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**STRESS REACTIVITY, COGNITIVE
FUNCTIONING AND HIPPOCAMPAL
MORPHOLOGY IN EXHAUSTION
DISORDER, AND DEVELOPMENT OF A
SELF RATING SCALE FOR
EXHAUSTION DISORDER, KEDS**

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ABSTRACT

Stress is considered a major health problem in modern society and a prominent reason behind the long term sick leave (LTSL). Chronic stress may give rise to feelings of irritation and fatigue or exhaustion and may precipitate depression and anxiety as well as a number of unexplained medical conditions such as burnout. Burnout is not classified in the International Classification systems, but is instead noted among “Problems related to life-management difficulty”. Hence Exhaustion disorder (ED) was introduced in 2003 as a medical diagnosis to classify the closely associated terms vital exhaustion, mental fatigue and clinical burnout. According to the glucocorticoid-cascade hypothesis of stress and ageing, over-exposure or prolonged exposure to stress hormones (cortisol) may have adverse effects on the ability to turn off a stress response as well as memory functioning.

On the contrary to our hypothesis, study I-III, demonstrated that publicly employed women, who were initially on LTSL due to work stress related depression and Exhaustion disorder have a blunted ability to mount a stress response as measured by the Dex/CRH test. The cognitive test battery revealed that attention and working memory was slightly impaired at baseline but not in the 1 year follow-up. Magnetic resonance imaging (MRI) demonstrated that Hippocampus volume was not changed, nor any other cortical area.

In study IV, a new self rating scale for assessment of ED-symptoms, The Karolinska Exhaustion disorder scale, KEDS was constructed and evaluated. The scale has 9 items, ranging from 0-6 points, with a maximum summated score of 54. Lower scores reflect no or mild symptoms, and 19 points is associated with sensitivity and specificity above 95% suggesting that the scale has a high discriminative capacity.

In summary, LTSL patients who suffered from work stress related depression and ED at baseline, demonstrated a neuroendocrine deficiency that remained at 1-year follow-up and at 7-years follow-up despite clinical improvement. Symptoms of Exhaustion disorder may be assessed using the 9 item self rating scale, KEDS.

LIST OF PUBLICATIONS

- I. Ingrid Rydmark, **Kristina Wahlberg**, Per Hamid Ghatan, Sieglinde Modell, Åke Nygren, Martin Ingvar, Marie Åsberg, and Markus Heilig.

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- II. **Kristina Wahlberg**, Per Hamid Ghatan, Sieglinde Modell, Åke Nygren, Martin Ingvar, Marie Åsberg, Markus Heilig.

Suppressed Neuroendocrine Stress Response in Depressed Women on Job-Stress-Related Long-Term Sick Leave: A Stable Marker Potentially Suggestive of Pre-existing Vulnerability. *Biological psychiatry* 2009;65:742-747
- III. **Kristina Wahlberg**, Anna Nager, Åke Nygren, Marie Åsberg, Markus Heilig, Martin Ingvar.

Suppressed Stress-reactivity in Women with a history of Job-Stress induced depression and Exhaustion Disorder: A 7-years follow-up. (In manuscript).
- IV. **Kristina Wahlberg**, Ulla Peterson, Aniella Besér, Åke Nygren, Marie Åsberg.

Construction and evaluation of a self rating scale for stress-induced Exhaustion Disorder, the Karolinska Exhaustion Disorder Scale. (Submitted).

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic Hormone
ANOVA	Analyses of Variance
ANS	Autonomic Nervous System
AUC	Area under the curve
AUDIT	Alcohol Use Disorder Identification Test
AVP	Arginin Vasopressin
BBB	Blood Brain Barrier
BMI	Body Mass index
BO	Burnout
BNST	Bed nucleus of the stria terminalis
CAR	Cortisol Awakening Response
CBG	Cortisol Binding Globulin
CBI	Copenhagen Burnout Inventory
CNS	Central Nervous System
CPRS	Comprehensive Psychopathological Rating Scale
CFS	Chronic Fatigue Syndrome
CSF	Cerebrospinal Fluid
CRH	Corticotrophine releasing hormone
Dex/CRH	Dexamethasone / Corticotrophine
DHEAS	DehydroEpiandrosterone
DSM-IV	The Diagnostic and Statistical Manual, version IV
DST	Dexamethasone suppression test
DUDIT	Drug Use Disorder Identification Test
ED	Exhaustion Disorder
EFA	Exploratory Factor analyses
11 β -HSD1	11 β -hydroxysteroid dehydrogenas 1
11 β -HSD2	11 β -hydroxysteroid dehydrogenas 2
FM	Fibromyalgia
GAD	General Anxiety Disorder
GAF	Global assessment of functioning
GC	Glucocorticoid
GR	Glucocorticoid receptor
HAD	Hospital Anxiety and Depression Scale
HDL	High density lipoprotein
HPAA	Hypothalamus Pituitary Adrenal Axis
HSS	Human Service Sector
ICD-10	International Classification of Diseases, Tenth Revision
IGL-1	Insuline Growth Like Factor-1
IL-6	Interleukin-6
LC	Locus Coeruleus
KEDS	Karolinska Exhaustion Disorder Scale
LTSL	Long Term (here defined as ≥ 3 months) Sick Leave
MADRS	Montgomery-Åsberg Depression Rating Scale
MBI	Maslach's Burnout Inventory

MDD	Major depressive disorder
M.I.N.I.	Mini Internationell Neuropsykiatrisk Intervju
MR	Mineralocorticoid receptor
MRI	Magnetic Resonance Imaging
NA	Noradrenaline
NBHW	National Board of Health and Welfare (Socialstyrelsen)
OLBI	Oldenburg Burnout Inventory
PTSD	Post Traumatic Stress Disorder
PVN	Para Ventricular Nucleus
RFV	National Social Insurance Board (Riksförsäkringsverket)
ROC	Receiver Operating characteristics
SAMA	Sympathetic Adrenal Medulla Axis
SCB	Statistiska Centralbyrån; Statistics
SCL-90	Symptom Checklist - 90
SCID I	Structured Clinical Interview for DSM-IV-Axis I
SCID II	Structured Clinical Interview for DSM-IV-Axis II
SH	Subclinical hypercortisolism
SNS	Sympathetic Nervous System
SSRI	Selective Serotonin reuptake inhibitor
Swed-Qual	The Swedish Health-Related Quality of Life Survey
VE	Vital Exhaustion
WHO	World Health Organisation

1 MAIN SECTION

1.1 INTRODUCTION

During 1999-2003, stress related psychiatric illness - particularly mood and anxiety disorders and other stress related conditions - almost doubled in Sweden, predominantly in the publicly employed women. Work related health problems, like Burnout (BO), generally increased in this sector during the 1990^{ths}, and it was assumed that the increase in psychiatric long term (≥ 3 months) sick leave (LTSL), was preceded by prolonged periods of stress related to work environmental issues (1, 2). Chronic stress may give rise to feelings of irritation and fatigue or exhaustion – signs associated with BO and a number of unexplained medical conditions as well as somatic and psychiatric diseases and disorders (3-6). BO has been considered as a mild psychiatric problem (7). “Burnout” has a code in the international diagnostic classification system, (ICD-10), but not as an illness category. Instead, it is classified among “factors influencing health status and contact with health services” in the subgroup covering “Problems related to life-management difficulty”. Hence a medical diagnosis for the psychiatric condition caused by chronic unrelieved stress was introduced in Sweden(8). It was called Exhaustion disorder (ED) and classified among “Reactions to severe stress, and adjustment disorder” as a new category (F43.8).

Although sciences are struggling to fully understand much of the biological mechanisms, chronic stress and major depression are commonly considered to be related to hyperactivity of centrally mediated stress systems, i.e. the Hypothalamic-Pituitary-Adrenal- Axis (HPAA), while termination of chronic stress and states of fatigue or exhaustion, are associated with decreased activity of the same system (4, 6, 9-13). The work with this thesis has been focused on analyzing HPAA reactivity, cognitive functioning, and brain morphology associated with ED. A second aim was to develop a symptom self-rating scale for the assessment of ED that could serve as a tool in clinical settings and in research.

1.1.1 Stress and mental health problems – a matter of public health concern

Stress is considered one of the most significant health problems in modern society and a prominent reason behind the global burden of disease and a worldwide public health concern in the 21st century (14-16). Stress may precipitate depression and the stress response includes alterations in anxiety levels, loss of cognitive and affective flexibility and set into motion a number of processes that are likely to promote survival during a life-threatening situation (10). In industrialized countries, stress related psychiatric conditions have surpassed other disease categories as a cause for long term sick leave (LTSL), (17, 18).

In Sweden, psychiatric illness, particularly depression-, anxiety disorders and stress related conditions, almost doubled during 1999-2003, and the dramatic increase was most prominent in publically employed and in women. During the same period other diseases, for instance, muscular-skeletal diseases were fairly stable. A register study performed by Vaez et al (2007) demonstrated that psychiatric LTSL individuals did not have a high pre-morbid rate of sick leave (19). The number of repeated downsizings or re-organizations, and psychosocial work environmental health problems, such as BO, generally increased in the public sector during the 1990^{ths} and it was assumed that this was related to prolonged periods of stress, that in the end lead to the psychiatric LTSL increase (2). Although stress related fatigue conditions like BO and Vital exhaustion (VE) has been associated with future risk of sickness absence and disability pension, due to mental and behavioral disorders (20, 21) and increased risk of cardiovascular disease (22), studies investigating the association between downsizing and psychiatric sick-leave are sparse. It has been suggested that the reason for this might be related to lack of diagnosis-specific sick-leave data. However, recent data suggest that 1% staff reduction increased the psychiatric sickness absence rate by 9% within the subsequent five years in publically employed middle-aged women (23).

1.1.2 Stress related mental health problems and diagnostic considerations

For well over a century, primary care clinicians have observed that illnesses, which are apparently associated with stress and psychosocial factors, share core features of extreme fatigue, disability out of proportion to physical examination findings, and

symptoms such as insomnia, cognitive or memory problems, and psychological distress (9, 24-26). Some of these conditions have been referred to as “functional” or “medically unexplained, although various names have also been used, such as somatisation, psychosomatic or somatoform syndromes (24, 27). These conditions in general are associated with poor functional status, unemployment and psychiatric illness, (9, 28). Chronic fatigue syndrome (CFS), fibromyalgia (FM), atypical or non-cardiac chest pain, multiple chemical sensitivity and migraine, are all examples of more or less controversial and/or accepted conditions found in this category (24, 27). Generally, inconsistent information is available on the cause, pathophysiology, natural history and prognosis, and medical management in many of these syndromes (9), but they are found to frequently co occur with psychiatric disorders. The co-occurrence of e.g. fatigue and depression pose a high risk for disability pension and is associated with greater functional impairment than when these conditions occur alone (25, 26, 29). Hence, early detection and prevention as well as systematic research on comparative biological concomitants and epidemiology in patients and healthy controls are needed (30). Fatigue is a dominant complaint in various psychiatric disorders (9, 25-27) as well as in metabolic disorders and mild traumatic brain injury (31, 32). A substantial amount of research has been performed but the fatigue concept is still considered elusive to grasp (25, 31). Burnout (BO) and VE are other conditions in which a state of fatigue or exhaustion is a central feature (12). BO is not clearly defined in the International Classification systems (ICD-10), but is instead noted among “Problems related to life-management difficulty” (33). The term Burnout was developed to serve within organizational psychology research (34) but has nonetheless been used as a diagnostic label by physicians. Korczak (2010) in a review of diagnostic practices of German psychiatrists, suggested that they often, for reimbursement reasons, use the term “depression” (35).

A correct diagnosis is a prerequisite to an adequate care and intervention as well as an adequate follow-up (36), and it is argued that screening for different psychiatric conditions is important (30). Our group performed a psychiatric screening, using the validated SCID I and II, in a sample of 200 private employees on LTSL, and found that 80 % fulfilled criteria for Major depressive disorder, while personality disorders and substance overuse were rare. Self assessed data further demonstrated that 45 % attributed their illness to prolonged job stress only, 41 % to job stress in combination

with private life issues, while 11% reported private life issues as the only reason for their illness (37). These patients described core symptoms of pain, fatigue, irritability pronounced cognitive and memory impairments, i.e. symptoms included among criteria for ED which were later introduced in 2003 (8). Similar findings have been presented, showing that 55% of their patients assessed work related stress as the main reason for their LTSL, 31% to job stress in combination with private life issues (38).

1.1.2.1 Psychiatric diagnostic screening

Psychiatric diseases are diagnosed based on subjectively reported symptoms. The fact that symptoms are overlapping between different psychiatric disorders and that there is a fairly high proportion of co morbid individuals, constitute challenges that may make the diagnostic process difficult (36). Furthermore, symptoms may overlap between psychiatric and somatic diseases and it is proposed that in primary care, in as much as 50 % of patients suffering from depression, might be unidentified as they seek consultation for bodily complaints (9, 36, 39). Similarly, ED symptoms are overlapping with other conditions. Symptoms of depression and anxiety frequently co occur during some stage of the illness or as a complication of stress-related emotional exhaustion (40).

A reliable diagnostic system and the health insurance system depend on validated instruments that can discriminate different diagnoses (36). A sensitive symptom rating scale would be valuable in the diagnostic process in clinical practice as well as in research about the biological mechanisms involved in ED and evidence based treatment

1.1.2.2 Stress related mental health problems and gender differences

By the end of December, 2010, close to 16.900 individuals were sick absent due to mood disorders and another 13.900 due to other stress related psychiatric disorders. The proportion of females in these categories was 69 % and 73 % respectively (41). The higher prevalence of stress related illness and mental health issues in women have become a matter for increased interest during recent years. Work related BO is much more common in women (1, 42, 43) and other non-medical conditions occur predominantly in women, approximately 1.5-2.0 times as often as in men (24),

although the relative risk of having Major Depressive Disorder (MDD) with severe burnout was greater for men in a study performed by Ahola and co-workers (7). Both intense acute stress and exposure to a multitude of stressors simultaneously or during a period of time may be a significant risk for later somatic symptoms and permanent changes in the human stress response (5), but female gender and other factors such as “chronic worry or expectation” and “lack of control” (of the stressor) are suggested to be more important for the development of fatigue, pain or other somatic symptoms as well as related conditions like CFS and FM (5, 24, 44, 45). Similarly, there are gender related prevalence rates for several (somatic and) psychiatric diseases, and women are also more likely to develop anxiety and depression (including atypical subtype) and to subjectively experience more stress than men (10, 42, 43). Consistently, women report more physical symptoms and show higher stress vulnerability although several studies have shown that stress responses appear not to parallel or reflect the subjective response to psychological or noxious stress. Therefore, it cannot be easily extrapolated from emotional or verbal reports of perceived stressfulness to a physiological response of the organism to a stressful encounter (3).

The recently introduced ED has not yet been validated in terms of gender related similarities and differences, but is an interesting research question. Clinical observations suggest that 85-90 % of the ED-patients are women.

1.1.3 Definition of stress, and promoting versus damaging effects of stress

All organisms' survival is critically dependent on an immensely complex dynamic "steady state of the internal milieu" as originally conceptualized by Claude Bernard (1813-1878), a physiologist. This "steady state" or equilibrium was later called homeostasis by the American physiologist, Walter Cannon (1871-1945), who coined the term "stressor" to describe any stimuli, i.e. "disturbing forces", whether internal or external, real or perceived - that challenge or threaten the homeostasis. Cannon expanded the concept by relating homeostasis to emotional and physical adaptations and associated these responses with stress-hormone (catecholamine) secretion from the adrenal medulla in an action called "the fight or flight response". Hans Selye (1907-1982), a Hungarian endocrinologist, was influenced by Bernard and Cannon. He observed a common physiological response to stress that consists of three parts, which he called the general adaptation syndrome or GAS. The initial response to a stressor is termed the Alarm reaction. This response leads to an immediate increase in physiological arousal. To maintain homeostasis, the body responds with the second stage which is called Resistance. During this phase, stress hormones are released to mobilize resources located throughout the body. This stage may last for long time and if the stress persists too long, the bodily resources may become completely depleted, leading to the final stage called Exhaustion (46).

In modern terminology "stress" commonly occurs when homeostasis is threatened - or perceived to be so by our brain (47, 48), either by an external stressor such as cold temperature, social rejection, or an intrinsic stressor like hypoxia or dehydration(49). The response to stress is controlled by the Paraventricular nucleus (PVN) in the hypothalamus which gathers information about the current external and internal status from numerous loci throughout the brain. When incoming information is summarized to a level exceeding a threshold magnitude, the hypothalamus starts an electrical and chemical signaling and the PVN output or release of Corticotrophin releasing hormone (CRH) and Arginine Vasopressin (AVP), determines whether a stress response occurs (50). The response to a potentially stressful situation is dependent on how the individual perceives the situation and on the general state of health (51).

Increased arousal, alertness and heightened attention are all examples of a behavioral shift that is controlled by the hypothalamus-pituitary-adrenal-axis (HPAA) (50). These organs are thus involved in the system responsible for the secretion of a number of hormones such as adrenalin and cortisol, that redirect energy and oxygen to the site that need them most (47, 52). In that sense, stress hormones mediate a behavioral and physical adaptation that is essential for the body to be able to deal with a challenge. Scientists have long been struggling to fully understand how stress gets under the skin and influences health (13), but the stress response influences all functions, i.e. behavior and bodily functions such as metabolism, immunity and growth (53, 54). The vast influence of the HPAA and its hormonal cascade has prompted numerous theories linking stress, cortisol and disease (13). In 1998 the protective and damaging effects of stress mediators were conceptualized in the Allostatic Load model. In contrast to the homeostatic systems, the allostatic adaptive system has a much broader margin as it allows us to direct e.g. our sleep, physical activity, or expose ourselves to psychological challenges or extreme temperature and infectious diseases (54).

1.1.3.1 Allostasis

Allostasis is defined as a process that maintains the homeostasis actively, or that strive to achieve stability through change for a limited period of time, by secretion of stress hormones and other mediators (5). An adequate stress response is crucial for well-being, successful task performance and positive social interactions (55), and the normal allostatic response is generally meant to be present for a limited period of time, i.e. initiated by a stressor and sustained for an appropriate period of time and then turned off (51, 53). Hypoxia for instance, requires activation of hypothalamus and brainstem to redirect posture (10, 51, 53), while a much more complex neural network including e.g. amygdala and prefrontal cortex, is involved when dealing with danger or psychological stressors such as unpredictability, uncontrollability, novelty, anticipation, ego-involvement, habituation and classically conditioned stimuli (10, 56). Psychological stress may thus be an equally potent trigger of a stress response as a physical threat (5, 13). The pattern of this response varies considerably because of individual differences in interpretation of the situation and in the choice of coping strategies (57). The pathways by which e.g. the limbic system may mediate cognitive, emotional or affective input remain unclear, but it is assumed that such influences are projected indirectly to the PVN via other sites in the hypothalamus and the bed nuclei

of the stria terminalis (50). In humans, the “fight or flight response” is commonly regarded as prototypic but it has been proposed that women’s behavioral stress response is evolutionary shaped by the differential parental investment (58). Within this context, survival of self and the offspring is suggested to be maximized by nurture of the offspring and affiliation with social groups to manage stressful situations and thus reducing the risk. This “tend-and-befriend” response may be built on oxytocin mediated attachment-care giving processes that are moderated by sex hormones and opiod peptide mechanisms that down regulate the sympathetic and HPAA responses to stress (58).

1.1.3.2 Allostatic load

In contrast to acute stressors, daily hassles are operating chronically and often at a low level. These types of stressors may trigger certain behaviors that are associated with a state of being stressed out, such as eating comfort foods and increase the calorie intake, decreased sleep, excessive smoking and alcohol use, neglect to see friends or engage in regular physical activity (5). Although medical sciences are still struggling to fully understand the biological mechanisms by which this process causes disease (13, 54), inadequate functions are associated with increased vulnerability to stress-related somatic and psychiatric states (59). During long periods of stress, hormones may participate in pathological changes such as immunosuppression, obesity, hypertension and atherosclerosis (5). If allostasis is not turned off when no longer needed, or are not turned on when they are needed, or overused due to excessive exposure to adverse psychosocial or physical situations for periods of weeks, or month – or even years, cumulative changes lead to a wear and tear, called “allostatic load” (4, 54). Hence, chronic stress can result in dysregulation characterized by elevated or reduced operating levels of physiological parameters of the sympathetic nervous system (SNS), sympathetic-adrenal-medullar axis (SAMA) and HPAA (60). People who are exposed to excessive life-stress such as multiple periods of poverty level income might thus frequently turn on a stress hormone response, resulting in a subsequent pathophysiology, followed by earlier aging and decline of both physical and mental functioning (51).

A second example of allostatic load is illustrated by a lack of adaptation to chronic or repeated stress (54). For instance, approximately 10% of subjects fail to habituate to repeated public speaking but continue to respond with increased cortisol levels every

time while most people adapt to this type of repeated challenge and no longer respond with raised cortisol secretion (54, 61). Another example might be illustrated by someone who has been dominated by an abusive supervisor and/or fired, who will likely approach a new job quite differently than someone with positive job experiences (51), but experiences in early life might perhaps play an even more important role in future reactions to new situations as well as psychiatric and somatic health outcomes (62). Animal studies suggest that early stress exposure may influence mechanisms that change the number of glucocorticoid receptors in the hippocampus resulting in altered negative feedback sensitivity. Early stress may thus have lifelong impact on the stress response (45).

A third type of allostatic load is related to a delay in shut-down and subsequent prolonged stress hormonal response. Individuals with this type of failure might thus suffer from elevated blood pressure and/or cortisol levels, although the stressful situation is over. Example four is related to a blunted hormonal stress response in which the individual fails to successfully mount an adequate secretion of glucocorticoids, and it is argued that such failure might lead to compensatory hyperactivity of other mediators such as cytokines (51).

It has been proposed that measurement or evaluation of allostatic load, may be performed using 10 variables that reflect the ANS-, SAMa- and HPA activity and physiological regulation (17). Some additional inflammatory parameters have been added so that all together 16 biomarkers are suggested to be a potentially useful measurement of allostatic load (60). Some of these are associated with high levels of stress, i.e. urinary noradrenalin excretion, cortisol secretion and interleukin (IL)-6 and Insulin Growth Like factor (IGF) -1, while others may be considered as effects of long term stress such as systolic and diastolic blood pressure, waist-hip ratio, Body Mass Index (BMI), total cholesterol, glycosylated haemoglobin, Dehydroepiandrosterone (DHEAS), Triglycerides, ratio of total cholesterol / HDL and serum HDL, and fasting glucose. Life style factors have a significant effect on many of these parameters while others are highly intercorrelated. A weak correlation is assumed to provide support for both the concept of allostatic load and the stress-buffering hypothesis (ibid) which is based on social constructs among which social support and social integration may be especially health promoting through different

mechanisms (14). Social support, defined as instrumental- informational- and emotional support -may confer resilience against stress, as it influences the choice of specific coping strategy when confronted with a stressful event (63, 64). A study published by Hellhammer and co workers found that hypocortisolemic individuals have higher scores on measures of depression, perceived stress and physical complaints but not on allostatic load. Apart from seasonal variations, allostatic load measures remained stable within individuals and the authors conclude that the hypocortisolemic response may be protective rather than damaging with respect to allostatic load (65).

1.1.4 Mental and behavioral disorders

Psychiatric symptoms are common in individuals on LTSL and as pointed out, the social insurance system may promote the transformation from stress descriptions towards diagnoses that belong to the psychiatric sphere (33, 35). Exposure to chronic stress increases the vulnerability to adverse outcomes like anxiety- and depressive states and executive and/or cognitive dysfunction and these conditions are thus often referred to as stress-related (10, 17, 47) while genetic predisposition may be required for the development of major depression in response to chronic stress (47). An acute short-term stress response is crucial for homeostasis recovery and survival (49), while extreme stress may trigger psychiatric disorders like post traumatic stress disorder (11).

“Mental and behavioral disorders” are listed in the International Classification of Diseases, Tenth Revision (ICD-10), in chapter V (33), and in the Diagnostic and Statistical Manual of Mental Disorders, axis I (66), although categorization according to these systems are not fully compatible. Conditions specified under “Mood disorders” are defined as emotional shifts towards either a state of lowered mood i.e. depression with or without anxiety - or a state of arousal accompanied with an increased level of activity, coded F30-F39 (33).

MDD is coded F32.0-F32.9 based on symptom severity or F33.0-F33.9 depending on number of episodes (and severity). Core features are lowered mood and/or reduced interest or joy (emotional engagement). These signs should have been present for at least two weeks, in combination with a minimum of 5 symptoms, such as reduced emotional engagement, sleep disturbances, concentration difficulties or impaired memory, reduced energy and feelings of worthlessness and guilt (33). DSM-IV lists two distinct clinical depressive subtypes, independent of unipolar-bipolar distinction. Melancholic depression is considered a state of hyperarousal associated with high levels of anxiety and focus on the self in the form of feelings of worthlessness, failure and helplessness. Patients with atypical depression seem to have a disturbing sense of disconnectedness and emptiness and being walled off from themselves. Other atypical features are fatigue, excessive sleepiness, increased food intake, weight gain and depressive symptoms that gets worse as the day goes by. Approximately 30 % of patients with major depression have pure melancholic features while 15-30% has

atypical features. Those with mixed subtype features are proposed to show a more severe course of illness (10, 67).

Anxiety disorders, Adjustments disorders and Exhaustion disorder are all examples of conditions specified in "Neurotic, stress related and somatoform syndromes", coded F40-F48. Anxiety disorders are defined as phobic anxiety (ICD-10 code F40.0- F40.9), or classified as "Other anxiety syndromes" including generalized anxiety disorder (GAD), (ICD-10 cod F41.0-F41.9). GAD is associated with an excessive situational or generalized fear or worry that have been persistent for the last 6 month in combination with at least three of the following; being easily exhausted, concentration difficulties, irritability, muscle tension, and sleeping problems. Several of these are thus overlapping with symptoms of depression (33), and ED (8).

"Adjustment disorders and reaction to severe stress" include conditions coded F43.0-F43.9 These diagnoses are described as a set of emotional or behavioral symptoms or a response to one or more identifiable stressors which have been present for 3 months (6 months in the case of ED). Adjustment disorder may develop in response to becoming a parent or as a result of failure to achieve a personal goal (33). Exhaustion disorder was introduced in 2003, as a separate medical diagnose to classify the closely related Burnout (8). Core symptoms of ED are an overwhelming state of exhaustion in combination with symptoms such as sleep disturbance, and cognitive problems (criteria are listed in table 1). ED is coded F43.8a although not yet acknowledged by the international WHO. To adjust this Swedish classification to international categorizations in research papers and reports, the term "chronic burnout" has been used (68) and "major depression or adjustment disorder with depressed mood due to work related factors that has been present for > 6 months" (69, 70), and "Stress-related exhaustion" and "work stress-related long-term sick leave" (71) and "clinical symptoms of burnout" (72).

Table 1. Diagnostic criteria for Exhaustion disorder(8)*

<i>A</i>	Physical and mental symptoms of exhaustion with duration of at least 2 weeks. The symptoms have developed in response to one or more identifiable stressors which have been present for at least 6 months.
<i>B</i>	Markedly reduced mental energy, which is manifested by reduced initiative, lack of endurance, or increase of time needed for recovery after mental efforts.
<i>C</i>	At least four of the following symptoms have been present most of the day, nearly every day, during the same 2-week period: <ul style="list-style-type: none"> 1 persistent complaints of concentration difficulties or impaired memory 2 markedly reduced capacity to tolerate demands or to work under time pressure 3 emotional instability or irritability 4 insomnia or hypersomnia 5 persistent complaints of physical weakness or fatigue 6 physical symptoms such as muscular pain, chest pain, palpitations, gastrointestinal problems, vertigo or increased sensitivity to sounds
<i>D</i>	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
<i>E</i>	The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism, diabetes, infectious disease).
* Coding instruction: Exhaustion disorder is diagnosed if each criteria with a capital letter in front, are fulfilled.If the criteria for major depressive disorder, dysthymic disorder or generalized anxiety disorder are met, then exhaustion disorder should be noted only as a sub specification (i.e. <i>with</i> exhaustion disorder). (Translated by Jörgen Herlofson.).	

1.1.5 Stress and Cognition

Cognitive dysfunction as well as problems with concentration and memory has been described in chronic stress related conditions and psychiatric diseases (17, 47).

A majority of those who suffer from ED report that they have pronounced cognitive problems related to planning and remembering daily activities. In neurobiology, higher order cognition is more specifically associated with the ability to attend, identify and plan meaningful responses to external stimuli or internal motivation. These processes are mediated by the association cortex in the parietal, temporal and frontal lobes – regions that account for approximately 75 % of all the tissue in the human brain.

Attention refers to the ability to consciously pay attention to – or not, i.e. to voluntarily and selectively process such information (stimuli) that is relevant and to ignore others.

The parietal association cortex is essentially involved in attending to complex stimuli in the external and internal environment, and lesions here may thus cause attention deficits. Identification and recognition of familiar objects is performed by the association cortex of either temporal lobe, while the frontal cortex integrates immensely complex perceptual information from the parietal and temporal association cortices as well as from sensory and motor cortices. This process allows for the appreciation of ourselves in relation to the world and the planning as well as execution of the appropriate behavior (73). Learning is the process by which new information is acquired by the nervous system and storage and/or retrieval of that information is referred to as memory. This process requires encoding of data, which is dependent on the activity in the frontal and temporal lobes. Encoding of non-verbal objects is associated with bilateral activation of hippocampus. Memory can be conceptualized according to how it is qualitatively stored, i.e. declarative and procedural. The term declarative refers to memories that can be expressed as remembered daily episodes, words and their meanings or history. Procedural memory is defined as information that is acquired and retrieved without thinking about it”. This category includes motor- and cognitive skills, simple classical conditioning and priming. Memory can also be described as immediate memory, short-term memory and long-term memory.

Immediate memory is referred to as routine ability to hold experience in mind for a few seconds, while short term memory is the ability to hold information in mind for a period of seconds-minutes. Working memory falls into the latter category as the ability to hold things in mind long enough to perform sequential actions. Intermediate-term memory lasts for minutes to hours, while long-term memory last for potentially

unlimited duration. The ability to pay attention may be evaluated by measurement of reaction time to simple stimuli, and by using more cognitively demanding tasks involving stimulus response selection in the face of competing streams of information (74). A conventional way of testing short term or working memory is to present a string of digits which is then repeated by the respondent (73). These tests are known to rely on frontocortical activity (75). Tasks that require activation of the temporal lobe and hippocampus, can be applied using one-trial encoding of visual associations while memory of complex visual cues rely on parietal cortex activation (76).

1.1.6 Stress and brain morphology

Hippocampus is located in the temporal lobe. In this region, Mineralocorticoid receptors (MR's) and Glucocorticoid receptors (GR's) in the CA1 region are involved in learning and the acquisition of declarative memory and the transformation from short term to long term memory. Impaired functioning is common in conditions associated with hypercortisolism (77-83). There are redundant pathways between the hippocampus and the PVN (50) and hippocampus is believed to be involved in the negative feedback loop of the HPAA activity that terminates the stress response (45). Studies in rodents have demonstrated that excessive amounts of glucocorticoids may have a deleterious effect on the neurons, particularly in the hippocampus structure (ibid) presumably related to a toxic increase in calcium-inflow and a decreased glucose-inflow to these cells (50). In these animal-studies, stress or over exposure to GC's during periods of weeks rendered atrophy in hippocampal dendrites while months of GC overexposure caused permanent loss of hippocampal neurons (45). The stress mediating adverse effects has been formulated in the so called Glucocorticoid-cascade hypothesis of stress and ageing" which postulate that overexposure to glucocorticoids may cause hippocampal atrophy followed by worsened hypercortisolism, and hippocampal memory functioning (54). In humans, magnetic resonance imaging studies have provided support for a role of cortisol as a mediator of volume changes in Cushing's disease and major depression although hypercortisolism as a mediator of hippocampal loss and cognitive impairment is not yet unequivocally established (81, 83-85).

1.1.7 The neuroendocrine response to stress

Exposure to a threatening or challenging stimulus, elicits the activation of a brain circuit responsible for the stress response which enables the organism to successfully adapt to the challenge (86). The sites that initiate the response are located within the central nervous system, i.e. PVN in the hypothalamus and the locus coeruleus (LC) in the brainstem. LC secretes noradrenaline (NA) which enhances attention, and activates the sympathetic division of the peripheral (autonomic) nervous system by electrical signals via neurons in the spinal cord, targeting the heart, lungs, bronchi, blood vessels and adrenal medulla for the secretion of adrenaline and noradrenalin. The release of catecholamines from the adrenal medulla into the bloodstream during sympathetic activation provides powerful reinforcement and modulation of the release from other sites. In less than a minute, heart rate, blood pressure and metabolism will increase while bronchi are dilated, and blood vessels to the stomach, skin and kidneys are constricted. The oxygenation increases, and nutrition is directed to the brain, heart and skeletal muscles and this process may be perceived as a state of arousal (47). The SNS and its efferent influence on vascular, glandular and metabolic adjustments is thus considered the branch specialized for the mobilization of energy – that optimizes the behavioral adaptation or response to stress (14, 50, 73, 86).

In parallel, to the activation of LC/NA and SNS, the hypothalamus triggers chemical signaling pathways (50) by the release of parvocellular CRH from the PVN directly to the anterior part of the pituitary, via the hypothalamohypophyseal portal. CRH triggers the pituitary to release adrenocorticotrophic hormone (ACTH) to the bloodstream targeting the adrenal cortex which secretes cortisol. The HPAA is the major - and commonly referred to as the most crucial physiological stress response system in the body, besides the LC/NA system (10, 15).

1.1.7.1 HPAA regulation

Besides its role as the principal secretagogue of ACTH, CRH innervates noradrenergic centres in LC and amygdala with anxiogenic and fear-related aspects of stress, corresponding to signs and symptoms of today's diagnostic classification of depression and anxiety (87), while ACTH triggers the release of cortisol from the Adrenals, as mentioned above. The most prominent examples of cortisol's action and influences can be described as the involvement in the Central Nervous System (CNS) where it plays a

role in learning, memory, and emotion; in the metabolic system, where it regulates glucose storage and utilization; in the immune system, where it regulates the magnitude and duration of the inflammatory responses and the maturation of lymphocytes (13, 49). Peripherally, cortisol mobilizes energy from bone and muscle cells (47) to allocate glucose so that the brain can fulfill its function (56). Excessive levels of cortisol may be involved in features of the metabolic syndrome including insulin resistance, hyperglycemia, hyperinsulinemia, increased abdominal fat mass, chronic pro-inflammatory states and low bone density. Other effects of high levels of cortisol are increased susceptibility to infections, poor wound healing, hypertension psychological disturbances, memory loss, sleep disturbances, increased vascular reactivity, increased appetite, peripheral muscle wasting (17, 32, 88, 89). Cortisol deficiency is associated with symptoms such as fatigue, weakness, fasting hypoglycemia, weight loss, anorexia, depression, apathy and hypotension (32)

The ability of cortisol to cross the brain-blood-barrier (BBB) enables its central activation of GR's located in the prefrontal cortex, hippocampus, amygdala and the hypothalamus (47) that terminate the release of CRH and ultimately the stress response (10, 50). Cortisol is thus the effectors in the negative feedback loop of the HPA axis activity.

Glucocorticoid receptor type 1, or MR's responds with about tenfold higher affinity to glucocorticoid-levels while glucocorticoid receptors type 2, or GR's, responds with lower affinity to glucocorticoids. MR's mainly govern the negative feedback during circadian rhythm (50), and becomes saturated while approximately 67-74% of the GR's becomes occupied during the stress response (90). MR's are present in the limbic system, preferentially in the hippocampus, parahippocampal gyrus, entorhinal, and insular cortices, while GR's are present in both subcortical (paraventricular nucleus and other hypothalamic nuclei, the hippocampus and parahippocampal gyrus) and cortical structures, with a preferential distribution in the prefrontal cortex (ibid). The activation of receptors at low and high concentrations allows the brain to differentially respond to the wide range of concentrations over which corticosteroids are secreted (91). Cortisol (but not the synthetic dexamethasone) binds to corticosteroid-binding globulin (CBG), present in the blood, and becomes the inactive form of cortisol which is directed to its target tissues. Cortisone becomes biologically active when converted to free cortisol by 11 β -hydroxysteroid dehydrogenase 1 (11 β -HSD1) isoform, whereas the

11 β -HSD2 converts cortisol to the inactive cortisone (49). The level of CBG 11 β -HSD enzymes thus regulates the entrance of cortisol to hippo-campus and other regions crucially involved in the termination of this stress system (5).

1.1.7.2 Dysregulated or altered HPA-activity

Alterations in HPA axis regulation under basal conditions and in response to acute stress appears to be correlated with the onset of different diseases or progression of the disease. Although only subtle increase in activity are found in panic disorder (87), MDD is commonly characterized by hypercortisolism (11). It has been proposed that the hyperactive HPAA is preferentially associated with the melancholic subtype of depression while the atypical subtype is rather associated with a down-regulated HPAA of central origin (10, 87). Dysregulation along the HPA-axis is defined by the ICD-10, in chapter IV; Diseases in other endocrine glands” with codes ranging from E20 – E35 depending on its source of deficiency (33).

Primary pathology is referred to Adrenal dysregulation in ICD-10. Hypersecretion of cortisol results in super-suppressive negative feedback loop, thus inhibiting further endogenous secretion of CRH and ACTH from the hypothalamus and pituitary, while adrenal failure to release cortisol, results in less effective negative feedback, thus increased CRH- and ACTH-levels.

Secondary pathology or dysregulation at the level of pituitary is at hand in e.g. cases of ACTH secreting tumor at the pituitary, which may result in elevated levels of ACTH. An excessive ACTH-release in turn, may result in increased cortisol secretion which inhibits the release of endogenous CRH and ACTH. Insufficient pituitary ACTH supply, on the other hand, may ultimately result in decreased levels of cortisol and insufficient supply of other hormones as well (32).

A third source of pathology is defined as hypothalamic neuronal dysregulation. Deficient hormonal secretion due to hypothalamic tumor has been associated with attenuated cortisol response to ACTH after synthetic CRH stimulation. It has been proposed that this indicates that the adrenals have not been subject to hyperstimulation due to excessive CRH-driven hypercortisolism, but rather had been hypostimulated for a long period of time (10).

Hypercortisolism is included in the ICD-10, code E24 as a criterion in Cushing’s syndrome and Cushing’s disease (33). Recently, subclinical hypercortisolism (SH)

was characterized although cut-off criteria for decision-making remains to be defined (92).

Hypocortisolism is defined by at least two of three criteria: a/ reduced cortisol secretion, at least temporarily during the circadian cycle and b/ reduced adrenocortical reactivity or c/ enhanced negative feedback inhibition of the HPA axis (11). Reduced ACTH and/or cortisol secretion is included - as adrenal insufficiency - in ICD-10, chapter IV, among Endocrine, nutritional and metabolic diseases, coded E27(33).

1.1.7.3 Methods for assessing HPAA activity in humans

Evaluation of the HPAA function is based on circulating levels of ACTH and cortisol. Basal activity can be measured by analyses of salivary cortisol in response to awakening (CAR). The cortisol level increase rapidly in men and women with a mean of about 50% during the first 30 minutes (93, 94). Thereafter, the cortisol concentration decreases in men while women show a delayed decrease resulting in larger AUC values compared to men. Over the remainder of the day, levels continuously decrease except for stress-induced elevations (94). Salivary cortisol is characterized by inter- and intra individual variability (15, 93) and several collecting days of saliva cortisol is thus required to be able to get reliable data (95). In the presence of decreased cortisol levels, a low dose of stimulating ACTH may be given to measure the adrenal response; a lowered cortisol response may indicate insufficiency of pituitary or hypothalamic origin, as prolonged ACTH deficiency causes adrenal atrophy (32). When an elevated cortisol level is at hand, test of the negative feedback regulation may be performed by oral intake of dexamethasone, in the dexamethasone-suppression-test (DST) and measurement of levels of ACTH and cortisol. Dexamethasone is a synthetic glucocorticoid which mimics endogenous cortisol by acting on glucocorticoid receptors primarily at the pituitary level. Inefficient suppression of ACTH and/or cortisol levels may thus indicate a pituitary resistance to glucocorticoid negative feedback (10). Relatively low (0,25 – 0,5 mg) doses are preferred when measurement is performed, not to completely suppress the secretion of endogenous cortisol levels the following day (12). Compared to the standard DST, the combined dexamethasone CRH suppression (Dex/CRH) test yielded a greatly improved sensitivity to detect depression as evaluated by Heuser et al (1994). In accordance with the protocol, 100 µg of human CRH stimulation is

given after 1,5 mg dexamethasone pretreatment to investigate the dynamic status of the HPAA (96). Besides clinical research on HPAA functioning in various diseases and conditions, these tests are established within clinical endocrinology in the diagnosis of Cushing's syndrome, and in clinical psychiatry to assess depression and other psychiatric disorders (11, 15, 56, 89, 94, 96) although it is argued that the low sensitivity of the DST limits its use as laboratory routine test (87). To assess the HPAA reactivity in study I-III, we performed the Dex/CRH test as this method is thought to have a high sensitivity for detecting depression (96).

1.1.8 Symptomatology assessment of Exhaustion Disorder

Exhaustion or fatigue, and increased mental fatigability after mental efforts are core features in ED and various other conditions like in the aftermath of chronic stress (5), and in Burnout (97), as well as in unexplained medical conditions, depression and anxiety disorders, after brain injury, and in endocrine (HPAA-) dysfunction (5, 24-26, 31, 32). Yet, the causes of fatigue are protean and there is no consensus concerning a definition, or factors contributing to this symptom or underlying mechanism (24, 31, 97), nor is it conceptualised or defined in a way that separates it from normal experiences such as tiredness or sleepiness (98). A large number of scales are designed to assess fatigue in several medical conditions and unexplained medical conditions and within the field of organisational psychology research, although they may tap different underlying dimensions (31, 99, 100) or signs of fatigue in relation to environmental factors such as Mashlach's Burnout Inventory (MBI) (101), Oldenburg Burnout Inventory (OLBI) (102) or Copenhagen Burnout Inventory (CBI) (103) which is proposed to discriminate between work-related burnout, client-related burnout, and personal burnout (97). In Sweden, there is an ongoing discussion of whether conditions like burnout, ED and other prolonged fatigue states should be included among affective disorders, and best diagnosed as cases of depression or anxiety, rather than classified as diseases in their own right (99, 100, 104). Interestingly, self rated symptoms of depression and CFS suggest that these conditions are related to different constructs (99, 100), and it has been demonstrated that chronic stress may be more closely associated with fatigue, but less so with sadness and anhedonia in individuals with depressive symptoms (105). It is argued that the assessment of fatigue depends on the phenomenology and etiology of the symptoms in different disorders, and that the clinician and researcher also should consider the populations in which the scale has been used previously to assess its validity in their own patient group (31, 106). To our knowledge, one scale related to ED has been developed recently by Glise and coworkers (2009), called "Stress-related Exhaustion Disorder" (s-ED), to predict risk for future sick leave in currently working employees (107). The diagnostic system and the social insurance system both depend on validated instruments for discriminating different psychiatric conditions, but the need for such applicable tools in research is also identified (36). The aim was to construct a short scale as this study was missing a self rating instrument for the assessment of clinically relevant symptoms of ED, using

psychiatric evaluation as standard. A second aim was to evaluate the relation between self rated symptoms of ED and depression, and between symptoms of ED and anxiety.

1.1.9 Summary of the introduction

The dramatic increase in stress related psychiatric LTSL a decade ago, was assumed to be related to chronic work stress – sometimes for several years - with adverse health outcomes reflected by a clinically significant state of exhaustion with symptoms such as impaired cognition, sleep disturbances, and reduced stress tolerance. Some of these symptoms resemble problems associated with the burnout syndrome, commonly used in occupational psychology, and it was recommended that the medical diagnosis “Exhaustion disorder” should be used to classify these patients (2, 36).

Theories proposing possible mechanisms to explain the link between adverse effects of stress and health, share the assumption of a physiological pathway (60) in which stress hormones are released to direct various (“health promoting”) behavioral and physiological adaptive responses. In the long run, these hormones may reach pathological levels (5) and may thus increase our vulnerability to somatic and mental health problems (13). The HPAA is a key system assumed to be such a link between life events and development of disease through excessive or chronic secretion of cortisol. Chronic exposure to glucocorticoids may mediate the deleterious effect on neurons and reduced hippocampus volume has been reported in conditions associated with stress exposure and/or increased HPAA, i.e. major depression, post-traumatic stress disorder and Cushing’s.

Thus, in study I-III, it was hypothesized that exposure to chronic work related stress, would have lead to prolonged, elevated levels of cortisol and a decreased hippocampus structure with concomitant decline in cognitive functioning. The decision to enroll publicly employed women only was based on the fact that this group was overrepresented among stress related psychiatric LTSL individuals. The limited number of participants would allow us to find controls, matched for potentially influencing variables, such as hormonal status, height and weight etc, providing homogenous samples. A majority of the patients fulfilled ED criteria.

There are overlapping symptoms between ED, depression and anxiety, and the fact that co-morbidity is likely to occur, at least during some stage of the illness may contribute to considerable difficulties in the diagnostic process. A sensitive tool that is able to discriminate patients with exhaustion disorder from patients with other closely related

diagnoses may thus be valuable not only in clinical settings but in future research on efficient treatment regimes and for deepened understanding about the biological underpinnings involved in exhaustion disorder.

1.2 GENERAL AIM

The general aim of this thesis was to obtain insights into the biological process associated with work stress related depression and exhaustion disorder in women, and to construct and evaluate a self-rating scale for assessment of symptoms of exhaustion disorder.

The specific aims in each study were as follows:

Study I investigated if women diagnosed with depression and exhaustion disorder, or adjustment disorder with depressed mood, would have altered HPAA-reactivity, and if the subjectively reported cognitive impairment could be detected by cognitive tests, and if so, whether the cognitive impairment would be related to hippocampal volume decrease.

In study II, re-test of HPAA reactivity and cognitive functioning was performed 12 months after baseline testing. Structural imaging was not repeated because no difference between groups had been found on the initial assessment.

In study III, the HPAA reactivity was reevaluated 7 years after baseline test, to elucidate if the difference between groups had changed. Cognitive functioning was not repeated as the difference between groups was abolished in the previous follow-up. A second aim was to analyze the correlation between HPAA reactivity and diurnal cortisol secretion in patients.

In study IV a self rating scale, for self assessment of ED symptoms was constructed and validated against psychiatric screening performed by experienced physicians. A second aim was to examine the relationships between self rated symptoms of ED and depression, and between self rated ED and anxiety.

1.3 METHODS

1.3.1 Overall procedures, participants and psychiatric screening

The description below gives a brief overview of the procedures. Details are given in each article.

1.3.1.1 Study I-II

29 female ED-patients and 28 healthy individuals were included for baseline tests and a 1-year follow-up. At inclusion, all were 40-55 years of age, Human Service Sector (HSS)-employed in Stockholm and working ≥ 30 hours per week for a minimum of three years within this profession before becoming ill or before being included as a control in the study.

Patients were selected from a database over public service employees who had been on sick leave for a minimum of 3 month (LTSL). Those who consented to participate in the study underwent a structured psychiatric evaluation using the computerized structured interview for axis I and II of the multi-axis in the Diagnostic and Statistical Manual of Mental Disorder (DSM)-IV system (108, 109). Twenty-six patients fulfilled criteria for work-stress induced depression, while 25 of these were additionally diagnosed with ED. Three women fulfilled criteria for maladaptive stress syndrome, with depressed mood. No one fulfilled criteria for any personality disorder.

The control group consisted of 28 fully working women who had previously been informed about the study through advertising at workplaces (i.e. at schools, hospitals, day-care, primary care facilities etc) and invited to contact the test-leader for further information and screening during an initial telephone interview and corresponding visit. Women who denied any past or present psychiatric or medical diagnoses or psychiatric treatment and scored within ± 2 standard deviations from their population norm on all subscales, as well as the Global Severity Index of the Symptom Check List (SCL) – 90 (110), were finally invited. Controls were selected to provide optimal matching for verbal intelligence, handedness, age, hormonal status, education, height, weight, family situation (including number of children living in the household), and nicotine use. Age and hormonal status were virtually identically distributed in the two groups.

The recruitment process and baseline testing was performed from January 2003 to January 2004. Participants were admitted on day 1 to the Karolinska Hospital to perform cognitive testing and MRI scanning of the hippocampus. On day 2 the combined Dex/CRH test were performed at Hospital Clinical Research Centre (CRC) for measurement of the HPAA reactivity.

Following the test procedure at baseline, all but three patients received a cognitive group therapy addressing work-related issues in groups of 6-8 participants. Weekly sessions were held for 10 weeks and every session was followed by home-work assignment.

In the 12-months follow-up patients were re evaluated according to DSM IV. All 29 patients and 28 controls participated. Twenty one patients were fully remitted, while 4 were still in partial remission without ED, and 4 were in remission with ED. Another 2 fulfilled criteria for ED.

Re-test of HPAA reactivity and cognitive functioning was performed from January 2004 to January 2005. One woman from the control group was excluded as the admission of CRH triggered a migraine-like attack and the blood-sampling was disrupted due to the severe head ache. MR imaging was not performed as no changes in hippocampus, or in other cortical areas were found at baseline.

1.3.1.2 Study III

Fifteen patients and eighteen controls from the initial study accepted invitation to the 7-years follow-up and re-test of HPAA reactivity. The current study did not include re-test of cognitive functioning as the difference between groups was no longer significant in the 12-months follow-up, whereas the difference in HPAA activity had remained virtually identical between groups.

Study information was given by a member of the research group during the initial telephone conversation, and a second time by letter, and a third time during an initial visiting prior to the test procedure. All participants gave their written consent.

Participants underwent psychiatric evaluation according to DSM IV M.I.N.I. 5.0.0b (111). 8 women in the former patient group were judged to be healthy, i.e. neither

criteria for depression nor exhaustion disorder (ED) were fulfilled. Four women suffered from ED and one fulfilled criteria for depression and ED. Women from the former control group were judged to be healthy. Participants were admitted to Danderyd Hospital, Hjärtforskningslaboratoriet, to perform the combined DEX/CRH test one week after the visit to the physician.

1.3.1.3 Study IV

In this study a self rating scale was developed for the assessment of ED-symptoms. Most items were selected from the Comprehensive Psychopathological Rating Scale (CPRS) (112) i.e. No. 4, 5, 15, 16, 17 and 19, assumed to reflect criteria C- 1, 3, 4 and 5 (see table 1, section 1.4 “Mental and behavioral disorders”). Another four items were formulated to correspond to criteria A, B, C- 2 and 6 on the basis of symptoms often reported by ED-patients. The initial version thus comprised 10 items although item 8 (emotional engagement) was excluded during the pilot test as it reflects one of the two main DSM criteria of depression but is not particularly typical of ED.

The evaluative work was performed using the nine items version, presented here. The items reflect the diagnostic criteria for ED (table 1). Each item has seven response alternatives ranging from 0-6 points. Low scores indicate no or mild symptoms, while the highest scores are indicating severe symptoms. Psychometric properties were evaluated using assessments made during 2005-2010, by 200 patients suffering from ED and 117 healthy individuals. Participants were in the age of 25-64 years and both genders were represented (although a majority was women). Patients were recruited from a stress rehabilitation clinic (n=166) and an intervention study at Karolinska institute (n=34) while healthy respondents were randomly selected in the Stockholm county by Statistics Sweden (SCB). All participants performed HAD-assessments and underwent diagnostic screening according to DSM IV by an experienced physician. The diagnostic classification was used as standard in the evaluation of the psychometric properties of the scale.

1.3.2 Ethical considerations

Participants were informed about their right to deny participation at any given time, at three separated occasions: i/ verbally, during an initial telephone conversation, ii/ in written form, and iii/ verbally, prior to the test procedure. Patients in study IV were informed orally and in written form by the clinical staff.

Long term investigations including psychiatric interviews and administration of chemical substances may clearly be experienced as impertinent inquiries and considered a violation of integrity. Insights about the disease and its biological underpinnings are nonetheless important to be able to gain deepened knowledge about causes and triggering mechanisms. Deepened knowledge may ultimately lead to preventive proficiency and to development of efficient treatment.

The qualities of assessments aimed to measure symptom severity are dependent on evaluated instruments and scales. Validated tools are thus needed to achieve an ethically acceptable and reliable diagnostic- and social insurance system. The benefits for those who are currently ill and for those who may eventually become sick in the future, may thus override the negative inconvenience for the participants in these studies.

1.3.3 Measurements, instruments, questionnaires and analyses

Psychiatric screening and questionnaires in each study are listed in table 2.

1.3.3.1 Clinical evaluations and psychiatric screening

In study I and II, patients underwent a structured psychiatric evaluation by a trained physician using SICD I and II (108, 109). In study III, all participants were evaluated according to DSM IV using M.I.N.I., version 5.0.0b (111). In study IV, patients and controls were evaluated according to DSM IV by an experienced physician and psychologist or by a psychiatrist.

1.3.3.2 Neuroendocrine, and cognitive tests, and brain morphology

HPAA-reactivity was measured using the combined dexamethasone suppression / and CRH- challenge (Dex/CRH)- test, in accordance with the protocol designed and described by Heuser and coworkers (96). Each participant was instructed to take one tablet of 1,5 mg dexamethasone at 23.00 in their home and then go to sleep as usual. The following day, participants arrived at approximately 13:00 and an intravenous catheter was inserted at 14:00. They were asked whether they had taken the dexamethasone tablet as instructed (which all had done). Participants then rested in a

supine position throughout the test. Blood was drawn at 15:00, prior to the CRH challenge, for analyses of basal ACTH and cortisol, immediately followed by the CRH-injection. Blood was then drawn at 15:30, 15:45, 16:00 and 16:15 for analyses of ACTH and cortisol. At baseline, blood was collected at two additional time-points (17:00 and 17:15) to check for a peak delay.

At baseline, evaluation of handedness was performed with the Edinburgh handedness inventory. Verbal intelligence was investigated using the Synonym test from a Swedish standard intelligence battery. This test is highly correlated with general intelligence as measure by other scales (113).

Cognitive functioning was evaluated using a computerized cognitive test battery during 1 hr starting in the afternoon at 2:00 or 3:30 PM. The battery comprised assessment divided in three blocks; attention - using two tests: 1/ simple reaction task and 2/ complex reaction task; working memory using backward digit-span test; declarative memory - using three tests: 1/ test of associative memory for complex visual cues, and 2/ delayed word recognition, and 3/ picture recognition. In the 12-months follow-up, attention, working memory and declarative memory were re tested using the same computerized device although with different digits, pictures and words to exclude a potential learning effect.

Magnetic Resonance Imaging (MRI) of the hippocampus was carried out using the same 1.5 Tesla Sigma 5.X scanner (General Electric, Milwaukee, Wisconsin), the standard quadrature head coil and the individuals in head first supine position. Voxel based morphometry (VBM) was used for voxelwise comparison of the local concentration of grey matter between two groups of subjects (114). The optimized VBM protocol of Good and co workers (115) was used here.

1.3.3.3 Questionnaires

Alcohol Use Disorder Test (AUDIT) is a self report questionnaire, for detection of hazardous alcohol use. It has 10 questions, scored 0-4 points reflecting consumption, dependence and alcohol related problems. A cutoff score of 6 was used to define hazardous alcohol consumption (116) and an exclusion criterion (69) in study I. Drug Use Disorder Test (DUDIT) is an 11 item questionnaire for self assessment of current

drug-related problems. The DUDIT has good potential for use as a parallel instrument to the AUDIT in screening for drug-related problems (117). No one reported any use of drugs other than alcohol (69).

Symptom Checklist (SCL) – 90 is a self rating questionnaire with 90 items, each related to any of nine subscales reflecting recently experienced physical and psychiatric symptoms. SCL-90 reflects current pathology for which Swedish, normative population data are available (110). The scale was used to check for deviant psychiatric assessments amongst healthy women during the recruitment process in study I.

The Montgomery-Åsberg Depression Rating Scale (MADRS-S) was used in study I – IV. MADRS has 9 items with scale steps ranging from 0-6 (118). Depressed patients rarely score below 15 points (119).

Hospital Anxiety Depression (HAD) includes 14 items; 7 items reflect symptoms of depression (HAD-D) and 7 items reflect symptoms of anxiety (HAD-A) (120). These subscales were applied in the evaluative process in study IV. For both subscales, a score of 8-10 is defined as doubtful caseness, while 11 or more is defined as definite caseness (120). A review of 71 articles, including somatic, psychiatric and primary care patients in the general population, found that both HAD-subscale performed well in assessing symptom severity (121).

The Swedish Health-Related Quality of Life Survey (SwedQual) is a self rating scale with 70 items related to different aspects of physical and mental health and functioning (122). Subscales for pain, sleep and cognitive functioning were used to investigate the relationship with HPAA reactivity.

Descriptive characteristics were gathered at inclusion in each study. In study I-III, data about hormonal phase was collected during conversation while length- and weight were measured, by the laboratory staff prior to test of the HPAA reactivity. The use of antidepressant medication was verbally reported by the patients during the initial visit to the physician. Other descriptive data, i.e. educational level, nicotine use, sick leave data, family situation or employment status are based on written self reports. In study IV, educational level and sick leave data were based on verbal reports by the patients during a visit to the physician.

Table 2. Overview of screening and self rating instruments used in each study

Paper	I	II	III	IV
SCID I	X (patients)	X (patients)		
SCID II	X (Patients)	X (Patients)		
M.I.N.I 5.0.0.			X	
AUDIT	X			
DUDIT	X			
MADRS	X	X	X	X
Handedness	X			
HAD				X
SCL-90	X (Controls)			
Swed-Qual	X	X	X	
Descriptive data	X	X	X	X

1.3.3.4 Biochemical analyses

Biochemical analyses were performed by the Clinical chemical laboratory, at Karolinska universitets sjukhuset, Solna.

In Study I and II Total serum cortisol was determined by a commercial fluoroimmunoassay (AutoDELFIA cortisol-kit; Wallac Oy, Turku, Finland). The lower detection limit was 5 nmol/L, and the intra and interassay coefficients of variation were below 8.5%. Plasma ACTH was measured using a chemiluminescence immunometric assay (Nichols, San Diego, California). The lower detection limit was 1 ng/L. Intra- and interassay coefficient of variation was below 8.5%, respectively, for both kits.

In study III Total serum cortisol was determined by an Electro Chemical Luminescens technique using Modular E solution (Roche, Mannheim, Germany). The lower detection limit was 0,5 nmol/L, and the intra- and interassay coefficients of variation were below 4,23%. Plasma ACTH was detected by an Electro Chemical Luminescens Reaction using Immulite 2000 Immunoassay System (Siemens Diagnostics, Llanberis, Gwynedd, United Kingdom). The lower detection limit was 0,1 pmol/L. Intra- and interassay coefficients of variation were below 5,55% and 1,95% respectively.

Saliva cortisol was measured with Spectria Cortisol RIA method (Inlaga Orion Diagnostica). The lower detection limit was 0,8nmol/L; intra- and interassay coefficients of variation for 2,656 nmol/L were 14,6 % and 19,7 % respectively.

1.3.3.5 Data analyses

Statistical analyses were carried out using Statistica 6.0 (Statsoft, Tulsa, Oklahoma) (study I), SPSS 15.0 for windows (study II) and PASW Statistics 18.0 (study III-IV).

Study I-III: Descriptive data from patients and controls were compared using two-tailed T-test (continuous data) or Fisher's exact test (frequency variables). Analyses of variance (ANOVA) were performed to test the differences in HPAA-reactivity and Cortisol/ACTH ratio, with subject category as a between-subjects factor, repeated measures over time as a within-subjects factor, and the interaction of these two to assess differential response between groups over time. To evaluate if being in first episode versus recurrent depression was of importance for the attenuation of the Dex/CRH response, those two groups were examined separately in study I. Selective serotonin reuptake inhibitor (SSRI) use, nicotine use and weight were considered potentially confounding variables. Subgroup analyses were thus performed to control for their influence on the endocrine outcome in study I-III (with hormonal phase as fixed factors and weight as covariate). The same analyses were conducted with GAF- and MADRS-ratings as covariate and fixed factor respectively in study I.

Area under the curve (AUC) for serum Cortisol were calculated and analyzed using two-way ANOVA, with test session (baseline or 1-year follow-up) as within factor and group as between factor. Correlations of AUC responses on the respective test round with each other, and correlations of AUC responses on follow-up with MADRS scores were evaluated using Pearson's Product-Moment correlation.

Cognitive tests did not violate criteria of homogenous variances, and were therefore analyzed using oneway ANOVA (study I-II). Holm-Bonferroni procedure was used to compensate for multiplicity of testing (123).

In study III, analyses were also carried out to explore if an ED-diagnose in the 7-years follow-up, would have an influence on the cortisol reactivity. Repeated measure over

time was used as within-subjects factor, diagnose category (ED-patient, noneED-patient and control) as between-subjects factor, and the interaction of these factors to evaluate the differential response between groups. Post hoc analyses were performed using Simple effects test for significant interactions, with pair wise comparisons of mean values at each time point. Bonferroni-correction was used to adjust for multiple testing.

Repeated measure analysis was performed to test if the cortisol response (AUC) of dropouts from study III was significantly different at baseline and in the 1-year follow-up compared to those who participated. Test session (baseline and 1-year follow-up) was used as within-subjects factor and category (participants and dropouts) as between-subjects factor.

The correlation between cortisol in serum and saliva were analyzed using Spearman non-parametric rank correlation analyses with AUC_{CAR} as calculated with respect to ground (AUC_G) and increase (AUC_I), earlier described by Pruessner and co-workers (124). Daily variations in CAR and diurnal cortisol were evaluated using repeated measure with time as within-subjects factor and day as between-subjects factor. Differences between ED- and nonED-patients were evaluated using repeated measure and CAR and diurnal slope as within-subjects factor and diagnostic category as between-subjects factor.

Study IV: Descriptive data in study IV were compared using independent sample T-test for continuous variables, and chi-square (or the Fisher exact test when the expected count was less than 5) for proportions. KEDS and HAD self-ratings were compared between groups using non-parametric independent-sample median test. The same analyses were performed to evaluate gender differences in these self assessments. Skewness and kurtosis were calculated at item-level and for summated scores. Internal consistency was evaluated by the Cronbach's alpha coefficient. Exploratory factor analyses (EFAs) using the principal component method with oblimin rotation and eigenvalues >1.0 as a criterion, were used to assess the factor structure in ratings made by patients, and potentially discriminate between the KEDS and HAD subscales. The appropriateness of EFA was supported by the Kaiser-

Meyer-Olkin measure of sampling adequacy and the Bartlett's test of sphericity.

Exploratory factor analyses were used to assess the factor structure in ratings made by patients, and potentially discriminate between the KEDS and HAD subscales.

Sensitivity and specificity of summated scores were evaluated using Area under Receiver Operating Characteristics (ROC) curve with ED-caseness as the state value.

Correlations between the KEDS and the HAD scales were tested with the non-parametric Spearman's rho.

1.4 MAJOR FINDINGS

Study I-III demonstrated that women who suffered from MDD and ED at baseline had a blunted stress response to CRH after dexamethasone pretreatment in each test session over a period of 7 years. The impaired attention and working memory functions found at baseline were no longer significantly different compared to that of healthy controls in the 1-year follow-up suggesting that these skills were improved although the neuroendocrine deficiency remained. Imaging of the hippocampus structure showed that depression and ED was not associated with atrophy in this region, or in other cortical areas.

In study IV a self-rating scale, the KEDS, was developed for the assessment of ED symptoms. Evaluation of the psychometric properties of this 9 item questionnaire, suggested that the scale reliably and validly indicates a clinically relevant state of ED and that this disorder is related to a different underlying construct than that of depression or anxiety.

1.4.1 Summary of findings in study I-III

At baseline, women in the control group were closely matched to women in the clinical sample for variables which could potentially influence the outcome. These are given in table 3. Educational level, family situation, verbal intelligence and handedness were also matched (for details, please see paper I).

Table 3. Descriptive characteristics

	Baseline			1-year follow-up			7-years follow-up		
	Patients	Controls	<i>p</i>	Patients	Controls	<i>p</i>	Patients	Controls	<i>p</i>
Participants, n	29	28	-	29	27	-	14	16	-
Age, yrs \pm s.d.	47,8 \pm 4,9	47,6 \pm 4,2	.92	48,9 \pm 5,0	48,5 \pm 4,2	.78	54,6 \pm 4,6	54,1 \pm 4,2	.75
Weight, kg \pm s.d.	71,0 \pm 12,2	66,8 \pm 9,9	.16	71,2 \pm 12,2	66,0 \pm 9,4	.09	77,4 \pm 9,4	68,5 \pm 11,3	.03
Nicotine use, n (%)	10 (34,5)	7 (24,1)	.56	10 (0)	7 (24,1)	.77	3 (21,4)	1 (6,3)	.25
Hormonal phase:									
Meno- or Post-menopausal, n (%)	12 (41,4)	13 (46,4)	1.00	14 (48,2)	16 (59,3)	.58	11 (78,6)	14 (87,5)	.43
Oestrogen medication, n (%)	6 (20,7)	5 (17,9)	73.0	3 (10,3)	2 (7,4)	1.00	0	0	1.00

Psychiatric symptoms were evaluated in patients prior to the test procedure at each test occasion. Women, who fulfilled ED criteria in the 1-year follow-up and in the 7-years follow-up, were not the same (Table 4). Self rated depression did not have an influence on the HPAA reactivity nor did global functioning (GAF).

Table 4. Clinical findings in patients

Psychiatric diagnose	Baseline	1 year follow-up	7 years follow-up
Number of patients included	29	29	14
MADRS-S scores, median (range)	16 (4-31)	9 (1-21)	3,5 (0-10,5)
MDD, no (%)	2 (6,8)	4 (13,7)	-
MDD and ED, no (%)	24 (82,7)	4 (13,7)	1
Maladaptive stress reaction, no (%)	1 (3,4)	-	-
Maladaptive stress reaction with ED, no (%)	2 (6,8)	-	-
ED, no (%)	-	2 (6,8)	4
Current use of antidepressant medication, no (%)	12 (41,3)	10 (34,5)	3 (21,4%)

1.4.1.1 HPAA reactivity

Repeated measure demonstrated that the cortisol response to CRH after dexamethasone pretreatment was significantly lower and flatter in patients compared to healthy controls at all three test sessions (Figure 1). These findings were not explained by antidepressant medication, nicotine use or by weight. Furthermore, the influence of depression severity was analyzed at baseline using the self rated median MADRS to classify patients as either low- or high scoring depressives. Both groups had a lower cortisol response than controls but they did not differ from each other.

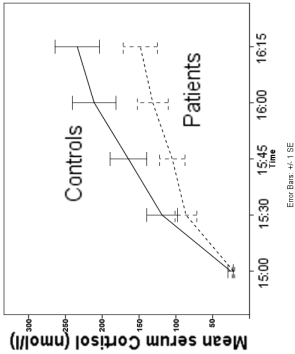


Figure 1a. Baseline.

Cortisol response to CRH after dexamethasone pretreatment in 29 patients and 28 controls.

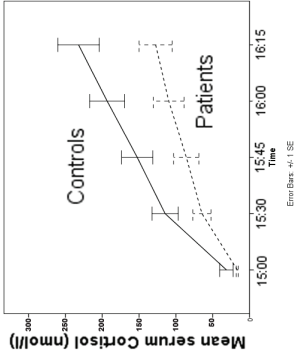


Figure 1b. 1-year follow-up.

Cortisol response to CRH after dexamethasone pretreatment in 29 patients and 27 controls.

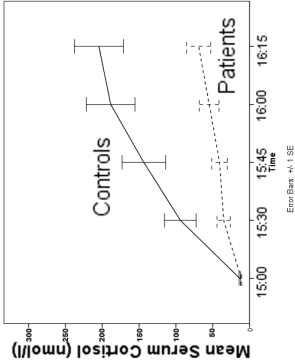


Figure 1c. 7-years follow-up.

Cortisol response to CRH after dexamethasone pretreatment in 14 patients and 16 controls.

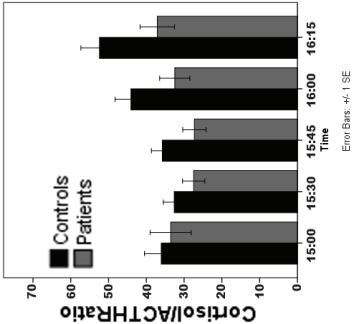


Figure 2a. Baseline.

S-cortisol/P ACTH response to CRH after dexamethasone pretreatment in 29 patients and 28 controls.

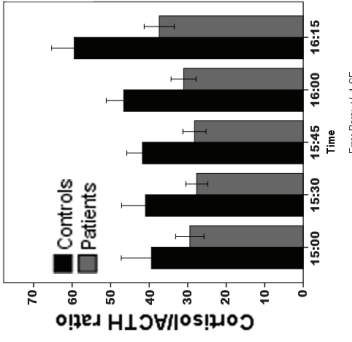


Figure 2b. 1-year follow-up.

S-cortisol/P ACTH response to CRH after dexamethasone pretreatment in 29 patients and 27 controls.

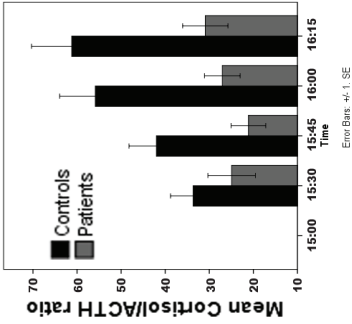


Figure 2c. 7-years follow-up.

S-cortisol/P ACTH response to CRH after dexamethasone pretreatment in 14 patients and 16 controls.

Analyses of Cortisol/ACTH ratio did not demonstrate that patients compensate the pituitary deficiency by increased adrenal activity. At baseline, an almost different response over time with a main group difference was found. One year later, the response over time was still significantly indifferent between groups while there was a significant overall difference [$F(1;54) = 8.3, p .006$]. At 7-years follow-up, patients had a significant differential response over time as shown by the interaction term [$F(3;84) = 5.7, p .001$] and a significant overall difference [$F(1;28) = 7.4, p .011$] compared to controls. These findings support that patients had a blunted HPAA response of central origin at all test sessions. The Cortisol/ACTH-ratio at each time session is illustrated in figure 2.

Subgroup analyses at baseline demonstrated that the Dex/CRH responses in first episode- and recurrent depressives was similar although the attenuation in patients with recurrent depression did not reach significance, presumably due to the small sample size ($n=6$).

Subgroup analyses using current ED diagnosis at 7-years follow-up as between-subjects factor revealed that the increase in ACTH and cortisol response to the CRH challenge was non-significant in ED-patients and nonED-patients. Pair wise comparison demonstrated a significant difference in ACTH-reactivity between healthy controls and ED-patients at 15:30 and 15:45 while the ACTH secretion in nonED-patients appeared with non-significant deviation in between the two other groups. Similarly, cortisol secretion was significantly higher in healthy controls compared to that of nonED-patients from 15:45 and onwards, and compared to ED-patients at 16:00 and 16:15 (figure 3).

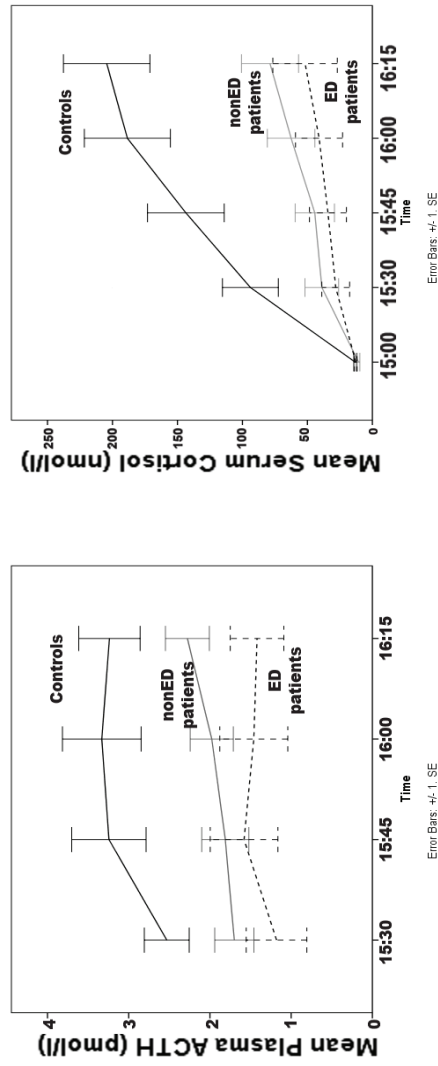


Figure 3a. 7- years follow-up.

P-ACTH after CRH stimulation in 16 healthy controls (black, solid line) and 9 non-ED patient (grey line) and 5 ED-patients (dotted line). Baseline not shown due to undetectable ACTH-values in a majority of the patients as noted above.

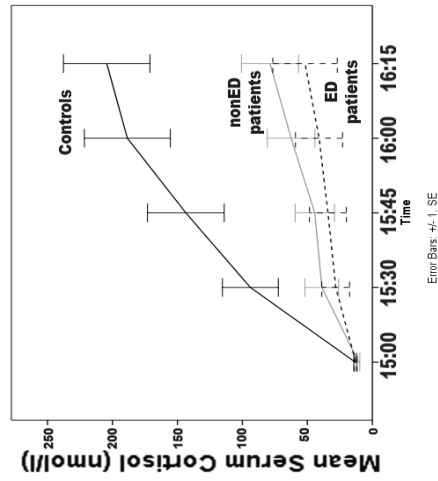


Figure 3b. 7- years follow-up.

S-Cortisol after CRH stimulation in 16 healthy controls (black solid line) and 9 non-ED patient (grey line) and 5 ED-patients (dotted line).

Figure 3

1.4.1.2 Cognitive functioning and hippocampus morphology

Cognitive testing at baseline revealed that attention and working memory were slightly impaired in patients, while retest one year later demonstrated that the difference between groups were abolished. MR-imaging at baseline did not reveal any morphological differences in hippocampus or in any other cortical areas in patients compared to controls.

1.4.1.3 Self-rated sleep, pain and cognitive functioning

Self ratings demonstrated that patients experienced significantly more pain (or lower “pain relief”) and significantly worse sleep quality as well as cognitive functioning at each test session. Sub group analyses further demonstrated that pain and sleep in these two groups, differed significantly from the general population’s assessments (Table 5). Non-parametric correlation analyses failed to reveal any significant correlation between any of these subscales and stress-reactivity, using AUC ACTH and AUC Cortisol.

Table 5. Self rated pain, sleep and cognitive functioning in patients, healthy controls and women in the general population.

	Baseline			1 year follow-up			7 year follow-up		
	Patients	Controls	<i>p</i>	Patients	Controls	<i>p</i>	Patients	Controls	<i>p</i>
SWQ Subscale	n=28	n=28		29	27		14	16	
Pain relief, mean \pm s.d	67.8 \pm 24.9	88.5 \pm 13.1	**	66.1 \pm 24.6	90.7 \pm 12.2	**	69.8 \pm 31.0	91.8 \pm 10.7	*
Sleep quality, mean \pm s.d	41.1 \pm 11.5	65.5 \pm 11.0	**	48.0 \pm 14.5	64.5 \pm 12.7	**	56.2 \pm 24.4	77.3 \pm 21.8	*
Cogn. func., mean \pm s.d	30.4 \pm 20.1	90.8 \pm 10.0	**	47.0 \pm 27.5	89.8 \pm 11.6	**	60.9 \pm 26.4	93.0 \pm 7.0	**
									Ref
									81.0
									71.4
									-

* Significant at the level of < .05

** Significant at the level of < .01

Ref: Mean values in the General female population, 25-54 years of age (Brorson et al 1993)

1.4.1.4 Diurnal cortisol secretion in patients

In the 7-years follow-up, saliva cortisol was collected for analyses of diurnal secretion and its relation with the pharmacologically stimulated cortisol response in serum.

Sampling was performed by 14 patients during 6 days. Sampling from one patient was excluded due to failure in the collection of the required amount. A large number of the samples collected at bedtime contained cortisol levels below the detection limit, thus bedtime sampling was excluded from the analyses.

Repeated measure showed that CAR increased over time with main time effect [$F(3,198) = 27.5, p < .001$] while time x day interaction and main day effect were non-significant. When diagnosis was used as between-subjects factor, time x diagnosis interaction appeared different in ED versus nonED patients [$F(3,210) = 11.1, p < .001$] with non-significant main group effect (figure 4a). Overall, cortisol secretion decreased during the rest of the day [main time effect [$F(2,132) = 303.9, p < .001$] with a significant time x day interaction [$F(10,132) = 3.2, p = .001$] indicating an irregular pattern of the daily curve. The cortisol slope in ED patients and nonED patients did not differ (figure 4b).

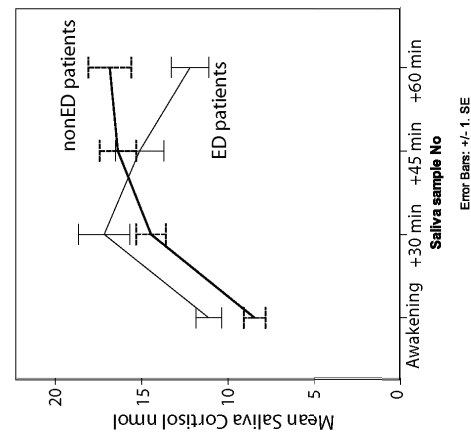


Figure 4a. 7-years follow-up.

CAR in 5 women suffering from ED and 7 women who did not fulfil ED criteria.

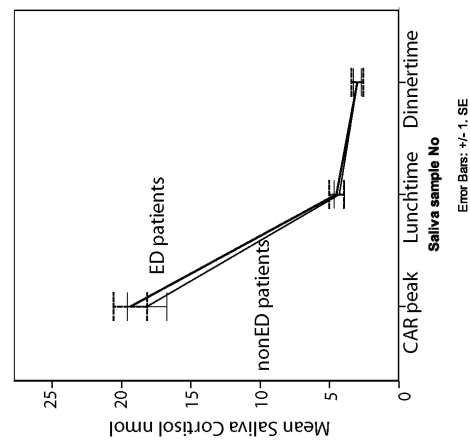


Figure 4b. 7-years follow-up.

Diurnal saliva cortisol in 5 women suffering from ED and 7 women who did not fulfil ED criteria (bedtime sampling not shown due to the large number of undetectable values)

Non parametric analyses demonstrated a statistically significant negative correlation between cortisol-reactivity and CAR_{AUCI} on day 2 ($r; -.62, p = .018$) but not on any of the other 5 days, nor between cortisol-reactivity and CAR_{AUCG} (figures not shown). The biological importance of these findings is however, limited due to the limited sample size.

1.4.2 Study IV: Self rating scale for Exhaustion Disorder

In this study the Karolinska Exhaustion disorder scale, KEDS was constructed and validated against psychiatric screening performed by trained physicians and self rated symptoms of depression and anxiety using HAD, validated elsewhere (121) and MADRS developed by Montgomery and Åsberg (118)

1.4.2.1 Construction of the KEDS scale

The scale consist of 9 items and each item offers 7 response alternatives ranging from 0-6 points, with a maximum summated score of 54. Lower scores reflect no or mild symptoms. The scale is presented in appendix 4.1 (for an English version) and 4.2 (for a Swedish version).

1.4.2.2 Evaluation of the KEDS scale

The evaluation of KEDS psychometric properties was based on assessments made by 200 sick-listed patients, who fulfilled ED-criteria and 117 healthy individuals. Each participant underwent psychiatric screening by a trained physician and assessed symptoms of depression and anxiety using the widely established and validated HAD scale and the MADRS. Exploratory Factor Analyses (EFA) was performed, using assessments made by patients and controls to evaluate the structure of HAD ratings in these samples. Two factors were produced, explaining 65.2 % of the total variance. All items showed acceptable communalities ranging from .47 - .82. As expected each item in subscale depression loaded in factor 1 (ranging from .58 - .87) while all items in the subscale anxiety loaded in factor 2 (ranging from .55 - .86). Age and educational levels were equal in both groups and women were overrepresented in patients as well as in controls. Descriptive characteristics of the two samples are presented in table 6.

Table 6. Proportions of doubtful and definite cases of HAD-A and HAD-D, according to cut-off values suggested by Zigmond & Snaith (120).

	Patients (n=200)	Controls (n=117)
Age years – Mean (s.d.)	45.4 (8.6)	45.2 (7.0)
Range years	25 - 64	25 - 55
Women, n (%)	176 (88.0)	79 (67.5)
Educational level:		
Compulsory school, n (%)	9 (4.5)	6 (5.1)
Upper secondary school, n (%)	62 (31.0)	36 (30.8)
University, n (%)	127 (63.5)	75 (64.1)
Data not available, n (%)	2 (1.0)	-
Sick-leave at inclusion:	n=197	n=117
Full-time, n (%)	132 (67.0)	-
Sick-leave 25 – 75%, n (%)	63 (32.0)	-
No sick-leave - %, n (%)	2 (1.0)	117 (100.0)
HAD, subscale Anxiety	(n=194)	(n=117)
Individuals scoring ≥ 8 and ≤ 10 , n (%)	50 (25.8)	5 (4.3)
Individuals scoring ≥ 11 , n (%)	105 (54.1)	2 (1.7)
HAD, subscale Depression	(n=194)	(n=117)
Individuals scoring ≥ 8 and ≤ 10 , n (%)	69 (35.6)	5 (4.3)
Individuals scoring ≥ 11 , n (%)	89 (45.9)	0 (0.0)

Item scores and response ranges in patients indicate that all KEDS items are relevant and that the scale is related to the construct being measured (125). No significant gender related differences were found. Reliability was found sufficient as shown by Cronbach's α of .74 in patients and .81 in controls, and exploratory factor analyses produced two factors which explained 50.5 % of the total variance with acceptable communalities for all items but sleep. Self-ratings are presented as medians and ranges for each item and summated score across groups in table 7.

Table 7. Median and range for each KEDS-item and summated score

KEDS-item		Patients (n = 200)	Controls (n = 117)	<i>p</i> -value
1	Ability to concentrate, median (range)	3 (0-5)	0 (0-4)	< .01
2	Memory, median (range)	4 (0-6)	1 (0-4)	< .01
3	Physical stamina, median (range)	3 (0-6)	0 (0-4)	< .01
4	Mental stamina, median (range)	4 (0-6)	0 (0-4)	< .01
5	Recovery, median (range)	4 (0-6)	1 (0-4)	< .01
6	Sleep, median (range)	3 (0-6)	1 (0-4)	< .01
7	Sensory impressions, median (range)	4 (0-6)	0 (0-6)	< .01
8	Experience of demands, median (range)	4 (0-6)	0 (0-3)	< .01
9	Irritability and anger, median (range)	4 (0-6)	1 (0-3)	< .01
	Summated rating score, median (range)	30 (6-47)	6 (0-29)	< .01

ROC analyses demonstrated that the KEDS has a high discriminant ability as witnessed by the AU_{ROC} (.991, $p < .01$, 95% CI .982; 1.000), with the best balance between sensitivity (95.5) and specificity (96.6) at the level of 19 points. These findings suggest that KEDS construct validity was satisfactory and that the concurrent validity was high.

Finally, analyses using pooled items of KEDS- and each HAD subscale demonstrated that items related to exhaustion emerged in separate factors compared to items related to depression and anxiety. These findings were supported by the fact that the best balance between sensitivity and specificity was accompanied with cutoff scores well below the levels defined as clinically relevant for both subscales, i.e. 5,5 for HAD-D and 6,5 for HAD-A, suggesting that there are different dimension underlying ED, depression and anxiety.

1.5 METHODOLOGICAL CONSIDERATIONS

A major strength of this thesis is that the same patients were reexamined in study I-III. In conformity with other literature (122), the dropouts in study III displayed an almost significantly higher HPAA response to the CRH stimulation, at baseline and in the 12-months follow-up, compared to those who participated. The number of dropouts was similar in patients and controls.

ACTH and cortisol analyses were performed using identical biochemical method and equipment in study I-II but not in study III. An internal evaluation performed by the laboratory showed that the detection was similar or identical in study III although Cortisol was detected at slightly higher levels by the new device compared to that of study I and II.

1.6 GENERAL DISCUSSION

The HPAA findings presented here suggest that ED patients with or without concomitant depression have a sustained altered HPAA-reactivity. However, contrary to the hypothesis, this neuroendocrine dysfunction was defined by a decreased – rather than an increased – CRH response after dexamethasone pretreatment. These findings were accompanied by morphologically intact hippocampus volume and a small decline in attention- and working memory functioning in patients at baseline but not at the 1-year follow-up.

The last article describes the Karolinska Exhaustion Disorder Scale, KEDS, which is a 9 item self rating scale that may be used for the assessment of ED symptoms, as defined by the NBWH (8). The evaluation showed that the scale has satisfactory psychometric properties and a high sensitivity and specificity for ED. It was also demonstrated that symptoms of ED and symptoms of depression, as well as symptoms of ED and symptoms of anxiety, emerged in separate factors, suggesting that KEDS and HAD tap different underlying constructs. The use of KEDS together with validated instruments for the assessment of depression and/or anxiety is recommended in the screening process, in clinical settings and in future research aimed to investigate the biological underpinnings and treatment in ED.

1.6.1 Study I-III: Stress reactivity, cognitive functioning and hippocampal morphology in Exhaustion disorder

The HPAA-reactivity was investigated in dexamethasone pretreated ED women with or without concomitant depression and a group of healthy women, at three separate occasions during 7 years. Although a majority of our patients had a first episode depression, findings demonstrated that patients have a reduced ability to respond to a potent synthetic CRH stimulation, as shown by a lower ACTH- and cortisol secretion and cortisol/ACTH ratio (69, 70, 126). The applied Dex/CRH test is thought to have a high sensitivity for detecting depression and it has been suggested that it might primarily tap a stress-induced recruitment of vasopressin co-expression in CRH neurons in the hypothalamus, which may reflect that vasopressin is increased in depressives (91) which in turn, may be related to depressive symptoms such as intense anxiety (127). Overall, data have indicated that typical depression is characterized by a hyperactive central CRH system (HPAA), while the atypical subtype of depression may instead be characterized by hypoactive central CRH systems and accompanied by lowered pituitary and adrenal activity (ibid). Our findings suggest that ED is associated with a lowered HPA activity earlier described for CFS and atypical depression (10, 91) although, its central origin remains obscure. A deficiency at the second or third level is difficult to assess and the literature refers to findings in animal studies and indirect evidence (11). It is, for instance, suggested that CRH is involved in the regulation of arousal and anxiogenic and fear-related aspects of stress (87) and that dysregulated CRH activity may be related to disturbances of arousal in PTSD. However, PTSD patients have higher levels of CRH in the cerebrospinal fluid (CSF), yet present with hypocortisolism suggesting that central CRH activity may not be adequately reflected by CSF CRH (11, 128). CFS is also associated with hypocortisolism (10) and it has been suggested that the symptoms of exhaustion and fatigue in these patients may reflect a hypothalamic deficiency (11). In parallel to symptoms of exhaustion and fatigability, anxiety is fairly common in ED-patients as assessed by self ratings, and a panic attack is sometimes the presenting symptom of the disorder.

Beside variables such as coping strategies, genetics, gender and early stress experiences that all may be involved in the development of hypocortisolism – a number of factors e.g. reduced biosynthesis or depletion at several levels of the HPA axis, hypothalamic hypersecretion and adaptive down-regulation of pituitary

receptors, increased feedback sensitivity of the HPAA, and morphological changes, may determine the manifestation and persistence of a dysregulated HPAA activity (11). The question of whether the HPAA system respond with hyper- or hyporeactivity to acute stress in chronically stressed or exhausted individuals, who are no longer able to cope with environmental stress, is still open to debate (15). Findings of both decreased and increased HPAA activity have been reported in stress related psychiatric disease (56, 129) and during chronic stress-exposure (11). The few studies that have applied psychological stressors or even more seldom - pharmacological stimulation procedures, potentially favor a subtle cortisol hypo reactivity in participants with higher levels of chronic stress, burnout and exhaustion (15). Our findings are in line with these reports and it has also been suggested that other fatigue related conditions, such as the CFS, share these characteristic of a decreased HPA activity too (5, 11, 86). It remains to be elucidated if the lowered HPAA reactivity in our ED-patients is related to hypocortisolism or not. We did not find a significant correlation between salivary cortisol and HPAA reactivity in patients, but several variables such as adrenal capacity, cortisol binding, and cortisol metabolism influence total and free cortisol levels in blood and – finally - in saliva. The association can thus only be expected to be moderate (5, 11, 15, 56, 86). Recent findings did not support that the diurnal cortisol secretion or feedback sensitivity is altered in ED patients compared to controls (71), but further studies performed by this research group showed that the application of a low dose synacth triggered an almost significantly increased cortisol secretion, and an increased cortisol/ACTH ratio in response to CRH-stimulation (ibid). Despite the different methodological approaches in our studies, it is interesting to note that the potent pharmacological stimulation applied in the Dex/CRH test in our study, demonstrated that the reactivity is lowered in patients, while Sandström and coworkers found a trend towards increased adrenal response to low dose synacth, and a decreased pituitary response to CRH with a slightly higher cortisol/ACTH response in women suffering from ED (ibid). A bimodal dose dependent neuroendocrine response pattern resembling these findings has earlier been associated with atypical depression and CFS. It has further been proposed that such a response may reflect an increased adrenal sensitivity due to long lasting CRH hypostimulation, which has ultimately resulted in sensitized adrenal receptors and hyper responsive pattern to low doses of stimulation while at the same time the adrenals are incapable of fully responding to a more potent stimulus because they have become atrophied (10, 47). The HPAA system is involved in a complex

bidirectional communication with the immune-system (10, 54), and hypo activity of the HPA axis system has been associated with autoimmune processes such as rheumatoid arthritis (3) as well as fibromyalgia, and atypical depression (130). A decreased HPAA in atypical depression may lead to insufficiently restrained immune-functioning that in turn may promote chronic, low grade inflammatory states (10). Pain is frequently reported by ED patients and it was recently suggested that pain and fatigue in fibromyalgia patients may be related to disturbed glucocorticoid receptor functioning as the IL-6 production in circulating monocytes seemed to be less sensitive to the immunosuppressive actions of glucocorticoids (131).

Our MRI findings are in line with recent findings (132) suggesting that neither hippocampus volume nor any other cortical areas are decreased in ED patients, and that hippocampus dependent memory was unaffected (69, 132). Earlier findings have indicated that extreme cortisol secretion may mediate morphological hippocampus reduction and cognitive impairment in Cushing's disease and in depression, although findings are inconsistent (83-85, 133). It has also been found that hippocampal atrophy is related to the cumulative duration of untreated depression (80, 134). For the majority of patients, the current episode was the first ever. Thus the absence of a decreased volume is no surprise. Prefrontal cortex working memory is modulated by cortisol in an inverted U-shaped manner, potentially reflecting the occupancy ratio between mineralocorticoid receptor and glucocorticoid receptors. The small but statistically significant impairment in attention and working memory functioning may instead be related to an inability to mount an adequate HPAA response to support normal test performance (135).

A majority of our patients had recovered from their exhaustion disorder and depression, but the HPAA-deficiency had not resolved after 7 years. Successful treatment with various antidepressants in major depression is associated with a reduction of the hormonal response to the Dex/CRH test, i.e. that the HPAA-hyperactivity is normalized (91, 136). We thus performed subgroup analyses showing that the seemingly lowered response in AD-treated patients was not significant compared to patients who did not receive AD medication. Similarly, the seemingly different HPAA reactivity between former ED patients and patients with a current ED in the 7-years follow-up, was non-significant although both groups displayed different reactivity compared to controls. If

and when, a dysregulated HPAA activity normalizes in this category of patients remains to be investigated. Vulnerability or trait markers are ideally independent of disease state and may be expected to be present before the onset of a disease and during remission (137), as well as after successful treatment (138). However, findings from the Munich-vulnerability demonstrated that high risk probands, who developed an affective disorder, did not differ in their premorbid neuroendocrine profile compared to age- and sex matched healthy controls. The authors in this study conclude that the dysregulated HPAA measured by the Dex/CRH test may rather be regarded as a neurobiological scar that has developed during the course of an affective disorder (138). Altered HPAA, caused by a pituitary tumor is also associated with features of depressive symptoms and it has been revealed that cortisol secretion return to normal levels within two years after removal of the tumor (47), although periods of 3-12 years are reported too (139).

1.6.2 Study IV: self rated symptoms of ED – KEDS

The purpose in this study was to construct a new self rating scale for assessment of symptoms of exhaustion disorder, The Karolinska Exhaustion Disorder Scale KEDS. The scale was easy to use and it was found to have satisfactory internal consistency. The ability to discriminate ED-patients implied a high concurrent validity as defined by a sensitivity and specificity above 95%, at a cut off score of 19. The total range is 0-54 points, and lower scores reflect no or mild ED-symptoms.

A second aim was to investigate the relation between symptoms of ED and depression, and between ED and anxiety. Items related to depression and anxiety emerged in separate factors, compared to exhaustion-related items as demonstrated by factor analyses, suggesting that KEDS is related to a different underlying dimension than that of HAD. These findings do not preclude that KEDS scores may be high also in major depressive disorder. The KEDS has not yet been tested in patients with primary major depression.

There is an ongoing discussion whether prolonged fatigue states such as burnout and exhaustion disorder should be included among affective disorders, and best diagnosed as cases of depression or anxiety, rather than classified as diseases in their own right (140, 141). Based on a population study, a Finnish research group have demonstrated a marked overlap between burnout and depressive disorder as approximately 50 % of participants with severe burnout had a depressive disorder (7).

The authors of these studies suggest that there is an inter related or reciprocal predisposition to these conditions although they appear to be separate concepts (20). Our analyses revealed that among patients, almost 46% could be classified as definite cases of depression and that 54% could be classified as definite cases of anxiety, using the suggested HAD caseness definition (120). In line with studies on another fatigue-related condition, CFS, our factor analyses demonstrated that symptoms of exhaustion are related to a different underlying dimension than that of depression- or anxiety symptoms, presumably supporting that these conditions need to be considered as separate constructs. Interestingly, Keller and co-workers in a population study of individuals with depressive symptoms found that chronic stress was more closely related to fatigue, but less so with sadness and anhedonia (105). It is currently argued that differential psychiatric screening is needed (36). The KEDS, may be a useful screening tool in clinical settings as well as in research, together with validated instruments for depression and anxiety.

1.7 OVERALL CONCLUSION AND FUTURE DIRECTION

HPAA findings from three separate test occasions over a period of 7 years suggest that ED patients, with or without concomitant depression, have a sustained, lowered HPAA-reactivity. Whether this low reactivity is of hypothalamic or pituitary origin remains obscure. Lowered reactivity has been described earlier in the atypical subtype of depression as well as in fatigue related conditions such as chronic fatigue fibromyalgia, and also in PTSD. Future systematic and comparative studies aimed at elucidating similarities and differences between ED and other closely fatigue related conditions are needed. CRH is involved in the regulation of attention and anxiety and it could be assumed that symptoms of exhaustion and fatigability in ED are related to CRH deficiency. However, more than 50 % of ED patients report that they have clinically relevant symptoms of anxiety, using the suggested caseness definition on the HAD scale (120). An interesting research question may be if ED is associated with a premorbid state of arousal or anxiety and if these symptoms reflect a CRH dysregulation.

The lower HPAA reactivity in ED was accompanied by a normal hippocampus volume and a small decline in attention and working memory in patients at baseline but not at the 1 year follow-up. Future studies investigating the feedback mechanism and the diurnal cortisol slope may reveal if ED, like some other fatigue related conditions, is associated with hypocortisolism. Assessment of duration and previous periods of ED may also be important to elucidate whether the experience of prolonged stress may create a kind of neurobiological “scare” which will reduce the reactivity of the HPAA (138). Prospective studies in healthy first degree relatives may elucidate if ED is associated with a pre-existing HPAA dysregulation or not.

A new self rating scale for assessment of ED symptom, KEDS, is presented. The scale is short (9 items scored of 0-6 points) and easy to use. The evaluation showed that the scale has satisfactory psychometric properties with high sensitivity and specificity for ED. Explorative factor analyses demonstrated that self rated KEDS and each HAD subscale emerge in separate factors suggesting that symptoms of ED and symptoms of depression, as well as symptoms of ED and symptoms of anxiety, are related to different underlying constructs. KEDS has not yet been validated against HPAA reactivity in ED patients, but it may be useful for research purposes, in the

evaluation of treatment effects, and also for assessment of ED severity in different contexts. It is also meant to be useful for clinical purposes, as a diagnostic aid in combination with other validated instruments, and in the assessment of degree of incapacity.

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4 APPENDICIES

4.1 KEDS, ENGLISH VERSION

1

Karolinska Exhaustion Disorder Scale

The purpose of this form is to provide an overall picture of your current (physical/emotional) state. We would like you to try to rate how you have been feeling during the past two weeks.

This form contains a series of statements about how one can feel in several different respects. These statements express different degrees of uneasiness, from lack of discomfort to a maximum and pronounced feeling of unease.

Draw a cross in the square in front of the number that you think corresponds best to the way you have been feeling the past two weeks. (See the example below.)

0

<input type="checkbox"/>	1
<input type="checkbox"/>	2
<input checked="" type="checkbox"/>	3

<input type="checkbox"/>	3
--------------------------	---

<input type="checkbox"/>	4
--------------------------	---

<input type="checkbox"/>	5
--------------------------	---

<input type="checkbox"/>	6
--------------------------	---

If you want to change your assessment, please do this by filling the entire square and draw a new cross in the appropriate square. (See example below)

<input type="checkbox"/>	0
--------------------------	---

<input checked="" type="checkbox"/>	1
-------------------------------------	---

<input checked="" type="checkbox"/>	2
-------------------------------------	---

If you wish to explain/clarify something, feel free to do so on the last page, under "Notes".

1 Ability to concentrate

We would like you to assess your ability to keep your thoughts together and concentrate on various activities. Think about how you function in various activities that demand different levels of concentration, e.g. reading a complicated text, reading a newspaper article and watching TV.

- ☐ 0 I do not have any difficulty concentrating, and can read, watch TV and converse normally.
- ☐ 1
- ☐ 2 I occasionally have difficulty keeping my thoughts together on things that would normally hold my attention.
- ☐ 3
- ☐ 4 I have often difficulty concentrating.
- ☐ 5
- ☐ 6 I cannot concentrate on anything at all.

2 Memory

We ask here that you describe your ability to remember things. Think about whether or not you have had difficulty recalling names, dates, or tasks that you intend to do during a regular day.

- ☐ 0 I remember names, dates, and what I am supposed to do.
- ☐ 1
- ☐ 2 Sometimes I forget things that are not so important, but if I pull myself together I can usually remember.
- ☐ 3
- ☐ 4 I often forget appointments or names of people whom I know very well.
- ☐ 5
- ☐ 6 Every day, I forget important things or what I have promised to do.

3 Physical stamina

This is a question concerning your physical stamina. Do you feel, for example, more exhausted than usual after the activities of an ordinary day or some form of physical exertion?

- ☐ 0 I feel the way I usually do and perform my daily physical activities or exercise as usual.
- ☐ 1
- ☐ 2 I feel that physical effort is more exhausting than normal, but still move the way I usually do in this respect.
- ☐ 3
- ☐ 4 I do not have the energy to exert myself physically. It is OK as long as I move at a normal phase, but I cannot increase my pace without becoming shaky and short of breath.
- ☐ 5
- ☐ 6 I feel very weak and cannot even move short distances.

REMEMBER that your assessment refers to the past two weeks.

4 Mental stamina

We would like you to reflect here on your mental stamina and to what extent you are more mentally exhausted than usual in various everyday situations.

- ☐ 0 I have just as much energy as usual. I do not have any particular difficulty performing my daily activities.
- ☐ 1
- ☐ 2 I can manage my everyday activities, but they take more energy and I am exhausted more quickly than usual. I need to take breaks more often than usual.
- ☐ 3
- ☐ 4 I become inordinately tired when I attempt my daily activities and find social situations exhausting.
- ☐ 5
- ☐ 6 I do not have the energy to do anything.

5 Recovery

We ask you to describe here how well and how quickly you recover mentally and physically when you have been exhausted.

- ☐ 0 I do not have to rest during the day.
- ☐ 1
- ☐ 2 I become tired during the day, but all I have to do is to take a little break in order to recover.
- ☐ 3
- ☐ 4 I become tired during the day and need to take long breaks in order to feel fit.
- ☐ 5
- ☐ 6 No matter how much I rest, it feels as if I am unable to recharge my batteries.

6 Sleep

We ask you to describe your sleep. Think about how long you have slept and the quality of your sleep during the past two weeks. Your assessment should reflect your actual sleep, regardless of whether or not you have taken sleeping pills.

- ☐ 0 I sleep well and long enough. I usually feel thoroughly rested when I wake up after a night's sleep.
- ☐ 1
- ☐ 2 Sometimes, I sleep more restlessly than usual, or wake up during the night and have difficulty going back to sleep. Sometimes, I do not feel thoroughly rested when I wake up after a night's sleep.
- ☐ 3
- ☐ 4 I often sleep more restlessly than usual, or wake up during the night and have difficulty going back to sleep. I often have a feeling of not being thoroughly rested after a night's sleep.
- ☐ 5
- ☐ 6 I sleep superficially or restlessly every night. I never feel thoroughly rested after a night's sleep.

REMEMBER that your assessment refers to the past two weeks.

7 Hypersensitivity to sensory impressions

This is a question about the extent to which one or several of your senses have become more sensitive to impressions, such as sound, light, smell or touch.

- ☐ 0 I do not think that my senses are more sensitive than usual.
- ☐ 1
- ☐ 2 Sound or light or other sensory impressions are sometimes unpleasant.
- ☐ 3
- ☐ 4 I often experience that sound, light or other sensory impressions are disturbing or unpleasant.
- ☐ 5
- ☐ 6 Sound, light or other sensory impressions bother me so much that I withdraw in order to give my senses a chance to rest.

8 Experience of demands

Here we ask you to give expression to the way you react to demands in your daily life. These demands can come from your surroundings or be your own demands on yourself.

- ☐ 0 I do what I am supposed to do or want to do without experiencing it as especially demanding or difficult.
- ☐ 1
- ☐ 2 Sometimes I experience daily situations that I used to handle without any particular problem as demanding, leading to unease, or causing me to become more easily stressed.
- ☐ 3
- ☐ 4 I often feel that situations that I previously handled without problem are now demanding and cause a strong feeling of uneasiness or stress.
- ☐ 5
- ☐ 6 I experience nearly everything as demanding and cannot handle it at all.

9 Irritation and anger

This question regards how easily irritated or angry you become, regardless of whether or not you show it. Think especially about how quick tempered you have been in relationship to the source of your irritation, and how often and intensively you have become angry or irritated. If you have not had any such feelings at all, then you should mark "0".

- ☐ 0 I do not feel that I am especially easily irritated.
- ☐ 1
- ☐ 2 I am more impatient and easily irritated than usual, but the feeling quickly passes.
- ☐ 3
- ☐ 4 I become more impatient and easily irritated than usual. Sometimes I lose control in a way that is unusual for me.
- ☐ 5
- ☐ 6 I am often furious and have to make an enormous effort in order to restrain myself.

REMEMBER that your assessment refers to the past two weeks.

4.2 KEDS, SWEDISH VERSION

Karolinska Exhaustion Disorder Scale 2010

Avsikten med detta formulär är att ge en bild av ditt nuvarande tillstånd. Vi vill alltså att du försöker gradera hur du mått de senaste två veckorna.

Formuläret innehåller en rad olika påståenden om hur man kan må i olika avseenden. Påståendena uttrycker olika grader av obehag, från frånvaro av obehag till maximalt uttalat obehag.

Sätt ett kryss i rutan framför det svarsalternativ som du tycker bäst stämmer med hur du mått de senaste två veckorna. (Se exemplet här nedan.)

☐ 0

☐ 1

☒ 2

☐ 3

☐ 4

☐ 5

☐ 6

Om du vill göra en ändring – fyll då hela den rutan du kryssat i och sätt krysset i den ruta du önskar. (Se exemplet här nedan.)

☐ 0

☒ 1

☐ 2

Om du vill förklara/förtydliga någonting skriv då detta på anteckningssidan som finns sist i formuläret.

1 Koncentrationsförmåga

Här ber vi dig ta ställning till din förmåga att hålla tankarna samlade och koncentrera dig. Tänk igenom hur du fungerar vid olika sysslor som kräver olika grad av koncentrationsförmåga, t ex läsning av komplicerad text, lätt tidningstext och TV-tittande.

- ☐ 0 Jag har inte svårt att koncentrera mig utan läser, tittar på TV och för samtal som vanligt.
- ☐ 1
- ☐ 2 Jag har ibland svårt att hålla tankarna samlade på sådant som normalt skulle fånga min uppmärksamhet.
- ☐ 3
- ☐ 4 Jag har ofta svårt att koncentrera mig.
- ☐ 5
- ☐ 6 Jag kan överhuvudtaget inte koncentrera mig på någonting.

2 Minne

Här ber vi dig beskriva din förmåga att komma ihåg saker. Tänk efter om du har svårt att komma ihåg namn, datum eller vardagliga ärenden.

- ☐ 0 Jag kommer ihåg namn, datum och ärenden jag ska göra.
- ☐ 1
- ☐ 2 Det händer att jag glömmer bort sådant som inte är så viktigt men om jag skärper mig minns jag för det mesta.
- ☐ 3
- ☐ 4 Jag glömmer ofta bort möten eller namnen på personer som jag känner mycket väl.
- ☐ 5
- ☐ 6 Jag glömmer dagligen bort betydelsefulla saker eller saker som jag skulle gjort.

3 Kroppslig uttrötthet

Frågan gäller hur du har det med din fysiska ork. Känner du dig t.ex. mer fysiskt trött än vanligt efter vardagliga sysslor eller någon form av kroppsansträngning?

- ☐ 0 Jag känner mig som vanligt och utför fysiska aktiviteter som ingår i vardagen eller tränar som jag brukar.
- ☐ 1
- ☐ 2 Jag känner att fysiska ansträngningar är mer tröttande än normalt men rör mig ändå som vanligt i det avseendet.
- ☐ 3
- ☐ 4 Jag har svårt att orka med kroppsansträngning. Det fungerar så länge jag rör mig i normal takt men jag klarar inte att öka takten utan att bli darrig och andfädd.
- ☐ 5
- ☐ 6 Jag känner mig mycket svag och orkar inte ens att röra mig kortare sträckor.

KOM IHÅG, att bedömningen gäller de senaste två veckorna.

4 Uthållighet

Här vill vi att du tänker efter hur din uthållighet är och om du blir lättare psykiskt trött än vanligt i olika vardagliga situationer.

- ☐ 0 Jag har lika mycket energi som vanligt. Jag har inga särskilda svårigheter att genomföra mina vardagliga sysslor.
- ☐ 1
- ☐ 2 Jag klarar av att genomföra vardagliga sysslor men det går åt mer energi och jag blir fortare trött än vanligt. Jag behöver ta pauser oftare än vanligt.
- ☐ 3
- ☐ 4 Jag blir onormalt trött av att försöka utföra mina vardagssysslor och umgänge med andra människor tröttar ut mig.
- ☐ 5
- ☐ 6 Jag orkar inte göra någonting.

5 Återhämtning

Här ber vi dig beskriva hur väl och hur snabbt du återhämtar dig psykiskt och fysiskt när du har blivit uttröttad.

- ☐ 0 Jag behöver inte vila under dagen.
- ☐ 1
- ☐ 2 Jag blir trött under dagen men det räcker med en liten paus för att jag ska återhämta mig.
- ☐ 3
- ☐ 4 Jag blir trött under dagen och behöver långa pauser för att bli piggare.
- ☐ 5
- ☐ 6 Det spelar ingen roll hur mycket jag vilar, det är som om jag inte kan ladda om mina batterier.

6 Sömn

Här ber vi dig beskriva hur du sover. Tänk efter hur god sömnen varit och/eller om du känt dig utsövd under de senaste två veckorna. Bedömningen skall avse hur du faktiskt sovit, oavsett om du tagit sömnmedel eller ej.

- ☐ 0 Jag sover gott och tillräckligt länge för mina behov och känner mig för det mesta utvilad när jag vaknar.
- ☐ 1
- ☐ 2 Ibland sover jag oroligare eller vaknar under natten och har svårt att somna om. Det händer att jag inte känner mig utsövd efter en natts sömn.
- ☐ 3
- ☐ 4 Jag sover ofta oroligt eller vaknar under natten och har svårt att somna om. Det händer ofta att jag inte känner mig utsövd efter en natts sömn..
- ☐ 5
- ☐ 6 Jag sover oroligt eller vaknar varje natt och har svårigheter att somna om. Jag känner mig aldrig utvilad eller utsövd när jag vaknar.

KOM IHÅG, att bedömningen gäller de senaste två veckorna.

7 Överkänslighet för sinnesintryck

Frågan gäller om du tycker att något eller några av dina sinnen blivit mer känsliga för intryck. T.ex. ljud, ljus, dofter eller beröring.

- ☐ 0 Jag tycker inte att mina sinnen är känsligare än vanligt.
- ☐ 1
- ☐ 2 Det händer att ljud, ljus eller andra sinnesintryck känns obehagliga.
- ☐ 3
- ☐ 4 Jag upplever ofta ljud, ljus eller andra sinnesintryck som störande eller obehagliga.
- ☐ 5
- ☐ 6 Ljud, ljus eller andra sinnesintryck stör mig så mycket att jag drar mig undan för att mina sinnen ska få vila.

8 Upplevelsen av krav

Här ber vi dig ta ställning till hur du reagerar på krav som du upplever ställs på dig i vardagen. Kraven kan komma från omgivningen eller dig själv.

- ☐ 0 Jag gör det jag ska eller vill göra utan att uppleva det som särskilt krävande eller besvärligt.
- ☐ 1
- ☐ 2 Vardagliga situationer som jag tidigare hanterat utan särskilda problem kan ibland kännas krävande och orsaka obehag eller få mig att bli lättare stressad än vanligt.
- ☐ 3
- ☐ 4 Situationer som jag tidigare hanterat utan problem känns nu ofta krävande och orsakar ett starkt obehag eller en stark stress.
- ☐ 5
- ☐ 6 Det mesta känns krävande och jag klarar inte av att hantera det överhuvudtaget.

9 Irritation och ilska

Frågan gäller hur lättirriterad eller arg du känner dig inombords oavsett om du visat något utåt eller ej. Tänk särskilt efter hur lättväckt din irritation varit ("kort stubin"), i förhållande till vad som utlöste den, och på hur ofta och hur intensivt du känt dig arg eller irriterad. Om du överhuvudtaget inte kan känna några sådana känslor, skall du sätta din markering vid 0.

- ☐ 0 Jag känner mig inte särskilt lättirriterad.
- ☐ 1
- ☐ 2 Jag känner mig mer otålig eller lättirriterad än vanligt men det går också snabbt över.
- ☐ 3
- ☐ 4 Jag blir lättare arg eller provocerad än vanligt. Ibland förlorar jag fattningen på ett sätt som inte är normalt för mig.
- ☐ 5
- ☐ 6 Jag känner mig ofta alldeles rasande invärtes och måste anstränga mig till det yttersta för att behärska mig.

I

Neuroendocrine, Cognitive and Structural Imaging Characteristics of Women on Longterm Sickleave with Job Stress-Induced Depression

Ingrid Rydmark, Kristina Wahlberg, Per Hamid Ghatan, Sieglinde Modell, Åke Nygren, Martin Ingvar, Marie Åsberg, and Markus Heilig

Background: A recent increase in long-term sick leave (LTSL) in Sweden affects mostly women in the public sector. Depression-related diagnoses account for most of the increase, and work-related stress has been implicated.

Methods: We examined dexamethasone/corticotropin-releasing hormone (dex/CRH) test responses, magnetic resonance imaging measures of prefrontocortical and hippocampal volumes, and cognitive performance in 29 female subjects fulfilling three core criteria: 1) LTSL > 90 days; 2) unipolar depression or maladaptive stress reaction with depressed mood; 3) job-related stress given as a reason for disability. This group was compared with 28 healthy matched controls.

Results: The cortisol response to CRH differed markedly between the two groups ($p = .002$), with a dampened response in patients. This difference remained after removing subjects on antidepressant drugs ($p = .006$) or smokers ($p = .003$). Neither hippocampal nor prefrontocortical volumes differed. Performance on hippocampus-dependent declarative memory tests did not differ between groups, but the LTSL group had impaired working memory.

Conclusions: Our most salient finding is an attenuated dex-CRH response in patients on LTSL due to job-stress related depression. This is opposite to what has been described in major depression. It remains to be established whether this impairment is the end result of prolonged stress exposure, or a pre-existing susceptibility factor.

Key Words: Depression, cortisol, CRH, hippocampus, stress, workplace

Sweden has experienced a dramatic increase in long-term sick-leave (LTSL), mainly accounted for by psychiatric diagnoses. The largest increase of LTSL has occurred in the public sector. The underlying causes and potential commonalities that would prompt a study of LTSL as a syndrome in its own right are presently unclear. There are, however, several indications that a study focusing on this growing population is of considerable interest. Thus, the increase in LTSL is largely accounted for by diagnoses of depression, anxiety and maladaptive stress reactions, while the prevalence of psychotic disorders and substance abuse has not increased as a cause for LTSL. The most overrepresented group on LTSL are workers in the health and human services (HHS) sector. Women constitute a majority of the workforce in this sector, and the largest increase in LTSL has been among women, accounting for two thirds of total Swedish LTSL. The Swedish HHS sector has experienced repeated reorganizations and downsizing during the last decade, providing a plausible cause for increased social stress in the work place, and leading to suggestions that this may have contributed to the increase in LTSL. Taken together, these observations suggest that the increase in LTSL may reflect a range of responses to an increased load of social stress. Furthermore, LTSL per se carries with it significant consequences related to altered life style, decreased social interaction, and loss of income.

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Although depressive syndromes and maladaptive stress reactions account for the recently observed increase in LTSL, the underlying statistics are based on insurance databases of clinical diagnoses. This is a potential source of error. However, using validated, structured face-to-face interviews, SCID I and SCID II (First et al 1997a, 1997b) on a sample of 200 private employees on LTSL, we found that about 80% of the participants indeed met diagnostic criteria for major depressive disorder while, for example, personality or substance disorders were rare. Subjectively, 45% of subjects attributed their illness to prolonged job stress, 41% to job stress in combination with factors in their private life and 11% to factors in their private life only (Rylander et al, unpublished data). Participants described a characteristic course, with symptoms gradually evolving over time, initial symptoms of aches and pains, palpitations, fatigue, and irritability. A majority reported pronounced memory and concentration problems. This clinical presentation has also been reported in relation to other chronic stressors (McEwen 2000).

The hypothalamic-pituitary-adrenal (HPA) axis is a key mechanism linking life events and disease. Its activation is an adaptive mechanism in the short term, primarily aimed at coping with acute physical challenges. In contrast, its chronic activation caused by complex psychological demands imposes an "allostatic load." This refers to the wear and tear caused by the demand to maintain regulatory stability at abnormal levels of activation. Depression, decreased hippocampal volume and impaired cognitive function have perhaps attracted the most interest among potential consequences of allostatic load, and may be interrelated through a dysregulation of the HPA axis leading to chronic hypercortisolemia (Holsboer 2000; McEwen 2000).

Early studies of depressive illness described non-suppression of cortisol secretion in the dexamethasone suppression test, DST. It has subsequently become clear that the relation between HPA axis dysfunction and depression is more complex, and hypercortisolism is only seen in approximately half of depressed patients, yielding an only 25% overall sensitivity for the DST (Strohle and Holsboer 2003). Despite this, there is broad agreement that HPA axis dysfunction is of central importance in

depression (Holsboer 2000; Nemeroff and Owens 2002). To more precisely probe the dynamic status of the HPA axis, an improved challenge test has been developed, in which corticotropin-releasing hormone (CRH) stimulation is given after dexamethasone pre-treatment (the combined Dex-CRH test). This test is thought to have a 80–90% sensitivity for detecting depression (Heuser et al 1994).

The hippocampus is involved in acquisition of declarative memory, and in the regulation of endocrine stress responses. It is rich in glucocorticoid receptors involved in feedback inhibition of the HPA axis, and lesions to this structure lead to elevated resting as well as stress-induced glucocorticoid levels. Glucocorticoids in turn increase hippocampal susceptibility to a wide range of insults. Decreased hippocampal volume has been reported in three conditions which involve stress exposure and/or pathological HPA axis activation, and where also impaired memory function is a common symptom: major depression, post-traumatic stress disorder (PTSD) and Cushing's disease (Bremner et al 1993, 1995, 2000; Sheline et al 1999, 2003; Starkman et al 1992, 2001). Hypercortisolism is present in about 50% of depressed subjects, and is an invariable component of Cushing's disease. In Cushing's disease tumor extirpation has led to normalization of glucocorticoid levels and also to increased hippocampal volumes (Starkman et al 1999). In depression, hippocampal volume reduction has been reported after multiple depressive episodes, but not in first-episode patients (MacQueen et al 2003). Furthermore, a correlation between duration of untreated depressions and hippocampal atrophy was found in female depressed subjects (Sheline et al 1999, 2003). Together, these findings indicate that hippocampal volume loss and by extension potentially also accompanying cognitive impairment may be the result rather than the cause of depression.

Here, we investigated women employed in the HHS sector, recruited on the basis of three core criteria: 1) presence of LTSL with a duration of >90 days; 2) a diagnosis of depression or maladaptive stress syndrome with depressed mood; 3) self-report of job stress as a factor significantly contributing to the disability. This selection was aimed at recruiting a group representative of the factors that account for the recent increase in LTSL, where these three phenomena coincide. To obtain insights into the processes leading to this phenomenon, we evaluated whether this group shows altered HPA-axis function, if their hypothesized chronic stress exposure is reflected in decreased hippocampal volumes, if subjectively reported cognitive impairment would be detected by cognitive tests, and if so whether a relation would exist between hippocampal volume loss and cognitive symptoms. Our primary hypothesis was that the cortisol response would be exaggerated, as previously described in major depression; the secondary hypothesis was that this might be accompanied by structural and cognitive impairments characteristic of a chronic hypercortisolemic state.

Methods and Materials

Subjects and Overall Design

The study was approved by the Karolinska Human Subject Ethics Committee North (Dnr. 01/373). All subjects gave their written informed consent.

Participation Criteria. Participants were subject to the following criteria: Inclusion: female gender; 40–55 years of age; employed in the health care sector or as a teacher, child caretaker, psychologist or social worker in Stockholm; working ≥ 30 h/week for ≥ 3 years in their profession before becoming

ill or being included as controls; right handed; learned Swedish in childhood; Exclusion: any ongoing daily medication except estrogen or contraceptives; in the patient group, antidepressants were also allowed, but a subgroup analysis was carried out for antidepressant medication-free subjects; past or present serious medical condition such as neurological, endocrine or psychotic disease; history of head injury with loss of consciousness for a minimum of 10 minutes; hazardous alcohol consumption, as defined by a score of >6 points on the Alcohol Use Disorders Identification Test (Saunders et al 1993); self-reported illicit drug use.

Additional Criteria for the Patient Group. Inclusion: on full-time sick-leave 3–8 months, major depression or adjustment disorder with depressed mood according to DSM IV; factors related to work reported as the main problem on axis IV and present for >6 months.

Additional Criterion for Controls. Exclusion: any past or present psychiatric diagnosis.

Recruitment Process. Details of the patient recruitment procedures are given in Supplement 1. Ultimately, 44 women underwent a diagnostic interview, after which 11 were excluded while two chose not to participate. Following initial inclusion, two of the 31 remaining patients had pathological findings on the MRI brain scan (intracellar cyst and intracellar mass, respectively), leaving 29 patients for the data analysis. The characteristics of this sample are given in Tables 1 and 2. The age of this group was 47.3 ± 4.8 (mean \pm SD) and mean days on sick leave when contacted were 168.4 ± 33.2 , very similar to the 115 subjects that we failed to reach or who declined either contact or participation (age: 46.1 ± 4.1 ; mean days on sick leave 167.4 ± 33.0).

Controls were recruited through advertising at workplaces in the human services sector in Stockholm county. The ad text and details of recruitment procedure are given in Supplement 1. Seven hundred fifty subjects responded to the ad and were informed and screened by telephone. Ultimately 210 persons were selected as potential controls, to be matched for hormonal

Table 1. Descriptive Characteristics of the Patient and Control Samples

	Patients (n = 29)	Controls (n = 28)	p-Value
Age, years	47.8 \pm 4.9	47.6 \pm 4.2	.92
Height, cm	167.4 \pm 6.1	167.5 \pm 5.3	.95
Weight, kg	71.0 \pm 12.2	66.8 \pm 9.9	.16
Current nicotine use	10	7	.56
Hormonal phase			
Premenopause	17	15	.79
Perimenopause	2	3	.67
Postmenopause + oestrogen	4	5	.73
Postmenopause – oestrogen	6	5	1.00
Education			
1–9 years	6	3	.47
10–12 years	8	9	.78
>12 years	15	16	.79
Family situation			
Single household	5	4	1.00
Single + children living at home	3	4	.71
Partner + children living at home	13	15	.60
Partner – children living at home	8	5	.53

No differences were found for a number of potentially confounding variables which were analysed. Continuous variables are given as mean \pm SD, with corresponding p-values generated using two-tailed t-test. Count variables are given as absolute frequencies, and compared using Fishers Exact Test.

Table 2. Psychiatric Characteristics of the Patient Group

Diagnosis (nr of subjects with each)	
Adjustment disorder with depressed mood	3
Major depression, single episode, partial remission	17
Major depression, single episode, present, moderate	3
Major depression, recurrent, partial remission	6
Intensity of depressive symptoms	
MADRS score (mean \pm SD)	16.5 \pm 5.6
Age of onset of mood disorder (mean years \pm SD)	
For the total group, $n = 29$	44.1 \pm 8.4
For the group with recurrent episodes, $n = 6$	32.7 \pm 10.6
Comorbidity (nr patients with each comorbid diagnosis)	
Panic syndrome	1
Social phobia	1
Specific phobia	2
Personality disorders	0
Reported axis IV stressors (nr of patients)	
Only work related stressors	14
Work and private related factors	15
Use of antidepressants (nr of patients)	
SSRI	12
Days on sick leave at investigation day (mean \pm SD)	211.3 \pm 39.4

status, education, age, etc. to each recruited patient. Finally, 30 right-handed healthy women were recruited. Among these, one subject subsequently had abnormal thyroid-stimulating hormone, while another one reported asthma and daily use of inhalation steroids, leaving 28 subjects for analysis.

During an outpatient visit, all patients underwent a structured psychiatric evaluation (SCID I and II; (First et al 1997a, 1997b). This was in all cases carried out by author IR, a physician with several years of psychiatric experience, who had additionally completed formal coursework on the use of the SCID, and a series of interviews under supervision prior to this study. For resolution of potential diagnostic issues regarding study subjects, an experienced SCID educator was available throughout the study. During the outpatient visit, rating of Montgomery-Asberg Depression Rating Scale (MADRS) depression scores were also obtained (Svanborg and Asberg 1994). Assessment of healthy controls was carried out during a corresponding visit. Within 6 weeks of assessment, subjects were admitted to the Karolinska Hospital Clinical Research Centre for the combined Dex-CRH test, an MRI scan of the brain, and a battery of cognitive function tests. Self-report questionnaires were collected for demographic factors. The entire investigation lasted 2 days, and patients slept at home on the intervening night.

Dex-CRH Test and Biochemical Analyses

The test was performed largely as described in Heuser et al (1994). Briefly, subjects received one tablet of 1.5 mg dexamethasone (Dexacortal; Organon, Oss, The Netherlands) with the instruction to take the medication at 11 PM the day before the CRH challenge. On the following day an intravenous catheter was inserted before 2 PM. The subjects rested in a supine position throughout the test. Blood samples were drawn first at 3 PM for the analysis of basal ACTH and cortisol. Within 2 minutes, 100 μ g of human CRH (Ferring, Kiel, Germany) were injected. Blood was drawn at 3:30, 3:45, 4:00 and 4:15 PM for analysis of ACTH and cortisol. These time points represent the protocol evaluated in Heuser et al (1994). Analyses were performed by the SWEDAC accredited clinical chemistry laboratory at the Karolinska University Hospital, with details given in Supplement 1. Data for plasma cortisol and ACTH were analyzed independently, using two-

factor ANOVA, with subject category as a between-subjects factor, repeated measures over time as a within-subjects factor, and the interaction of these two to assess differential response between groups over time.

Magnetic Resonance Imaging

All examinations were carried out using the same 1.5 Tesla Sigma 5.X scanner (General Electric, Milwaukee, Wisconsin), the standard quadrature head coil and the individuals in head first supine position. The parameters of image acquisition are given in Supplement 1.

Voxel based morphometry (VBM) was used for voxelwise comparison of the local concentration of grey matter between two groups of subjects (Ashburner and Friston 2000). The optimized VBM protocol of Good et al (2001) was used here. Details of the VBM analysis are given in Supplement 1.

Cognitive Evaluation

A battery of tests was run on a Macintosh computer (Apple, Cupertino, California). The entire test procedure lasted 90 minutes, starting either at 2:00 or 3:30 PM. Details of test methodology are given in Supplement 1. Handedness was assessed with the Edinburgh handedness inventory (Oldfield 1971). Verbal intelligence was assessed using the Synonymous test from a Swedish standard intelligence battery, highly correlated with general intelligence as measured by other scales (Dureman and Sälde 1959). Attention was gauged using both a simple, and a complex reaction task. Working memory was examined using a backward digit-span test known to rely on lateral frontocortical activity (Owen 2000). Declarative memory was examined using three tests. 1) A test of associative memory for complex visual cues, based on the procedure in (Ingvar et al 1997); 2) Delayed word recognition; and 3) Picture recognition.

Data from the cognitive tests did not violate criteria of homogenous variances, and were therefore analyzed using one-way ANOVA. The Holm-Bonferroni procedure was used to compensate for multiplicity of testing (Aickin and Gensler 1996).

Results

Patient and Control Characteristics

Characteristics of the two groups are shown in Table 1; psychiatric characteristics of the patient group are shown in Table 2. The groups were closely matched for several variables which could potentially influence the outcomes measured. Importantly, age and hormonal status were virtually identically distributed in the two groups. Two remaining potential confounds were selective serotonin reuptake inhibitor (SSRI) use, and smoking. Subgroup analyses were therefore carried out, as described below, to exclude a confounding influence of these variables.

Dex-CRH Test

Cortisol data from the dex-CRH test are shown in Figure 1A. A highly significant overall change in cortisol over time was present in response to the CRH challenge [$F(4,220) = 67.1, p \leq .0001$]. There was also a significant overall difference between the groups [$F(4,220) = 4.2, p = .046$]. Most importantly, the response to the CRH challenge over time differed markedly between the two groups, as witnessed by the interaction term [$F(4,220) = 4.5, p = .002$]. Despite the reduced power, this differential response remained after removing all 12 subjects treated with antidepressant drugs [$F(4,172) = 3.8, p = .006$] or all 17 (10 patients, 7 controls) smoking subjects [$F(4,152) = 2.9, p = .02$]. To evaluate

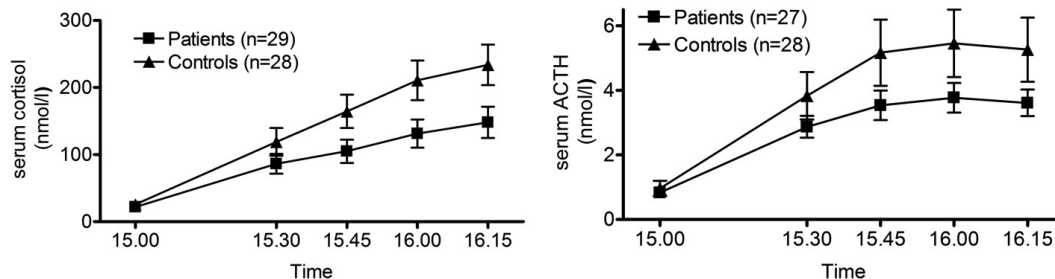


Figure 1. Attenuated cortisol response to an 100 µg i.v. CRH challenge in the patient group compared with controls ($p = .002$). Samples for ACTH analysis from 2 patients were lost by the laboratory, reflected in the lower n for this analysis. Results for ACTH were similar to those of cortisol, but variability was higher, and the difference did not achieve overall statistical significance. Smoking is a known confound in the dex-CRH test; when the 17 smokers (10 patients, 7 controls) in the study were removed, ACTH variability was markedly reduced, and the difference in ACTH response reached significance. For statistics, see Results.

the possible influence of depression severity, a separate analysis was carried out, subdividing patients into those below compared with those above median MADRS. These two subgroups did not differ from each other, and both were lower than controls (data not shown). Finally, to examine if being in first episode versus recurrent depression was of importance for the attenuation of dex-CRH response, those two groups were examined separately. Both groups showed a very similar magnitude of cortisol response attenuation. The analysis had a markedly higher power for the first episode than the recurrent group, due to their respective size ($n = 17$ vs. $n = 6$, respectively). This presumably accounted for the fact that statistical significance for an attenuation was robust in the former [$F(4,196) = 3.2$, $p = .014$, but only at trend level in the latter group [$F(4,128) = 2.1$, $p = .08$].

ACTH data from the dex-CRH test are shown in Figure 1B. ACTH samples for 2 patients were lost by the laboratory, which is reflected in the lower df for this analysis. There was a highly significant overall response of ACTH to the CRH challenge [$F(4,212) = 40.1$, $p \leq .0001$]. Similar to cortisol, the average ACTH response curve for the patient group was flatter than for controls, but variability was greater than for CORT values, and the interaction between time and group did not reach significance [$F(4,212) = 1.9$, $p = .11$]. Interestingly, once the 17 (10 patients, 7 controls) smoking subjects were removed, the variability was

reduced, and despite the reduced power, the differential ACTH response reached significance [$F(4,144) = 2.4$, $p = .05$].

MRI Analysis of Hippocampal and Prefrontocortical Volumes

VBM revealed no difference in a directed search in the temporal lobe, nor was any significant difference found, neither for temporal nor frontal lobe structures, when a global search was subsequently performed. Adding age and performance in declarative memory did not provide a better model fit to the data.

Cognitive Function

Some test data were lost due to computer errors. Actual degrees of freedom for each analysis therefore differ slightly between the analyses, and are given together with the respective results. All results together with their corresponding statistics are shown in Table 3.

The groups did not differ on verbal intelligence. Simple reaction time did not differ between groups, but complex reaction time was significantly longer in patients than controls. The number of missed responses on both tasks, and the number of errors in the complex task did not differ between groups.

A highly significant working memory impairment was found

Table 3. Scores on the Neurocognitive Tests to Assess Verbal Intelligence, Reaction Times, Working Memory, and Long Term Memory

	Patients	Controls	
Verbal intelligence			
Synonym test	23.8 ± 3.1	24.2 ± 2.3	$F(1,53) = .35$, $p = .56$
Reaction time			
Simple reaction task	372.2 ± 104.3	353.5 ± 77.5	$F(1,51) = .55$; $p = .46$
Complex reaction task	411.9 ± 86.6	365.6 ± 60.9	$F(1,52) = 5.2$; $p = .03$
Working memory			
Backward digit span, no corr. seq.	2.5 ± 1.5	4.0 ± 1.8	$F(1,52) = 11.6$; $p = .001$
Backward digit span, no tot. seq.	5.9 ± 1.7	7.6 ± 2.0	$F(1,52) = 11.2$; $p = .002$
Long term memory			
Picture recognition	34.5 ± 4.3	35.9 ± 3.4	$F(1,51) = 1.7$; $p = .19$
Delayed word recognition	17.1 ± 2.5	18.2 ± 1.8	$F(1,52) = 3.5$; $p = .07$
Visual Cues	24.7 ± 8.2	26.3 ± 7.2	$F(1,51) = .6$; $p = .43$

Mean ± SD values are given for the nr of correct responses on each test, as described in Methods, except for the reaction times, which are given in milliseconds. Some test data were lost due to computer failures; actual degrees of freedom are given for each analysis.

in patients versus controls in the backward repeated digit span test, while none of the three long-term memory tests differed.

The analyses above were also carried out for medication-free subjects only versus controls, but results did not differ from those obtained based on the full patient sample.

Discussion

Summary of Findings and Discussion of Their Validity

This study was carried out to explore the pathophysiological mechanism in subjects fulfilling three core criteria: 1) being on LTSL of 90 days duration or longer; 2) having a diagnosis of depression or maladaptive stress syndrome with depressed mood; and 3) presenting a self-report of job stress as a major factor underlying the disability. Subjects with these characteristics account for the recent increase in LTSL in Sweden, and insights into their pathophysiology might therefore aid an understanding of this phenomenon. In this population, we assessed three dimensions implicated in the pathophysiology of depression and related maladaptive stress responses: responsiveness of the HPA axis to a CRH stimulus under dexamethasone feedback inhibition, hippocampal, and prefrontocortical (PFC) volumes, and cognitive function (Holsboer 2000; McEwen 2000). The most salient finding is a marked attenuation of the HPA axis response to CRH challenge in LTSL patients, a pattern opposite to that consistently reported in major depression (Heuser et al 1994; Kunugi et al 2004; Modell et al 1997; Rybakowski and Twardowska 1999). The attenuated HPA axis response is likely of central origin, since the ACTH responses follow a similar pattern. Hippocampal as well as prefrontocortical volumes were unaffected. Declarative memory was unaffected, but working memory and attention were impaired.

The internal validity of our results is likely high. We assessed numerous subject characteristics that could potentially confound the outcome measures. A comparison shows that the groups are very closely matched for all but two variables. Importantly, age and hormonal status, factors demonstrated to influence the dex-CRH test (Kudielka et al 1999), were virtually identically distributed in the two groups. Two variables prompted a closer analysis to exclude their potential confounding influence. First, current smoking, while not significantly different in frequency between groups, showed a trend difference that justified a separate analysis, because smoking is a known confound in the dex-CRH test (Kunzel et al 2003). Second, antidepressant treatment can affect both declarative memory and/or hippocampal volumes (Vermetten et al 2003; Vythilingam et al 2004), and use of antidepressants was obviously restricted to the patient group. We addressed the potential confounding influence of both these variables by subgroup analyses of non-smoking and medication free subjects, respectively, but results were not affected. In fact, the difference in ACTH profiles was strengthened by excluding smoking subjects, making the differential response between groups significant, in a manner consistent with the cortisol findings. Confounding variables are thus unlikely causes of abnormalities found in the patient group, and a blunted HPA axis response of central origin seems to be present in the LTSL group.

Assessing the degree to which the data can be generalized to the population of subjects on LTSL under a depression related diagnosis is more challenging. Ultimately, approximately 10% of the registry based sample was examined. One main set of selection filters along the way, i.e., excluding subjects with medical conditions or ongoing medication, was imposed by the study, had a rationale related to methodological considerations,

and is in our opinion unlikely to affect generalizability. Subjects who could not be included due to our failure to reach them, or due to their unwillingness to participate, may on the other hand differ in important characteristics from those who participated in a systematic manner. The likelihood for this type of selection bias is somewhat reduced by the observation that subjects that were ultimately examined did not differ from those who could not be evaluated with regard to the two measures available for all members of the original registry sample, i.e. age and duration of sick leave. However, in absence of other data, we cannot establish that the results are representative of the group of LTSL patients with a depression diagnosis as a whole.

Neuroendocrine Results—Attenuated dex-CRH Response

The finding of attenuated HPA axis response in depressed LTSL subjects was contrary to our expectation. An exaggerated cortisol response in the dex-CRH test has consistently been reported in depression (Heuser et al 1994; Kunugi et al 2004; Modell et al 1997; Rybakowski and Twardowska 1999), increasing in parallel with the number of episodes (Hatzinger et al 2002). The sensitivity of the dex-CRH test to detect depression has been reported at 80%, or as high as 90% if properly adjusted for age (Heuser et al 1994). A failure to find an elevated dex-CRH response in our subjects could possibly have been attributed to the fact that the vast majority of them had first-episode depression. The up-regulated dex-CRH response in acute depression seems to represent a neuroadaptation developed during the course of illness, as shown by the finding that healthy high-risk subjects did not have a premorbid HPA activation prior to disease onset (Ising et al 2005), and that patients with a first episode of depression still had a normal response in the dex-CRH test, and an attenuated response when in complete remission (Rybakowski and Twardowska 1999). However, the predominance of first episode depression in our sample cannot account for the observation of the opposite result, i.e., a marked attenuation of the dex-CRH response.

Dexamethasone suppression has commonly been thought to gauge the sensitivity of hippocampal glucocorticoid receptors to mediate feedback inhibition of the HPA axis. It has subsequently been realized that the dex-CRH test largely taps into HPA function downstream of the hippocampus. Importantly, the test might primarily probe stress-induced hypothalamic recruitment of vasopressin co-expression in CRH neurons, which acts to potentially augment actions of CRH (Holsboer 2000). Despite this, available central and peripheral indices of the stress axis indicate that in typical, melancholic depression, the dex-CRH response largely reflects upregulated central CRH activity (for review, see Kasckow et al, 2001). Interpreted within this framework, our findings would indeed indicate that a lowered drive of central stress system components is present in our patient sample. This suggests an underlying pathophysiology distinct from what has typically been described in major depression, and instead similar or identical to that previously described for atypical depression, an entity characterized by an attenuated activity of the CRH and norepinephrine systems involved in both endocrine and behavioral stress responses (Gold and Chrousos 2002). Interestingly, LTSL subjects commonly reported chronic musculoskeletal pain. It has previously been described that a hypoactive HPA axis in atypical depression may lead to an insufficiently restrained function of the immune system, in turn leading to chronic, low grade inflammatory states (Gold and Chrousos 2002). The link between such a pro-inflammatory shift and atypical depression may, however, only be relative. More recently, a generally

attenuated ability of cortisol to inhibit proinflammatory cytokines has been described in subjects fulfilling major depression criteria, without stratification for atypical features (Miller et al 2005).

Before concluding that our findings in LTSL subjects reflect a hypoactive state of central stress systems in this population, studies on PTSD need to be considered. For reasons which are not well understood, an upregulated activity of central CRH systems is present in this condition despite attenuated HPA axis activity (reviewed in Kasckow et al 2001). However, important differences exist between the two conditions. The stressors underlying PTSD are acute and life threatening. In contrast, stressors in depression in general, and in our LTSL sample in particular, are of lower magnitude, primarily social, and chronic. Furthermore, although findings of reduced hippocampal size in PTSD similar to those in chronic depression have been reported (Bremner et al 1995), a subsequent twin study indicated that this may represent a pre-existing vulnerability factor rather than the result of the intense, acute stress-exposure characteristic of this condition (Gilbertson et al 2002).

Integrating these considerations, we therefore favor the interpretation that our dex-CRH results are indicative of hypoactive central stress-axis circuitry similar to what has been described for atypical depression (Gold and Chrousos 2002). A final consideration is whether this hypoactivity is part of a primary underlying pathophysiology, or is a secondary result of being on LTSL, as opposed to being actively engaged in work. Although effects secondary to being on LTSL would be of considerable interest to study, we do not think they offer a likely explanation for our findings. This is because our observations of attenuated dex-CRH response are in line with, and expand on, a previous report, which also found evidence for HPA-axis hypoactivity in women scoring high on measures of "burn out." In that study, low baseline as well as dex-inhibited salivary cortisol was obtained, despite subjects being engaged in work to normal extent (Pruessner et al 1999).

Depression severity as measured by the MADRS did not distinguish between dex-CRH responses, with the potential limitation that depression ratings in our patient group were generally low, as the majority of patients were in partial remission. The lack of relation between depression severity and magnitude of dex-CRH blunting may suggest that the latter is related to trait rather than state. Our observations still leave unresolved whether such a hypoactivity reflects an end-stage of chronic, primarily social stress in the work-place, possibly justifying the commonly used concept of a "burn out"; or, perhaps more interestingly, whether a pre-existing inability to mount an adequate stress response might predispose subjects in our population to developing a maladaptive syndrome which superficially resembles major depressive illness, but is in fact a pathophysiologically distinct entity, similar or identical to what has been described for atypical depression (Gold and Chrousos 2002; Kasckow et al 2001).

Structural and Cognitive Measures

We found no differences in hippocampal or PFC volumes between our LTSL population and controls. Hippocampal volume reductions have been observed in major depression, and are proposed to result from actions of elevated cortisol feeding back onto hippocampal cells (Holsboer 2000; McEwen 2000; Sheline et al 1999, 2003). In addition to the hippocampus, prefrontal cortex (PFC) has also been implicated in regulation of stress responses (Diorio et al 1993), in structural and functional consequences of stress in rodents (Brown et al 2005; Cook and Wellman 2004; Radley et al 2005; Wellman 2001), and in depression in humans (Drevets et al 1997). Importantly, recent studies

indicate a higher abundance of glucocorticoid receptors in the subhuman primate and human PFC compared with the rodent brain, indicating a potentially higher relative importance of this region in both responses to, and consequences of, stress in humans (Lupien et al 2005).

Support for a role of cortisol as mediator of volume changes have been reported in the extreme form of hypercortisolism, Cushing's disease (Brown et al 2004; Starkman et al 2001), although hypercortisolism as a mediator of hippocampal volume loss and cognitive impairment in depression is not yet unequivocally established (O'Brien et al 2004). Two characteristics of our study population make the lack of structural differences unsurprising in retrospect. First, a vast majority of our population had first episode depression. Hippocampal volume loss has been reported to correlate with duration of untreated depression (Sheline et al 2003), and in agreement with that observation, a recent study in women with first episode depression related to another stressor, a cancer diagnosis, also failed to find hippocampal volume changes (Inagaki et al 2004). Our data would thus be consistent with those studies. Furthermore, assuming cortisol to be the mediator of structural hippocampal and prefrontocortical pathology in depression, our finding that the HPA axis is hypoactive rather than hyperactive in our sample of LTSL depression is not predictive of structural changes.

However, it is well established that both hippocampus-dependent declarative memory and PFC-dependent working memory can be influenced by stress and cortisol even in the absence of structural changes. Of interest for the present study, PFC-mediated working memory has been shown to be more sensitive to changes in glucocorticoid levels than declarative memory. Furthermore, PFC function and working memory specifically are modulated by cortisol in an inverted U-shaped manner, presumably reflecting the relative occupancy ratio of glucocorticoid and mineralocorticoid receptors (Lupien et al 2005). Impaired working memory and attention observed in our LTSL population are therefore consistent with the attenuated HPA axis response which was found in parallel. In fact, the finding of impaired working memory may directly reflect an inability to mount an adequate HPA axis response to support normal performance on this test. Similar to the neuroendocrine stress response, this could reflect consequences of chronic stress, pre-existing vulnerability, or both.

Two interpretations are commonly given for the rapid rise in disability attributed to stress in the workplace: abuse of the benefit system and depression-like pathology. In fact, data are lacking to substantiate either. We report an unexpected attenuation, rather than accentuation, of HPA axis response in depressed subjects on LTSL under a diagnosis of depression, resembling the pattern previously described for atypical depression. A neuroendocrine dysregulation in these subjects would conventionally be interpreted as reflecting consequences of long-term stress exposure. An intriguing alternative possibility is that a pre-existing impaired ability to mount an adequate HPA axis response to social stressors may contribute to an inability to cope. Longitudinal data from this cohort will be forthcoming that will help evaluate this hypothesis.

IR and KW contributed equally to this article.

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Supplementary material cited in this article is available online.

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II

ARCHIVAL REPORTS

Suppressed Neuroendocrine Stress Response in Depressed Women on Job-Stress-Related Long-Term Sick Leave: A Stable Marker Potentially Suggestive of Preexisting Vulnerability

Kristina Wahlberg, Per Hamid Ghatan, Sieglinde Modell, Åke Nygren, Martin Ingvar, Marie Åsberg, and Markus Heilig

Background: We recently reported marked hyporeactivity of the hypothalamo-pituitary-adrenal (HPA) axis in depressed women on job-stress-related long-term sick leave (LTSL). This unexpected finding prompted the question of whether HPA axis hypofunction in this group results from stress exposure or reflects preexisting vulnerability. Here, as a first step toward addressing this question, we assessed temporal stability of HPA axis reactivity in these subjects.

Method: We used the combined dexamethasone/corticotropin-releasing hormone (DEX-CRH) test to retest HPA axis reactivity in 29 patients and 27 control subjects after 12 months of follow-up. Clinical status and cognitive performance was also retested.

Results: Despite marked clinical improvement and normalization of initially observed impairments in attention and working memory, marked HPA axis hyporeactivity persisted in patients. A high test–retest correlation was found both at the level of corticotropin ($R = .85$, $p < .001$) and cortisol ($R = .76$, $p < .001$) responses.

Conclusions: Hyporeactivity of the HPA was stable over 12 months in LTSL subjects, independent of clinical improvement and normalized cognitive function. The stability of this response over time suggests that decreased DEX-CRH responses in this group may be a trait rather than a state marker. This finding is compatible with a hypothesis that HPA axis hyporeactivity may reflect a preexisting vulnerability in these subjects.

Key Words: ACTH, burnout, cortisol, depression, Dex-CRH-test, stress, vulnerability

Psychiatric diagnoses have surpassed other conditions as a cause of long-term sick leave (LTSL) in Sweden and other industrialized countries. Diagnostic categories that account for the majority of this increase are mood and anxiety disorders, conditions thought to involve dysregulation of stress systems. This morbidity has been hypothesized to represent prolonged psychological responses to chronic job-related emotional and interpersonal stressors (1,2). Commonly reported symptoms among subjects on job-stress-related LTSL are emotional and physical exhaustion, manifested in depletion of energy and drive, and cognitive problems. These symptoms overlap with core symptoms of major depression, and in fact many of these subjects fulfill established diagnostic criteria for mood disorders. This prompts the question whether these two categories of conditions reflect a shared or distinct pathophysiology.

The glucocorticoid receptor hypothesis postulates that a key pathophysiologic mechanism in major depression is an impaired negative feedback control of the hypothalamic-pituitary-adrenal

(HPA) axis, resulting in progressively unrestrained cortisol release (3,4). Among a wide range of pathologic consequences, this is thought potentially to result in hippocampal “endangerment” and volume reduction, in turn leading not only to further impairment of negative HPA axis inhibition but also to impaired cognitive function commonly reported in stress-related conditions (5). Original data on HPA axis hyperactivity in depression were obtained using the dexamethasone suppression test (DST), subsequently found to possess limited sensitivity and specificity for depression (6). An improved test has therefore been developed to probe the dynamic status of the HPA axis. In this combined DEX-CRH test, CRH (corticotropin-releasing hormone) is administered to stimulate corticotropin (ACTH) release after dexamethasone pretreatment. Using this test, an 80%–90% sensitivity for detecting depression has been reported (7).

We recently applied the DEX-CRH test to probe whether depressed subjects on LTSL because of self-reported job stress share HPA axis pathophysiology with major depression (8). Our hypothesis was that chronic stress exposure in LTSL subjects could have resulted in upregulated reactivity of the HPA axis in a manner commonly seen in major depression. We further hypothesized that this might be accompanied by hippocampal volume reduction with concomitant cognitive impairment. Unexpectedly, we found just the opposite, that is, a marked decrease of HPA axis reactivity in depressed LTSL subjects. HPA axis responses to the DEX-CRH challenge in this group were decreased compared with healthy control subjects, in the absence of baseline differences. Rather than providing support for an impaired feedback inhibition of the HPA axis, these data suggested a failure to mount an adequate response to the CRH stimulus, caused at a level upstream of the adrenal cortex. No hippocampal volume reduction was found, and cognitive impairment was limited to frontocortically localized functions, such as

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attention and working memory. Our study added to a growing literature on stress-related disorders in which hyposecretion rather than hypersecretion of cortisol is found (9–11).

A key question prompted by these findings is whether the hyporeactive HPA axis observed in our LTSL subjects is likely to be the result of prolonged stress exposure, warranting the “burnout” label commonly used in occupational psychology (12), or whether it might instead reflect a preexisting vulnerability. The latter possibility would be in line with the observation that, although an unrestrained HPA axis activity leads to well-recognized pathology, an inability to mount an adequate stress response is also detrimental for successful coping with stress (5). In fact, it has previously been proposed that a persistent lack of cortisol availability in traumatized or chronically stressed individuals may promote an increased vulnerability for the development of stress-related disorders with primarily bodily manifestations (9).

An interesting hypothesis is thus that a hyporeactivity of the HPA axis, as measured by the DEX-CRH test, reflects preexisting vulnerability. Several testable predictions arise from this hypothesis. One of these is that the hyporeactivity is expected to persist as a stable trait rather than vary with state. The objective of this study was to obtain the initial data required to address this question by following up the LTSL subjects reported previously (8) after 12 months, an interval during which a significant clinical improvement occurred in most of them. On follow-up, we reevaluated DEX-CRH responses and cognitive function. Structural imaging was not repeated because no difference between groups had been found on the initial assessment.

Methods and Materials

Subjects

The study was approved by the Human Subject Ethics Committee North of the Karolinska Institute (Dnr. 01/373). All subjects gave their written informed consent. The original population was 29 female patients and 28 matched healthy control subjects (described subsequently). (For details regarding the initial recruitment process, see ref. 8.) In brief, subjects were women, 40–55 years old, and employed ≥ 30 hours/week for ≥ 3 years in the health care, social services, or education sector in Stockholm County. Patients on LTSL were selected from a database over public service employees on long-term (i.e., ≥ 3 month) sick leave from November 2002 to November 2003. Additional criteria for patients were full-time LTSL, presence of major depression (26 subjects) or adjustment disorder with depressed mood (3 subjects) according to DSM-IV (as determined using Structured Clinical Interview for DSM), job-related stressors reported as the main problem on Axis IV, and presence of these stressors for > 6 months. Subjects with any illicit drug use, hazardous alcohol consumption as determined by the Alcohol Use Disorder Identification Test (AUDIT), or a SCID diagnosis of a substance use disorder were excluded.

On the initial assessment, 12 of the 29 patients were receiving antidepressant medication. By the time of this study, 15 were receiving antidepressants. Additional criteria for the control group were absence of past or present psychiatric or medical diagnosis, and absence of any medical or psychiatric treatment. Control subjects were screened for these criteria during an initial telephone interview and then in writing. Those who denied any history of disease or treatment, with the exception of contraceptive use, and who scored within ± 2 standard deviations from their population norm on all subscales as well as the Global Severity Index of the Symptom Check List-90 (13), were invited

to participate. From 200 subjects eligible according to these criteria, 28 subjects were selected to provide maximal matching for age, hormonal status, education, height, weight, family situation (including number of children living in the household), and nicotine use.

Following the initial study (8), all but three patients participated in cognitive group therapy, a therapy model that addresses job-related issues in groups of 6–8 participants. Weekly sessions were held by an experienced therapist for 10 weeks. Every session was followed by homework assignment. Controls received no treatment. For the 12-month follow-up, subjects were contacted by telephone and admitted to the Clinical Research Centre (CRC) at the Karolinska University Hospital to undergo a retest with the combined DEX-CRH test and a cognitive reevaluation. CRH challenge and cognitive testing were done on two consecutive afternoons, and all subjects slept at home on the intervening night.

DEX-CRH Test

The DEX-CRH test was carried out as previously described (7). The setting (Karolinska University Hospital CRC), procedure, and biochemical analyses were identical to those used in the initial study (8). Briefly, subjects received 1.5 mg dexamethasone (Dexacortol, Organon) to take at 11 PM the day before the CRH challenge. On the following day, intravenous catheters were inserted at 2 PM, subjects rested for 1 hour, and blood samples were drawn for basal ACTH and cortisol at 3 PM. Within 2 min, 100 μ g of human CRH (Ferring, Kiel, Germany) was injected, and blood was drawn every 15 min 3:30–5:15 PM. This represents a 1-hour extension of sampling time compared with established procedures (7) and was performed to capture the response more fully. Total serum cortisol was determined by a commercial fluoroimmunoassay (AutoDELFIA cortisol-kit; Wallac Oy, Turku, Finland). The lower detection limit was 5 nmol/L, and the intra- and interassay coefficients of variation were below 8.5%. Plasma ACTH was measured using a chemiluminescence immunometric assay (Nichols, San Diego, California). The lower detection limit was 1 ng/L. Intra- and interassay coefficient of variation (CV) were below 8.5%, respectively, for both kits.

To evaluate groupwise as well as individual stability of ACTH and cortisol responses, the area under the curve (AUC) was calculated for each subject on the respective test session. To make data from the two test sessions comparable, this was restricted to the time points assessed on both tests (3:00–4:15 PM). Although these sampling intervals are established (7), they do not capture the full course of the response until it returns to baseline and could potentially fail to capture differences that primarily affect the late phase of the response. We therefore repeated all analyses using individual peak responses as an alternative index of response magnitude. The AUC and peak responses were highly correlated, and results on all analyses were virtually identical using either measure. The AUC-based analyses yielded lower residual variance and are therefore the ones presented. AUC data were also used to evaluate a potential correlation between neuroendocrine responses on the two assessments and a potential correlation between the neuroendocrine responses and ratings on the self-report version of the Montgomery-Åsberg Depression Rating Scale (MADRS) (14).

Cognitive Evaluation

Cognitive testing was carried out as described for the initial study (8). Briefly, testing lasted 60 min, starting 2:30 or 3:30 PM. Attention was assessed using both a simple and a complex

Table 1. Descriptive Characteristics of Subjects at Follow-Up

	Patients (<i>n</i> = 29)	Control Subjects (<i>n</i> = 27)	<i>p</i>
Age (years)	48.9 ± 5.0	48.5 ± 4.2	.78
Weight (kg)	71.2 ± 12.2	66.0 ± 9.4	.09
Current Nicotine Use	9	7	.77
Hormonal Phase			
Premenopause	15	11	.59
Estrogen medication	3	2	1.00
Family Situation			
Living with partner	21	19	1.00
Living with children ≤ 16 years	9	8	1.00

The groups continued to be well matched on key variables, although there was a trend for lower body weight in controls. Continuous variables are given as mean ± SD, with corresponding *p* values generated using two-tailed *t* test. Count variables are given as absolute frequencies, and compared using Fisher's Exact Test.

reaction task. Working memory was examined using a backward digit-span test. Declarative memory was examined using a test of associative memory for complex visual cues, delayed word recognition, and picture recognition. None of the pictures or words used in the initial testing was used on the follow-up to avoid learning effects.

Statistics

Data for cortisol and ACTH on the 12-month follow-up session were analyzed separately using two-way analysis of variance (ANOVA), with subject category as a between-subjects factor and repeated measures over time within the session as a within-subjects factor. The AUC responses on the two test rounds were analyzed using a two-way ANOVA with subject category as a between-subjects, and test session (baseline or follow-up) as a within-subjects factor. Correlations of AUC responses on the respective test round with each other, and correlations of AUC responses on follow-up with MADRS scores were evaluated using Pearson's Product-Moment correlation. Data from the cognitive tests were analyzed using one-way ANOVA. Patient characteristics were compared between groups using two-tailed *t* tests (continuous variables) or Fisher's Exact Test (frequency variables). All statistical analyses were carried out using Statistica 6.0 (Statsoft, Tulsa, Oklahoma).

Results

Subject Characteristics and Clinical State

All 29 patients, and all but one of the 28 control subjects from the original study participated in the follow-up. Descriptive subject data at the time of follow-up are shown in Table 1. The groups continued to be comparable on key variables, although there was a trend for lower body weight in the control group. Among the LTSL patients who had all fulfilled criteria for major depression or adjustment disorder with depressed mood at the time of the initial study, 21 had now fully remitted and no longer fulfilled criteria for these disorders, whereas 8 patients were still in partial remission. There was a marked decrease in depressive symptomatology over the 1-year follow-up interval, as measured by the MADRS ratings [16.5 ± 1.0 vs. 9.2 ± 1.2 , baseline study vs. follow-up, mean ± SEM; $F(1,28) = 39.4$, $p < .0001$]. The reliability of these ratings was supported by the observation that, despite the overall decrease, there was a highly significant correlation between baseline and follow-up MADRS scores ($R = .51$, $p = .007$). Of the 29 LTSL patients, 18 had returned to part-time or full-time work at the time of follow-up, and 11 remained on LTSL.

Cognitive Function

Results of the cognitive tests are given in Table 2. The impairments in attention (complex reaction time) and working memory found in the baseline study were no longer present.

DEX-CRH Test

Cortisol data from the DEX-CRH test are shown in Figure 1A. There was a robust cortisol response to the CRH challenge [main time effect: $F(8,434) = 39.4$, $p < .0001$]. There was also a robust group difference, with a significantly lower response in the patient group [main group effect: $F(1,54) = 8.3$, $p = .006$], as well as group × time interaction [$F(8,434) = 3.2$, $p = .002$] indicative of a differential time course of the response between the groups.

Despite the reduced power, this pattern remained after excluding all smokers (10 patients and 7 controls; [main time effect: $F(8,304) = 38.1$, $p < .0001$; main group effect: $F(1,37) = 8.11$, $p = .007$; group × time interaction: $F(8,304) = 4.1$, $p = .0001$]. The same was also true when the 15 antidepressant-treated patients were excluded from analysis [main time effect: $F(8,312) = 21.3$, $p < .0001$; main group effect: $F(1,39) = 5.4$, $p = .02$; group × time interaction: $F(8,312) = 2.2$, $p = .027$].

Table 2. No Group Differences Were Found on the Neurocognitive Tests Carried out to Assess Reaction Times, Working Memory, and Long Term Memory

	Patients	Control Subjects	
Reaction Time			
Simple Reaction Task	375.2 ± 100.2	371.5 ± 93.2	$F(1,51) = .02$; $p = .89$
Complex Reaction Task	407.5 ± 64.6	396.3 ± 62.8	$F(1,52) = .42$; $p = .52$
Working Memory			
Backward Digit Span (Correct Repeats)	2.9 ± 1.7	3.6 ± 1.4	$F(1,54) = 3.15$; $p = .08$
Backward Digit Span (Total Repeats)	6.5 ± 2.0	7.0 ± 1.7	$F(1,54) = 1.09$; $p = .30$
Long-Term Memory			
Picture Recognition	27.5 ± 8.5	28.0 ± 7.2	$F(1,52) = .06$; $p = .80$
Delayed Word Recognition	18.1 ± 2.4	18.4 ± 1.3	$F(1,53) = .25$; $p = .62$
Visual Cues	36.0 ± 4.2	36.7 ± 3.8	$F(1,53) = .43$; $p = .52$

Mean ± SD values are given for the number of correct responses on each test, as described in Methods and Materials, except for the reaction times, which are given in milliseconds. Some test data were lost because of computer failures. Actual degrees of freedom are given for each analysis.

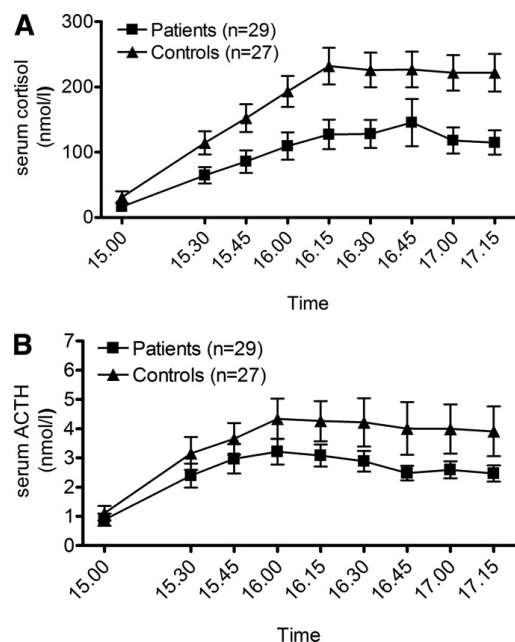


Figure 1. (A) Persistent attenuated cortisol responses ($p = .006$) to an 100 μ g intravenous corticotropin-releasing hormone (CRH) challenge in depressed patients on long-term sick leave related to job stress compared with control subjects on 12-month follow-up. Data points are means \pm SEM. Potential confounds from smoking or antidepressant treatment were excluded by replicating the results with these subjects excluded. For details and statistics, see Results. (B) Despite greater inherent variability, a persistent attenuated corticotropin response ($p = .03$) to the CRH challenge was also found in the patient group on 12-month follow-up; it had only been observed as a trend on the initial assessment. Data points are means \pm SEM. For details and statistics, see Results. ACTH, adrenocorticotropic hormone.

ACTH data from the DEX-CRH test are shown in Figure 1B. There was a robust ACTH response to the CRH challenge [$F(8,424) = 14.1, p < .0001$]. Despite the inherently higher variance of ACTH data, the ACTH response in the patient group was significantly lower [main group effect: $F(1,53) = 4.1, p < .05$]. The ACTH responses, measured as AUC, were highly correlated with the corresponding measure for cortisol ($R = .76, p < .0001$). Because of this correlation and the fact that ACTH data have a considerably higher variance, subgroup analyses aimed at eliminating potential confounds were limited to the cortisol responses, as indicated earlier.

Expressed as AUC, cortisol responses within each group were very similar between the baseline assessment and the 12-month follow-up (Figure 2A). A mixed model ANOVA of AUC responses, with time point (baseline vs. follow-up) as within-subjects factor and diagnostic group (patient vs. control) as between-subject factor, demonstrated a significant main effect of diagnostic group [$F(1,54) = 6.0, p = .02$], but no effect of, or trend for an effect of time, or of the group \times time interaction. Furthermore, individual cortisol responses were highly correlated between the baseline study and this follow-up (Figure 2B; $R = .76, p < .0001$). Similar findings were obtained for ACTH

responses, which were also highly correlated between baseline and follow-up ($R = .85, p < .0001$). In contrast, no correlation or trend was found between MADRS scores and ACTH or cortisol responses expressed as AUC. Consistent with this observation, MADRS scores were not a significant covariate in either the cortisol or the ACTH analysis.

Discussion

We recently reported the unexpected finding that depressed women on long-term sick leave related to job stress had markedly suppressed reactivity of the HPA axis in the DEX-CRH test, a pathology opposite to that typically reported in major depression (7). Here, we find that at 12-month follow-up, this pathology persists despite a marked clinical improvement shown by full remission in close to 75% of subjects, a highly significant reduction in depression symptom ratings and normalized cognitive function. In our original study, the attenuation of cortisol responses found at baseline was statistically robust, whereas ACTH response attenuation was only at a trend level, following a typical pattern in which ACTH responses have a higher degree of variability. On the follow-up reported here, attenuation was significant both for cortisol and ACTH, and the effect sizes for both variables were slightly larger than those observed initially. Together, this demonstrates that HPA axis hyporeactivity on follow-up was no less pronounced than that found on initial assessment. In both studies, we were able to rule out a confounding influence of factors such as smoking or antidepressant treatment. Attenuated responses at the level of both the adrenals

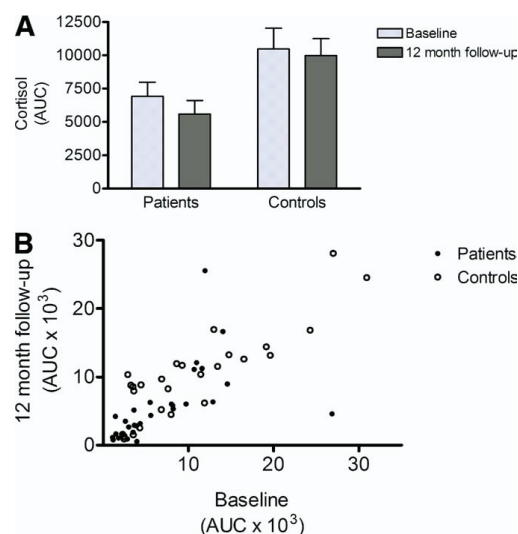


Figure 2. (A) Comparison of cortisol responses measured as area under the curve (AUC) indicated high stability between the baseline assessment and the 12-month follow-up reported here. Responses for patients and control subjects, respectively, are given (mean \pm SEM). On a repeated-measures analysis across the two rounds of testing, there was a significant main effect of group ($p = .02$), but no time effect or group \times time interaction. For details and statistics, see Results. (B) Cortisol responses also showed high individual stability, as shown by a highly significant correlation between the baseline and the present follow-up study ($R = .76, p < .0001$).

and the pituitary and the observation that responses at these two levels were highly correlated strongly suggest that the hyporeactivity is of central origin.

The stability of HPA axis hyporeactivity in this group and its lack of relation to clinical improvement are consistent with a hypothesis that the observed pathology may be a trait rather than a state marker. Trait markers are ideally independent of disease state, are expected to be found even before the onset of illness as well as during remission, and might be found in persons vulnerable to the illness who do not manifest it (e.g., unaffected first-degree relatives) (15). Our findings of stability during symptomatic remission provides initial evidence that is thus suggestive, although not conclusive, of HPA axis hyporeactivity in this population being a trait marker. An alternative possibility that cannot be excluded at this stage is that the stable deficit observed during remission could be a residual marker of the disease, as previously suggested for elevated DEX-CRH responses in major depression (16). It has long been debated whether long-lasting changes in hormonal responses following stress are pathological (17) or in fact adaptive (9). According to the latter view, adaptive down-regulation of pituitary CRH receptors in response to increased central CRH drive might ultimately result in hypocortisolism. These two views are not necessarily contradictory, because what starts out as an adaptive response may ultimately result in a persistent dysregulation and allostatic set-point shift (18). Prospective studies as well as studies of unaffected relatives will ultimately be helpful in determining whether the HPA axis hyporeactivity observed here in fact reflects a preexisting vulnerability factor and, if so, whether this vulnerability interacts with stress exposure to produce disease.

Our sample was selected on the basis of criteria of a depressive disorder as well as job-stress-related sick leave. It is difficult to obtain reliable measures of cumulative stress burden that combine exposures both within and outside the workplace using retrospective report. A limitation of our study may therefore be that we were not able to assess directly the quantitative relation between degree of stress exposure and HPA axis pathology. However, inclusion criteria of the constellation of job-stress-related LTSL and a diagnosis of a depressive disorder appears to have identified a population distinct from subjects with depression alone, because up- rather than down-regulated reactivity of the HPA axis has generally been observed in major depression (2,3). Thus, increased DEX-CRH responses, indicative of impaired negative HPA axis feedback control, have been reported during depressive episodes (7,19), and these changes partially remitted with an improvement of depressive symptoms (20). Less pronounced abnormal responses were also found in nondepressed relatives of depressed subjects (21), but the relation of these abnormalities to depression susceptibility is complex. In the healthy high-risk probands, HPA findings were remarkably stable over a period of 4 years (22). When these individuals were followed up for more than 10 years, those among them who ultimately developed an affective disorder did not have premorbid HPA hyperactivity. Given these findings, it was concluded that in major depression, exaggerated DEX-CRH responses are not likely to reflect preexisting vulnerability but rather are a state marker, reflect changes acquired as a result of illness, or both (23). In contrast to major depression, consistent abnormalities in DEX-CRH responses have not been found in chronically depressed patients (24) or in dysthymia (25).

Less research interest has been devoted to a potential pathophysiologic role of attenuated HPA axis reactivity. The best documented case in which this is found is posttraumatic stress

disorder (PTSD) in which peripheral cortisol levels are decreased, presumably because of up-regulated feedback inhibition (26). In agreement with these findings, it has recently been shown that the DEX-CRH response in this disorder is also attenuated (27). PTSD may, however, be a special case in which peripheral hypocortisolism is found despite increased central CRH drive (28) and hippocampal volume reduction may be related to a specific preexisting vulnerability (29). Hypocortisolism postulated to exist in chronic fatigue syndrome, fibromyalgia, and other chronic-stress-related conditions with primarily physical manifestations (9,11,30) may be of more direct relevance for our present findings but has not until now been extensively studied mechanistically.

Our initial observation of attenuated DEX-CRH response in depressed subjects on LTSL related to job stress were consistent with, and expanded on, a previous report, which showed decreased morning saliva cortisol and increased dexamethasone suppression in subjects scoring high on measures of "burnout" (31). As indicated earlier, a key question prompted by these converging findings is whether HPA axis hyporeactivity in these subjects reflects consequences of prolonged stress exposure or might be a stable endophenotype related to preexisting vulnerability factors. If HPA axis hyporeactivity is indeed a vulnerability trait, future research will have to take into account genetic or epigenetic factors as candidate mechanisms for its biological underpinnings. Both genetic variation and epigenetic regulation leading to hyperactive stress responses have been described in animal models (32,33), but no data are yet available on mechanisms in either category with an ability to produce chronically and pathologically dampened responses.

It has been argued that workforce structure in industrialized economies has undergone changes over approximately the past 25 years, facing employees with powerful social stressors resulting from greater demands and less job security and contributing to the incidence of stress-related disorders such as depression (1). Unrestrained HPA axis reactivity to stressors has been linked to psychiatric morbidity, but it is equally clear that the ability to mount an adequate stress response is critical for coping with stressful challenges and ultimately for survival and health (5). At low doses, corticosteroids preferentially activate the high-affinity mineralocorticoid rather than the low-affinity glucocorticoid receptor, are neuroprotective, increase hippocampal neurogenesis and plasticity, and have positive effects on memory and affect. The adaptive value of stress responses has typically been framed in metabolic terms, because cortisol-mediated mobilization of energy for short-term use at the expense of long-term processes obviously subserves physical coping responses. However, emotional, behavioral, autonomic, and endocrine stress responses act in concert to support coping and are coordinated by central CRH systems. It has previously been pointed out that hypoactivity of these systems may render subjects vulnerable to a particular category of depressive disorders, commonly labelled "atypical" (10). It is currently unknown what psychological coping deficits that might result from a persistent hypoactivity of stress systems. In the context of prolonged emotional and social stress in a changing workplace, it is, however, easy to speculate that an inability to mount adequate biological stress responses may impair active strategies to cope with chronic excessive job stress, such as refusing to accept unrealistic demands or leaving a dysfunctional workplace.

In conclusion, this 1-year follow-up showed a persistent decrease of HPA reactivity in women on long-term sick leave initially diagnosed with depression, despite remission of clinical

symptoms and normalized cognitive function. A provocative hypothesis emerging from these data is that an inability to mount an adequate stress response to emotional and social stressors in the workplace may constitute a preexisting vulnerability factor that results in impairment of coping ability and increases the risk of LTSL.

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III

Suppressed Stress-reactivity in Women with a history of Job-stress induced depression and Exhaustion Disorder: A 7 year follow-up.

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Background

A Persistent, lowered Hypothalamus-pituitary-adrenal axis (HPAA) reactivity was previously reported in woman with a history of long-term sick-leave due to job stress related depression and exhaustion disorder (1, 2). To investigate whether the difference in HPAA-reactivity would have changed over a longer period of time, a 7 year follow-up was conducted.

In parallel, the correlation with saliva cortisol levels was analyzed in patients. This biomarker is considered an indicator of activity and reactivity of the HPAA (3), and is routinely used and related to both psychological stress and mental disease (4).

Methods and Materials*Subjects*

Descriptive data are given in table 1.

The study was approved by the Human Subject Ethics Committee North of the Karolinska Institute. The initial study was performed in 2003 with 29 female patients (hereinafter referred to as patients) and 28 matched healthy individuals (hereinafter referred controls). The first follow-up was conducted 12 month's later. For details, see (1, 2). From this sample, 15 patients and 18 controls accepted invitation to this 7 years follow-up. Participants were informed about the study and invited by telephone and letter. Each participant responded to the MADRS-s scale (5) and underwent a structured psychiatric evaluation, a mini-version of SCD I and II; (6, 7) including criteria for Exhaustion disorder (8), and were screened for recent somatic disorders by a physician during an outpatient visit prior to the DEX/CRH test. All participants gave their informed consent.

Eight individuals in the former patient-group were screened healthy, i.e. neither criteria for depression nor exhaustion disorder (ED) were fulfilled. These women were also not on sick-leave. Four women suffered from ED and one fulfilled criteria for depression and ED. Of these five patients, two were on partial (50%) sick-leave, and one on fulltime sick-leave (due to a recent knee-operation and not the ED-diagnose) while two women were not allowed sick-leave compensation although ED-criteria were fulfilled.

HPAA-reactivity

The DEX-CRH test was carried out during May 12th – Juli 15th, 2010, at Danderyds Hospital (Hjärtforskningslaboratoriet), with substances and test-procedure being identical to those used in previous sessions (1, 2). In short 1,5 mg dexametasone was given on day 1, at 11:00 pm.

On day 2, at 3:00 pm, blood was drawn for baseline ACTH- and cortisol levels. Within 2 minutes, 100 µg of human CRH (Ferring Kiel, Germany) was injected. Blood was drawn through the intravenous catheter at 15:30, 15:45, 16:00 and 16:15 and collected in pre-cooled EDTA- and serum Sep Clot Activator containing tubes. EDTA-tubes were centrifuged at 4 °C while serum tubes were centrifuged after 30 minutes at room temperature. After separation from the blood cells, plasma and serum were stored at -80°C until biochemical analyses.

HPLC reactivity in our previous studies was analyzed with different biochemical equipment (1, 2). Here, the following devices were used:

Plasma ACTH was detected by an Electro Chemical Luminescence Reaction using Immulite 2000 Immunoassay System (Siemens Diagnostics, Llanberis, Gwynedd, United Kingdom). The lower detection limit was 0,1 pmol/L. Intra- and interassay coefficients of variation were below 5,55% and 1,95% respectively.

Serum cortisol was determined by an Electro Chemical Luminescence technique using Modular E solution (Roche, Mannheim, Germany). The lower detection limit was 0,5 nmol/L, and the intra- and interassay coefficients of variation were below 4,23%.

The internal evaluation performed by the chemical laboratory showed that the measuring procedures were similar or identical, and that cortisol was detected at slightly higher levels by the new device compared to that of AutoDelfia, which was used earlier.

Cortisol in saliva

Saliva sampling was performed using the Salivette (Sarstedt; Germany). To achieve reliable trait measures, saliva was collected during six days (3). Participants were instructed to spit immediately after awakening and 15, 30 and 60 minutes (CAR) thereafter, and at lunch-, dinner- and bedtime. To avoid contamination of the saliva, sampling should be performed before meals, drinking and tooth-brushing. Participants were also instructed to store all saliva samples in the freezer and personally handle them over to the study crew upon arrival to the laboratory, prior to the DEX/CRH test. At the laboratory, salivettes were stored at -80°C until biochemical analyses were conducted.

Salivary cortisol was analyzed using Spectria Cortisol RIA method (Inlaga Orion Diagnostica). The lower detection limit was 0,8 nmol/L; intra- and interassay coefficients of variation for 2,56 nmol/L were 14,6% and 19,7 % respectively and for 9,12 nmol/L; 8,5% and 7,0 % respectively.

All Biochemical analyses were conducted at Kliniskt Kemlab, Karolinska universitetssjukhuset, Solna.

Statistics

Descriptive data were analyzed using two-tailed T test for continuous variables. Pearson chi-square (Fisher exact when expected count were less than 5) or non-parametric test for two independent samples were used for categorical variables.

The influence of weight and/or hormonal phase on the HPA-reactivity was analyzed using Univariate Analyses of Variance with Area Under the Curve (AUC) ACTH- and Cortisol as dependent factor, group and hormonal phase as fixed factors and weight as covariate. The same analyses were conducted with GAF- and MADRS-ratings as covariate and fixed factor respectively.

Drop-out analyses were carried out using AUC_{cortisol} as dependent variable, repeated measure with test-occasion (baseline and 1 year follow-up) as within subject factor and category (drop-out/participant) as between subjects factor.

ACTH and cortisol data were analyzed separately using repeated measure with time as within subject factor, diagnose category (ED patient, none-ED patient and control) as between subjects factor, and the interaction of these factors to evaluate the differential response between groups. Simple effects were tested for significant interactions, with pair wise comparisons of mean values at each time point. Bonferroni-correction was used to adjust for multiple testing.

The Cortisol/ACTH ratio in patients and controls were analyzed using repeated measure with time as within subject factor, subject category as between subjects factor and the interaction of these two factors.

AUC_{CAR} was calculated with respect to Ground (AUC_G) and Increase (AUC_I), as described by Pruessner and co-workers (9) and their correlation with serum cortisol (AUC_{cortisol}) were evaluated using Spearman non-parametric rank correlation analyses.

Daily variations in CAR and diurnal cortisol were evaluated using repeated measure with time as within subject factor and day as between subjects factor. To evaluate the difference between women with- and without- ED, analyses were performed using repeated measure with CAR and evening cortisol as dependent variables, time and day as within subject factors and diagnose category as between subjects factor.

PASW Statistics 18.0 was used for all analyses.

Results

Descriptive data are shown in table 1.

Each ED-patient (n=5) in the current follow-up fulfilled criteria at baseline but not in the 12 month's follow-up.

Eighty-three percent had entered the menopause- or postmenopausal phase compared to 47 % at baseline. On average, patients had significantly higher BMI, and impaired GAF and depression ratings compared to controls although none of these factors had any significant influence on the HPA axis reactivity outcome (figures not shown).

Table 1. Descriptive Characteristics

	Patients	Controls	<i>p</i> - value
<i>n</i>	14	16	
Age, years \pm s.d.	54,6 \pm 4,6	54,1 \pm 4,2	.749
BMI \pm s.d.	27,2 \pm 2,6	24,3 \pm 3,1	.011
Current Nicotine Use, n (%)	3 (21,4)	1 (6,3)	.249
Hormonal Phase:			
Meno- or post-menopausal, n (%)	11 (78,6)	14 (87,5)	.433
Estrogen medication, n (%)	0	0	-
Family situation:			
Living with partner, n (%)	11 (78,6)	12 (75,0)	.581
Living with children \leq 16 years, n (%)	3 (21,4)	3 (18,8)	.605
Employment status:			
No of unemployed or part-time working, n (%)	6 (42,9)	1 (6,3)	.025
Social functioning and self-rated symptoms of depression:			
GAF-scores, median (range)	80 \pm (65-90)	90 (85-95)	.019
MADRS-S scores, median (range)	4,2 (1,5-10,5)	2,0 (0-4,5)	.001
Psychiatric diagnoses:			
Depression and Exhaustion disorder	1 (7,1)	0 (-)	.483
Exhaustion disorder	4 (28,6)	0 (-)	.037
Use of Antidepressants medication:			
SSRI, n (%)	3 (21,4)	0 (-)	.090
Reason for Sick-leave absence 25-100%:			
Depressive episode and/or Exhaustion disorder, n (%)	2 (14,3)	0 (-)	.209
Somatic (pain condition and knee-surgery), n (%)	2 (14,3)	0 (-)	.209

Drop-outs and missing values

15 patients and 18 controls accepted invitation to the follow up. In the analyses of HPAA-reactivity, samples from 14 patients and 16 controls were used – samples from 3 women were contained insufficient amount of blood (n=2) while one had pathological TSH level. Baseline (15:00) - ACTH levels were not detectable in 9 patients and 2 controls. Analyses of ACTH response were thus carried out including values at 15:30, 15:45, 16:00 and 16:15.

Saliva-samples from 12 patients were used for analyses of cortisol levels as samples from 3 women had insufficient amount of saliva. In addition, 14 bedtime-samples (2,7%), contained cortisol-levels below the detection limit. Bedtime sampling was thus not included in the analyses of the diurnal secretion.

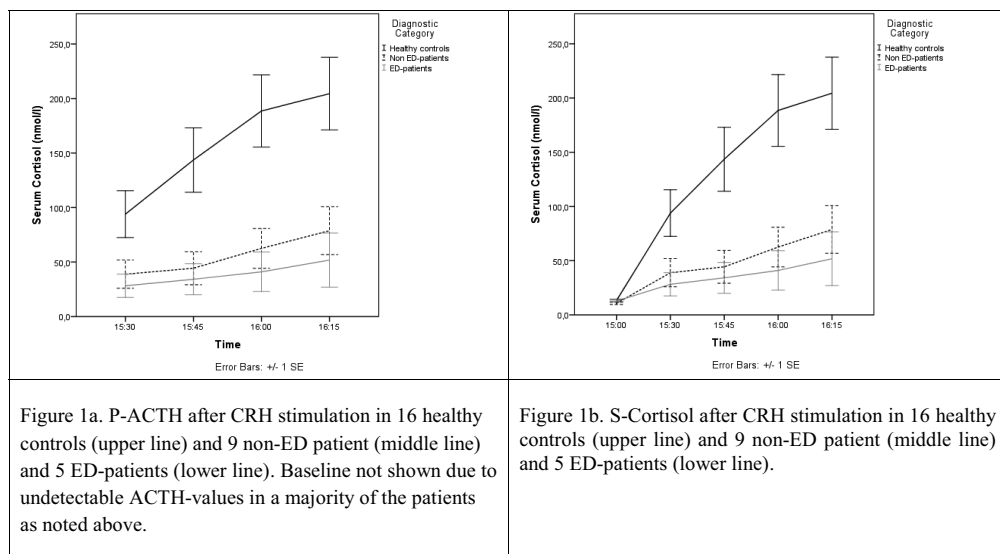
Patients who denied invitation to the current follow-up had an almost significantly higher HPA-reactivity at baseline and in the 1 year follow-up compared to patients who attended as shown by the main group effect; [F(1,27)= 4.0, *p* = .055]. Data from controls did not differ significantly in this regard, neither at baseline nor at the 1 year follow-up (figures not shown).

HPAA reactivity

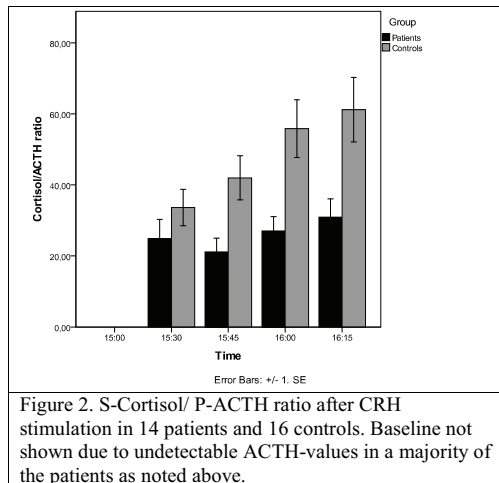
ACTH and cortisol reactivity data are shown in figure 1.

The pituitary response to CRH increased over time as shown by the main time effect [$F(3,81) = 4.3, p = .007$], with a significantly lower ACTH-response in patients [main group effect: $F(2,27) = 4.5, p = .02$] and non-significant group \times time interaction. Pair wise comparisons showed that there was a significant difference in ACTH-reactivity between healthy controls and ED patients at 15:30 ($p = .034$) and at 16:15 ($p = .025$).

The Cortisol response increased over time [main time effect: $F(4,108) = 15.0, p < .001$] with significantly lower response in patients [main group effect: $F(2,27) = 5.4, p = .010$], and group \times time interaction [$F(4,108) = 4.9, p < .001$]. Simple main effects test showed that there was a significant cortisol response in healthy controls ($p < .001$) while patients response was flatter as shown by a non-significant increase, although there was a trend towards significant p-value in nonED patients ($p = .116$). Pairwise comparisons showed that there was a significant difference between healthy controls and nonED patients at 15:45 ($p = .047$), at 16:00 ($p = .022$) and at 16:15 ($p = .028$). There was a trend towards lower cortisol response in healthy controls compared to ED patients at 15:45 ($p = .085$), while the differences reached significant levels at 16:00 ($p = .031$) and at 16:15 ($p = .030$).



Cortisol/ACTH ratio increased over time as shown by the main time effect; [$F(3,84) = 15.3, p < .001$] with significant difference between groups as shown by the main group effect; [$F(1,28) = 7.4, p = .011$] and group \times time interaction [$F(3,84) = 5.7, p = .001$] (figure 2), indicating that the cortisol response to ACTH after CRH administration was delayed and lower in patients.

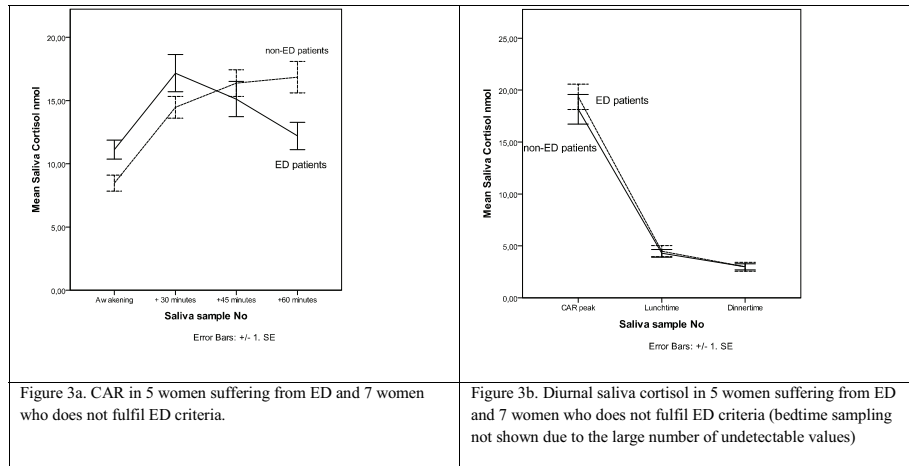


Saliva cortisol

Serum Cortisol reactivity was negatively correlated with saliva cortisol AUC_1 on day 2 ($r = -.62, p = .018$) but not with any of the other 5 days, nor with AUC_G .

CAR increased over time with main time effect [$F(3,198) = 27.5, p < .001$] while time \times day interaction and main day effect were non-significant. When diagnose was used as between subject factor, time \times diagnose interaction appeared different in ED versus nonED patients [$F(3,210) = 11.1, p < .001$] with non-significant main group effect (figure 3a).

There was an overall decrease during the day showed by main time effect; [$F(2,132) = 303.9, p < .001$] with time \times day interaction [$F(10,132) = 3.2, p = .001$] indicating that the diurnal curve altered between days while ED patients and nonED patients showed indifferent cortisol slopes (figure 3b).



Discussion

Major findings:

Almost 60 % of the participants in the former patient group were screened healthy and none of these were sick-listed in the current long term follow-up. Despite this, the differences in HPA reactivity between groups were highly similar to those found 7 respectively 6 years ago (1, 2), with a lower and flattened stress response in patients who also had a delayed and lower Cortisol/ACTH ratio compared to controls.

Our result contradicts recently published findings of an increased cortisol/ACTH ratio in ED-patients with a blunted ACTH-response (10). Such hyper-responsive adrenals have been described as a centrally mediated hypercortisolism and a key feature in melancholic depression (11). Our findings rather indicate that the adrenals have been hypostimulated by the blunted ACTH secretion, that may reflect a long term suppression of hypothalamic CRH secretion in the context of many years of activation of the stress system (11).

However, the CRH dose applied by Sandström and co-workers (10), was lower than the one used in our design, and the results in these two studies may thus present a broader picture of the neuroendocrine pattern associated with ED, i.e. a pattern resembling a bimodal dose dependent response previously associated with atypical depression and Chronic Fatigue Syndrome (CFS). It has been proposed that such response reflect an increased adrenal sensitivity due to long lasting CRH hypostimulation, that has ultimately resulted in sensitized adrenal receptors, that are hyper respondent to low doses of stimulation while, at the same

time the adrenals are incapable of fully responding to a more potent stimulus because they have become atrophied (11).

Chronic stress has commonly been associated with increased HPAA activity (12) although findings of decreased HPAA activity are now growing (4). It has also been suggested that the latter is rather present in a state following chronic stress, and in fatigue related conditions like CFS (12). Indeed, ED-criteria include exposure to increased long-term stress, often for years, followed by an overwhelming exhaustion (8). If and when, the altered HPAA functioning normalizes in these patients, remains to be elucidated. In cases of dysregulated HPAA caused a pituitary tumor, the levels return to normal within approximately two years after removal of the tumor (12). Psychiatric research, on the other hand, have found that HPAA dysregulation during the course of depression may be present even when psychopathological symptoms are remitted (13) and that the number of episodes is positively correlated with the neuroendocrine response to the DEX/CRH test suggesting that a dysregulated HPAA activity may be seen as a biological score (14). In our previous (12 month) follow-up, the HPAA pathology was present despite the fact that 80% of these women no longer fulfilled ED criteria and that almost 75% were in full remission with normalized cognitive functioning (2). Here, 60 % of the participants in the former patient group were screened healthy, yet suffering from a dysregulated HPAA activity. Future studies that take into account the severity and number of ED episodes or duration may thus elucidate the correlation with a HPAA dysregulation associated with this disorder.

Analyses failed to support that there is an obvious correlation between saliva cortisol and HPAA as earlier reported (15). However, multiple sites and factors controls HPAA reactivity and all may influence the levels of cortisol in saliva and it has been concluded that cortisol levels should rather be considered a source of variance, particularly in pathological HPAA-conditions, such as hypocortisolism (4). Saliva cortisol is, nonetheless, suggested to be a useful measure in e.g. depression, burnout, chronic fatigue, stress (3, 16-19), and in stress related exhaustion which has been associated with reduced diurnal variation (20). At this moment, we are unable to conclude if saliva cortisol is altered in patients - or unaltered as reported by Sandström and colleagues (10), but in the search for a deepened understanding

about the mechanisms behind this disorder and efficient treatment, it is important to elucidate if ED is associated with a state of hypocortisolism (21).

Patients in this 7 year follow-up had a significantly lower HPAA reactivity at baseline and in the 12 month follow-up compared to those who denied participation. These dropouts constitute almost half of the original patient sample, and the biochemical analyses were performed with different equipment so the result clearly needs to be interpreted with caution. Although ED-patients in the current follow-up fulfilled criteria for a second time, we have not been able control for clinically relevant episodes in between the 1 – and 7 years follow-up. Whether the neuroendocrine change found in these patients could be regarded a “biological scare” and a predictor for relapse in a manner described in depressives (14), remains to be investigated. The number of episodes and its relation to HPAA activity in ED-patients might thus be analyzed to answer this question in future studies.

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IV

Construction and evaluation of a self rating scale for stress-induced Exhaustion Disorder, the Karolinska Exhaustion Disorder Scale

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Abstract

Background: Prolonged stress (six month or more) may cause a typical condition which has been named Exhaustion Disorder (ED) with ICD-10 code 43.8. ED is characterised by exhaustion, cognitive problems, poor sleep, and decreased tolerance to further stress. ED might cause long term disability and depressive symptoms may develop.

Aims: To construct and evaluate a self-rating scale for the assessment of ED using diagnostic screening as standard. The second aim was to examine the relationship between the constructed scale and the Hospital Anxiety and Depression Scale (HAD).

Methods: A 9 item self-rating scale, The Karolinska Exhaustion Disorder Scale (KEDS) was developed and tested in 200 ED patients and 117 healthy controls, screened for psychiatric and somatic health by experienced physicians.

Results: Construct validity was satisfactory and concurrent validity was high. A summated score of 19 (scale range 0-54), was accompanied by sensitivity and specificity of 95.5 and 96.6 % respectively. When KEDS items were pooled with items from each HAD subscales in factor analyses, exhaustion, depression and anxiety emerged in separate factors, suggesting that these instruments reflect latent variables.

Conclusions: The KEDS is here suggested to be a useful tool in the assessment of symptoms of exhaustion disorder in clinical settings as well as in research such as e.g. treatment studies.

Key Word: Stress, exhaustion disorder, depression, anxiety, KEDS, self-rating scale, burnout

Background

Chronic stress without sufficient recuperation may end in a prolonged state of profound exhaustion which cannot readily be relieved by rest (1). Typically, this condition is preceded by months or years of stress, but the onset of symptoms is often abrupt and characterised by mental and physical fatigue, cognitive problems such as memory disturbance, episodic difficulties in finding words and finding one's way in familiar surroundings, and restless and interrupted sleep. There is an increased sensitivity to stress which may lead to anxiety, irritability, and feelings of befuddlement and confusion.

This clinical condition is well known to general practitioners as well as to psychiatrists, but it is difficult to classify in the current diagnostic systems ICD-10 (2) and DSM IV (3). The chronic stress is sometimes related to work, which explains the common use of the term burnout (4). Burnout is, however, not a medical diagnosis, and another term may be preferable. Many chronic stress patients develop depressive symptoms at some time of their illness, and in the research literature terms such as job stress-induced depression, or work adjustment disorder, have also been used (1, 4, 5). The Swedish National Board of Health and Welfare (NBHW) suggested, based on a literature review, that the condition should be called Exhaustion Disorder (ED), and diagnostic criteria were formulated (6). The recommended diagnostic code in the International Classification of Diseases (ICD-10) is F43.8 (2).

Stress-induced psychiatric conditions were among the most important diagnostic groups in a dramatic increase in long-term sick leave in Sweden during the years 1997-2003 (7). A register based follow-up of patients on long term sick leave for a psychiatric diagnosis in 1999, found that a majority remained on sick leave or disability pension for several years (8). Patient reports, as well as a recent register based study of staff downsizing and subsequent psychiatric morbidity, suggest that factors at work are important for the development of ED (9). There is as yet no evidence-based treatment for ED (10), but the condition may be possible to prevent (11). Development of methods for early recognition, as well as for prevention and treatment, is thus a major public health concern.

Aims

The aims of this study were to construct and validate a rating scale for the assessment of ED symptoms, and to examine the relationship between symptoms of ED and depression, and between ED and anxiety.

Methods

Scale construction

The construct to be measured was defined by the tentative criteria for ED, formulated by the NBHW (2003);

- A Physical and mental symptoms of exhaustion with duration of at least 2 weeks. The symptoms have developed in response to one or more identifiable stressors which have been present for at least 6 months.
- B Markedly reduced mental energy, which is manifested by reduced initiative, lack of endurance, or increase of time needed for recovery after mental efforts.
- C At least four of the following symptoms have been present most of the day, nearly every day, during the same 2-week period:
 - 1/ persistent complaints of concentration difficulties or impaired memory
 - 2/ markedly reduced capacity to tolerate demands or to work under time pressure
 - 3/ emotional instability or irritability
 - 4/ insomnia or hypersomnia
 - 5/ persistent complaints of physical weakness or fatigue
 - 6/ physical symptoms such as muscular pain, chest pain, palpitations, gastrointestinal problems, vertigo or increased sensitivity to sounds
- D The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
- E The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism, diabetes, infectious disease).

Items were chosen on the basis of their correspondence to ED criteria A – C. Most items were selected from the Comprehensive Psychopathological Rating Scale (CPRS) (12) i.e. No. 4, 5, 15, 16, 17 and 19, assumed to reflect criteria C- 1, 3, 4 and 5. Another four items were formulated to correspond to criteria A, B, C- 2 and 6 on the basis of symptoms often reported by ED patients. The 10 items in the initially constructed scale reflected signs of impaired or worsened (1) concentration, (2) memory functioning, (3) physical stamina, (4) mental stamina, (5) recovery, (6) sleep, (7) sensory impressions, (8) emotional engagement, (9) experience of demands, and (10) irritability. The CPRS items were rephrased where appropriate, to fit with the vocabulary and definitions found in autobiographical reports or descriptions made by patients suffering from ED. One example is the “stamina”-items, which were originally a single item. As patients have pointed out that “stamina” could refer to mental as well as to physical phenomena, which were not necessarily strongly correlated, these distinctions were made clear by formulating two separate questions. Each item offered 7 unipolar response-alternatives ranging from 0–6 points, where 0 reflects no symptoms. Definitions were formulated at score 0, 2, 4 and 6 points but not at 1, 3 and 5. The unweighted sum of all item scores was used to assess a possible ED.

Pilot testing

A panel of psychiatrists, experienced psychotherapists and ED-patients (altogether 15 individuals), found that items and terminology were relevant except for item 8 (emotional engagement) which was excluded as it reflects one of the two main DSM criteria of depression but is not particularly typical of ED. Hence, the final version of the scale consists of 9 items (Supplemental file).

Translation

The KEDS was originally formulated in Swedish, translated into English by a native American professional translator and back translated into Swedish by a bilingual Swedish psychologist. The similarity of these two Swedish versions was judged to be satisfactory by the constructors of the scale. All testing was performed with the original Swedish version.

Participants

203 sick-listed patients, age 25-64 years, were screened by a trained physician during April 2005 to April 2010 at a Stress Rehabilitation Clinic in Stockholm and at the Department of clinical sciences, Karolinska Institute (the latter as part of an intervention study). Patients who fulfilled criteria for ED, either with or without symptoms of depression and/or anxiety were selected. In all, 3 patients (< 1%) failed to rate either one of three KEDS-items, *i.e.*, No 5, 8 and 9 respectively. Thus, 200 successfully completed self-ratings were included in the analyses (166 from the Stress Rehabilitation Clinic and 34 from the intervention study). This group is referred to as “patients”.

117 healthy individuals, working full- or part-time, age 25-55 years, were randomly selected, during January 2009 to April 2010, from the general population in the County of Stockholm by Statistics Sweden (SCB). Subjects who consented to participation were screened twice; during a telephone conversation with a trained nurse, and in an interview by an experienced physician. Individuals without a history or present psychiatric disorder, personality disorder or severe somatic disorder illness were included. This group is referred to as “controls”.

Measures

The KEDS was distributed together with the Hospital Anxiety and Depression Scale (HAD) on the initial visit to the clinic, or on study inclusion. The HAD is a self-assessment scale, developed for assessing clinically significant degrees of anxiety (HAD-A) and depression (HAD-D) (13). A review of 71 articles, including somatic, psychiatric and primary care patients and the general population, found that both HAD-subscales performed well in assessing symptom severity (14). For both HAD scales, a score of 8-10 is defined as doubtful caseness, while 11 or more is defined as definite caseness (13). In our patient group Cronbach’s alpha was .78 for HAD-D and .82 for HAD-A, and .74 and .76, respectively, in the healthy control group. A subgroup of 34 patients also received the self assessment version of the Montgomery Asberg Depression Rating Scale (MADRS-S) (15), with scale steps ranging from 0-6. A score of 15 and above on the MADRS-S suggests a clinically relevant depression (16).

Statistical analyses

Descriptive characteristics were compared using independent sample T-test for age, and chi-square (or the Fisher exact test when the expected count was less than 5) for gender proportions and educational level. KEDS and HAD self-ratings were compared between groups (and gender) using the non-parametric independent-sample median test. Skewness and kurtosis were calculated at item-level and for summated scores. According to Curran, Finch and West (1996) the assumption of normal distribution is severely violated if skewness > 2 and kurtosis > 7 (17). Internal consistency was evaluated by the Cronbach's alpha coefficient. Exploratory factor analyses (EFAs) using the principal component method with oblimin rotation and eigenvalues >1.0 as a criterion, were used to assess the factor structure in ratings made by patients, and potentially discriminate between the KEDS and HAD subscales. The appropriateness of EFA was supported by the Kaiser-Meyer-Olkin measure of sampling adequacy and the Bartlett's test of sphericity. To assess the best balance between sensitivity and specificity, Area under Receiver Operating Characteristics (ROC) curve was calculated for summated scores using ED-caseness as the state value. Correlations between the KEDS and the HAD scales were tested with the non-parametric Spearman's rho. PASW Statistics 18.0 was used for all analyses.

Ethics

The studies were approved by the Ethics committee at the Karolinska Institute.

Results

Descriptive characteristics

Descriptive characteristics are presented in table 1. Neither age nor educational level differed significantly between groups. Women were overrepresented in patients and in controls. No statistically significant gender differences in self-ratings were found.

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The distributions of KEDS summated score across groups are presented in figure 1. The assumption of normal distribution was not severely violated. At item level, “hypersensitivity to sensory impressions” (No 7) was severely skewed in controls but as the scale was developed to detect clinically relevant symptoms of ED, these findings were considered acceptable. The scale also showed sufficient internal consistency with Cronbach’s alpha of .74 in patients, and .81 in controls.

- insert figure 1 about here -

Each item-score was increased in patients ($p < .01$), indicating that no item was irrelevant. As response-alternatives ranged from 0 to 6, an item median of 3 would indicate that the item does not fail to detect certain values of the construct (18). Patients scored 3 in three of the nine items, and 4 in the remainder. Ratings ranged from 0-6 points in all but one item, which instead ranged from 0-5. Item medians in controls were 0-1 and rated scale steps ranged from 0-3 or 0-4. The median summated score was 30 (95% CI: 28-32) in patients, and 6 (95% CI: 4-8) in controls.

Exploratory Factor Analyses (EFA)

An EFA of the KEDS-items, assessed by patients, produced two factors, which explained 50.5% of the total variance (table 2). The first factor accounted for 36.3% and the second for 14.2% of the total variance. All items, except number 6 (“sleep”), showed acceptable communalities ranging from .33 to .72. Factor loadings ranged from .43 to .86. Removal of the items in the second factor, i.e. No 6 (“sleep”), 7 (“hypersensitivity to sensory impressions”) and 9 (“irritation and anger”) improved the internal consistency in patients to .79 while Cronbach’s alpha was reduced to .74 in controls. The corrected item-total correlation for these items were .22, .40 and .17, respectively, whereas the rest of the items ranged from .38 to .62.

- insert table 2 about here -

Discriminant ability of the KEDS, HAD and MADRS-S

ROC coordinates for KEDS, HAD subscales and MADRS-S are shown in table 3. All three scales discriminated between patients and healthy controls as shown by the AU_{ROC} although the clinical sample was best discriminated by KEDS ($> .99, p < .01, 95\% \text{ CI } .982; 1.000$). For both HAD subscales, the best balanced sensitivity and specificity was accompanied by scores well below the threshold defining caseness as suggested by Zigmond & Snaith (1983). Analyses of MADRS-S assessments yielded similar findings indicating a cut-off below the pathological range as suggested (16)

- insert table 3 about here -

The relation between symptoms of ED, depression and anxiety

Patient's summated scores of KEDS and HAD-D were moderately correlated compared to controls (Spearman's ρ .58 and .43 respectively) while the correlation between KEDS and HAD-A in patients was lower compared to controls (Spearman's ρ .40 and .57 respectively).

When KEDS and HAD-D items were pooled, the EFA produced four factors explaining 57 % of the total variance (table 4). Overall, KEDS and HAD-D items emerged in separate factors; four KEDS items and one HAD-D item accounted for 32.2% of the variance in factor 1, relating to a state of exhaustion. Factor 2 accounted for 10.6 % of the variance and emerged as a depression factor comprising five of seven of the HAD-D items. The items in factor 4 were related to cognitive symptoms.

- insert table 4 about here -

Similarly, when KEDS-items were pooled with items of HAD-A, the EFA produced four factors, which explained 57.9% of the total variance. Factor 1 accounted for 29.7%, factor 2 for 13.8% and the

remaining factors for 7.6 and 6.8 %, respectively. Four of the seven HAD-A items related to anxiety, loaded in the factor 1, while factor 2 reflected exhaustion and factor 3, a state of tension.

Discussion

A 9 item summated rating scale for the assessment of exhaustion disorder, the KEDS, was developed and evaluated in patients clinically diagnosed with ED and a healthy control group. The scale was easy to use and its internal consistency was satisfactory. The ability to discriminate ED patients implied a high concurrent validity as defined by a specificity and sensitivity above 95 % at a cut-off score of 19 (total range 0-54). The KEDS thus reliably and validly indicates a clinically relevant state of ED. The symptoms of other prolonged fatigue states, for instance the chronic fatigue syndrome, as well as neurasthenia (19) are quite similar to exhaustion disorder, and it is possible that the KEDS could be useful in these conditions as well, although this remains to be showed. Whether these syndromes are actually identical or overlapping conditions is outside the scope of the present study, but an interesting research question.

There is an ongoing discussion whether burnout, ED and other prolonged fatigue states should be included among the affective disorders, and best diagnosed as cases of depression or anxiety, rather than classified as diseases in their own right (20-22). Our study shows that ED, depression and anxiety conditions do have an amount of shared variance (33 percent between KEDS and HAD-D, and 16 percent between KEDS and HAD-A) and that 46% of our patients were classified as definite cases of depression using the established caseness definitions (13). However, in line with studies on the chronic fatigue syndrome (20, 21) the factor analysis showed that depressive-related items and items related to exhaustion, loaded on different factors, suggesting the existence of two different underlying dimensions. Furthermore, ROC analyses showed that optimal discrimination between patients and healthy controls were in the non-pathological range of HAD- and MADRS- scales, suggesting that all three are less useful for assessing ED.

The available neurobiological evidence suggests that ED, with or without concomitant depression, is accompanied by a lowered sensitivity of the HPA-axis to stimulation (5, 23) rather than the increased

sensitivity described as a characteristic of major depression. In the same vein, Tsigos (24) suggest that atypical or seasonal depression, and states of fatigue following chronic stress are associated with decreased HPA activity. Interestingly, Keller and co-workers in a population study of individuals with depressive symptoms found that chronic stress was more closely associated with fatigue, but less so with sadness and anhedonia (25).

Clinical experience with ED suggests that antidepressant drugs do not work well in this condition. Sick listed patients treated for depression quite often experience difficulties in returning to work, even after their depressive symptoms are relieved (26). We suggest that prolonged exhaustion, which may have a longer duration than depressive symptoms, may partly account for this and that the KEDS might yield useful information in such cases. Together with a depression scale like HAD or MADRS, KEDS could be used in clinical trials and possibly explain the absence of desirable effects of antidepressant medication.

Another possible use for the KEDS is in screening for signs of exhaustion at work. It has been shown that sick leave for chronic stress among health care personnel may be preventable, if cases at risk are identified at an early stage (11). The KEDS is currently included in a screening questionnaire used in an ongoing occupational health survey.

There are two obvious limitations to this study. The first is that the scale was developed and tested in Swedish and although it went through the usual translation-back translation procedure, we cannot be certain that the English and the Swedish versions tap identical phenomena (27, 28). The second limitation is that we have only studied the discrimination between patients and healthy controls. Symptoms of exhaustion and fatigue are common in most psychiatric disorders, and the instrument should therefore not be relied on for differential diagnosis.

So far, the KEDS has not been compared with other scales developed for prolonged fatigue or stress induced disorders, such as the Schedule of Fatigue and Anergia (SofA) (29) or the stress-related Exhaustion Disorder (s-ED) scale, recently described by Glise and co-workers to predict increased risk for sick leave in employees (30). The sharp discrimination between controls and patients in our study

suggests that the KEDS will be useful for distinguishing between cases of normal tiredness and pathological exhaustion disorder and for identifying employees at risk for exhaustion disorder. Ongoing studies will reveal whether it is also sensitive enough to assess effects of treatment and rehabilitation.

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Declaration of interest

Marie Åsberg and Åke Nygren participated in the expert group formulating the diagnostic criteria for ED (6).

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Table 1. Characteristic of patients and controls at inclusion.
Proportions of doubtful and definite cases of HAD-A and HAD-D, according to cut-off values suggested by Zigmond & Snaith (Zigmond and Snaith, 1983b)

	Patients, n=200	Controls, n=117
Age years – Mean (s.d.)	45.4 (8.6)	45.2 (7.0)
Range years	25 - 64	25 - 55
Women, n (%)	176 (88.0)	79 (67.5)
<u>Educational level:</u>		
Compulsory school, n (%)	9 (4.5)	6 (5.1)
Upper secondary school, n (%)	62 (31.0)	36 (30.8)
University, n (%)	127 (63.5)	75 (64.1)
Data not available, n (%)	2 (1.0)	-
<u>Sick-leave at inclusion:</u>	<u>n=197</u>	<u>n=117</u>
Full-time, n (%)	132 (67.0)	-
Sick leave 25 – 75 %, n (%)	63 (32.0)	-
Sick leave 0 %, n (%)	2 (1.0)	117 (100.0)
<u>HAD, subscale Anxiety</u>	<u>n=194</u>	<u>n=117</u>
Individuals scoring ≥ 8 and ≤ 10 , n (%)	50 (25.8)	5 (4.3)
Individuals scoring ≥ 11 , n (%)	105 (54.1)	2 (1.7)
<u>HAD, subscale Depression</u>	<u>n=194</u>	<u>n=117</u>
Individuals scoring ≥ 8 and ≤ 10 , n (%)	69 (35.6)	5 (4.3)
Individuals scoring ≥ 11 , n (%)	89 (45.9)	0 (0.0)

Table 2. Factor loadings and communalities in the exploratory factor analysis of KEDS-items as assessed by patients (n=200).

<u>KEDS-item, no</u>	<u>Factor 1</u>	<u>Factor 2</u>	<u>Communality</u>
1 Ability to concentrate	.51		.51
2 Memory	.49		.45
3 Physical stamina	.71		.48
4 Mental stamina	.86		.72
5 Recovery	.79		.60
6 Sleep		.54	.29
7 Sensory impressions		.43	.33
8 Experience of demands	.51		.59
9 Irritation and anger		.78	.58

Table 4. Factor loadings of KEDS and HAD-D (n=194).

		Factor 1	Factor 2	Factor 3	Factor 4
<u>KEDS-item:</u>					
1	Ability to concentrate				.51
2	Memory				.39
3	Physical stamina	.72			
4	Mental stamina	.77			
5	Recovery	.68			
6	Sleep				.76
7	Sensory impressions			.44	
8	Experience of demands	.46			
9	Irritation and anger			.89	
<u>HAD-item:</u>					
2	Irritation and anger		.62		
4	I still enjoy the things I used to enjoy		.83		
6	I can laugh and see funny side of things		.76		
8	I feel as if I am slowed down	.58			
10	I have lost interest in my appearance		.58		
12	I look forward with enjoyment to things		.77		
14	I can enjoy a good book or TV programme				.66

Table 3. ROC-Coordinates showing scores with the best balance between sensitivity and specificity for KEDS, HAD subscales and MADRS-S. In both HAD subscales, non-caseness is defined by 0-7 points according to Zigmond & Snaith (1983). Guiding principle suggest that MADRS-S scores of 0-15 should be defined as non-caseness (Svanborg pers. comm. 28 February, 2011).

3a. Ratings from 200 patients and 117 controls.			3b. Ratings from 196 patients and 117 controls.			3c. Ratings from 34 patients and 117 controls.		
<u>KEDS</u>			<u>HAD-D</u>			<u>HAD-A</u>		
Scores	Sensitivity	Specificity	Scores	Sensitivity	Specificity	Scores	Sensitivity	Specificity
17.0	97.5	94.9	4.5	95.9	82.9	5.5	90.2	86.3
18.5	95.5	96.6	5.5	92.3	88.0	6.5	85.1	89.8
19.5	94.0	98.3	6.5	86.6	94.9	7.5	79.9	94.0

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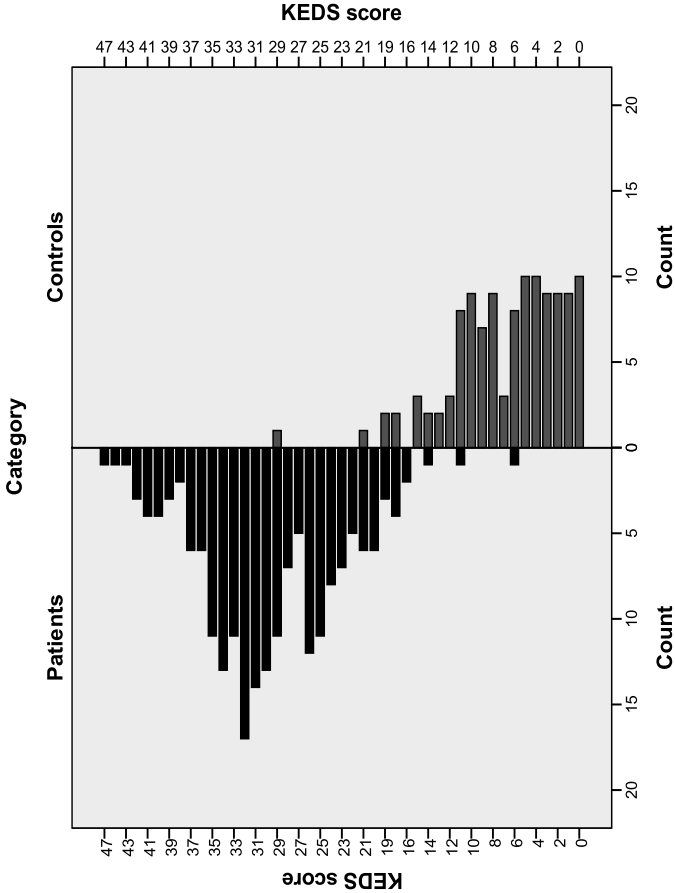


Fig. 1. Distribution of summated scores as assessed by the KEDS-scale in ED-patients (n=200) and in controls (n=117).



**Karolinska
Institutet**

From THE DEPARTMENT OF CLINICAL NEUROSCIENCE,
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**STRESS REACTIVITY, COGNITIVE FUNCTIONING
AND HIPPOCAMPAL MORPHOLOGY IN EXHAUSTION
DISORDER, AND DEVELOPMENT OF A SELF RATING
SCALE FOR EXHAUSTION DISORDER, KEDS**

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras i Kugelbergssalen, Neurokliniken,
Karolinska sjukhuset Solna fredagen den 20/1, 2012, kl 09:00.

av

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ABSTRACT

Stress is considered a major health problem in modern society and a prominent reason behind the long term sick leave (LTSL). Chronic stress may give rise to feelings of irritation and fatigue or exhaustion and may precipitate depression and anxiety as well as a number of unexplained medical conditions such as burnout. Burnout is not classified in the International Classification systems, but is instead noted among “Problems related to life-management difficulty”. Hence Exhaustion disorder (ED) was introduced in 2003 as a medical diagnosis to classify the closely associated terms vital exhaustion, mental fatigue and clinical burnout. According to the glucocorticoid-cascade hypothesis of stress and ageing, over-exposure or prolonged exposure to stress hormones (cortisol) may have adverse effects on the ability to turn off a stress response as well as memory functioning.

On the contrary to our hypothesis, study I-III, demonstrated that publicly employed women, who were initially on LTSL due to work stress related depression and Exhaustion disorder have a blunted ability to mount a stress response as measured by the Dex/CRH test. The cognitive test battery revealed that attention and working memory was slightly impaired at baseline but not in the 1 year follow-up. Magnetic resonance imaging (MRI) demonstrated that Hippocampus volume was not changed, nor any other cortical area.

In study IV, a new self rating scale for assessment of ED-symptoms, The Karolinska Exhaustion disorder scale, KEDS was constructed and evaluated. The scale has 9 items, ranging from 0-6 points, with a maximum summated score of 54. Lower scores reflect no or mild symptoms, and 19 points is associated with sensitivity and specificity above 95% suggesting that the scale has a high discriminative capacity.

In summary, LTSL patients who suffered from work stress related depression and ED at baseline, demonstrated a neuroendocrine deficiency that remained at 1-year follow-up and at 7-years follow-up despite clinical improvement. Symptoms of Exhaustion disorder may be assessed using the 9 item self rating scale, KEDS.

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