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Exhaustion-related changes in cardiovascular and cortisol reactivity to acute psychosocial stress

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HIGHLIGHTS

- High scorers on SMBQ showed a blunted HPA-axis response to stress provocation.
- The SAM-axis responses to stress provocation were unrelated to stress symptom scores.
- HPA- and HR-responses, and state anxiety habituated to the second V-TSST.
- Dysfunctional stress response flexibility was related to signs of exhaustion.

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ABSTRACT

Prior findings indicate that individuals scoring high on vital exhaustion show a dysfunctional stress response (DSR), that is, reduced cortisol reactivity and habituation to psychosocial stressors. The main aim of the present study was to examine whether a DSR may be a vulnerability factor in exhaustion disorder (ED). We examined whether a DSR is present during the early stages of ED, and still is present after recovery. Three groups were studied: 1. Former ED patients ($n = 14$); 2. persons who during the past 6 month had experienced stress at work and had a Shirom–Melamed Burnout Questionnaire (SMBQ) score over 3.75, considered to indicate a pre-stage of ED ($n = 17$); 3. persons who had not experienced stress at work during the past 6 months and had a SMBQ score below 2.75 ($n = 20$). The participants were exposed twice to a virtual version of the Trier Social Stress Test (V-TSST), during which salivary cortisol samples were collected. In addition, high frequency heart rate variability (HF-HRV), heart rate (HR), t-wave amplitude (TWA), and α-amylase were assessed to examine stress reactivity and habituation in the autonomic nervous system (ANS).

The initial analyses showed clear hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS) activations in both V-TSST sessions, together with habituation of cortisol and heart rate in the second session, but without any significant group differences. However, the former ED patients showed considerable variation in self-reported signs of exhaustion (SMBQ). This led us to assign former ED patients with lower ratings into the low SMBQ group (LOWS) and those with higher ratings to the high SMBQ group (HIGHS). When repeating the analyses a different picture emerged; the HIGHS showed a lower cortisol response to the V-TSST than did the LOWS. Both groups' cortisol response habituated to the second V-TSST session. The ANS responses did not differ between the two groups.

Thus, persons in a pre-stage of ED and *unrecovered* former ED patients showed signs of DSR, in contrast to healthy controls and *recovered* former ED patients. The results may be interpreted as indicating that DSR in the HPA axis is present early on in the stress process, but subsides after successful recovery.

1. Introduction

During the past decade, mental illnesses such as depression and burnout/exhaustion disorder (ED) have constituted a large part of

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long-term sick leaves in many post-industrial countries. The major contributing factor suggested is the rapidly changing structure of work, with a shift from manual to mental demands [4]. The working conditions that may lead to mental illness are largely known: high job demands combined with low control and poor social support from colleagues and supervisors, imbalance between effort and reward, and organizational injustice [57]. Workplace programs for primary prevention of mental disorders are rare, though probably effective [58]. Besides preventive measures on the workplace or community level, it may also be important to identify vulnerable individuals. Although personality factors, for example "overcommitment" [54] and "performance-based self-esteem" [15], have been suggested to predispose the individual to accepting unreasonable levels of responsibility and workload, it remains doubtful whether personality factors fully explain individual susceptibility to ED. Apparently, a considerable part of the population has had a heavy workload for years without developing ED. It is possible that some kind of biological vulnerability is necessary to turn normal reactions to work stress into ED. Such biological vulnerability may explain the sleep disturbances and cognitive problems that are commonly encountered already in pre-stages of ED [9].

The responsiveness of the stress system to stressors is essential for a sense of wellbeing, adequate performance of tasks and positive social interactions [6]. The development and severity of conditions such as ED depend on the genetic, epigenetic and constitutional vulnerability or resilience of the individual to stress, the exposure to stressors during 'critical periods' of development, the presence of concurrent adverse or protective environmental factors, and the timing, magnitude and duration of stress [6]. Inappropriate basal activity and/or responsiveness of the stress system, in terms of both magnitude and duration, might impair growth, development and body composition, and might account for many behavioral, endocrine, metabolic, cardiovascular, autoimmune, and allergic disorders [6].

In work stress studies, salivary cortisol has often been used as a biomarker for hypothalamic–pituitary–adrenal (HPA) axis activation. However, in studies of ED, conflicting results showing increased, decreased or normal cortisol levels have been reported [41–43], and recent studies of well-defined ED patients have failed to show deviating diurnal cortisol patterns compared to controls [46,47,55]. One possibility is that the earlier stages of ED are characterized by increased levels of free cortisol, while later stages are associated with hypocortisolism, representing a breakdown of the endocrine feedback mechanisms [32,38,40]. In support of this, a review of 62 articles found that the cortisol awakening response (CAR) co-varied positively with work stress and general life stress, while clinical burnout/exhaustion and fatigue were associated with reduced CAR [5]. The cumulative long-term effect of the physiological systems' attempts to adapt to life demands has been labeled *allostatic load*, comprising four types: 1) too frequent "hits" of stress activation, 2) lack of adaptation to repeated stressors, 3) prolonged response, i.e. inability to shut off the response, and 4) inadequate response [37]. Thus, it is relevant to study the stress response in different stages of ED.

In this context, studies using experimental stress provocation have yielded interesting results. The Trier Social Stress Test (TSST) is the most widely used tool to induce stress in laboratory settings, and has been shown to reliably evoke a stress response with concurrent activation of the HPA axis and the two branches of the autonomic nervous system (ANS) (the sympathetic nervous system — SNS, and the parasympathetic nervous system — PNS) [1]. Teachers in active work but scoring high on vital exhaustion [32], and individuals scoring high on an allostatic load index (associated with burnout and chronic stress) [24] have been reported to respond with blunted cortisol responses to the TSST. Matthews et al. [36] found that higher levels of chronic stress were related to lower blood pressure and norepinephrine responses to an acute stress task similar to the TSST. In a study by Kudielka et al. [32], vital exhaustion was also associated with reduced HPA-axis stress response habituation to repeated exposures to the TSST, habituation that in healthy persons normally occurs rapidly and most notably at the second stress exposure [26,51]. The results suggest that one pathway leading to ED may be an inability to respond adequately physiologically when confronted with new stressors (i.e., Scenario 4: inadequate response), as well as a reduced ability to adapt to repeated stress exposure (i.e., Scenario 2 above: lack of adaptation). The possible mechanisms behind an inadequate physiological response might be an up-regulated cortisol feedback inhibition of ACTH in the pituitary [65] or a down-regulation of pituitary CRF receptors after a period of CRF hypersecretion from the hypothalamus [21]. It is interesting to note that pharmacological blocking of the HPA and sympathetic-adreno-medullar (SAM) axes has been shown to impair cognitive functions [35]. Reduced flexibility in the HPA- and SAM-axis responses to acute stress may thus result in insufficient mastery of demanding situations due to lacking cognitive activation [60]. This means that increasing effort has to be invested in order to cope with attention- and energy-demanding work tasks, which in the long run may lead to a vicious cycle of deficient mastery and exhaustion, including cognitive complaints [48].

Deviances in the parasympathetic branch of the ANS, as measured by heart rate variability (HRV), have also been associated with stress. Low HRV has been related to poor attentional control, anxiety, post-traumatic stress disorder [12], vital exhaustion [63] and work stress [59]. It is possible that persons with ED show inadequate activation of the vagal system during stress provocation, although this has as yet been insufficiently studied.

A study on dysfunctional HPA-axis activation in exhausted teachers [32] is thus far the only one of its kind, and there is a need to further extend and deepen the research on decreased HPA- and SAM-axis flexibility as possible key factors in the onset and perpetuation of ED. It will probably remain an open issue whether this dysfunction develops during long-term stress or if it existed already beforehand, representing e.g. a genetically based vulnerability [8]. Irrespective of causality, there is a strong need to study the flexibility of the HPA-axis during repeated stress provocations at various stages of ED, together with possible deviations in the SAM-axis and the PNS, in order to gain new knowledge about possible physiological correlates of relevance for the development and perpetuation of ED.

Thus, the main aim of the present study was to examine whether dysfunctional flexibility of the stress response in the HPA and SAM axes is present during early stages of ED, and still present after recovery. In addition, we also assessed ANS reactivity. Saliva cortisol and α-amylase were collected to measure HPA- and SAM-axis reactivity [45]. Cardiovascular reactivity was assessed using heart rate, T-wave amplitude as a proxy of sympathetic cardiac control [30,52], and high frequency heart rate variability (HF-HRV) as a measure of vagal cardiac control [3].

Three alternative outcome patterns were:

Outcome type 1: Dysfunctional stress response exists early on in the exhaustion process and also after essential recovery from ED. This may indicate that DSR is a predisposing factor or has developed early on in the stress process.

Outcome type 2: Dysfunctional stress response exists early on in the exhaustion process, but subsides after recovery. This may indicate that DSR is a sign of incipient exhaustion, but not a predisposing factor for ED.

Outcome type 3: Dysfunctional stress response evolves late in the exhaustion process and remains after essential recovery from ED. This may indicate that DSR does not develop until mental "breakdown," and remains a chronic vulnerability, predisposing for relapse.