Neural correlates of emotional action control in anger-prone women with borderline personality disorder

Katja Bertsch, PhD; Karin Roelofs, PhD; Paul Jonathan Roch, MD; Bo Ma, MSc;
Saskia Hensel, MSc; Sabine C. Herpertz, MD; Inge Volman, PhD

Background: Difficulty in controlling emotional impulses is a crucial component of borderline personality disorder (BPD) that often leads to destructive, impulsive behaviours against others. In line with recent findings in aggressive individuals, deficits in prefrontal amygdala coupling during emotional action control may account for these symptoms. **Methods:** To study the neurobiological correlates of altered emotional action control in individuals with BPD, we asked medication-free, anger-prone, female patients with BPD and age- and intelligence-matched healthy women to take part in an approach-avoidance task while lying in an MRI scanner. The task required controlling fast behavioural tendencies to approach happy and avoid angry faces. Additionally, before the task we collected saliva testosterone and self-reported information on tendencies to act out anger and correlated this with behavioural and functional MRI (fMRI) data. **Results:** We included 30 patients and 28 controls in our analysis. Patients with BPD reported increased tendencies to act out anger and were faster in approaching than avoiding angry faces than with healthy women, suggesting deficits in emotional action control in women with BPD. On a neural level, controlling fast emotional action tendencies was associated with enhanced activation in the antero- and dorsolateral prefrontal cortex across groups. Healthy women showed a negative coupling between the left dorsolateral prefrontal cortex and right amygdala, whereas this was absent in patients with BPD. **Limitations:** Specificity of results to BPD and sex differences remain unknown owing to the lack of clinical control groups and male participants. **Conclusion:** The results indicate reduced lateral prefrontal–amygdala communication during emotional action control in anger-prone women with BPD. The findings provide a possible neural mechanism underlying difficulties with controlling emotional impulses in patients with BPD.

Introduction

Borderline personality disorder (BPD) is a severe mental disorder characterized by instability of affect, self-image, and personal goals, along with interpersonal dysfunctions and high levels of hostility, impulsivity and risk-taking behaviour.¹ Enhanced difficulty in controlling emotional impulses is a crucial component of BPD.² Unfortunately, the patients' impulsive responses are often directed against other individuals, thereby obstructing healthy social relationships.³ Investigating the neurobiological correlates of altered social emotional behaviour in patients with BPD is of great relevance, as an increased knowledge of underlying mechanisms may guide the development of new mechanism-based treatment.⁴ In the present study, we investigated these neurobiological correlates in a group of female patients with BPD who performed an experimental task that required rule-driven control of emotional behaviour.

Previous studies of patients with BPD reported altered reactivity to emotional stimuli in several brain regions, including prefrontal areas and the amygdala.⁵ Although increased amygdala activation has been associated with emotional hypersensitivity, decreased activity in the dorsolateral prefrontal cortex (dlPFC)^{5,6} and reduced prefrontal amygdala functional and structural connectivity⁷ suggest deficient or ineffective communication between these regions in patients with BPD. In studies with healthy participants, the dlPFC as well as the lateral anterior PFC (aPFC) have been found to be crucially involved in the control of emotionally relevant actions by downregulating the amygdala.^{8–12} A recent investigation found reduced lateral aPFC activation and aPFC–amygdala coupling in aggressive male offenders during emotional action control.¹² This suggests that an inefficient inhibition of the amygdala by lateral PFC regions could be a neurobiological correlate underlying decreased cognitive control of emotional behavioural tendencies,^{9,10} especially in individuals with a tendency to act out

Correspondence to: K. Bertsch, Department for General Psychiatry, Center of Psychosocial Medicine, University of Heidelberg Voßstr. 269115 Heidelberg, Germany; katja.bertsch@med.uni-heidelberg.de

Submitted May 19, 2017; Revised Aug. 24, 2017; Accepted Sept. 6, 2017; Published online first Jan. 16, 2018

DOI: 10.1503/jpn.170102

their feelings of anger or threat aggressively.¹² Testosterone modulates lateral PFC–amygdala connectivity.^{11,12} This hormone has been linked to the tendency to approach interpersonal threats and to act out aggressively.^{13–15} Interestingly, testosterone levels have recently been reported to be enhanced in female patients with BPD.^{16–18} Taken together, these findings raise questions about whether lateral PFC activity and PFC–amygdala connectivity are altered when patients with BPD have to control emotionally relevant actions and whether such an alteration may be associated with the patients' aggression and endogenous testosterone levels.³

To address these questions, anger-prone women with BPD and healthy female volunteers took part in an approach-avoidance task during which they were instructed to respond to briefly presented happy and angry facial expressions with approach and avoidance movements.^{9–12,19} During affect-congruent conditions, participants could follow their emotional tendency to approach happy and avoid angry faces, whereas they had to control their emotional action tendencies during affect-incongruent conditions in order to perform the counterintuitive action of avoiding happy and approaching angry faces. In previous studies, healthy volunteers responded slower and showed stronger aPFC activations in trials requiring emotional action control (affect-incongruent v. congruent trials).^{9–11} Using this task, deficient aPFC–amygdala coupling has been found in highly aggressive male offenders,¹² suggesting less prefrontal regulation of emotional actions.¹⁰

In the present study, we investigated whether similar reductions in the communication between the prefrontal cortex and amygdala during emotional action control could be found in anger-prone women with BPD. We hypothesized that patients with BPD would show deficits in cognitive control of emotional action tendencies, as reflected in reduced behavioural and lateral prefrontal congruency effects compared with healthy volunteers. In addition, we expected reduced PFC–amygdala coupling during the affect-incongruent versus the affect-congruent condition. Based on previous research, we additionally assessed whether these alterations could be related to patients' elevated levels of endogenous testosterone¹⁷ and the strength of their tendency to act out their feelings of anger.

Methods

Participants

We recruited medication-free female patients with BPD as well as age- and intelligence-matched healthy women to take part in our study. We excluded women with neurologic disorders; alcohol/drug abuse in the 2 months preceding the study, or alcohol/drug dependence in the 12 months preceding the study; a lifetime diagnosis of schizophrenia, schizoaffective, or bipolar disorder; severe medical illness; or use of psychotropic medication for at least 2 weeks preceding the study. Given the focus of the present study and to avoid excessive heterogeneity, we included only those who currently fulfilled at least 5 DSM-IV criteria of BPD, including anger

proneness, in the patient group.²⁰ To be included in the healthy control group, participants had to have no history of a psychiatric diagnosis (assessed with structured interviews) or psychotherapeutic or psychiatric treatment.

The study was part of the KFO-256,²¹ a German consortium on mechanisms underlying emotion dysregulation in patients with BPD. Participants were recruited through a KFO-256 general recruitment unit, with psychometric data of all participants being monitored in a central data bank. Samples across KFO-256 studies may overlap. The present study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg. Participants provided written informed consent. Details on the experimental protocol are provided in Appendix 1, available at jpn.ca/170102-a1.

Measures

All patients and controls took part in an extensive onsite diagnostic interview to assess BPD and other current and lifetime psychiatric disorders. Interviews consisted of the Structured Clinical Interview for DSM-IV for axis-I disorders (SCID-I)²² and the International Personality Disorder Examination (IPDE) for axis-II disorders.²³ These interviews were performed by experienced diagnosticians who had at least a master's degree in psychology or medical doctorate and underwent standardized training; there was high interrater reliability (ICC $\geq$ 0.91 for both the number of BPD criteria and the dimensional score assessed by the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD). Body mass index was calculated according to height and weight measurements on the study day. Possible confounders of testosterone data (menstrual cycle, use of the contraceptive pill, smoking) were assessed in a standardized questionnaire. Raven's progressive matrices²⁴ were used as an estimate for intelligence. We assessed BPD symptom severity using the ZAN-BPD,²⁵ depressiveness using the Beck Depression Inventory,²⁶ attention-deficit/hyperactivity disorder (ADHD) symptoms using the self-rating behaviour questionnaire for ADHD,²⁷ trait anxiety with the State-Trait Anxiety Inventory,²⁸ and disposition to act out feelings of anger using the State-Trait Anger Expression Inventory.²⁹

Testosterone levels

We collected a saliva sample before the experiment (between 1.30 pm and 2.00 pm) in 2 mL polypropylene tubes; the samples were immediately frozen at -20°C for biochemical analysis. Testosterone concentration was measured using a competitive chemiluminescence immunoassay (LIA) with a sensitivity of 0.0025 ng/mL (IBL) and intra- and interassay coefficients between 10% and 12%. As testosterone levels were skewed, we used log-transformed and z-standardized (per group) values.

Approach-avoidance task

The experiment was based on a 2×2 design with the factors congruency and facial affect. Participants had to categorize the effect of angry and happy faces (presentation time 100 ms) either by pushing a joystick away from themselves or pulling

it toward themselves as soon as the face appeared.^{9–12} After having moved the joystick, participants had to return it to the starting position before the end of the intertrial interval (2–4 s). The task consisted of 16 blocks with 12 trials per block. Each block started with a written instruction indicating the required responses: pulling for happy and pushing angry faces (congruent condition) or vice versa (incongruent condition), and ended with a baseline period (black screen; 21–24 s). The sequence of blocks (incongruent/congruent) was counterbalanced across participants. Within each block, facial affect and sex were presented in a pseudorandom order (< 4 sequential presentations of the same affect and/or sex). The task lasted 35 minutes, starting with a joystick calibration and training (4 blocks of 8 trials with different stimuli; Appendix 1).

Data acquisition

Stimulus presentation and acquisition of joystick positions (Fibre Optic Joystick, Current Designs; sampling rate 550 Hz; placed on the participants' abdomen) were controlled with Presentation software version 16.3 (Neurobehavioural Systems). Functional images were acquired in a 3 T whole-body MRI scanner (Tim Trio, Siemens) equipped with a 32-channel head coil using a multi-echo GRAPPA sequence with the following parameters: repetition time (TR) 2190 ms; echo times (TE) 9.3, 20.9, 32 and 44 ms; 34 transversal slices, ascending acquisition, distance factor 17%, effective voxel size $3.3 \times 3.3 \times 3.0$ mm³; and field of view (FOV) 212 mm.³⁰ After completion of the task, isotropic high-resolution structural images were recoded using a T_1 -weighted coronal-oriented MPRAGE sequence with the following parameters: TR 2300 ms, TE 2.98 ms, 240 sagittal slices, effective voxel size $1.0 \times 1.0 \times 1.0$ mm³, FOV 256 mm.

Data analysis

BPD symptomatology

We used 2-sample *t* tests to analyze group differences in BPD symptom severity, depressiveness, ADHD symptoms, trait anxiety, tendencies to act out anger and testosterone. We considered results to be significant at $p < 0.05$ and used Cohen *d* to assess effect size.

Behavioural data

Trials with incorrect responses, reaction times faster than 100 ms or slower than 1500 ms, or with joystick peak velocities or path lengths greater than ± 3 standard deviations (SDs) of the participant-specific data distribution were excluded. To investigate emotional action control, we calculated difference scores by subtracting the mean reaction time (time from stimulus presentation until movement onset) for affect-congruent conditions from affect-incongruent conditions. These difference scores were then submitted to a group (BPD, control) by affect (happy, angry) analysis of variance (ANOVA) using a 2-tailed significance threshold of $p < 0.05$. Effect sizes of significant results are reported as proportions of explained variances (η^2). The sphericity assumption was not violated ($\epsilon = 1.0$). For further analysis of interaction

effects, we used Dunn multiple comparisons with Bonferroni correction for multiple testing as post hoc tests.

Functional MRI data

Statistical parametric mapping (SPM8; www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used for preprocessing and analyzing imaging data following previously described procedures for multi-echo GRAPPA MRI sequences³⁰ (Appendix 1).

For each participant, we constructed a design matrix by modelling face presentation onset and reaction time (convolved with the canonical hemodynamic response function) as separate regressors for the 4 combinations of affect (angry, happy) $\times$ movement (approach, avoid), 2 regressors for the excluded trials (misses) and the instructions/feedback (information), and regressors for the movement parameters and the signal intensities in white matter, in cerebrospinal fluid, and in the proportion of the MRI image outside the skull³¹ (Appendix 1). Finally, fMRI time series were high-pass filtered (cutoff 120 s), and temporal autocorrelation was modelled as a first-order autoregressive process.

In line with previous studies,^{9–12} consistent effects across participants and between groups were assessed in a random-effects multiple regression analysis with the estimated effects of the 8 conditions based on the group $\times$ affect $\times$ movement interaction.

As we were interested in neural correlates of emotional action control, analyses were focused on the congruency effect (i.e., task-related differences of affect-incongruent [avoid-happy, approach-angry] v. affect-congruent [approach-happy, avoid-angry] trials across groups and for each group separately). We performed a hypothesis-driven region of interest (ROI) analysis^{8–12} on the left and right aPFC³² and dlPFC³³ as well as an exploratory whole brain analysis. We assessed congruency effects within one group and tested whether those effects were specific to that group and thus significantly weaker in the other group. This was done by applying a strict family-wise error (FWE) voxel-level correction for multiple comparisons ($p_{\text{FWE}} < 0.05$ based on recent recommendations³⁴) on the effect of interest (group-specific congruency effect) and masking that contrast with the group $\times$ congruency contrast ($p < 0.05$, uncorrected; see the study by Volman and colleagues¹²). Bonferroni-corrected *p* values of ROI analysis are reported.

Furthermore, psychophysiological interaction analyses (PPIs)³⁵ were performed to test whether the coupling of aPFC and dlPFC with the amygdala (ROI³⁶) during the congruency effect differed between groups. To define the volumes of interest (VOI), voxels within an 8 mm radius around the peak voxel of the congruency effect across both groups were selected (Montreal Neurological Institute [MNI] coordinates: *x*, *y*, *z* = −24, 52, 6 in the left aPFC and *x*, *y*, *z* = −32, 52, 22 in the left dlPFC). Participant-specific contrast images were generated describing the PPI between the time courses of the VOIs and affect-incongruent versus affect-congruent conditions.

We additionally performed explorative correlations analyzing associations of behavioural and fMRI data with testosterone and tendency to act out in anger. We considered findings to be significant at $p < 0.05$.

Results

Participants

We included 30 medication-free women with BPD (mean age 26.9 ± 6.1 [range 18–40] yr) and 28 age- and intelligence-matched controls (mean age 26.5 ± 5.7 [range 19–48] yr) in our analysis (Table 1). Although we measured 32 women with BPD and 30 control women, 4 participants had to be excluded from our analyses owing to head movements or joystick malfunctioning).

BPD symptomatology

Besides significantly higher levels of BPD symptom severity, depressiveness, ADHD symptoms and trait anxiety (all $p < 0.001$), patients with BPD reported stronger outwardly directed anger ($p = 0.003$) and had significantly increased testosterone levels ($p = 0.023$) compared with healthy volunteers (Table 1).

Behavioural data

Mean reaction times are presented in Table 2. The analysis of difference scores (incongruent minus congruent trials) revealed a significant group $\times$ affect interaction ($F_{1,56} = 5.72$, $p = 0.020$, $\eta^2 = 0.09$). Post hoc tests showed significantly larger difference scores for happy than angry faces in both groups (all $p < 0.01$) and a significant group effect for angry faces (all $p < 0.05$; Fig. 1). The negative mean difference score of pa-

tients with BPD (-0.045 ± 0.014) suggested relatively faster approach versus avoidance responses to angry faces — an effect that was absent in healthy volunteers (-0.001 ± 0.015 , $p > 0.05$). This effect in patients with BPD is opposite to previously reported emotional action tendencies in healthy samples to avoid rather than approach signals of interpersonal threats¹⁹ and may support the role of aggression in patients with BPD.³ Effects remained significant after controlling for depressiveness, ADHD symptoms and trait anxiety.

Functional MRI data

The multiple regression analysis showed a significant congruency effect (contrast: incongruent $>$ congruent trials) across both groups in the left dlPFC (Brodmann area [BA] 46 extending into BA 10; peak voxel $x, y, z = -32, 52, 22$; ROI $p_{\text{FWE}} = 0.002$, $k = 181$; Fig. 1B and C and Table 3) and in the left lateral aPFC (BA 10; peak voxel $x, y, z = -24, 52, 6$; ROI

Table 2: Reaction times for each group and factor in the approach-avoidance task

Factor	Group; mean $\pm$ SE, ms	
	BPD	Control
Happy-approach	578 $\pm$ 15	562 $\pm$ 15
Happy-avoid	654 $\pm$ 20	619 $\pm$ 21
Angry-approach	602 $\pm$ 17	601 $\pm$ 21
Angry-avoid	627 $\pm$ 18	598 $\pm$ 18

BPD = borderline personality disorder; SE = standard error.

Table 1: Demographic and clinical characteristics of study participants

Characteristic	Group; mean $\pm$ SD*		<i>t</i>	<i>p</i> value	Cohen <i>d</i>
	BPD, <i>n</i> = 30	Control, <i>n</i> = 28			
Age, yr	26.9 $\pm$ 6.1	26.5 $\pm$ 5.7	0.28	0.78	0.07
Intelligence (Raven)	54.2 $\pm$ 4.2	54.1 $\pm$ 4.1	0.09	0.93	0.02
Body mass index	23.0 $\pm$ 2.9	22.0 $\pm$ 2.5	1.40	0.17	0.37
Salivary testosterone, pg/mL	26.9 $\pm$ 33.5	11.1 $\pm$ 12.3	2.34	0.023	0.62
BPD symptom severity (ZAN-BPD)	13.2 $\pm$ 5.0	0.5 $\pm$ 0.8	13.18	< 0.001	3.46
Depressiveness (BDI-II)	27.5 $\pm$ 10.7	3.9 $\pm$ 3.4	11.12	< 0.001	2.92
ADHD symptom severity (ADHD-SR)	14.45 $\pm$ 1.5	6.4 $\pm$ 1.1	4.32	< 0.001	1.14
Trait anxiety (STAI)	59.5 $\pm$ 6.8	29.4 $\pm$ 5.9	18.03	< 0.001	4.74
Anger out (STAXI)	15.1 $\pm$ 4.5	11.7 $\pm$ 3.8	3.10	0.003	0.82
Comorbid disorder, no. current (lifetime)					
Affective disorders	8 (22)	—	—	—	—
Substance disorders	0 (3)	—	—	—	—
Anxiety disorders	12 (15)	—	—	—	—
PTSD	7 (8)	—	—	—	—
Social phobias	5 (7)	—	—	—	—
Somatoform disorders	3 (3)	—	—	—	—
Eating disorders	7 (12)	—	—	—	—
Antisocial personality disorder	1 (1)	—	—	—	—
Avoidant personality disorder	10 (10)	—	—	—	—

ADHD = attention-deficit/hyperactivity disorder; ADHD-SR = Self-Rating Behaviour Questionnaire for ADHD; BDI-II = Beck Depression Inventory, revised; BPD = borderline personality disorder; PTSD = posttraumatic stress disorder; SD = standard deviation; STAI = State-Trait Anxiety Inventory; STAXI = State-Trait Anger Expression Inventory; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

*Unless indicated otherwise.

$p_{\text{FWE}} = 0.050$, $k = 51$). In the left dlPFC, this effect was driven by healthy volunteers (BA 46 extending into BA 10; peak voxel $x, y, z = -32, 54, 12$; ROI $p_{\text{FWE}} < 0.001$, $k = 31$; Fig. 1C), and it was significantly weaker in patients with BPD (as the reported result in healthy volunteers remained after masking the main effect in healthy volunteers in the group [control > BPD] $\times$ congruency interaction, thresholded at $p < 0.05$).^{9–12}

Furthermore, patients with BPD activated a relatively wide network during incongruent compared with congruent trials. There was a significant congruency effect in a more posterior cluster in the right dlPFC (BA 46; ROI $p_{\text{FWE}} < 0.001$, $k = 39$; Fig. 1C), which was significantly weaker in healthy volunteers (as the reported result remained after masking the effect in patients with BPD in the group (BPD > control) $\times$ congruency

interaction, thresholded at $p < 0.05$). Additionally, patients with BPD showed a significant congruency effect in parts of the right middle and inferior frontal gyri, right supramarginal, left inferior temporal, bilateral fusiform gyri, and in several clusters of the occipital cortex, including the precuneus and cuneus (all $p_{\text{FWE}} < 0.05$; Table 3). The described effects were evoked by both happy and angry faces according to post hoc conjunction analyses (all $p < 0.001$).³⁷

Connectivity analysis with the left aPFC ($x, y, z = -24, 52, 6$) as a seed region did not reveal any significant effects. However, using the left dlPFC ($x, y, z = -32, 52, 22$) as a seed region on the congruency effect indicated a group difference with the right amygdala (ROI $x, y, z = 34, 0, -20$, $p = 0.005$, $k = 4$) with healthy volunteers showing a negative coupling

Fig. 1: (A) Difference scores for reaction times ± 1 standard error (affect-incongruent minus affect-congruent conditions) of patients with borderline personality disorder (BPD) and healthy volunteers. Note that the behavioural congruency effect for both emotions is influenced by a general movement effect (i.e., generally larger reaction times for avoiding than approaching joystick movements, which is typically found in the MR version of the approach-avoidance task; see www.ingevolman.com/Projects/suppl-to-volman-et-al-submitted). ** $p < 0.01$; * $p < 0.05$. (B) Mean activation ± 1 standard error of the active voxels within the left dorsolateral prefrontal cortex (dlPFC) for affect-incongruent versus affect-congruent conditions for each affect (happy, angry) and group (BPD, control). (C) Brain regions reflecting increased activations for affect-incongruent versus affect-congruent conditions across groups (ALL), in healthy volunteers and in patients with BPD. For visual purposes, activations are presented at $p < 0.001$ and $k > 10$. (D) Group difference on the congruency-related left dlPFC-amygdala connectivity, $p < 0.001$ for visual purposes. (E) Strength of the congruency-specific changes ± 1 standard error in dlPFC-amygdala connectivity for healthy volunteers, which was not present in patients with BPD. * $p < 0.05$. RTs = reaction times.

between the left dlPFC and right amygdala (ROI $x, y, z = 34, 0, -20$, $p_{\text{FWE}} = 0.030$, $k = 10$), while patients with BPD showed no differential connectivity effect (Fig. 1D-E).

Correlation analyses

The tendency to act out in anger modulated the group (BPD > control) $\times$ congruency effect (incongruent > congruent trials) in the left aPFC (ROI $x, y, z = -28, 52, 10$, $p_{\text{FWE}} = 0.021$, $k = 11$) and the right amygdala (whole brain: $x, y, z = 30, -8, -12$, $k = 52$, $p_{\text{FWE}} = 0.002$). Post hoc analyses revealed that these effects were mainly driven by angry faces. In healthy volunteers, congruency effects decreased in the left aPFC and increased in the right amygdala with an increasing tendency to act out anger. Contrary to this, congruency effects were unrelated to aPFC activations in patients with BPD and decreased

in the right amygdala with an increasing tendency to act out in anger (Fig. 2). No associations were found between the tendency to act out in anger and behavioural data (all $p > 0.05$), and no significant association was found with testosterone, except positive correlations with the behavioural tendency to approach rather than avoid happy and angry faces (BPD: $r = 0.50$, $p = 0.005$; control: $r = 0.35$, $p = 0.072$; Appendix 1, Fig. S1).

Discussion

The present study aimed to test neural correlates of aggression in female patients with BPD during emotional action control. The results pointed at several behavioural and neural deficits of emotional action control in patients with BPD. Behaviourally, the patients showed increased self-reported

Table 3: Clusters showing significantly larger activations for the affect-incongruent than for the affect-congruent conditions across groups

Activation effect	BA	Side	MNI coordinates			k	t	p _{FWE} value
			x	y	z			
Congruency effect across groups								
VOI on aPFC	10	L	−24	52	6	51	3.66	0.025
VOI on dlPFC	46	L	−32	52	22	181	5.27	0.001
Whole brain effect								
Calcarine sulcus	17	L	−4	−78	10	76	6.05	0.001
Superior occipital cortex	17	L	−10	−98	8	7	5.62	0.004
Inferior temporal cortex	37	L	−50	−50	−24	17	5.62	0.004
Cuneus	18	R, L	2	−82	22	39	5.57	0.004
dlPFC	46(/10)	L	−32	52	22	6	5.27	0.015
Congruency effect in controls								
VOI on dlPFC	46	L	−32	54	24	31	5.43	< 0.001
Whole brain effect								
dlPFC	46(/10)	L	−32	54	24	12	5.43	0.008
Congruency effect in patients with BPD								
VOI on dlPFC	46	R	26	42	24	39	5.39	< 0.001
Whole brain effect								
Superior occipital cortex/precuneus	7/18/19	R	22	−76	32	180	6.57	< 0.001
Middle/superior occipital cortex	18/19	L	−32	−84	12	107	6.35	< 0.001
Cuneus/calcarine sulcus	17/18	L, R	−6	−80	22	159	6.24	< 0.001
Middle frontal gyrus	8	R	32	16	60	99	6.21	< 0.001
Lingual gyrus/fusiform gyrus	18/19	L	−18	−70	−12	59	6.04	0.001
Middle frontal gyrus	9	R	28	26	34	28	5.94	0.001
Middle occipital cortex	19	L	−30	−64	26	37	5.38	0.001
Inferior occipital cortex	37	L	−48	−64	−14	26	5.7	0.003
Fusiform gyrus	37	L	−38	−44	−26	6	5.67	0.003
dlPFC	46	R	26	42	24	42	5.66	0.003
Superior occipital cortex	19	L	−14	−92	22	17	5.65	0.003
Inferior temporal gyrus	37	L	−48	−52	−26	9	5.55	0.005
Calcarine sulcus	17/18	R	12	−86	6	27	5.47	0.007
Precuneus		R	12	−56	42	5	5.45	0.007
Supra marginal gyrus	40	R	54	−46	42	5	5.33	0.012
Inferior frontal gyrus	45	R	48	40	10	13	5.29	0.014
Superior occipital cortex	18	L	−12	−96	12	6	5.23	0.018

aPFC = anterior prefrontal cortex; BA = Brodmann area; BPD = borderline personality disorder; dlPFC = dorsolateral prefrontal cortex; FWE = family-wise error; L = left; MNI = Montreal Neurological Institute; R = right; VOI = volume of interest.

tendencies to act out feelings of anger and relatively faster approach than avoidance behaviour for angry faces. At the neural level, they showed a reduction in the negative prefrontal–amygdala coupling that was observed in healthy participants during emotional action control.

In line with the expected deficits in cognitive control of emotional action tendencies and previous findings in anger-prone or aggressive individuals,^{38–40} patients with BPD showed relatively faster approach than avoidance responses to angry faces. Our data add to previous reports of an increased likelihood to detect subtle signals of facial anger,^{41,42} a stronger initial orientation toward negative emotional faces,⁴³ and an increased percentage of attention shifts toward threatening emotional faces^{44,45} in patients with BPD. Together these studies suggest a hypersensitivity for negative or threatening emotional information as well as difficulties in the control of emotional impulses — 2 symptoms that we have recently proposed as possible mechanisms for the increased tendency to act out aggressively in response to interpersonal threats or provocations.³ Both threat hypersensitivity and the reduced or slower avoidance of interpersonal threat stimuli may be associated with growing up in an unpredictable, invalidating and abusive environment.⁴⁶ Experiences like these, which are reported by the majority of patients with BPD, may not foster avoidance of potential interpersonal threats as a favourable option and could generally hinder the development of an efficient and reliable emotion action control system.⁴⁷ However, so far it remains to be determined whether deficits in emotion action control are a risk factor or a consequence of negative social experiences throughout life and whether they may be modulated by specific interventions.

In the present study we were primarily interested in studying the neural correlates of deficient emotional action control in patients with BPD using fMRI. Importantly, the negative

connectivity between the lateral PFC and amygdala in healthy volunteers was absent in patients with BPD. This connectivity pattern has previously been shown to be associated with lateral PFC inhibition of the amygdala, which can facilitate emotional action control.¹⁰ A similarly reduced — albeit more anterior — PFC–amygdala coupling was recently found in aggressive male delinquents in addition to a lack of communication from the aPFC to the amygdala in a sample susceptible to affective disorders during emotional action control.^{10,12} This suggests that deficiencies in communication between these regions are a common neurobiological correlate for difficulties in emotional impulse control.¹⁹ This is supported by further similarities between our data and increased behavioural approach tendencies in anger-prone or aggressive individuals.^{19,38,39} Deficits in dlPFC–amygdala communication, but not PFC activation per se, have also been reported in patients with BPD during (negative) affect regulation^{48,49} and thus highlight the centrality of emotion dysregulation for this disorder and its treatment.⁴⁷

Furthermore, both groups replicated previously reported aPFC and dlPFC activations in trials that required control of fast emotional action tendencies.^{8–12,19} The aPFC is known to facilitate the selection of responses by integrating and co-ordinating different cognitive processes,⁵⁰ whereas the dlPFC seems critically involved in executive processes, particularly during continuous updating and manipulation of stimuli in working memory⁵¹ and emotion regulation.⁸ Patients with BPD did not show blunted PFC activations while overriding fast emotional action tendencies, but rather showed increased activations in the PFC as well as in a broad network of brain regions involved in the processing of visual (occipital cortex) and facial (fusiform face area) information and emotion processing (precuneus, cuneus), among others. Interestingly, our results are highly similar to a recently reported network of activations in highly aggressive men performing the same

Fig. 2: Modulation of the congruency effect by the tendency to act out anger in the left amygdala for angry faces in patients with borderline personality disorder (BPD) and healthy volunteers. For visual purposes, activation is presented at $p < 0.001$. Scatterplots reflect correlations between the significant amygdala cluster for approach minus avoidance of angry faces and self-reported, z-standardized tendency to act out in anger (BPD: $r = -0.35$, $p = 0.06$; control: $r = 0.52$, $p = 0.005$, $Z = -3.19$, $p = 0.001$).

task.¹² Finally, it is well worth considering the associations between self-reported tendencies to act out in anger and lateral PFC and amygdala activations. In healthy volunteers, the tendency to act out in anger was negatively associated with left lateral aPFC and positively associated with amygdala activations for approach of angry faces. This indicates that healthy volunteers who are less able to recruit prefrontal areas to downregulate the amygdala while approaching angry faces are those who are less able to refrain from acting out feelings of anger. Contrary to this, in patients with BPD with a high tendency to act out in anger, approaching angry faces was associated with decreased amygdala responses, without a significant prefrontal effect. Acting out to interpersonal threat may hence be a way to regulate aversive states of anger or other negative emotions by reducing arousal and inner tension and increased limbic activation. This suggests a similar regulatory function of aggressive and autoaggressive, self-injurious behaviours.⁵² Clinically, our results may suggest a stronger treatment focus on feelings of anger as well as the emotional action control ability in patients with BPD. Although facial signals of anger are threatening for most individuals and typically induce fear and avoidance, anger-prone individuals, such as patients with BPD, interpret them as provocative and exhibit appetitive motivation and approach or attack behaviour.⁵³ Learning strategies to avoid or withdraw from potentially threatening interpersonal situations could therefore be important for specific interventions in those patients with BPD who have increased tendency to act out in anger.

Limitations

Despite several strengths of the present study, such as the inclusion of a large sample of medication-free patients with BPD and a well-matched healthy control group, several limitations need to be considered. First, patients with BPD had a number of comorbid disorders, which confirms the representativeness of our sample, but may call into question the specificity of the results for BPD. Therefore, more studies including clinical control groups as well as male participants are needed. Second, it would be interesting for future research to investigate whether approach-avoidance tendencies change as a function of psychotherapy. Third, important differences between the present and former studies with aggressive male delinquents^{12,38} have to be noted: although all patients with BPD reported current anger-proneness, only 1 patient fulfilled the criteria for antisocial personality, and no information was available on psychopathic traits (while high levels of psychopathy were reported in the studies by Volman and colleagues¹² and von Borries and colleagues³⁸). Despite prominent differences between anger-prone BPD and psychopathy, the present results may, however, indicate a shared mechanism for deficits in emotional impulse control. Although problems in anger regulation are experienced by more than 70% of patients with BPD,⁵⁴ the restriction on anger-prone patients may limit the generalizability of our results. This is important to mention, as no differences were found in response to angry faces in a previous behavioural study on

emotional action control in an unselected sample of patients with BPD.⁵⁵ Fourth, except for the correlations with the tendency to act out in anger, we did not find any emotion-specific neural congruency effects. This is unexpected when considering that behavioural group differences were found only for angry faces. It remains unclear whether the differences between neural and behavioural effects are due to a greater sensitivity in the neural data or to the approach-avoidance task, which may not fully differentiate between automatic and effortful stages of socioemotional behaviours. Fifth, for time reasons, we did not include neutral facial expressions or a nonemotional control task, as congruency effects have previously not been found in control tasks or for neutral faces^{11,12,38} and because patients with BPD are known to interpret neutral faces as aversive.⁵⁶ Finally, despite its general association with approach-related behaviour, we could not replicate modulatory effects of testosterone on aPFC activations found in male participants,^{11,12} calling for further studies to clarify sex-specific effects of testosterone on neural correlates of cognitive control of emotional action tendencies.

Conclusion

Taken together, the present results show deficits in emotional action control in anger-prone female patients with BPD. Highly similar to aggressive male offenders, women with BPD were relatively faster at approaching than avoiding angry faces. Crucially, deficits in emotional action control in anger-prone individuals have, across diagnoses, been associated with reduced lateral PFC–amygdala communication. These findings may represent a common mechanism underlying difficulties in controlling emotional impulses.

Acknowledgements: The study was supported by the German Research Foundation (HE 2660/12-1 and BE5292/1-1). I. Volman was supported by a Marie Curie Individual Fellowship (MSCA-IF-2014_EF_660397) within the European Union's Horizon 2020 Framework Program. The authors thank P. Gaalman, Dr. S. Heiland and Dr. T. Kaestel for technical support and Dr. J. Cook for language editing. Furthermore, the authors thank the members of the Core Unit for recruitment and diagnostics of the Clinical Research Unit 256: A. Spohn, S. Cackowski, K. Haeussler, Dr. D. Gescher and Dr. F. Mancke.

Affiliations: From the Department of General Psychiatry, Center for Psychosocial Medicine, University of Heidelberg, Heidelberg, Germany (Bertsch, Herpertz); the Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands (Roelofs); Division of Experimental Radiology, University of Heidelberg, Heidelberg, Germany (Ma); the Department of Psychosomatic Medicine, Central Institute of Mental Health Mannheim, Medical Faculty Mannheim/Heidelberg University, Heidelberg, Germany (Hensel); and the Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, London, UK (Volman).

Competing interests: None declared.

Contributors: K. Bertsch, K. Roelofs, S. Herpertz and I. Volman designed the study. K. Bertsch, K. Roelofs, P. Roch, B. Ma and S. Hensel acquired the data, which K. Bertsch, K. Roelofs, S. Herpertz and I. Volman analyzed. K. Bertsch, K. Roelofs and I. Volman wrote the article which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

References

- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 5th ed. Arlington (VA): American Psychiatric Publishing; 2013.
- Lieb K, Zanarini MC, Schmahl C, et al. Borderline personality disorder. *Lancet* 2004;364:453-61.
- Mancke F, Herpertz SC, Bertsch K. Aggression in borderline personality disorder: a multidimensional model. *Pers Disord* 2015;6:278-91.
- Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med* 2013;11:126.
- Schulze L, Schmahl C, Niedtfeld I. Neural correlates of disturbed emotion processing in borderline personality disorder: a multimodal meta-analysis. *Biol Psychiatry* 2016;79:97-106.
- Ruocco AC, Amirthavasagam S, Choi-Kain LW, et al. Neural correlates of negative emotionality in borderline personality disorder: an activation-likelihood-estimation meta-analysis. *Biol Psychiatry* 2013;73:153-60.
- New AS, Hazlett EA, Buchsbaum MS, et al. Amygdala-prefrontal disconnection in borderline personality disorder. *Neuropsychopharmacology* 2007;32:1629-40.
- Dörfel D, Lamke JP, Hummel F, et al. Common and differential neural networks of emotion regulation by detachment, reinterpretation, distraction, and expressive suppression: a comparative fMRI investigation. *Neuroimage* 2014;101:298-309.
- Volman I, Roelofs K, Koch S, et al. Anterior prefrontal cortex inhibition impairs control over social emotional actions. *Curr Biol* 2011;21:1766-70.
- Volman I, Verhagen L, den Ouden HE, et al. Reduced serotonin transporter availability decreases prefrontal control of the amygdala. *J Neurosci* 2013;33:8974-9.
- Volman I, Toni I, Verhagen L, et al. Endogenous testosterone modulates prefrontal-amygdala connectivity during social emotional behavior. *Cereb Cortex* 2011;21:2282-90.
- Volman I, von Borries AKL, Bulten BH et al. Testosterone modulates altered prefrontal control of emotional actions in psychopathic offenders. *eNeuro* 2016; 3:1-12.
- Enter D, Spinhoven P, Roelofs K. Alleviating social avoidance: effects of single dose testosterone administration on approach-avoidance action. *Horm Behav* 2014;65:351-4.
- Enter D, Terburg D, Harrewijn A, et al. Single dose testosterone administration alleviates gaze avoidance in women with social anxiety. *Psychoneuroendocrinology* 2016;63:26-33.
- Bos PA, Panksepp J, Bluthé R-M, et al. Acute effects of steroid hormones and neuropeptides on human social-emotional behavior: a review of single administration studies. *Front Neuroendocrinol* 2012;33:17-35.
- Dettenborn L, Kirschbaum C, Gao W, et al. Increased hair testosterone but unaltered hair cortisol in female patients with borderline personality disorder. *Psychoneuroendocrinology* 2016; 71:176-9.
- Rausch J, Gäbel A, Nagy K, et al. Increased testosterone levels and cortisol awakening responses in patients with borderline personality disorder: gender and trait aggressiveness matter. *Psychoneuroendocrinology* 2015;55:116-27.
- Roepke S, Ziegenhorn A, Kronsbein J, et al. Incidence of polycystic ovaries and androgen serum levels in women with borderline personality disorder. *J Psychiatr Res* 2010;44:847-52.
- Kaldewaij R, Koch SB, Volman I, et al. On the control of social approach-avoidance behavior: neural and endocrine mechanisms. *Curr Top Behav Neurosci* 2017;30:275-93.
- Gunderson JG. Revising the borderline diagnosis for DSM-V: an alternative proposal. *J Pers Disord* 2010;24:694-708.
- Schmahl C, Herpertz SC, Bertsch K, et al. Mechanisms of disturbed emotion processing and social interaction in borderline personality disorder: state of knowledge and research agenda of the German Research Unit. *Borderline Personal Disord Emot Dysregul* 2014;1:12.
- First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV (SCID-I)*. New York (NY): Biometrics Research Department, New York State Psychiatric Institute; 1995.
- Loranger AW, Sartorius N, Andreoli A, et al. The International Personality Disorder Examination. The World Health Organization/Alcohol, Drug Abuse, and Mental Health Administration international pilot study of personality disorders. *Arch Gen Psychiatry* 1994;51:215-24.
- Heller KA, Kratzmeier H, Lengfelder A. *Matrizen-Test-Manual, Band 1. Ein Handbuch mit deutschen Normen zu den Standard Progressive Matrices von J.C. Raven*. Göttingen (Germany): Beltz; 1998.
- Zanarini MC. Zanarini rating scale for borderline personality disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. *J Pers Disord* 2003;17:233-42.
- Beck AT, Steer RA, Brown GK et al. BDI-II. Beck-Depressionsinventar [Beck Depression Inventory II]. Frankfurt (Germany): Pearson Verlag; 2006.
- Rösler M, Retz W, Retz-Junginger P, et al. Instrumente zur Diagnostik der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) im Erwachsenenalter. Selbstbeurteilungsskala (ADHS-SB) und Diagnosecheckliste (ADHS-DC) [Tools for the diagnosis of attention-deficit/hyperactivity disorder in adults. Self-rating behaviour questionnaire and diagnostic checklist]. *Nervenarzt* 2004;75:888-95.
- Laux L, Glanzmann P, Schaffner P, et al. *Das State-Trait-Angstinventar. Theoretische Grundlagen und Handanweisung [the State-Trait Anxiety Inventory. Theoretical background and manual]*. Weinheim: Beltz Test GmbH; 1981.
- Schwenkmezger P, Hodapp V, Spielberger CD. *Das State-Trait-Ärgerausdrucks-Inventar STAXI: Handbuch, 1. Aufl. [the State-Trait Anger Inventory Manual]* Bern: Huber; 1992.
- Poser BA, Versluis MJ, Hoogduin JM, et al. BOLD contrast sensitivity enhancement and artifact reduction with multiecho EPI: parallel-acquired inhomogeneity-desensitized fMRI. *Magn Reson Med* 2006;55:1227-35.
- Verhagen L, Grol MJ, Dijkerman HC, et al. Studying visually-guided reach-to-grasp movements in an MR-environment. *Neuroimage* 2006; 31:S45.
- Neubert F-X, Mars RB, Sallet J, et al. Connectivity reveals relationship of brain areas for reward-guided learning and decision making in human and monkey frontal cortex. *Proc Natl Acad Sci U S A* 2015;112:E2695-704.
- Sallet J, Mars RB, Noonan MP, et al. The organization of dorsal frontal cortex in humans and macaques. *J Neurosci* 2013;33:12255-74.
- Eklund A, Nichols TE, Knutsson H. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci U S A* 2016;113:7900-5.
- Friston KJ, Buechel C, Fink GR, et al. Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 1997;6:218-29.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, 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.
- Nichols T, Brett M, Andersson J, et al. Valid conjunction inference with the minimum statistic. *Neuroimage* 2005;25:653-60.
- von Borries AKL, Volman I, de Bruijn ERA, et al. Psychopaths lack the automatic avoidance of social threat: relation to instrumental aggression. *Psychiatry Res* 2012;200:761-6.
- Lobbestael J, Cousijn J, Brugman S, et al. Approach and avoidance towards aggressive stimuli and its relation to reactive and proactive aggression. *Psychiatry Res* 2016;240:196-201.

40. Veenstra L, Schneider IK, Bushman BJ, et al. Drawn to danger: trait anger predicts automatic approach behavior to angry faces. *Cogn Emotion* 2016;31:765-71.
41. Domes G, Czeschnek D, Weidler F, et al. Recognition of facial affect in borderline personality disorder. *J Pers Disord* 2008;22:135-47.
42. Izurieta Hidalgo NA, Oelkers-Ax R, Nagy K, et al. Time course of facial emotion processing in women with borderline personality disorder — an ERP study. *J Psychiatry Neurosci* 2016;41:16-26.43.
43. Von Ceumern-Lindenstjerna IA, Brunner R, Parzer P, et al. Initial orienting to emotional faces in female adolescents with borderline personality disorder. *Psychopathology* 2010;43:79-87.
44. Bertsch K, Gamer M, Schmidt B, et al. Oxytocin reduces social threat hypersensitivity in females with borderline personality disorder. *Am J Psychiatry* 2013;170:1169-77.
45. Bertsch K, Krauch M, Stopfer K, et al. Threat sensitivity in borderline personality disorder — an eye tracking study. *J Pers Disord* 2017;315:647-70.
46. Zanarini MC. Childhood experiences associated with the development of borderline personality disorder. *Psychiatr Clin North Am* 2000;23:89-101.
47. Linehan MM. Understanding borderline personality disorder. New York (NY): Guilford Press; 1995.
48. Herpertz SC, Nagy K, Ueltzhöffer K, et al. Brain mechanisms underlying reactive aggression in borderline personality disorder — sex matters. *Biol Psychiatry* 2017;82:257-66.
49. Schmitt R, Winter D, Niedtfeld I, et al. Effects of psychotherapy on neuronal correlates of reappraisal in female patients with borderline personality disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2016;1:548-57.
50. Haggard P. Human volition: towards a neuroscience of will. *Nat Rev Neurosci* 2008;9:934-46.
51. Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. *Cogn Affect Behav Neurosci* 2003;3:255-74.
52. Schmahl C, Baumgärtner U. Pain in borderline personality disorder. *Mod Trends Pharmacopsychiatry* 2015;30:166-75.
53. Putnam KM, Silk KR. Emotion dysregulation and the development of borderline personality disorder. *Dev Psychopathol* 2005;17:899-925.
54. Newhill CE, Eack SM, Mulvey EP. Violent behavior in borderline personality. *J Pers Disord* 2009;23:541-54.
55. Kobeleva X, Seidel E-M, Kohler C, et al. Dissociation of explicit and implicit measures of the behavioral inhibition and activation system in borderline personality disorder. *Psychiatry Res* 2014;218:134-42.
56. Daros AR, Zakzanis KK, Ruocco AC. Facial emotion recognition in borderline personality disorder. *Psychol Med* 2013;43:1953-63.

REPRINTS

from the **CMAJ Group**

Going to a conference?

Teaching a course?

Need extra copies?

Contact Sheridan Press
1-800-635-7181 ext. 8065
marcus.glover@sheridan.com
www.sheridan.com/cma/eoc

20170006