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# Gender determines cortisol and alpha-amylase responses to acute physical and psychosocial stress in patients with borderline personality disorder

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## ABSTRACT

Borderline personality disorder (BPD) is characterized by affective instability, unstable relationships, and identity disturbance. We measured salivary alpha-amylase (sAA) and salivary cortisol levels in all participants during exposure to the Trier Social Stress Test (TSST) and an electric stimulation stress. Seventy-two BPD patients were compared with 377 age- and gender- matched controls. The State and Trait versions of the Spielberger Anxiety Inventory test (STAI-S and STAI-T, respectively), the Profile of Mood State (POMS) tests, and the Beck Depression Inventory (BDI), the Depression and Anxiety Cognition Scale (DACS) were administered to participants before electrical stimulation. Following TSST exposure, salivary cortisol levels significantly decreased in female patients and significantly increased in male patients compared with controls. POMS tension–anxiety, depression–dejection, anger–hostility, fatigue, and confusion scores were significantly increased in BPD patients compared with controls. In contrast, vigor scores were significantly decreased in BPD patients relative to controls. Furthermore, STAI-T and STAI-S anxiety scores and BDI scores were significantly increased in BPD patient compared with controls. DACS scores were significantly increased in BPD patient compared with controls. Different stressors (e.g., psychological or physical) induced different responses in the HPA and SAM systems in female or male BPD patients.

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## 1. Introduction

Borderline personality disorder (BPD) is the most common personality disorder and characterized by affective instability as well as by impulsivity, self-injurious behavior, anxiety of abandonment, and unstable and intense interpersonal relationships (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR); American Psychiatric Association, 2000). It is also associated with instabilities of identity and self-direction (Bender and Skodol, 2007; Feliu-Soler et al., 2013). Suicidal behavior is also highly predominant, appearing to be related to affective instability and depressive mood states (Soloff et al., 2000; Yen et al., 2004).

Stress exposure impairs the cognitive regulation of emotion (Raio et al., 2013). The stress group showed significantly higher cortisol levels after the stressor, whereas the control group

demonstrated significantly decreased levels. Cortisol regulates its own release via a negative feedback in the central nervous system. It binds to specific receptors throughout the limbic system, including the hippocampus, amygdala, and prefrontal cortex (Herman et al., 2005). A previous study on the effect of glucocorticoid on stress-related pathophysiology particularly concentrated on the hypothalamic–pituitary–adrenal (HPA) axis, which organizes the major neuroendocrine stress system (Myers et al., 2014; Nater et al., 2013). Although glucocorticoids initiate adaptive processes that produce energy for coping, prolonged or inappropriate glucocorticoid secretion is harmful. Inappropriate processing of stressful data may direct an active drive that does not match the environmental need, thereby resulting in a risk of pathology. Several studies have demonstrated that effective coping strategies often fail in BPD patients (Gratz et al., 2006; Conklin et al., 2006). For example, neuroimaging studies in BPD patients showed reductions in the hippocampal volumes and increase in the hypothalamic volume (Kuhlmann et al., 2013); the hypothalamic volume was associated with a history of trauma in BPD

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patients. BPD patients have enhanced cortisol levels under basal states compared with healthy controls (Carvalho Fernando et al., 2012). Female adolescents with non-suicidal self-injury showed an attenuated cortisol response to TSST (Kaess et al., 2012). Female BPD patients showed heightened resting cortisol levels and intense subjective negative emotional arousal among those with BPD, as well as reduced psychobiological reactivity to TSST (Scott et al., 2013). Enhanced stress in BPD might reduce cortisol response and salivary alpha-amylase (sAA) increase and change of heart rate variability after physical and psychological stress.

Increasing evidence indicates that changes in HPA activity may contribute to BPD (Wingenfeld et al., 2010). Furthermore, higher basal cortisol levels have been reported in BPD patients (Wingenfeld et al., 2007), although changes in the function of the HPA axis in BPD appear to be effected by comorbid symptomatology. The studies of HPA activity in BPD have been cross-sectional, and therefore, no causal inferences can be made about how “changes in HPA activity” “contribute to BPD”. The dexamethasone suppression test (DST) has been extensively used to identify abnormal HPA axis feedback regulation. In BPD patients, DST outcomes vary with comorbid psychopathology (Zimmerman and Choi-Kain, 2009). Decreased cortisol suppression by dexamethasone has also been reported in non-depressed BPD patients (Lieb et al., 2004). However, there have been inconsistent results regarding increased feedback inhibition in BPD patients (Carrasco et al., 2007). BPD symptoms suggested amplified cortisol reactivity to a test stressor only in participants with low degrees of post-traumatic stress disorder (PTSD) symptoms (Dixon-Gordon et al., 2013). In participants with prominent levels of PTSD symptoms, there was no indication of an association between BPD symptoms and cortisol reactivity. Nater et al. (2010) reported that the plasma adrenocorticotrophic hormone (ACTH)/cortisol ratio, salivary cortisol levels, and alpha-amylase responsiveness were decreased in unmedicated female BPD patients compared with healthy control. No significant differences for ACTH levels and catecholaminergic responses were detected. Stress hormone response to psychosocial stress in BPD showed that prominent dissociative symptoms in BPD were associated with greater HPA axis and noradrenergic reactivity to stress (Simeon et al., 2007). Female BPD participants showed more delayed cortisol response than control participants after psychosocial stress (Walter et al., 2008). These data failed to provide consistent conclusions, because of differences in gender, numbers, and participant stressor. Thus, it remains unclear whether BPD patients show different HPA axis stress reactivity. Some reports have shown an association between autonomic function and emotional dysregulation (Porges, 2003).

The parasympathetic component of the autonomic nervous system (ANS) differentiates response profiles between individuals diagnosed with BPD and controls (Austin et al., 2007), with BPD patients having comparatively increased sympathetic activity and decreased parasympathetic activity during a social stressor task (Weinberg et al., 2009). Elices et al. (2012) assessed the emotional response and heart rate in BPD patients and healthy controls while watching emotional films. The heart rates of BPD patients increased lesser than that of controls when watching frightening, sad, and anger-inducing films. No significant differences were found between BPD patients with or without psychotropics (benzodiazepines or antipsychotics) use and healthy controls. Research has variably suggested both increased and decreased ANS activity in BPD patients (Austin et al., 2007; Kuo and Linehan, 2009). Because heart rate is regulated by both sympathetic and parasympathetic innervations more precise measures of sympathetic and parasympathetic activity are needed to evaluate this accurately. Recent reports have demonstrated that the sAA and cortisol are valid and reliable markers of central sympathetic activity and HPA axis activity (Nater and Rohleder, 2009; Ishitobi

et al., 2010; Tanaka et al., 2012a, 2012b, 2013; Maruyama et al., 2012; Kawano et al., 2013; Tamura et al., 2013) and they may be used as a non-invasive markers of sympathetic activity (Chu et al., 2013). In addition, there has been controversy about whether sAA reflects sympathetic activity specifically, or if it is a more general marker of autonomic activity, with some evidence suggesting that it reflects activity of both autonomic branches (Bosch et al., 2011).

Further, although maladaptive cognitions are common among BPD patients and are useful for differentiating the disorder, this part of neither the HPA axis nor the ANS is adequately studied (Zanarini et al., 2013). A limited number of earlier studies have compared salivary cortisol levels, sAA levels, psychological tests and cardiac autonomic modulation among BPD patients (Simeon et al., 2007; Nater et al., 2010). The present study aimed to examine the psychological, physiological, and neuroendocrine responses to physical and psychosocial stressor in female and male BPD patients compared with healthy participants. We hypothesized that BPD patients would feel greater subjective stress to an acute physiological and psychosocial stressor compared with healthy controls, that secretion of salivary cortisol is interrupted in BPD patients, indicating deregulated stress reactivity of the HPA axis, and that ANS reactivity would be deregulated in BPD patients.

## 2. Materials and methods

### 2.1. Participants

In total, 72 BPD patients and 377 healthy controls participated in the study. Eligible patients were required to meet the DSM-IV-TR criteria for BPD and to have no current alcohol/substance abuse, no medications, and no major depression. The diagnoses of BPD and other Axis II disorders were determined using the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) for Personality Disorders (SCID-II) Questionnaire (First et al., 1997). The diagnoses were made by self-report and by clinicians via semi-structured interviews. Current Axis I diagnoses were made by a trained psychiatrist (JA) using the Mini International Neuropsychiatry Interview (MINI), a standardized psychiatric examination validated in the general population (Sheehan et al., 1998) according to DSM-IV-TR criteria (Ritchie et al., 2004). Comorbid current Axis I disorders in the BPD sample were not permitted. We excluded 12 BPD patients with comorbid axis I disorder (six major depressive disorder (MDD), four panic disorder, and two bipolar disorder).

None of the participants had major medical illness according to their medical history and physical examination, and there was substance, alcohol abuse or dependence within the 12 months prior to the study. Participants took no psychotropic medication for at least 12 weeks prior to the beginning of the study. Further exclusion criteria included use of hormonal contraceptives, irregular menstrual cycles, schizophrenia, bipolar disorder, MDD, PTSD, substance abuse, and anorexia [body mass index (BMI) of < 17.5]. Healthy control participants were enrolled via advertising and were required to be free of Axis I or II disorders (SCID II). Otherwise, the same exclusion criteria as applied to BPD patients were used.

Demographic information (age and education) was collected from all participants. Participants were asked to refrain from excessive physical activity for 48 h prior to the experiment and to avoid all sporting activities and alcohol consumption for the 24 h. Furthermore, caffeine, tea and smoking were not permitted within 3 h prior to the study, and tooth brushing and eating were not allowed within 120 min of the study. To minimize circadian deviations in physiological variables, all experiments were performed in the afternoon (between 1300 h and 1700 h) and during the follicular phase of the menstrual cycle. (Ishitobi et al., 2010; Tanaka et al., 2012a, 2012b, 2013; Maruyama et al., 2012; Kawano et al., 2013; Tamura et al., 2013). After a comprehensive explanation of the study, participants provided written informed consent for participation. The ethics committees of the Oita University Faculty of Medicine approved the study.

### 2.2. Stress challenge

All participants were exposed to the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) and the electric stimulation; the two stress tests were performed within 1 week of each other. To minimize habituation to the experimental environment, participants were divided into small groups of four to five. As our preparation room of the experiments is narrow, the presence of many participants might induce stress. Each group was alternately assigned to receive either electric stimulation or TSST, first. The remaining experiment was administered 1 week after the first.

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