder. *J Nerv Ment Dis* 2008; **196**: 230–6.

5 Klonsky ED. The functions of deliberate self-injury: a review of the evidence. *Clin Psychol Rev* 2007; **27**: 226–39.

6 Chapman AL, Gratz KL, Brown MZ. Solving the puzzle of deliberate self-harm: the experiential avoidance model. *Behav Res Ther* 2006; **44**: 371–94.

7 Nock MK, Prinstein MJ. A functional approach to the assessment of self-mutilative behavior. *J Consult Clin Psychol* 2004; **72**: 885–90.

8 Simeon D, Stanley B, Frances A, Mann JJ, Winchel R, Stanley M. Self-mutilation in personality disorders: psychological and biological correlates. *Am J Psychiatry* 1992; **149**: 221–6.

9 Ludaescher P, Greffrath W, Schmahl C, Kleindienst N, Kraus A, Baumgaertner U, et al. A cross-sectional investigation of discontinuation of self-injury and normalizing pain perception in patients with borderline personality disorder. *Acta Psychiatr Scand* 2009; **120**: 62–70.

10 Schmahl C, Greffrath W, Baumgaertner U, Schlereth T, Magerl W, Philipsen A, et al. Differential nociceptive deficits in patients with borderline personality disorder and self-injurious behavior: laser-evoked potentials, spatial discrimination of noxious stimuli, and pain ratings. *Pain* 2004; **110**: 470–9.

https://doi.org/10.1192/bjp.bp.114.153379 Published online by Cambridge University Press

11 Bohus M, Limberger M, Ebner U, Glocker FX, Schwarz B, Wernz M, et al. Pain perception during self-reported distress and calmness in patients with borderline personality disorder and self-mutilating behavior. *Psychiatry Res* 2000; **95**: 251–60.

12 Ludaescher P, Bohus M, Lieb K, Philipsen A, Jochims A, Schmahl C. Elevated pain thresholds correlate with dissociation and aversive arousal in patients with borderline personality disorder. *Psychiatry Res* 2007; **149**: 291–6.

13 Schmahl C, Bohus M, Esposito F, Treede RD, Di Salle F, Greffrath W, et al. Neural correlates of antinociception in borderline personality disorder. *Arch Gen Psychiatry* 2006; **63**: 659–67.

14 Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, et al. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. *Biol Psychiatry* 2003; **54**: 1284–93.

15 Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, et al. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biol Psychiatry* 2001; **50**: 292–8.

16 Koenigsberg HW, Siever LJ, Lee H, Pizzarello S, New AS, Goodman M, et al. Neural correlates of emotion processing in borderline personality disorder. *Psychiatry Res* 2009; **172**: 192–9.

17 Niedtfeld I, Schulze L, Kirsch P, Herpertz SC, Bohus M, Schmahl C. Affect regulation and pain in borderline personality disorder: a possible link to the understanding of self-injury. *Biol Psychiatry* 2010; **68**: 383–91.

18 Niedtfeld I, Kirsch P, Schulze L, Herpertz SC, Bohus M, Schmahl C. Functional connectivity of pain-mediated affect regulation in borderline personality disorder. *PloS One* 2012; **7**: e33293.

19 Ochsner KN, Gross JJ. The neural architecture of emotion regulation. In *The Handbook of Emotion Regulation* (eds JJ Gross and R Buck): 87–108. Guilford Publications, 2007.

20 Russ MJ, Roth SD, Lerman A, Kakuma T, Harrison K, Shindledecker RD, et al. Pain perception in self-injurious patients with borderline personality disorder. *Biol Psychiatry* 1992; **32**: 501–11.

21 Baumgaertner U, Iannetti GD, Zambreanu L, Stoeter P, Treede RD, Tracey I. Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: a high-resolution fMRI study. *J Neurophysiol* 2010; **104**: 2863–72.

22 Kawamata M, Takahashi T, Kozuka Y, Nawa Y, Nishikawa K, Narimatsu E, et al. Experimental incision-induced pain in human skin: effects of systemic lidocaine on flare formation and hyperalgesia. *Pain* 2002; **100**: 77–89.

23 Pogatzki-Zahn EM, Wagner C, Meinhardt-Renner A, Burgmer M, Beste C, Zahn PK, et al. Coding of incisional pain in the brain: a functional magnetic resonance imaging study in human volunteers. *Anesthesiology* 2010; **112**: 406–17.

24 Reitz S, Krause-Utz A, Pogatzki-Zahn EM, Ebner-Priemer U, Bohus M, Schmahl C. Stress regulation and incision in borderline personality disorder – a pilot study modeling cutting behavior. *J Pers Disord* 2012; **26**: 605–15.

25 Dedovic K, Renwick R, Mahani NK, Engert V, Lupien SJ, Pruessner JC. The Montreal Imaging Stress Task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. *J Psychiatry Neurosci* 2005; **30**: 319–25.

26 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder (4th edn) (DSM-IV)*. APA, 1994.

27 Loranger AW. *International Personality Disorder Examination (IPDE): DSM-IV and ICD-10 Modules*. Psychological Assessment Resources, 1999.

28 First MB, Spitzer RL, Gibbon M, Williams JBW, Benjamin LS. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) – Clinical Version*. American Psychiatric Press, 1997.

29 Bradley MM, Lang PJ. Measuring emotion: the Self-Assessment Manikin and the semantic differential. *J Behav Ther Exp Psychiatry* 1994; **25**: 49–59.

30 Electrophysiology TFotESoCatNASoPa. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996; **17**: 354–81.

31 Schafer A, Vagedes J. How accurate is pulse rate variability as an estimate of heart rate variability?: a review on studies comparing photoplethysmographic technology with an electrocardiogram. *Int J Cardiol* 2013; **166**: 15–29.

32 Cohen J. *Statistical Power Analysis for the Behavioral Sciences (2nd edn)*. Lawrence Erlbaum Associates, 1998.

33 Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002; **15**: 273–89.

34 Hayasaka S, Nichols TE. Combining voxel intensity and cluster extent with permutation test framework. *Neuroimage* 2004; **23**: 54–63.

35 Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 2012; **59**: 2142–54.

36 Beauchaine T. Vagal tone, development, and Gray's motivational theory: toward an integrated model of autonomic nervous system functioning in psychopathology. *Dev Psychopathol* 2001; **13**: 183–214.

37 Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord* 2000; **61**: 201–16.

38 Roose SP. Depression, anxiety, and the cardiovascular system: the psychiatrist's perspective. *J Clin Psychiatry* 2001; **62** (suppl 8): 19–22.

39 Stiglmayr CE, Shapiro DA, Stieglitz RD, Limberger MF, Bohus M. Experience of aversive tension and dissociation in female patients with borderline personality disorder – a controlled study. *J Psychiatr Res* 2001; **35**: 111–8.

40 Krause-Utz A, Winter D, Niedtfeld I, Schmahl C. The latest neuroimaging findings in borderline personality disorder. *Curr Psychiatry Rep* 2014; **16**: 438.

41 Veer IM, Oei NY, Spinhoven P, van Buchem MA, Elzinga BM, Rombouts SA. Beyond acute social stress: increased functional connectivity between amygdala and cortical midline structures. *Neuroimage* 2011; **57**: 1534–41.

42 Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci* 2012; **1251**: E1–24.

43 Mak AK, Hu ZG, Zhang JX, Xiao ZW, Lee TM. Neural correlates of regulation of positive and negative emotions: an fMRI study. *Neurosci Lett* 2009; **457**: 101–6.

44 McRae K, Hughes B, Chopra S, Gabrieli JD, Gross JJ, Ochsner KN. The neural bases of distraction and reappraisal. *J Cogn Neurosci* 2010; **22**: 248–62.

45 Haines J, Williams CL, Brain KL, Wilson GV. The psychophysiology of self-mutilation. *J Abnorm Psychol* 1995; **104**: 471–89.

46 Auerbach RP, Kim JC, Chango JM, Spiro WJ, Cha C, Gold J, et al. Adolescent nonsuicidal self-injury: examining the role of child abuse, comorbidity, and disinhibition. *Psychiatry Res* 2014; **220**: 579–84.

https://doi.org/10.1192/bjp.bp.114.153379 Published online by Cambridge University Press