Blunted neuroendocrine stress reactivity in young women with eating disorders

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ABSTRACT
Objective: Stress is known to influence risk and progression of eating disorders (EDs). However, studies investigating physiological and psychological stress responses under laboratory conditions in patients with Anorexia nervosa or Bulimia nervosa are scarce and often produce conflicting findings. We therefore aimed to compare the neuroendocrine and affective stress response in ED inpatients and healthy controls.

Methods: Twenty-eight female inpatients with Anorexia or Bulimia nervosa and 26 healthy women were exposed to the Trier Social Stress Test (TSST). Salivary cortisol and alpha-amylase (sAA) levels were assessed before as well as repeatedly after stress exposure, while heart rate and heart rate variability were determined before and during the TSST. Negative affective state was assessed at baseline and post-TSST.

Results: Compared to healthy controls, ED patients showed blunted cortisol stress responses combined with overall attenuated sAA levels. The latter was reflected in generally enhanced parasympathetic activity indicated by lower heart rate and stronger high-frequency heart rate variability throughout the TSST. Although patients reported more negative affect overall, they did not differ in their affective stress response.

Conclusions: In summary, patients suffering from eating disorders show a blunted HPA axis reactivity to stress exposure and a generally reduced sympathetic/exaggerated parasympathetic nervous system activity. This combination may contribute to elevated health risks seen in eating disorder patients, such as enhanced inflammatory activity, and thus provide insight into the underlying stress-related mechanisms.

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Introduction
Eating disorder (ED) related behaviors like keeping a diet, the desire to be thinner or performing compensatory behavior such as self-induced vomiting or excessive sport frequently occur among young women [1–3]. However, only a small number of these women develop an eating disorder like Anorexia nervosa (AN) or Bulimia nervosa (BN; [4]). The etiology of these disorders is still relatively unknown [5]. Stress has been identified as a potential risk factor for the development of eating disorders [6], since there is evidence that patients often experience severe life events or chronic stress before the onset of the ED [7]. Although chronic stress is not specific to patients with EDs [6], this finding might indicate that there is a strong activation of stress mediating physiological systems before the onset of an ED. This is in line with current stress–disease models suggesting that chronic stress or an inadequate stress response facilitates emotional disorders [8–11].

The two prominent physiological systems that mediate the stress response are the sympathetic nervous system (SNS) and the hypothalamus–pituitary–adrenal axis (HPAA; [12]). The former system belongs to the autonomic nervous system and allows short-term adaptation to challenging conditions within a few seconds through the release of epinephrine and norepinephrine from the adrenal medulla as well as through direct innervation of target tissues. The latter system complements the former through the release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and glucocorticoids (GCs), mainly cortisol in humans [13]. Cortisol permeates the blood–brain barrier and activates central corticosteroid receptors, thereby regulating its own release [12,14].

Besides acute cortisol increases indicating HPAA reactivity, cortisol also shows a circadian rhythm indicating basal HPAA activity [15]. This rhythm is characterized by a cortisol awakening response (CAR).
associated with 50–100% increase in cortisol over the first 30–45 min after awakening followed by a steady decline over the course of the day and a nadir in the first half of the night [16]. The CAR is significantly related to various psychosocial factors, chronic stress, health and physical conditions [17–20].

Past research on patients with EDs showed a relatively consistent pattern in terms of SNS and HPAA activity under resting conditions. In contrast to healthy controls (HC), patients with AN or BN show a blunted activity of the SNS as indicated by heart rate frequency (HRF; [21,22]), blood pressure [23,24], heart rate variability (HRV; [25]), salivary alpha-amylase (sAA; [26]), and serum norepinephrine [21,22] level. Furthermore, ED patients often display an enhanced HPAA activity with higher concentrations of CRH in cerebrospinal fluid [27] and cortisol in serum or saliva [28–31]. In terms of CAR, only one study investigated this HPAA activity marker in AN patients and found it to be enhanced compared to HC [26]. These changes were often attributed to (at least intermittent) starvation [32,33] but could be interpreted as a predisposing condition which preceded the development of an ED and make individuals more vulnerable for EDs as well [22,24].

The patterns become less consistent when looking at stress system reactivity instead of activity. While patients with AN or BN typically show a blunted SNS response to acute laboratory stressors compared to HC [21,22,30,31,34], the findings on HPAA activity are more heterogeneous. For example, in one study [31], no group differences were found between ED patients and HC in the cortisol response to a mirror exposure task. Contrarily, Zonnevylle-Bender et al. [34] and Ginty et al. [35] reported a blunted stress response to the Trier Social Stress Test (TSST; [36]) and to a ten minute mental arithmetic stress task in patients with AN and BN. Another study reported elevated cortisol levels in women with AN throughout the investigation period when compared to women with BN and HC [30]. In this study the TSST was used as well. These conflicting results may in part be due to methodological issues. Several of the studies used stress induction methods that activate the SNS but may not be very effective in eliciting a HPAA response [37]. For instance, studies used a modified Stroop color word test [38,39], an imagination task [40,41], a mental challenge task [21,24], an auditory stimulation test [42], speech tasks [43,44] or pain-induction [23]. Additionally, often rather small sample sizes were investigated. The aim of the present study was thus to investigate differences in physiological and psychological stress responses between ED patients and HC using a larger sample size and the TSST as an effective laboratory stress induction protocol [37]. Therefore the SNS, HPAA and the affective stress responses were assessed and analyzed. We expected differences in the HPAA stress response and the CAR between ED patients and HC and a lower SNS stress response and a stronger negative affect after the TSST in ED patients compared to HC. The latter prediction was based on a recent study showing that stress exposure resulted in stronger sadness responses as well as insecurity in ED patients compared to HC [45].

Importantly, for the purpose of the current study, patients with AN and BN were investigated as one group according to the transdiagnostic perspective [46,47]. This conceptualization is based on the longitudinal observation that patients with AN, BN and atypical eating disorders (AED; eating disorders of clinical severity that do not meet the criteria for AN or BN) share a core psychopathology characterized by over-evaluation and control of eating, shape and weight [47]. This is expressed in similar attitudes and behaviors, such as rigid restriction of food intake, vomiting, and over-exercise. However, the balance of under- and over-eating differs between the groups resulting in differences in body weight. Indeed, patients who do not recover from AN frequently cross-over to BN (1/4 of patients with BN had AN in the past) or AED [48–50]. Moreover, BN typically starts as AN or an AED and a particularly common outcome of BN is a chronic AED. In summary, AN, BN and AED are states on a psychopathology continuum with patients moving between these diagnostic states [51–53].

Methods

Participants

A total of N = 54 women were recruited. Prior to testing, participants underwent a diagnostic examination using the German versions of the Structured Clinical Interview for Axis I of the DSM-IV (SCID-I; [54]), the Beck-Depression-Inventory (BDI; [55]), the Symptom-Checklist-90-Revised (SCL90-R; [56]) and the Eating Disorder Examination-Questionnaire (EDE-Q; [57]). The SCID was administered by trained professionals with at least one year experience in the use of this diagnostic instrument. Twenty-eight inpatients with ED participated during the first week of their treatment. Of those, n = 18 fulfilled the diagnostic criteria of the text revised 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, [58]) of AN and n = 10 patients those of BN. All patients were consecutive patients and were asked for participation to the study directly on the first or the second day after admission to the clinic. They were medication-free (except of oral contraceptives) and were combined into one group according to the transdiagnostic theory of EDs [47]. Due to well-known changes in HPAA activity in post-traumatic stress disorder, borderline personality disorder or schizophrenia [59,60], patients with EDs fulfilling the criteria of at least one of those diagnoses were excluded. Duration of illness was not restricted but considered in subsequent analyses. To ensure comparability, ambulant patients were excluded as well. All patients were recruited from the Christoph-Dornier Clinic for Psychotherapy, Münster (Germany) and the Department of Psychosomatic Medicine and Psychotherapy, LWI-University Clinic, Bochum (Germany), both are specialized in the treatment of EDs. The group of HC was composed of n = 26 physically and mentally healthy, medication-free (except of oral contraceptives) and drug-free female students with a body mass index (BMI) within the normal range (18.5–26 kg/m²) recruited at the University of Bochum and Münster via advertisements at the bulletins boards. Participants with previous TSST exposure and participants who did not refrain from physical exercise or eating 1 h before testing were excluded. Since ED patients often use oral contraceptives and/or smoke, we did not exclude women who smoked and/or used oral contraceptives. However, due to potential effects on HPAA reactivity [61], frequencies of both behaviors were assessed and statistically controlled. All participants provided written informed consent. The study protocol was approved by the institutional review board of the Ruhr-University of Bochum.

Trier social stress test (TSST)

The TSST was performed as described by Kirschbaum et al. [36]. In short, participants were told to introduce themselves to a committee and to convince the committee that they were the perfect applicant for a vacant position in their ‘dream job’. After a five minute preparation period, each participant had to talk about her job-relevant personality traits for a duration of 5 min. If the participant finished her speech in less than 5 min, standardized questions were used. During the subsequent 5 min, the participants were asked to count backwards in steps of 17 from 2043 as fast and as accurately as possible. Whenever the participant made a mistake, she had to start over at 2043. Both members of the committee were dressed in white lab coats and acted in a reserved manner. The TSST has been shown to be highly effective in eliciting a HPAA response [37], a SNS response, and a negative affect state [62].

Saliva sampling and biochemical analyses

Saliva samples were obtained using the Salivette sampling device (Sarstedt, Nümbrecht, Germany) to assess free cortisol and SAA levels as HPAA and SNS markers, respectively [63,64]. To assess stress system reactivity, saliva samples were collected 1 min before (−1) and 1 (+1), 10 (+10) and 25 (+25) min after the TSST. To assess the CAR (basal

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HPAA activity/reactivity), saliva samples were collected on two consecutive days before the TSST to increase reliability of the CAR assessments [65,66]. On each day, the first sample was collected immediately after awakening (+0) and the second sample 30 min after awakening (+30). Participants were asked to protocol the awakening time and the times of saliva sampling by using a saliva diary. Doing so the diary allowed us to assess the (self-reported) compliance following the most common compliance procedure in this section. Participants were instructed not to brush their teeth and to refrain from eating, drinking and smoking during the sampling procedure. All samples were frozen and after study completion, cortisol concentrations were measured using a commercially available immunoassay with chemiluminescence-detection (IBL-Hamburg, Germany). Salivary alpha-amylase was measured using a quantitative enzyme kinetic method, as described earlier [63]. Inter- and intra-assay coefficients of variation were below 10% for both assays.

Assessment of cardiac parameters

HRF as beats per minute and HRV were registered as an indicator of autonomic changes. For this purpose, the Polar watch system (RS800CX, Polar, Finland) for heart-beat monitoring was used, since it has been shown to be of good validity and reliability [67–70]. Spectral analysis of HRV was performed with the Polar Pro Trainer 5 Professional Training Software, based on interbeat intervals (R–R intervals). The software extracts HRV in various frequency bands and expresses it as ms². Frequency domain variables as described by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [71] were derived from HRF measurements during a timespan of 5 min before the TSST (baseline) and during the first 5 min of the TSST. High-frequency HRF (HF-HRV, 0.15–0.4 Hz) is thought to reflect cardiac vagal function by representing the respiratory sinus arrhythmia, therefore indicating primarily parasympathetic activity. Low-frequency HRV (LF-HRV, 0.04–0.15 Hz) is thought to reflect both parasympathetic and sympathetic activity.

Assessment of affect

To complement the assessment of physiological stress responses with psychological stress response assessments as well as for manipulation check, participants filled out the Positive and Negative Affect Schedule (PANAS; [72]) at arrival at the laboratory, shortly before and immediately after cessation of the TSST and 10 and 25 min after the TSST. The PANAS is a reliable and valid measure for the current affective state [73]. It consists of 10 items for positive affect (e.g., interested, enthusiastic) and 10 items for negative affect (e.g., upset, ashamed). Participants are asked to rate the items on a 5-point scale ranging from 1 = “very slightly or not at all”, to 5 = “extremely”, with higher average scores indicating more positive and more negative affect, respectively.

Procedure

The study took place on three consecutive days. On the first study day, participants provided informed consent as well as information pertaining to their menstrual cycling phase and responses to questionnaires. Diagnoses were confirmed with SCID-I. Lastly, each participant received four saliva sampling devices and detailed instructions on how to use these devices over the following two days. More specifically, on the second as well as third study day, participants collected a saliva sample right upon awakening followed by a second sample collection 30 min post-wakening. Patients collected saliva samples in the hospital and healthy controls at home. On the third day, participants were exposed to the TSST either in the hospital (all patients, 50% of healthy controls) or in the laboratory. All TSSTs were administered in the afternoon between 2 pm and 5 pm to minimize between-participant variation in pre-TSST baseline cortisol levels [15]. After arrival at the lab, participants were seated in a quiet room. The Polar watch was fitted and started to continuously record HRF and HRV until the end of the test day. Additionally, participants answered the PANAS for the first time. Afterwards the participants completed a cognitive task on working memory and autobiographic memory (results will be reported elsewhere) lasting about 30 min. Subsequently, a first saliva sample (baseline) was obtained and the PANAS was answered for the second time. Next, the participants were exposed to the TSST and immediately afterwards, post-treatment saliva sample (+1) and PANAS self-report were collected. Finally, the third (+10 min) and the fourth (+25 min) saliva samples were obtained and the PANAS was filled out simultaneously.

Statistical analyses

Demographic and descriptive variables were investigated by Pearson’s Chi-square test and Student’s t-test. All data were tested for normal distribution with Kolmogorov–Smirnov test (K–S test). In case of a significant K–S test, data were log-transformed and the subsequent statistical analyses were performed with the transformed data. The CAR was operationalized by the difference between the baseline and the 30 minute sample and averaged across the two days [66]. Using the saliva diaries, compliance for CAR sampling was operationalized as deviation in minutes from the 30 minute time difference between the wake-up sample and +30 min samples. More than 10 minute deviation was coded as non-compliant behavior and considered in the following statistical analyses. Area under the curve (AUC, [74]) was calculated with respect to increase (AUCI) for the neuroendocrine variables (cortisol and sAA) to assess HPAA and SNS stress reactivity. Cortisol responders to the TSST were defined as showing a 1.5 nmol cortisol increase between baseline and 10 min post-stress value as recently recommended [75]. Mixed model analyses of variance (ANOVA) for repeated measures were performed on cortisol and sAA levels, on PANAS scores, HRF, and HRV to reveal possible effects of time and group. Greenhouse–Geisser adjusted p-values are reported in case of violated sphericity assumption. Differences of interest between the groups within a specific variable and a specific sampling time were evaluated post-hoc by using Student’s t-test for independent samples. In this case, level of significance was Bonferroni-adjusted. The CAR was analyzed using the paired t-test for the increase within each group and the t-tests for independent groups for between-group differences. Statistical analyses were performed using IBM SPSS 21 (Chicago, IL) for Mac OS X. Level of significance was defined as p ≤ .05. Effects with p ≤ .10 were interpreted as trends.

Results

Sample characteristics

ED patients and HC did not differ in terms of age and body height (Table 1). However, patients had lower body weight and a lower body mass index. They reported more disturbed eating behavior (EDE-Q), more depressive symptoms (BDI) and more psychological strain (GSI score of the SCL-90-R). The EDE-Q mean score of the current patients was not significantly different from the normative EDE-Q mean score (z = .91, p > .05). Disease duration varied between seven months and 347 months, with a mean duration of 76.22 ± 96.04 months. The two groups did not differ in smoking behavior, average cigarettes per day, menstrual cycle phase or intake of oral contraceptives. However, they differed in level of education (χ² = 23.69, p < .01) with a higher graduation level within HC. Importantly, ten patients showed comorbid Major Depressive Disorder (MDD) and thus subsequent analyses controlled for MDD diagnosis. Furthermore, patients reported a wide range of somatic comorbidities consistent with an ED diagnosis, such as sleep problems, headaches, joint pain, fatigue, dizziness, nausea, thinning hair, hair loss, lanugo, dry skin (hands), sensitivity to cold, tooth decay, amenorrhea, anemia, iron deficiency anemia, protein deficiency, hypoglycemia, hyperglycemia, hypertriglyceridemia, hypertension, bradycardia, hypocalemia, jaundice, hypothyroidism, leukopenia, IgE-dependent allergic disposition, atop dermatitis, arthrosis, osteoporosis, disturbed blood flow (cold hand and feet), stomachache, heartburn, gastro-esophageal reflex, diarrhea, postprandial nausea, indigestion.

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Cortisol stress response

Cortisol concentrations are displayed in Fig. 1A. Statistical analyses were conducted on log-transformed cortisol data, since K-S test revealed a skewed distribution for all sampling times (p < .001). A mixed 4 × 2-factorial ANOVA for repeated measures with Time as within-subject factor and Group as between-subject factor revealed a significant effect of Time (F(2.37/116.0) = 2.9, p = .04) and a significant Time-by-Group interaction (F(2.37/116.0) = 5.84, p < .01; Group: F(1/48) = 1.25, p = .27), indicating an increase in cortisol levels in response to the TSST in the HC group compared to a blunted response observed in ED patients (cortisol increase from baseline to +10 min post-TSST: t(49) = 4.08, p < .001). This was confirmed when assessing AUCI, which was significantly higher in HC compared to ED patients (ΔAUCI = 3.26, p = .002; see Fig. 1B). Examining responder rates, we found that 16 HC participants responded to the TSST in contrast to only four of the ED patients (χ² = 11.1, p = .001). The significant Time-by-Group interaction was even seen when MDD (F(2.3/112) = 5.47, p = .003), duration of illness in months (F(2.3/103.8) = 3.86, p = .018) or symptom severity as measured by the EDE-Q (F(2/46) = 1.35, p = .23) were considered as covariates or the patients were divided into AN and BN (F(4.7/110.9) = 3.1, p = .01). Specifically, neither patients with AN nor patients with BN showed a cortisol response to the TSST.

Alpha-amylase stress response

Salivary AA levels are presented in Fig. 2A. Similarly to cortisol, sAA data were log-transformed before being subjected to statistical analyses. The mixed 4 × 2-factorial ANOVA for repeated measures revealed significant main effects of Time (F(2.3/109.5) = 4.02, p = .04) and between-group differences in depressive mood as a consequence of MDD comorbidity in ED patients, the main effect of group disappeared when BDI scores were included as a covariate. Furthermore, a significant main effect of Group with respect to sympathetic activity (HF-HRV) was observed, such that ED patients showed lower parasympathetic activity as assessed by HF-HRV, such that ED patients showed lower parasympathetic activity and thus a higher parasympathetic activity than HC. However, the two groups did not differ in sympathetic activity (LF-HRV). Consequently, examining the ratio between the two measures, i.e., the sympathetic-vagal balance (LF/HF), revealed only a significant main effect of Time and a trend for HC to show a stronger sympathetic activity in relation to parasympathetic activity pre and post-TSST.

Time × Group interaction: F(2.3/104.8) = .09, p = .70) and symptom severity as measured by the EDE-Q (Time: F(2.3/104.8) = 23, p > .05; Group: F(1/32) = 12.5, p = .001; Time × Group interaction: F(2.3/104.8) = 1.1, p > .05) were considered as covariates. When dividing patients into AN and BN, only an effect of Time (F(2.3/107.3) = 14.2, p < .001), but no main effect of Group (F(2.3/107.3) = 2.7, p = .08) or a Time × Group interaction effect (F(4.7/107.3) = .30, p = .93) was observed.

Heart rate frequency and variability during stress exposure

The results of HRV and HRV are presented in Table 2. Using a mixed 2 × 2 ANOVA for repeated measures, we found a significant main effect of Group with respect to HRF and parasympathetic activity as assessed by HF-HRV, such that ED patients showed lower HRF and thus a higher parasympathetic activity than HC. However, the two groups did not differ in sympathetic activity (LF-HRV). Consequently, examining the ratio between the two measures, i.e., the sympathetic-vagal balance (LF/HF), revealed only a significant main effect of Time and a trend for HC to show a stronger sympathetic activity in relation to parasympathetic activity pre and post-TSST.

Affective stress response

Data on negative affect assessed by the PANAS are presented in Fig. 3. A 5 × 2-factorial ANOVA for repeated measures on log-transformed PANAS scores revealed a significant main effect of Time (F(2.3/112) = 13.9, p = .001; Group: F(1/48) = 4.3, p = .04; Time × Group interaction: F(2.3/104.8) = 0.29, p = .70) and symptom severity as measured by the EDE-Q (Time: F(2.3/104.8) = 23, p > .05; Group: F(1/32) = 12.5, p = .001; Time × Group interaction: F(2.3/104.8) = 1.1, p > .05) were considered as covariates. When dividing patients into AN and BN, only an effect of Time (F(2.3/107.3) = 14.2, p < .001), but no main effect of Group (F(2.3/107.3) = 2.7, p = .08) or a Time × Group interaction effect (F(4.7/107.3) = .30, p = .93) was observed.

![Fig. 1. Means and standard error of means of cortisol concentrations within each group, measured at four sampling times (A) and by the increase function of the area under the curve (AUCI) (B). Only healthy controls showed a peak in cortisol levels after the TSST. The asterisk indicates a significant between-group difference.](http://dx.doi.org/10.1016/j.jpsychores.2014.11.001)
Mean cortisol awakening responses are shown in Fig. 4. Values from corresponding day 1 and day 2 samples correlated significantly (awakening: \( r = .43, p = .004 \); +30 min: \( r = .34, p < .001 \)). A mixed 2 × 2-factorial ANOVA revealed significant increases in cortisol values from awakening to +30 min post-awakening (Time: \( F_{1/38} = 27.8, p < .001 \); Group: \( F_{1/38} = .52, p = .48 \); Time-by-Group: \( F_{1/38} = 1.48, p = .23 \)). Controlling for compliance did not change CAR-related results (Time: \( F_{1/38} = 25.3, p < .001 \); Time-by-Group: \( F_{1/38} = 53.1, p = .26 \); Group: \( F_{1/38} = 5.2, p = .04 \)).

Discussion

The present study investigated the neuroendocrine, cardiovascular and emotional reactivity of a representative sample of patients with ED. Compared to healthy controls, patients showed blunted cortisol stress responses to the TSST in combination with a stronger parasympathetic activity, as indicated by generally lower sAA levels, lower HRF, and higher HF-HRV. Furthermore, while negative affect increased in response to the stressor in both groups, patients’ affect was more negative and higher HF-HRV. Furthermore, while negative affect increased in response to the stressor in both groups, patients’ affect was more negative and higher HF-HRV. In line with previous studies utilizing the TSST, HC displayed a peak cortisol 10 min after the stress test followed by a decrease in levels throughout the entire study. Lastly, no group differences were observed for the cortisol awakening responses.

In line with previous studies utilizing the TSST, HC displayed a peak cortisol 10 min after the stress test followed by a decrease in levels thereafter [36,61,62]. Contrarily, ED patients showed a blunted cortisol response. This finding was robust in that it was observed independent of ED diagnosis (AN versus BN) and when taking into account comorbid MDD, making the presence of a comorbid MDD as an explanation for the results improbable. As such, our observations are in line with findings from Zonnevyle-Bender et al. [34] who investigated ten adolescent inpatients with AN and reported a lack of cortisol increases and only a marginal increase in heart rate. Similarly, Ginty et al. [35] compared twelve HC with twelve BN patients after exposure to a ten minute mental arithmetic stress task and reported a blunted cortisol reaction. However, in contrast, one recent study in outpatients reported a comparable cortisol peak in BN patients and an exaggerated cortisol response to the TSST in AN patients compared to HC [30]. One possible explanation for the discrepancy between this study and our findings might be the difference in sample sizes, as Monteleone et al. [30] investigated seven patients with AN and eight patients with BN and compared them to eight HC, making the findings susceptible to outlier effects.

An alternative explanation may be differences in nutrition. Patients in the current study were inpatients and were treated already on the first day of their treatment in each clinic with a specific high-caloric re-feeding program aiming at weight gaining in patients with AN or a nutrition program aiming at a consistent eating schedule in patients with BN. In contrast, patients investigated in the study by Monteleone et al. [30] were outpatients and their treatment as well as nutrition status is unclear. A recent study, however, linked malnutrition and elevated HPAA reactivity. More specifically, while no differences in cortisol responses to a standardized mixed meal were found between healthy individuals and weight-recovered AN outpatients, patients...

Table 2

<table>
<thead>
<tr>
<th>Cardiac marker</th>
<th>Measurement</th>
<th>Eating disorder</th>
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<td>Heart rate (beats/min)</td>
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<td>Baseline</td>
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<td>1281.3 (± 196.3)</td>
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<td>1309.7 (± 143.6)</td>
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<td>856.6 (± 174.3)</td>
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<td>2.48 (± .04)</td>
<td>( F_{1/40} = 3.98; p = .05 )</td>
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</table>

Mean cortisol awakening responses are shown in Fig. 4. Values from corresponding day 1 and day 2 samples correlated significantly (awakening: \( r = .43, p = .004 \); +30 min: \( r = .34, p < .001 \)). A mixed 2 × 2-factorial ANOVA revealed significant increases in cortisol values from awakening to +30 min post-awakening (Time: \( F_{1/38} = 27.8, p < .001 \); Group: \( F_{1/38} = .52, p = .48 \); Time-by-Group: \( F_{1/38} = 1.48, p = .23 \)). Controlling for compliance did not change CAR-related results (Time: \( F_{1/38} = 25.3, p < .001 \); Time-by-Group: \( F_{1/38} = 53.1, p = .26 \); Group: \( F_{1/38} = 5.2, p = .04 \)).

Discussion

The present study investigated the neuroendocrine, cardiovascular and emotional reactivity of a representative sample of patients with ED. Compared to healthy controls, patients showed blunted cortisol stress responses to the TSST in combination with a stronger parasympathetic activity, as indicated by generally lower sAA levels, lower HRF, and higher HF-HRV. Furthermore, while negative affect increased in response to the stressor in both groups, patients’ affect was more negative throughout the entire study. Lastly, no group differences were observed for the cortisol awakening responses.

In line with previous studies utilizing the TSST, HC displayed a peak cortisol 10 min after the stress test followed by a decrease in levels thereafter [36,61,62]. Contrarily, ED patients showed a blunted cortisol response. This finding was robust in that it was observed independent of ED diagnosis (AN versus BN) and when taking into account comorbid MDD, making the presence of a comorbid MDD as an explanation for the results improbable. As such, our observations are in line with findings from Zonnevyle-Bender et al. [34] who investigated ten adolescent inpatients with AN and reported a lack of cortisol increases and only a marginal increase in heart rate. Similarly, Ginty et al. [35] compared twelve HC with twelve BN patients after exposure to a ten minute mental arithmetic stress task and reported a blunted cortisol reaction. However, in contrast, one recent study in outpatients reported a comparable cortisol peak in BN patients and an exaggerated cortisol response to the TSST in AN patients compared to HC [30]. One possible explanation for the discrepancy between this study and our findings might be the difference in sample sizes, as Monteleone et al. [30] investigated seven patients with AN and eight patients with BN and compared them to eight HC, making the findings susceptible to outlier effects.

An alternative explanation may be differences in nutrition. Patients in the current study were inpatients and were treated already on the first day of their treatment in each clinic with a specific high-caloric re-feeding program aiming at weight gaining in patients with AN or a nutrition program aiming at a consistent eating schedule in patients with BN. In contrast, patients investigated in the study by Monteleone et al. [30] were outpatients and their treatment as well as nutrition status is unclear. A recent study, however, linked malnutrition and elevated HPAA reactivity. More specifically, while no differences in cortisol responses to a standardized mixed meal were found between healthy individuals and weight-recovered AN outpatients, patients...
with untreated AN showed significantly higher cortisol concentrations [76]. Since cortisol concentrations were negatively associated with hunger and appetite ratings in all participants, these findings suggest that enhanced HPAA activity reflects malnutrition in untreated individuals with AN. Similar studies in patients [28–31,76] support this interpretation and a study in fasting healthy individuals suggests that these processes are generalizable to a non-clinical population [77]. Thus, we suggest that patients in the study by Monteleone et al. [30] might have been malnourished to a larger extent than patients in our study, resulting in an enhanced HPAA response to the TSST. Since malnutrition in patients with AN is generally higher than in patients with BN, this resulting in an enhanced HPAA response to the TSST. Since malnutrition might be considered adaptive, as they might also help to save energy. Again, longitudinal studies are needed to test these hypotheses.

In terms of circadian cortisol rhythm, patients with EDs as well as HC showed cortisol responses to awakening comparable to HC in other studies [16–18]. These results indicate that there was no general unresponsiveness of the HPAA in our sample of patients with EDs. To our knowledge, only one other study reported CAR in patients with EDs. This study was conducted with eight AN outpatients [26] and in contrast to our research, this study found an increased CAR in patients. Again, the discrepancy to our findings could be a result of differences in the feeding status due to differences in the treatment setting (inpatient versus out-patient or in versus out treatment). Taken together, our results suggest that in treated patients with ED, HPAA dysfunctions are restricted to changes in reactivity to psychosocial stress (hypo-reactivity), and are not apparent in measures of basal activity (i.e., awakening responses).

Finally, some strengths and limitations of our study should be mentioned. One strength is the relatively large general sample size as compared to previous research in this area. However, in spite of the transdiagnostic view of eating disorders [46,47] taken in the present study, in a further step, a differentiation between the various subgroups of patients with EDs with a sufficient sample size for each form of EDs would be desirable. Furthermore, it has to be emphasized that our study is cross-sectional in nature. Studying high risk populations (e.g. young women doing a diet) as well as implementing longitudinal studies investigating stress reactivity of acutely ill patients, patients currently under treatment, and recovered patients are needed in order to clarify whether the reported psychoneuroendocrine changes are a cause or a consequence of the ED. Finally, assessment of gonadal steroids as well as additional sampling time points – both for diurnal cortisol rhythm assessment as well as SNS and HPAA activity assessment of an ED, i.e., represents a pre-morbid condition making individuals more vulnerable to EDs. Therefore, further studies should concentrate on the differences between treated and untreated or in- and outpatients with EDs and consider that changes in HPAA functioning could be dynamic during the course of a psychological disorder [86], warranting longitudinal studies (e.g. [87]).

With regard to sAA, HRF and HRV, we found similar stress responses, but reduced overall levels throughout the study period in patients with EDs compared to healthy individuals, indicating reduced SNS activity in patients. As such, our findings are in line with earlier reports [21,22,25,30,35,88]. It has been hypothesized that the observed SNS hypoactivity in ED patients is caused by starvation and/or intermittent dieting [89]. However, most patients with BN are not nutritionally deficient and therefore, metabolic deficiencies associated with reduced caloric intake might not be able to sufficiently explain the observed adrenergic dysregulation [22]. Additionally, in the present study, patients with BN and AN do not differ in their adrenergic hypoactivity. Perhaps adrenergic dysregulation acts as a predisposing factor in EDs or a consequence of HPAA dysregulations [22]. More specifically, glucocorticoids like cortisol can facilitate sympathetic actions, such that during stress, their overall physiological effects are to permissively prolong cardiovascular reactivity [12]. Vice versa, blunted cortisol concentrations are linked to less prolonged sympathetic activity. During fasting, a downregulation of adrenergic receptors could be a long-term consequence of a hyperactive HPAA, leading to a hypoactive SNS. These changes might be considered adaptive, as they might also help to save energy.

With respect to negative affect, we found patients with EDs to have overall higher negative affect scores than healthy individuals, probably moderated by a higher degree of depressive symptoms or differences in MDD frequency. However, the groups did not differ in the magnitude of the increase in negative affect in response to the TSST. This result is in line with other reports [22,31,34,44,45,90] and suggests that while ED is associated with elevated negative mood, affective reactivity to psychosocial stress is preserved. Kaye [53] reviewed related literature and summarized that the dysregulation in mood is a consequence of an altered brain serotonin function in patients with AN and BN and indicates a neurobiological vulnerability.

Finally, some strengths and limitations of our study should be mentioned. One strength is the relatively large general sample size as compared to previous research in this area. However, in spite of the transdiagnostic view of eating disorders [46,47] taken in the present study, in a further step, a differentiation between the various subgroups of patients with EDs with a sufficient sample size for each form of EDs would be desirable. Furthermore, it has to be emphasized that our study is cross-sectional in nature. Studying high risk populations (e.g. young women doing a diet) as well as implementing longitudinal studies investigating stress reactivity of acutely ill patients, patients currently under treatment, and recovered patients are needed in order to clarify whether the reported psychoneuroendocrine changes are a cause or a consequence of the ED. Finally, assessment of gonadal steroids as well as additional sampling time points – both for diurnal cortisol rhythm assessment as well as SNS and HPAA activity assessment

Fig. 3. Means and standard error of means of the negative affect sum score of the Positive and Negative Affect Schedule, obtained within each group at five time points. The baseline measurement was conducted approximately 45 min prior to the TSST.

Fig. 4. Means and standard error of means of salivary cortisol concentrations immediately after awakening and 30 min later on two consecutive days before stress testing.

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period prior to the TSST – are recommended for future stud-
es to increase reliability and determine possible confounding variables (e.g., carry-over effects of the cognitive testing).

In the present study, a large sample size as well as the use of the TSST as an effective acute laboratory stress procedure allowed us to provide evidence of a hypo-reactive HPA axis combined with blunted basal SNS activity and unchanged HPA activity in inpatients suffering from eating disorders. Our findings further emphasize the importance of studying neuroendocrine processes in eating disorders in order to unravel their contribution to disease etiology and treatment success.

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Conflict of interest

The authors declare that they have no conflict of interest.

References


