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Brain Mechanisms Underlying Reactive Aggression in Borderline Personality Disorder—Sex Matters

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ABSTRACT

BACKGROUND: Aggression in borderline personality disorder (BPD) is thought to be mediated through emotion dysregulation via high trait anger. Until now, data comparing anger and aggression in female and male patients with BPD have been widely missing on the behavioral and particularly the brain levels.

METHODS: Thirty-three female and 23 male patients with BPD and 30 healthy women and 26 healthy men participated in this functional magnetic resonance imaging study. We used a script-driven imagery task consisting of narratives of both interpersonal rejection and directing physical aggression toward others.

RESULTS: While imagining both interpersonal rejection and acting out aggressively, a sex × group interaction was found in which male BPD patients revealed higher activity in the left amygdala than female patients. In the aggression phase, men with BPD exhibited higher activity in the lateral orbitofrontal and dorsolateral prefrontal cortices compared with healthy men and female patients. Positive connectivity between amygdala and posterior middle cingulate cortex was found in female patients but negative connectivity was found in male patients with BPD. Negative modulatory effects of trait anger on amygdala–dorsolateral prefrontal cortex and amygdala–lateral orbitofrontal cortex coupling were shown in male BPD patients, while in female patients trait anger positively modulated dorsolateral prefrontal cortex–amygdala coupling. Trait aggression was found to positively modulate connectivity of the left amygdala to the posterior thalamus in male but not female patients.

CONCLUSIONS: Data suggest poor top-down adjustment of behavior in male patients with BPD despite their efforts at control. Female patients appear to be less aroused through rejection and to successfully dampen aggressive tension during the imagination of aggressive behavior.

Keywords: Anger, Emotion regulation, Functional magnetic resonance imaging, Prefrontoamygdala connectivity, Reactive aggression, Sex × group interaction

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Aggression is highly prevalent in borderline personality disorder (BPD), causing immense burden for the individual and society. Data provide evidence of repetitive aggressive events in male and female patients with BPD (1), with, for instance, 73% reporting aggressive behaviors within the last year. Moreover, studies in prison populations indicate an overrepresentation of BPD (2), particularly in inmates incarcerated because of impulsive aggression (3).

Aggression can be regarded as a behavior directed toward another individual with the proximate intent to cause harm (4), which in the case of reactive aggression is of an impulsive, anger-driven nature expressed in response to perceived social threat (5). Emotion dysregulation appears to be the underlying dysfunction that leads to anger and in turn to aggressive behavior in BPD (6,7), even when controlling for antisocial traits (8). Starting from uncontrolled outbursts of anger in response to interpersonal threat or rejection, aggression in BPD is regarded as a prototypical form of reactive aggression (9).

Functional magnetic resonance imaging (fMRI) studies in healthy volunteers indicate a major role of amygdala, thalamus, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), middle cingulate cortex (MCC), ventrolateral prefrontal cortex (PFC), dorsolateral PFC (DLPFC), and medial PFC in anger and aggression (10–12). Increased amygdala activity has been found in several studies during the processing of facial signals of threat [e.g., (13)] and neural hyperresponsivity to aggressive threat stimuli were found in the hippocampus and thalamus of domestic batterers (14). While the ventrolateral PFC is involved in inhibitory motor control (15), the lateral OFC (LOFC) plays a major role in the adjustment of behavior, emphasizing the relevance of this region for selecting rule-driven while overriding automatic stimulus–response

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associations (16). The DLPFC, together with the ACC, reflects decision-making processes about the consequences of one's own behavior, evaluating wrongdoings, activating self-regulatory cognitions, and reestablishing emotional balance after conflictual interactions with others (17,18).

In medication-free patients with BPD, compared with healthy volunteers, emotion dysregulation has been related to abnormal prefrontal-limbic reactivity, with studies revealing increased left-sided amygdala reactivity to negative stimuli, as well as prefrontal hypometabolism during regulatory control processes (most consistently in the ACC, LOFC, and DLPFC) that fail to control enhanced amygdala reactivity (9,19). Two studies focusing on emotions of anger in BPD found exaggerated amygdala reactivity and weaker activations of the ACC (20) or the OFC (21), respectively. However, study samples have been rather small and results inconsistent, with another study reporting decreased amygdala activity together with increased activity in the bilateral ACC (22).

Aggressive behavior in BPD might also work as a maladaptive emotion regulation strategy analogue to an impulse control disorder that is characterized by a relief of emotional arousal going along with the aggressive acts (23). Notably, such a key mechanism is thought to underlie the development of nonsuicidal self-injurious behavior in female BPD patients (24).

Male patients have rarely been studied in BPD although there is no female preponderance among individuals with BPD in the general population (25). Notably, there has not been a systematic comparison of brain activity underlying aggression between female and male patients in this population except for two studies that examined sex differences in BPD patients with a comorbid condition of intermittent explosive disorder (26,27). New *et al.* (26) found increased relative glucose metabolic rate in OFC and amygdala in BPD individuals during an aggression provocation paradigm but no significant sex effect. A focus on sex differences appears to be particularly important in view of recently published data showing fundamentally different gene × environment interactions in female compared with male BPD patients (28) and might be of particularly high significance for understanding aggression in BPD.

This study aimed to investigate the processing of 1) angry feelings in the context of social rejection and 2) anger-based reactive aggressive behavior in female and male BPD patients, and thus for the first time to explicitly differentiate between a failure in emotion regulation and a failure in behavioral control in states of emotional arousal in BPD. While during anger induction we expected decreased prefrontal activities (OFC, ACC, DLPFC) together with amygdala hyperreactivity, we speculated that the imagination of one's own aggressive behavior toward others might be associated with neuronal correlates of a breakdown of anger control or—analogous to nonsuicidal self-injurious behavior in BPD—with a dampening of limbic activity in the sense of a maladaptive emotion-regulation strategy (29,30). In an exploratory approach, we compared female and male patients.

METHODS AND MATERIALS

Participants

Groups comprised 33 women and 23 unmedicated men with a current diagnosis of BPD (18 to 45 years of age) and 30 age-matched healthy women and 26 healthy men who had never received a psychiatric diagnosis or undergone any psychological and/or psychopharmacological treatment (Table 1). Recruitment was done by the central project of the KFO 256 (24), a clinical research unit funded by the German Research Foundation dedicated to investigating mechanisms of disturbed emotion processing in BPD (24). Thus, all projects that originate from the KFO 256 include subjects from a joint database. Recruitment procedures and specific exclusion criteria are described in the Supplement.

After telephone screening, qualified diagnosticians assessed the diagnosis of BPD and Axis I and II comorbid disorders (per Structured Clinical Interview for DSM-I and International Personality Disorder Examination). In addition to the general inclusion criteria of BPD according to DSM-IV, all patients had to fulfill BPD criterion 8, "anger proneness." Details on comorbidities are provided in Table 1. Notably, only 1 female and 3 male patients had a current comorbid antisocial personality disorder. Additionally, a number of trait measurements were assessed (see Table 2 and details in the Supplement). The Ethics Committee of the Medical Faculty, Heidelberg University approved the study. All participants provided written informed consent and were paid for their participation.

Experimental Protocol

Using a script-driven-imagery paradigm, participants listened to four standardized scripts read by professional actors. They were told to imagine the scenes as vividly as possible in order to provoke intense emotional responses without explicitly being instructing to apply emotion-regulation strategies. Each script comprised four separate phases (baseline, anger, aggression, relaxation; length/script phase: 25 seconds each with 8-second interphase intervals; example and further details provided in the Supplement) always presented in the same order for reasons of a coherent story. Anger induction was based on narratives of harsh interpersonal rejections and supported by emotional emphasis of the reading actor: the first sentence always represented the rejection scene that was then followed by the description of intense feelings of anger. Aggressive scripts used narratives of directing (moderate)

Table 1. Comorbidities in BPD Patients

	mBPDs (n = 23)		fBPDs (n = 33)	
	Lifetime	Current	Lifetime	Current
Affective Disorders	19 (83)	10 (43)	28 (85)	10 (30)
Substance-Associated Disorders	6 (26)	0 (0)	5 (15)	0 (0)
Anxiety Disorders	14 (61)	13 (57)	21 (64)	18 (55)
PTSD	7 (30)	7 (30)	10 (30)	8 (24)
Somatoform Disorders	0 (0)	0 (0)	5 (15)	5 (15)
Eating Disorders	10 (43)	9 (39)	18 (55)	11 (33)
Adjustment Disorder	3 (13)	3 (13)	3 (9)	3 (9)
Antisocial PD	5 (22)	3 (13)	1 (3)	1 (3)
Avoidant PD	7 (30)	6 (26)	12 (36)	11 (33)

Values are presented as n (%).

BPD, borderline personality disorder; fBPDs, female BPD patients; mBPDs, male BPD patients; PD, personality disorder; PTSD, posttraumatic stress disorder.