

## Out of control? Acting out anger is associated with deficient prefrontal emotional action control in male patients with borderline personality disorder



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### HIGHLIGHTS

- Difficulty in anger control is a frequent symptom of patients with borderline personality disorder (BPD).
- The lateral antero- and dorsal prefrontal cortex are crucially involved in the control of fast emotional actions.
- Hardly anything is known about the neural correlates of deficient anger control in male patients with BPD.
- Results confirm antero- and dorsolateral prefrontal involvement in emotional action control of male patients with BPD.
- Deficient lateral prefrontal emotion control may be a common neural correlate of anger-related aggression.

### ARTICLE INFO

#### Keywords:

Anger  
Aggression  
Male sex  
Anterior prefrontal cortex  
Dorsolateral prefrontal cortex  
Amygdala

### ABSTRACT

Difficulty in anger control and anger-related aggressive outbursts against others are frequently reported by patients with borderline personality disorder (BPD). Although male sex is a known predictor for aggression, hardly any study has addressed the neural correlates of deficient anger control in male patients with BPD. Building on previous reports in female BPD, we investigated the involvement of lateral antero- and dorsal prefrontal cortex in the control of fast emotional actions and its relation to self-reported tendencies to act out anger. 15 medication-free male patients with BPD and 25 age- and intelligence-matched healthy men took part in a social Approach-Avoidance task in the MR-scanner. This task allows the measurement of neural correlates underlying the control of fast behavioral tendencies to approach happy and avoid angry faces. Hypothesis-driven region-of-interest and exploratory whole brain analyses were used to test for activations of antero- and dorsolateral prefrontal regions and their relation with the amygdala during emotional action control as well as their association with self-reported anger out in male patients with BPD and healthy volunteers. Male patients with BPD showed reduced anterolateral prefrontal activations during emotional action control compared to healthy volunteers. Furthermore, anger out was negatively related to antero- and dorsolateral prefrontal activations, while it was positively related to amygdala activity in male patients with BPD. The current results suggest the involvement of antero- and dorsolateral prefrontal regions in controlling and overriding fast emotional actions. Deficits in lateral prefrontal emotion control seem to be a common neural mechanism underlying anger-related aggression.

This article is part of the Special Issue entitled 'Current status of the neurobiology of aggression and impulsivity'.

### 1. Introduction

Intense anger and difficulty in anger control is one of the nine diagnostic criteria of borderline personality disorder (BPD) (American

Psychiatric Association, 2013). Many patients with BPD report frequently acting out aggressively against others in anger (Newhill et al., 2012). This often leads to severe and lasting psychosocial impairments (e.g., Gunderson et al., 2011; Zanarini et al., 2010) and may be

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particularly problematic for male patients with BPD who tend to end up in prison for acting out violently against significant others in an impulsive, uncontrolled manner (Moore et al., 2018; Sansone and Sansone, 2009; Wetterborg et al., 2015).

We have therefore started studying possible neural mechanisms of anger-related aggression in BPD (for reviews, see Mancke et al., 2015, 2018). One such mechanism may be deficient control of fast emotional biases mediated by the lateral prefrontal cortex. Fast emotional actions, such as approaching appetitive and avoiding aversive or threatening stimuli are primarily driven by limbic regions, particularly the amygdala (Quirk and Gehlert, 2003), a region that is hyperactive in patients with BPD in response to (negative) emotional stimuli (Schulze et al., 2016). Controlling and overriding such fast action tendencies has been associated with an inhibition of the amygdala by lateral prefrontal regions – in particular, the antero- (aPFC) and the dorsolateral prefrontal cortex (dlPFC) (for review see, Kaldewaij et al., 2017). Hypoactivation in these prefrontal regions has been suggested to underlie deficits in BPD patients' emotion regulation capacities (Schulze et al., 2016).

In two recent studies, we have shown reduced lateral prefrontal activity and reduced communication with the amygdala during emotional action control in male psychopathic offenders (Volman et al., 2016) as well as in anger-prone female patients with BPD (Bertsch et al., 2018). Reduced lateral prefrontal activity and inhibition of the amygdala might therefore represent a common mechanism of deficient emotional action control and lead to increased tendencies to act out aggressively in anger. Here, we test this hypothesis in a sample of male patients with BPD by assessing lateral prefrontal reactivity during emotional action control, its relation with the amygdala, as well as the relationship between deficient lateral prefrontal control and self-reported tendencies to act out anger.

Male patients with BPD have not received much research attention, despite equal prevalence rates in population-based samples (Grant et al., 2008). This is particularly astonishing in the context of anger and aggression, where male sex is a long known predictor of aggressive behavior irrespective of psychiatric diagnoses (Archer, 2004). Furthermore, we have recently found significant sex differences in the neural correlates of anger-related aggression in BPD (Herpertz et al., 2017). In this study, we used script-driven imagery to induce feelings of anger followed by an imagination of physical aggressive outbursts against another individual. The imagination of acting out aggressively in anger led to increased activations in the lateral orbitofrontal cortex and dlPFC as well as the amygdala in male patients with BPD compared to healthy men and to female patients with BPD (Herpertz et al., 2017). Since the connectivity between these prefrontal regions and the amygdala was negatively related to self-reported trait anger in male patients with BPD, this may suggest unsuccessful voluntary control over emotional actions in anger provoking situations.

Following previous studies on emotional action control, we used an Approach-Avoidance task (Roelofs et al., 2009; Tyborowska et al., 2016; Volman et al., 2011a,b, 2013; 2016) in the present study. This task consists of briefly presented happy and angry facial expressions which are presented in two experimental conditions: an affect-congruent condition, during which the participants can follow their fast emotional action tendencies to approach happy and avoid angry faces and an affect-incongruent condition, which requires participants to control their emotional action tendencies to perform the counter-intuitive action of avoiding happy and approaching angry faces. Across studies, healthy individuals have been found to respond faster in the affect congruent condition, i.e., when they were instructed to “move the joystick towards themselves” for appetitive stimuli, such as happy faces and to “move the joystick away from themselves” for aversive stimuli, such as angry faces than vice versa (see Chen and Bargh, 1999; Eder and Roethermund, 2008; Roelofs et al., 2005).

In line with previous studies (Bertsch et al., 2018; Radke et al., 2015, 2017; Roelofs et al., 2009; Tyborowska et al., 2016; Volman et al., 2011a,b, 2013; 2016), we expected enhanced aPFC and dlPFC

**Table 1**

Demographic and psychometric information (mean  $\pm$  one standard deviation) as well as comorbid disorders (current (lifetime)) of male patients with borderline personality disorder (BPD;  $N = 15$ ) and healthy male controls (CON;  $N = 25$ ). ZAN-BPD: Zanarini Rating Scale for Borderline Personality Disorder; BDI-II: Beck Depression Inventory, revised; STAXI: State-trait Anger Expression Inventory; STAI: State-trait Anxiety Inventory; BIS: Barratt Impulsivity Scale 10; ADHD: attention deficit hyperactivity disorder; ADHD-SR: Self-Rating Behavior Questionnaire for ADHD; PTSD: posttraumatic stress disorder.

	BPD	CON	T	p
Age (years)	27.9 $\pm$ 9.1	29.8 $\pm$ 5.6	-0.85	.402
Intelligence (Raven)	50.3 $\pm$ 6.1	53.7 $\pm$ 4.6	-1.75	.094
BPD symptom severity (ZAN-BPD)	11.6 $\pm$ 5.2	0.2 $\pm$ 0.4	10.79	< .001
Depression (BDI-II)	28.6 $\pm$ 8.8	2.8 $\pm$ 3.2	13.57	< .001
Anger Out (STAXI)	16.1 $\pm$ 6.6	9.7 $\pm$ 2.2	4.61	< .001
Trait Anxiety (STAI)	60.1 $\pm$ 7.1	31.6 $\pm$ 7.6	11.61	< .001
Impulsivity (BIS-11)	84.6 $\pm$ 13.1	61.9 $\pm$ 10.8	5.899	< .001
ADHD (ADHD-SR)	21.5 $\pm$ 11.1	5.7 $\pm$ 4.8	6.27	< .001
Affective disorders	7 (13)	0 (0)		
Substance disorders	0 (3)	0 (0)		
Anxiety disorders	7 (8)	0 (0)		
PTSD	1 (1)	0 (0)		
Social phobia	4 (4)	0 (0)		
Somatophorm disorders	0 (3)	0 (0)		
Eating disorders	4 (4)	0 (0)		
Antisocial personality disorder	1 (1)	0 (0)		

activations in affect-incongruent compared to affect-congruent trials (main effect of congruency). We expected reduced aPFC and dlPFC activations and reduced aPFC/dlPFC-amygdala connectivity in male patients with BPD compared to healthy men (group by congruency interaction). Finally, based on previous findings in female patients with BPD (Bertsch et al., 2018), we hypothesized that lateral prefrontal emotional action control would be related to self-reported tendencies to act out anger (anger out modulation of group by congruency interaction) in such a way that male BPD patients with high tendencies to act out anger would show reduced prefrontal control and enhanced amygdala activation.

## 2. Methods and materials

### 2.1. Participants

15 medication-free male patients with BPD (BPD;  $M_{age} = 28.3$ ,  $SD = 8.9$ , range = 19–44 years) and 25 age- and intelligence-matched healthy men (CON;  $M_{age} = 30.1$ ,  $SD = 5.9$ , range = 20–42 years) took part in the experiment (see Table 1 for details on sample characteristics). Originally,  $N = 17$  BPD and  $N = 29$  CON were measured;  $N = 1$  patient with BPD had to be excluded due to head movements ( $> 8$  mm scan-to-scan),  $N = 1$  patient with BPD due to positive drug screening (cannabis), and  $N = 2$  healthy controls due to joystick malfunctioning.

Exclusion criteria comprised: Neurological disorders, alcohol/drug abuse in the last two months or alcohol/drug dependence in the last 12 months, a lifetime diagnosis of schizophrenia, schizoaffective or bipolar disorder, severe medical illness, or psychotropic medication for at least two weeks prior to participation. Only patients were included who currently fulfilled at least five DSM-IV BPD criteria including BPD-criterion 8 “anger proneness” given the focus of the current study, and to avoid excessive heterogeneity of the sample (Gunderson, 2010). Healthy controls had never received a psychiatric diagnosis (assessed by structured interviews, see below) or undergone a psychotherapeutic or psychiatric treatment.

The study was part of the KFO-256 (Schmahl et al., 2014), a German consortium on mechanisms underlying emotion dysregulation in BPD. Participants were recruited through a KFO-256 general recruitment unit with psychometric data of all participants being monitored in a central

database. Samples across KFO-256 studies may show overlap in participants. The study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg. Participants provided written informed consent.

## 2.2. Experimental protocol

For all patients with BPD and healthy controls the diagnostic process comprised an extensive telephone screening for inclusion and exclusion criteria (approx. 45min) followed by an onsite diagnostic appointment (approx. 3 h; see below). At the day of their participation, participants performed a urine toxicology screening for exclusion of acute substance abuse. The experiment started with detailed instructions, a calibration of the joystick, and a brief training (4 blocks/8 trials with different stimuli). The total time of the experiment was approx. 35min. Afterwards anatomical scans were collected (see below). All participants were financially reimbursed.

## 2.3. Measures

The onsite diagnostic interview consisted of the Structured Clinical Interview for DSM-IV (SCID-I for axis-I disorders; First et al., 1995) and the International Personality Disorder Examination (IPDE for axis-II disorders; Loranger et al., 1994) for the assessment of BPD and other comorbid psychiatric disorders. The interviews were performed by experienced diagnosticians who had at least a M.Sc. in Psychology or M.D. and underwent standardized training resulting in high inter-rater reliabilities ( $ICC \geq 0.91$  for both the number of BPD criteria and the dimensional score assessed by the ZAN-BPD scale). Raven's progressive matrices (Heller et al., 1998) were used as an estimate for intelligence. BPD symptom severity was assessed with the Zanarini Rating Scale for BPD (ZAN-BPD; Zanarini, 2003), depressiveness with the Beck Depression Inventory revised (BDI-II; Beck et al., 2006), Attention Deficit Hyperactivity Disorder (ADHD) symptoms with the Self-Rating Behavior Questionnaire for ADHD (Rösler et al., 2004), trait anxiety with the State-Trait-Anxiety Inventory (Laux et al., 1981), impulsivity with the Barratt Impulsivity Scale 10th version (Patton et al., 1995), and the State-Trait-Anger Expression Inventory (Schwenkmezger et al., 1992) was conducted to assess the disposition to act out anger.

## 2.4. Approach-Avoidance task

The experiment was based on a 2x2-design with the factors congruency and facial affect. Facial stimuli consisted of happy and angry expressions of 36 different models (18 male) selected from several picture sets (Ekman and Friesen, 1976; Lundqvist et al., 1998; Martinez and Benavente, 1998; Matsumoto and Ekman, 1988). Faces were grayscale, trimmed from hair and non-facial contours, matched for brightness and contrast values, and presented on a black background. Stimuli were projected at the center of a screen, viewed via a mirror above the subject's head.

Participants had to categorize the affect of angry and happy facial expressions (presentation time: 100 ms) by either pushing a joystick away from themselves or pulling it towards themselves as soon as a facial stimulus appeared (also see Bertsch et al., 2018; Roelofs et al., 2009, or Volman et al., 2011a,b, 2013; 2016). After having moved the joystick, they had to return it to the starting position before the end of the inter-trial interval (2–4sec). The middle position was defined as the central area covering 15% along the sagittal plane. Joystick movements of  $\geq 60\%$  along the sagittal plane  $\leq 3$ sec after stimulus presentation were regarded as valid responses. Participants received visual feedback for invalid responses.

The task consisted of 16 blocks with 12 trials per block. Each block started with a written instruction indicating the required responses, i.e., pulling for happy and pushing for angry faces (congruent condition) or vice versa (incongruent condition), and ended with a baseline period

(black screen; 21–24sec). The sequence of blocks (incongruent/congruent) was counterbalanced across participants. Within each block, facial affect and sex were presented in a pseudorandomized order (no more than 4 sequential presentations of the same facial affect and/or sex in a row).

## 2.5. Data acquisition

Stimulus presentation and acquisition of joystick positions (Fiber Optic Joystick, Current Designs, sampling rate: 550 Hz; placed on the participants' abdomen) were controlled by Presentation software (Version 14.2, Neurobehavioral Systems). Functional images were acquired in a 3-T whole-body MR scanner (Tim Trio; Siemens) equipped with a 32-channel head coil using a multi-echo GRAPPA sequence (TR = 2,190 ms, TEs = 9.3/20.9/32/44 ms; 34 transversal slices, ascending acquisition, distance factor = 17%, effective voxel size =  $3.3 \times 3.3 \times 3.0 \text{ mm}^3$ , FoV = 212 mm (Poser et al., 2006)). After completion of the task, isotropic high-resolution structural images were recorded using a T1-weighted coronal-oriented MPRAGE sequence (TR = 2,300 ms, TE = 2.98 ms, 240 sagittal slices, effective voxel size =  $1.0 \times 1.0 \times 1.0 \text{ mm}^3$ , FoV = 256 mm).

## 2.6. Data analysis

**BPD-Symptomatology.** We used two sample t-tests to analyze group differences in BPD-symptom severity, depressiveness, ADHD symptoms, trait anxiety, and tendencies to act out anger ( $p < .05$ ).

**Behavioral Data.** Following previous studies with this task (e.g., Bertsch et al., 2018; Volman et al., 2011a,b, 2013; 2016), we excluded trials with incorrect responses (for the calculation or reaction times), reaction times  $< 100 \text{ ms}$  or  $> 1,500 \text{ ms}$ , or with joystick peak velocities or path lengths  $> \pm 3SDs$  of the participant-specific data distribution. We then submitted the error rates and mean reaction times to  $2 \times 2$  repeated-measure analyses of covariance (ANCOVA) with the factors group (BPD vs. HC), congruency (congruent vs. incongruent), and affect (happy vs. angry) and the covariate Anger-Out (z-standardized levels of the STAXI Anger-Out subscale) in order to investigate differences in emotional action control. The level of statistical significance was set at  $p = .05$ . Effect sizes of significant results are reported as proportion of explained variances ( $\eta^2$ ). The sphericity assumption was not violated ( $\epsilon = 1.0$ ). For further analysis of interaction effects, Dunn's Multiple Comparisons with Bonferroni correction for multiple testing were used as post-hoc tests. Behavioral data were preprocessed in MATLAB (MathWorks) and statistical analyses were performed using IBM SPSS version 24.

**fMRI Data.** Statistical parametric mapping (SPM8, [www.fil.ion.ucl.ac.uk/spm/software/spm8/](http://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 MR sequences (Poser et al., 2006). The preprocessing comprised the following steps: (1) Discarding of the first 4 volumes to allow for T1 equilibration. (2) Estimation of head motion parameters on the MR images with the shortest TE (9.3 ms), since these images are known to be least affected by possible artifacts in multiecho GRAPPA MR sequences. (3) Application of estimated motion-correction parameters (least-square approach with 6 rigid body transformation parameters [translations and rotations]) to the 4 echo images collected for each excitation. (4) Combination of the 4 echo images into a single MR volume using an optimized echo weighting method. (5) Temporal realignment of time series for each voxel to the first slice to correct for differences in slice time acquisition. (6) Co-registration of the T1-weighted image to the mean of the functional images. (7) Transformation and resampling of the fMRI time series at anisotropic voxel size of 2 mm into standard Montreal Neurological Institute (MNI) space using both linear and nonlinear transformation parameters as determined in a probabilistic generative model that combines image registration, tissue classification, and bias correction (i.e., unified

segmentation and normalization) of the co-registered T1-weighted image (Ashburner and Friston, 2005). (8) Spatial smoothing of the normalized functional images using an isotropic 8 mm full-width at half-maximum Gaussian kernel.

For each participant, a design matrix was constructed by modelling face presentation onset and reaction time (convolved with the canonical hemodynamic response function) as separate regressors for the four combinations of affect (angry, happy) x movement (approach, avoid), two 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 MR image outside the skull (Verhagen et al., 2006). Finally, fMRI time series were high-pass filtered (cutoff 120s) and temporal autocorrelation was modeled as a first-order autoregressive process.

In line with previous studies (e.g., Bertsch et al., 2018; Volman et al., 2011a,b, 2013; 2016), a random effects multiple regression analysis with group x affect x movement conditions was set up. All analyses assessed the congruency effect, reflecting task-related differences in affect-incongruent (avoid-happy, approach-angry) versus affect-congruent trials (approach-happy, avoid-angry). We considered two effects: (1) We tested for general effects of congruency over both groups (incongruent > congruent) and group by congruency interaction (CON > BPD and BPD > CON). (2) We tested whether activations were modulated by Anger-Out and therefore performed group by congruency contrasts on the regressor parameterizing inter-individual differences in Anger-Out on task-relevant conditions, i.e., we tested whether the correlation between congruency effect (incongruent > congruent) and Anger-Out was significantly different in male patients with BPD and in healthy men. We performed hypothesis-driven analyses on the left and right aPFC and dlPFC using a volume of interest (VOI) on coordinates previously found to be modulated by the congruency effect in healthy volunteers (8-mm-radius spheres centered on the following MNI coordinates: left aPFC:  $x = -30$ ;  $y = 58$ ;  $z = 2$ ; right aPFC:  $x = 32$ ;  $y = 54$ ;  $z = 8$ ; Volman et al., 2011a,b, 2016; left dlPFC:  $x = -32$ ;  $y = 52$ ;  $z = 22$ ; right dlPFC:  $x = 26$ ;  $y = 42$ ;  $z = 24$ ; Bertsch et al., 2018). Additionally, exploratory whole brain analyses were run. All reported results are  $p < .05$  family-wise-error (fwe) corrected (voxel level; Eklund et al., 2016), in addition, small volume correction and Bonferroni-Holms correction were used in the VOI analyses.

(3) We performed psychophysiological interaction analyses (PPIs; Friston et al., 1997) to test whether the coupling of aPFC with the amygdala (ROI; Tzourio-Mazoyer et al., 2002) during the congruency effect differed between the two groups. Here, the VOIs were defined by selecting voxels within a sphere of 8-mm radius around the peak voxel of the congruency effect over both groups (left aPFC:  $x = -26$ ;  $y = 58$ ;  $z = 8$ ; right aPFC:  $x = 28$ ;  $y = 52$ ;  $z = 14$ ; see 3.3). Participant-specific contrast images were generated describing the PPI between the time courses of the VOIs and affect-incongruent vs. affect-congruent conditions.

### 3. Results

#### 3.1. BPD-symptomatology

Patients with BPD reported significantly higher levels of BPD-symptom severity, depression, impulsivity, ADHD symptoms, trait anxiety, and anger-out compared with healthy volunteers (all  $ps < .001$ , see Table 1 for statistical details).

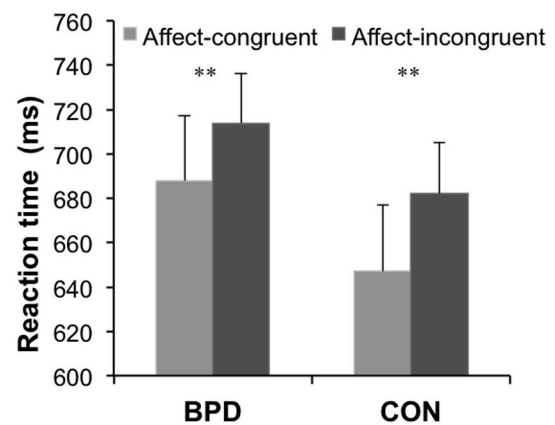
#### 3.2. Behavioral Data

Participants performed the task accurately (BPD: 5.6%; CON: 5.5% errors; see Table 2). Significant main effects of congruency (RT:  $F(1,37) = 13.86$ ,  $p = .001$ ,  $\eta^2 = 0.27$ ; ER:  $F(1,37) = 13.28$ ,  $p = .001$ ,  $\eta^2 = 0.26$ ) and of affect (RT:  $F(1,37) = 10.80$ ,  $p = .002$ ,  $\eta^2 = 0.23$ )

**Table 2**

Error rates and reaction times ( $\pm$  one standard error) for each group (male patients with borderline personality disorder, BPD, and healthy male controls, CON) and factor in the Approach-Avoidance task.

	BPD	CON
<i>error rates (%)</i>		
Happy – Approach	5.6 (1.0)	5.0 (0.8)
Happy – Avoid	6.2 (1.3)	6.2 (1.0)
Angry – Approach	7.2 (1.0)	6.6 (0.8)
Angry – Avoid	3.6 (0.9)	3.9 (0.7)
<i>reaction times (ms)</i>		
Happy – Approach	652 (28)	615 (22)
Happy – Avoid	722 (31)	690 (24)
Angry – Approach	706 (31)	674 (24)
Angry – Avoid	724 (32)	680 (25)



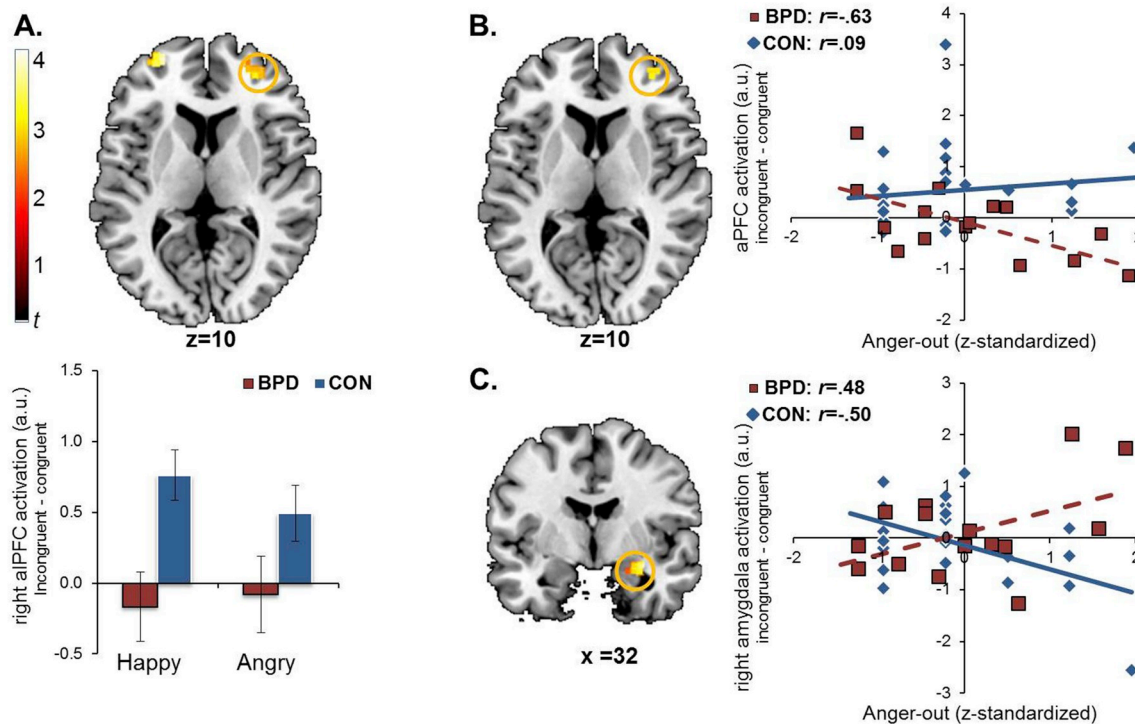
**Fig. 1.** Mean reaction times  $\pm$  one standard error for affect-congruent and affect-incongruent conditions in male patients with BPD (BPD) and healthy male controls (CON). Participants were significantly slower in affect-incongruent (approach-angry, avoid-happy) than affect-congruent conditions (approach-happy, avoid-angry), with no significant group differences.

indicated generally slower reactions and more errors in incongruent than in congruent trials as well as for angry than for happy faces. These main effects were qualified by significant congruency by affect interactions (RT:  $F(1,37) = 31.38$ ,  $p < .001$ ,  $\eta^2 = 0.46$ ; ER:  $F(1,37) = 10.68$ ,  $p = .002$ ,  $\eta^2 = 0.22$ , see Fig. 1). Post-hoc tests revealed significantly slower reactions in incongruent than in congruent trials with happy faces ( $p < .05$ ) and significantly more errors in incongruent than congruent trials with angry faces ( $p < .05$ ). The groups did not differ in terms of error rates or reaction times (no significant main or interaction effects including group, all  $F(1,37) < 1.0$ ,  $p > .20$ ). Results did not change significantly after controlling for ADHD, depression, and impulsivity.

#### 3.3. fMRI data

(1) The multiple regression analysis revealed a significant congruency effect (contrast: incongruent > congruent trials) over both groups in the left and right aPFC see Fig. 2A and Table 3). In the right aPFC, the congruency effect was significantly stronger in healthy controls than in patients with BPD (significant group by congruency interaction). The whole brain analyses additionally revealed a significant congruency effect over both groups in several clusters located in the cingulate, parietal, and occipital cortices including the left and right precuneus and cuneus, as well as the parahippocampal gyrus and putamen (for details, see Table 3 and Supplementary Fig. 1). In the group by congruency contrast tested over the whole brain, BPD patients showed significantly stronger activations than healthy controls in parts of the temporal gyrus,





**Fig. 2.** A. Brain regions reflecting a stronger congruency effect (affect-incongruent > congruent) in male healthy controls (CON) than in male patients with BPD (BPD). For visual purposes, activations are presented at  $p < .01$  and  $k > 10$ . The bar graph shows the mean activation  $\pm$  one standard error of the active voxels within the right aPFC. B. Modulation of the congruency effect by the tendency to act out anger in the right aPFC in male patients with BPD (BPD) and male healthy controls (CON). For visual purposes, activation is presented at  $p < .01$ ,  $k > 10$ . Scatterplots reflect correlations between the significant right aPFC cluster and self-reported, z-standardized tendency to act out anger. C. Modulation of the congruency effect by the tendency to act out anger in the right amygdala in male patients with BPD (BPD) and male healthy controls (CON). For visual purposes, activation is presented at  $p < .01$ ,  $k > 10$ . Scatterplots reflect correlations between the significant right amygdala cluster and self-reported, z-standardized tendency to act out anger.

cingulate, insular, and occipital cortices, including the fusiform gyrus, and of the cerebellum, while the congruency effect led to enhanced activation in the left rolandic operculum and precentral gyrus in healthy controls.

- (2) The congruency effect was differentially modulated by Anger-Out between the two groups (significant group by congruency by Anger-Out interaction) in the right aPFC and left and right dlPFC (see Fig. 2B and Table 3). According to post-hoc tests, the congruency effect (i.e., incongruent > congruent) in these three prefrontal areas was negatively correlated with self-reported Anger-Out levels in the patient group (right aPFC:  $r = -0.63$ ; left dlPFC:  $r = -0.38$ , right dlPFC:  $r = -0.68$ ), while no negative correlation was found in the healthy control group (right aPFC:  $r = 0.09$ ; left dlPFC:  $r = 0.39$ , right dlPFC:  $r = 0.19$ ; group differences of Fisher's Z-transformed r-values:  $z \geq -2.26$ ,  $ps \leq .012$ ). Exploratory analyses additionally revealed an opposing pattern for a cluster located in the right amygdala ( $x = 32$ ,  $y = -4$ ,  $z = -14$ , ROI  $T = 5.15$ ,  $p_{FWE} < .001$ ,  $k = 103$ ). Here, the congruency effect correlated positively with Anger-Out levels in the patient group ( $r = 0.48$ ), while negatively in the healthy control group ( $r = -0.50$ , group difference of Fisher's Z-transformed r-values:  $z = 2.99$ ,  $p = .001$ ). The whole brain analysis additionally revealed differential modulatory effects of Anger-Out on the right and left middle frontal gyrus (healthy controls > patients with BPD) and middle temporal gyrus (patients with BPD > healthy controls; for details, see Table 3). All reported effects were evoked by both happy and angry faces according to post-hoc conjunction analyses (all  $ps < .001$ ; Nichols et al., 2005).
- (3) Neither the connectivity analyses with the left and right aPFC as seed regions nor additional connectivity analyses with the left and right dlPFC as seeds revealed any significant coupling with the

amygdala (all small volume corrected  $p_{FWE} > .10$ ).

#### 4. Discussion

In the present study, we investigated deficits in lateral prefrontal emotional action control as a potential neural correlate of increased tendencies to act out anger in male patients with BPD. Consistent with our previous findings in male psychopathic offenders (Volman et al., 2016) and in female patients with BPD (Bertsch et al., 2018), we found reduced activations in the aPFC and dlPFC of male patients with BPD versus healthy men when they had to control and override fast emotional action tendencies. Interestingly, activations in these lateral prefrontal regions were negatively related to self-reported tendencies to act out anger in patients, suggesting deficient lateral prefrontal emotional action control as an important correlate of anger-related aggression. The opposite correlation with amygdala activity was found in BPD patients, supporting previously found reductions in negative lateral prefrontal-amygdala connectivity during emotional action control in patients with anger-related aggression.

The current results confirm the involvement of lateral prefrontal regions in controlling and overriding fast emotional action tendencies. Consistent with previous studies (e.g., Roelofs et al., 2009; Volman et al., 2011a,b, 2013; 2016), we found significantly stronger activations in the left and right aPFC during affect-incongruent conditions, in which participants were instructed to avoid happy and to approach angry faces, than in affect-congruent conditions of approaching happy and avoiding angry faces. It has been suggested that the lateral aPFC is involved in emotion regulation primarily by exerting control over the amygdala and is thus implicated in fast emotional processing and responding (Kaldewaij et al., 2017). Evidence for such an inhibitory effect over the amygdala comes from a study, in which the anterolateral

**Table 3**

Clusters showing significantly larger activations for the affect-incongruent vs. affect-congruent conditions over groups (congruency effect), significant group by congruency interaction, or significant modulatory effects of Anger-Out on the group by congruency interaction are reported.

Note. Coordinates are defined in MNI space (X, Y, Z). P-values represent FWE-corrected values. K: cluster size, L: left, R: right, aPFC: anterior prefrontal cortex, dlPFC: dorsolateral prefrontal cortex.

	Side	X	Y	Z	K	T	P <sub>FWE</sub>
<b>Congruency effect over groups</b>							
<i>VOI on aPFC</i>							
	L	-26	58	8	93	4.34	.002
	R	28	52	14	94	4.08	.004
<b>Whole brain effects</b>							
Precuneus/superior occipital/parietal cortex	L	-12	-66	34	184	7.23	< .001
Anterior cingulate cortex	L	-4	38	16	59	6.32	< .001
Calcarine sulcus/cuneus	L	-12	-76	18	32	5.99	.001
Superior occipital cortex/calcarine sulcus	R	20	-92	6	17	5.95	.002
Posterior cingulate cortex	L	-2	-34	28	14	5.80	.003
Precuneus	R	8	-64	36	28	5.75	.003
Rolandic operculum/frontal inferior operculum	L	-56	2	4	44	5.74	.003
Middle cingulate cortex	L	-6	-6	32	30	5.68	.004
Precuneus	R	2	-60	50	24	5.65	.005
Superior occipital cortex	R	16	-90	22	20	5.53	.008
Precuneus	R	2	-58	36	5	5.44	.011
Parahippocampal Gyrus	L	-30	-46	-6	9	5.39	.013
Putamen	R	34	10	6	7	5.29	.019
Superior parietal cortex	R	26	-70	52	9	5.21	.026
Middle cingulate cortex	R	6	16	38	12	5.17	.030
<b>Group by congruency interaction</b>							
<b>- CON &gt; BPD</b>							
<i>VOI on aPFC</i>							
	R	36	48	10	32	3.87	.007
<b>Whole brain effects</b>							
Rolandic operculum/precentral gyrus	L	-46	-2	20	13	5.94	.002
<b>- BPD &gt; CON</b>							
<b>Whole brain effects</b>							
Middle temporal gyrus	L	-52	-48	10	64	6.69	< .001
Fusiform gyrus/inferior temporal gyrus	L	-36	-36	-16	26	6.64	< .001
Calcarine sulcus/cuneus	R	14	-96	12	210	6.39	< .001
Fusiform gyrus/inferior occipital cortex	L	-38	-62	-12	80	6.32	< .001
Middle cingulate cortex	L	-10	-24	48	18	5.91	.002
Cerebellum	R	14	-56	-12	7	5.65	.005
Insula	R	44	0	-2	32	5.53	.008
<b>Anger out modulation of group by congruency interaction</b>							
<b>- CON &gt; BPD</b>							
<i>VOI on aPFC</i>							
	R	36	48	8	26	3.04	.050
<i>VOI on dlPFC</i>							
	L	-26	52	24	102	3.75	.009
	R	26	44	30	44	4.34	.002
<b>Whole brain effects</b>							
Middle frontal gyrus	L	-32	32	38	110	7.69	< .001
Middle frontal gyrus	R	28	8	48	32	6.30	< .001
<b>- BPD &gt; CON</b>							
<i>VOI on amygdala</i>							
	R	32	-4	-14	103	5.15	< .001
<b>Whole brain effects</b>							
Middle temporal gyrus	R	62	-12	-16	88	6.81	< .001

prefrontal activity was experimentally reduced with transcranial magnetic stimulation (TMS; Volman et al., 2011a,b). Reducing left aPFC activity resulted in significantly worse performance, i.e., more errors in affect-incongruent condition as well as significantly increased activity in regions associated with fast emotion processing and responding, such as the amygdala and fusiform face area.

In the current study, we found significantly reduced activations in the right aPFC in male patients with BPD compared to healthy male controls during affect incongruent trials. Similar deficits in recruiting aPFC during emotional action control have been reported in male psychopathic offenders (Volman et al., 2016). Amongst these individuals, testosterone significantly modulated the aPFC activity and aPFC-amygdala connectivity suggesting a reduced lateral prefrontal inhibition of the amygdala in those criminals with high endogenous testosterone levels. Since we have no testosterone samples, we may only speculate about a possible moderator of endogenous testosterone, which has been previously found to be elevated in male and female patients with BPD compared to healthy controls (Rausch et al., 2015). Genetic alterations of the serotonergic system may also be associated with deficits of lateral prefrontal emotional action control. Investigating healthy male participants, Volman et al. (2013) found elevated amygdala activations in short-allele (s) carriers of the serotonin transporter gene that, according to dynamic causal modelling was driven by reduced inhibitory control from the aPFC. Although reports on genetic variations in the serotonergic system in BPD remain inconsistent, the s-allele has been generally related to an enhanced risk for violent suicide, the development of psychopathological symptoms as well as elevated amygdala responses to emotional stimuli (Bondy et al., 2000; Courtet et al., 2004; Hariri et al., 2002; Lesch and Mössner, 1998; Melke et al., 2001).

In the current study, we found a similar pattern of elevated amygdala and reduced antero- and dorsolateral prefrontal activations in those patients with BPD who reported a strong tendency to act out anger. Similar to the aPFC, the dlPFC is known for its crucial role in emotion regulation (Dörfel et al., 2014). In a recent study, we found reduced dlPFC activations and a reduced negative dlPFC-amygdala coupling during emotional action control in female anger-prone patients with BPD compared to healthy women (Bertsch et al., 2018). Taken together, reduced lateral prefrontal emotional action control and its reduced inhibition of the amygdala, which according to other studies may be moderated by androgen hormones and the serotonergic system, may underlie reactive aggression across diagnoses and sexes.

Although this is one of the first studies investigating neural correlates of anger-related aggressive tendencies in a male sample of medication-free patients with BPD, several limitations need to be addressed. First, we were only able to recruit a relatively small sample of male patients with BPD ( $N = 15$ ) and results therefore need to be replicated in a larger sample. However, the consistency of the present results with those reported in male psychopathic offenders (Volman et al., 2016) and anger-prone female patients with BPD (Bertsch et al., 2018) as well as building on aPFC emotional control findings of a robust set of studies in healthy human participants (Radke et al., 2015, 2017; Tyborowska et al., 2016; Volman et al., 2011a,b, 2013; 2016) strengthen our interpretation. According to a post hoc power analyses, the current sample size was sufficient to detect large effects of  $d = 1.2$  and  $d = 1.5$  reported for the anger out modulation of the group by congruency effect in aPFC and amygdala, respectively (Bertsch et al., 2018) with a statistical power of  $1-\beta \geq 80\%$ . Nevertheless, non-significant results may not be interpreted due to insufficient power ( $1-\beta < 0.80\%$ ) for effects of  $d < 0.95$ . Second, the patients had a number of comorbid disorders and we did not include a clinical control group. Hence, despite controlling for ADHD symptoms and depressiveness, we are limited with drawing any disorder-specific interpretations. Since we suspect deficient prefrontal-amygdala (emotional) control as a common mechanism for aggressive outbursts across diagnoses and sexes, further investigations including large cohorts of anger-prone men and women would be relevant. Third, it remains unclear whether the lack of behavioral group differences is due to the task design or the small sample size. Critically, the version of the AA task used in this study is designed to induce a mild emotional challenge to avoid behavioral group differences. As mentioned above, the purpose of this design was to focus on effects at the neural level, without interpretational confounds due to behavioral

differences (Volman et al., 2016). Fourth, we did not include neutral facial expressions or a non-emotional control task as congruency effects have previously not been found in control tasks or for neutral faces (Volman et al., 2011a,b, 2016; von Borries et al., 2012) and because patients with BPD are known to interpret neutral faces as aversive (Daros et al., 2013).

## 5. Conclusions

The present results show reduced anterolateral prefrontal activity in male patients with BPD during emotional action control. Self-reports of acting out anger were related to reduced antero- and dorsolateral PFC activity as well as increased amygdala activity in male patients with BPD, suggesting deficits of lateral prefrontal emotional action control as a common neural correlate of reactive aggression.

## Conflicts of interest

The authors declare no conflict of interest.

## Acknowledgement

The authors declare no conflict of interest. The study was supported by the German Research Foundation (HE 2660/12-1 and BE5292/1-1). Furthermore, I.V. was supported by a Marie Curie Individual Fellowship (MSCA-IF-2014\_EF\_660397) within the European Union's Horizon 2020 Framework Program. The authors would like to thank P. Gaalman, S. Heiland, and T. Kaestel for technical support.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuropharm.2018.12.010>.

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