The Trials and Tribulations of Teaching

A Psychobiological Perspective on Chronic Work Stress in School Teachers

Silja Bellingrath

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Abbreviations

ACTH	Adrenocorticotropic hormone
AL	Allostatic load
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
BM	Burnout Measure
BMI	Body mass index
BO	Burnout
CAR	Cortisol awakening rise
CATS	Cognitive Activation Theory of Stress
CBG	Corticosteroid binding globulin
CHD	Coronary heart disease
CNS	Central nervous system
COR	Conservation of Resources Theory
CRH	Corticotropin-releasing hormone
CRP	C-reactive-protein
CVD	Cardiovascular disease
DHEA-S	Dehydroepiandrosterone-sulfate
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th ed.
DST	Dexamethasone Suppression Test
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ERI	Effort-reward-imbalance
GAS	General adaptation syndrome
GCs	Glucocorticoids
GLM	General linear model
GR	Glucocorticoid receptor
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale - Anxiety
HADS-D	Hospital Anxiety and Depression Scale - Depression

HbA1c	Glycosylated haemoglobin
HDL	High-density lipoprotein
HOMA	Homeostasis model assessment
HPA axis	Hypothalamus-pituitary-adrenal axis
HPLC	High performance liquid chromatography
HR	Heart rate
HRV	Heart rate variability
ICD-10	International Classification of Diseases, 10^{th} ed.
IL	Interleukin
LC	Locus coeruleus
LC/NE	Locus coeruleus-norepinephrine
LDL	Low-density lipoprotein
LPS	Lipopolysaccharide
MBI	Maslach Burnout Inventory
MBI-DP	Maslach Burnout Inventory - Depersonalization
MBI-EE	Maslach Burnout Inventory - Emotional Exhaustion
MBI-LA	Maslach Burnout Inventory - Lack of Accomplishment
MR	Mineralocorticoid receptor
OC	Overcommitment
OLBI	Oldenburg Burnout Inventory
PBMC	Peripheral blood mononuclear cell
PHA	Phytohemagglutinin
POMC	Proopiomelanocortin
PTSD	Post traumatic stress disorder
PVN	Hypothalamic paraventricular nucleus of the hypothalamus
SC	Suprachiasmatic nucleus of the hypothalamus
SD	Standard deviation
SES	Socioeconomic status
SEM	Standard error of mean
SMBM	Shirom-Melamed Burnout Measure
SNS	Sympathetic nervous system
SOC	Sense of coherence

SRH	Self-reported health
TBS	Teacher Burnout Scale
TBS-ATS	Teacher Burnout Scale - Attitude towards Students
TBS-CJRS	Teacher Burnout Scale - Coping with Job Related Stress
TBS-CS	Teacher Burnout Scale - Career Satisfaction
TBS-PAS	Teacher Burnout Scale - Perceived Administrative Support
TNF-α	Tumor-necrosis-factor-alpha
TSST	Trier Social Stress Test
URI	Upper respiratory illness
VE	Vital exhaustion
WHR	Waist/hip-ratio
17-OHCS	17-hydroxycorticosteroid

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Chapter 1

Introduction and outline of the thesis

Stress at work and its negative impact on the health status of employees are major problems for modern societies. A survey of the European Union's member states found that 28% of employees reported stress-related illness or health problems. This accounts for 41 million EU workers[1].

Why is work such an important determinant of peoples well-being? Most adults spend a large part of their daily life at work. Consequently, conditions in the workplace are likely to be an important determinant of mental health as well as physical well-being. Work has a central role in people's lives and a satisfying job may contribute to a more meaningful life, a higher self-esteem and economic independence. Individuals who work report a higher quality of life than those who do not (Ruchlin & Morris, 1991) and full time employment predicts slower declines in perceived health and in physical functioning for both men and women (Ross & Mirowsky, 1995). Social and technical modernisation followed by globalisation has caused a polarisation of the labour market in economically advanced societies. On the one hand, unemployment is a pressing problem because not enough jobs are available on the labour market or people have only insufficient education. For these individuals stress results from financial insecurity as well as understimulation (Lundberg, 2007). On the other hand, many people experience stress because they are exposed to high demands at work and to hard competition due to downsizing efforts and an increased need for efficiency. Work related stress is very costly for societies, leading to increased absenteeism, a higher employee turnover, diminished productivity, more accidents as well as to direct medical, legal and insurance costs. In 1993, German employers for example paid up to 60 billion DM for social security insurance to cover the pay of absentee

[1] *according to the Third European Survey on Working Conditions (2000), European Foundation for the Improvement of Living and Working Conditions. Dublin, Ireland.*

workers[2]. Thus, the financial implications of work stress alone should arouse public interest and it should be a major goal of all involved parties (governments, employers, employees, and insurance companies) to reduce absenteeism and ill health caused by stress at work.

Although there is growing research activity linking chronic work stress and the modern work environment with specific health outcomes, not much attention has yet been paid to the psychoneuroendocrinological processes that may underlie these links. The stress response has evolved as a highly adaptive reaction to ensure survival when an organism is confronted with a physical or psychological challenge. However, the same processes that are adaptive under acute stress conditions, may ultimately promote disease development when occurring chronically (Chrousos, 1998; Tsigos & Chrousos, 2002; McEwen, 2007). Previous work has implicated two main pathways through which stress can impact on physical health. On the one hand stress can influence people's health behaviour, like smoking, choice of diet, exercise or adherence to medical treatment and on the other hand stress can directly initiate unfavourable alterations in endocrine and immune function, thereby increasing an individual's vulnerability to a range of physical diseases. The aim of the present thesis was to investigate the physiological effects of work-related stress in school teachers in order to better understand the mechanisms by which such stress may lead to ill health. This population was selected because teaching has been proposed to be a highly stressful occupation, with enhanced levels of psychosocial stress experienced in the workplace (Guglielmi & Tatrow, 1998; Kyriacou, 2001; Weber et al., 2001).

By integrating the methodologies of work psychology, health psychology, psychosomatic medicine and psychoneuroendocrinology, this work has primarily sought to enhance our understanding of how chronic work stress and the consequences of such stress, may relate to various health problems.

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[2] *numbers based on the European Research Report, 1997, Preventing Absenteeism at the Workplace.*

The general introduction in **Chapter 1** gives a brief overview of the thesis and the research rationale behind the Trier Teacher Stress Study. **Chapter 2** summarizes important theoretical concepts that underpin the present work. Furthermore, an introduction into the physiology of the stress response as well as the applied research tools is provided. Finally, a review of the current literature regarding the impact of burnout and exhaustion on the regulation of the hypothalamus-pituitary-adrenal (HPA) axis, allostatic load and the particular stressors and demands of the teaching profession is given. In the following three chapters my own empirical findings on the relationships between work-related stress, burnout and exhaustion, and alterations in different physiological systems are presented. The Trier Teacher Stress Study was conducted under the supervision of Prof. Dr. Brigitte Kudielka-Wüst and Prof. Dr. Dirk Hellhammer. I have written three independent manuscripts that have been submitted for publication in different scientific journals. They are presented in this thesis such that each is self-contained, with its own introduction, methods, results and discussion sections, to allow readers to access individual parts of the thesis without recourse to the whole document. Because not all of the assessed parameters could be investigated in every subject, the number of subjects differs slightly in the three sets of results. In **Chapter 3**, evidence is provided that burnout, exhaustion and low reward from work all appear to be associated with subtle HPA axis dysregulation. This dysregulation was not reflected in cortisol day profiles but manifested as heightened HPA axis negative feedback.

Chapter 4 presents data supporting the hypothesis that chronic work stress, reflected in effort-reward-imbalance and exhaustion is associated with changes in a multi-system summary indicator of physiological risk, called allostatic load. In **Chapter 5** the impact of chronic work stress, in terms of effort-reward-imbalance and overcommitment on responses to acute psychosocial stress is scrutinized. This data supports the concept of HPA axis hyporeactivity being present in highly overcommitted school

teachers. **Chapter 6** provides a general discussion, with the aim of integrating the presented findings, followed by a brief discussion of potential future research directions.

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Chapter 2

Theoretical background

2.1 Stress

The first section of this chapter introduces stress theories that have been significantly influential in psychobiological research. The second section briefly elaborates the two work stress models most widely used to study the effects of chronic work stress on health and well-being.

2.1.1 The definition of stress

The concept of stress in the medical, biological and psychological literature arose from the work of Hans Selye, the founding father of modern stress research. He first used the term in 1936 to define a non-specific response of the body to any demand characterized by the secretion of glucocorticoids (Selye, 1936). Since then, the term 'stress' has become an ingrained part of our vocabulary and yet it is still remarkably imprecise and poorly defined. Due to continuing difficulties with definition, some researchers have even proposed to drop the term 'stress'. However, in doing so one would dismiss a substantial body of biomedical research from the past decades.

Selye based his concept of the general adaptation syndrome (GAS) on a series of endocrinological experiments, in which he injected mice with extracts of various organs. Initially, he thought he had discovered a new hormone until he realised that every of those irritating substances produced the same set of symptoms, namely swelling of the adrenal cortex, atrophy of the thymus as well as gastric and duodenal ulcers. Based on these findings, paired with his observation that people with different diseases exhibit similar symptoms, he developed the concept of the GAS. Selye assumed that a stress reaction is always comprised of an initial alarm reaction, a stage of resistance and finally, a stage of exhaustion, independent of the kind of challenge the organism has to face. Focusing primarily on the role of the sympathetic nervous system in the response to emergency situations, Walter Cannon in turn defined stress in terms of the stimulus required to elicit adrenomedullary responses (Cannon, 1914). He coined the term fight-flight response,

describing the responses to an acute threat. Selye on the other hand was concerned with the adaptation of the organism to chronic challenges (Levine, 2003). Mason later challenged Selye's idea of an unspecific stress response (Mason, 1968a, 1968b, 1971). He was able to demonstrate that specific situational characteristics, such as novelty, uncontrollability, unpredictability, ambiguity, anticipation of negative consequences as well as high ego-involvement, determine specific endocrine stress responses.

The cognitive model of Lazarus and Folkman (Lazarus & Folkman, 1984) puts a special emphasis on the transactional element of stress. They define stress as the experience of a mismatch between the demands put on an individual in a challenging situation and his or her abilities to cope. According to Lazarus and Folkman (Lazarus & Folkman, 1984), an individual's sense of control over the challenge and over his or her actions must be considered crucial for the appraisal process and therefore the quality and intensity of the stressor. By contrast, the conservation of resources theory (COR) of Hobfoll (1989) argues against the notion that stress is a state that primarily occurs when demands exceed coping resources. Hobfoll argues that people have a basic motivation to obtain, retain, and protect what they value. The things that people value are called resources, of which there are several types, including material, social, and energetic resources (e.g. a good marriage, job stability, money or personal characteristics like high self-esteem). Thus according to the COR theory, stress occurs when individuals are threatened with resource loss or when they fail to gain resources after investing resources. Stress contributes to an ongoing loss of resources, leading to a decrease in an individual's ability to withstand new stressors such that they become increasingly vulnerable to further stress-related difficulties.

Finally, the relatively recent cognitive activation theory of stress (CATS) by Ursin and Eriksen (Ursin & Eriksen, 2004) offers a comprehensive definition of stress, aiming to reduce the reliance on words with imprecise meanings and usage. The CATS theory distinguishes four aspects of stress: input or stress stimuli, the individual processing or the stress

experience, the non-specific, general stress response and finally the experience of the stress response. The stress response is believed to serve as a general alarm in a homeostatic system and is therefore described as an essential and necessary physiological response. The alarm elicits specific coping behaviours which are dependent on acquired expectancies of the outcomes of stimuli and available responses. According to Ursin and Eriksen (2004) it is an essential element of CATS that, only when coping is defined as positive outcome expectancy, predictions regarding health and disease can be made.

2.1.2 Stress at work - a problem of modern society

In adult life, core social roles, such as the work role, the family role and marital role link the individual with a structured goal-oriented social environment. Having a job is essential for a continuous income and with this, for the independence from traditional support systems, like family or community welfare. The level of income determines a wide range of life opportunities and education or training for a job, and ensures personal growth and the development of an individual. At the same time, exposure to harmful job conditions can be a major determinant of disability, increased disease susceptibility and premature death (Siegrist, 2007). The nature of work in economically advanced societies has changed considerably over the past decades, caused by social and technical development. Economic constraints produce work pressure in the form of forced occupational mobility, the need to work on temporary contracts, or even rationalisation and cut-down in personnel. Thus, distinct psychological and emotional demands and threats are becoming the major prevalent challenges to health in modern working life, rather than traditional occupational hazards like noise or exposure to heat and cold, which had to be dealt with when industrial mass production still dominated the labour market. Several theoretical models postulate an association of work stress and negative health outcomes. The best known amongst them, the effort-reward-imbalance model (Siegrist, 1996) and

the job demand-job control model of occupational stress (Karasek & Theorell 1990) will be outlined in the following section.

The model of effort-reward-imbalance at work

Siegrist´s effort-reward-imbalance (ERI) model is based on the principles of distributive justice. He postulated that health and well-being in adult life are dependent on adequate personal self-regulation, which in turn is contingent on successful social exchange. Threats to this exchange, such as a lack of reciprocity or exclusion from this exchange are experienced as deviations from the basic grammar of fairness and can impair personal self-regulation by weakening a person's sense of self-efficacy, self-esteem and belonging (Siegrist, 2002). Thus, the basic assumption of the ERI model is, that a lack of reciprocity between personal costs (effort) and personal gains (reward) at the workplace elicits negative emotions and stress, which may result in the development of stress-related disorders. Such efforts include job demands and obligations imposed on the employee, whilst the rewards are conceptualized as falling into three distinct categories: money, esteem and security/career opportunities. People may actively persevere with jobs despite an unfavourable effort-reward-imbalance for a variety of reasons. For example, they may be influenced by strategic concerns such as the improvement of their career prospects, or insufficient alternatives in the job market may force their persistence, or motivational overcommitment may be the driving force.

Overcommitment, a key component of the ERI model, reflects a cognitive-motivational pattern of coping with demands based on elements of Type A behaviour that reflect an extreme ambition in combination with a special need for control and approval (van Vegchel et al., 2005). There is a growing body of research underlining the predictive power of the ERI model in respect to a variety of health outcomes. In fact, associations have been reported between high effort-reward-imbalance and increased risk for cardiovascular disease (CVD), type 2 diabetes, depression, alcohol dependence, and sleep problems and chronic fatigue syndrome (CFS)

(Tsutsumi et al., 2001; Kivimäki et al., 2002; Kudielka et al., 2004b; Kumari et al., 2004; Kouvonen et al., 2006; Dragano et al., 2008; Wada et al., 2008). Overcommitment has similarly been associated with musculoskeletal pain (Joksimovic et al., 2002), CVD incidence (Bosma et al., 1998; Kivimäki et al., 2002), cardiovascular risk factors (Vrijkotte et al., 1999), depression (Dragano et al., 2008), CFS (Wada et al., 2008) as well as neuroendocrine stress reactivity (Wirtz et al., 2008).

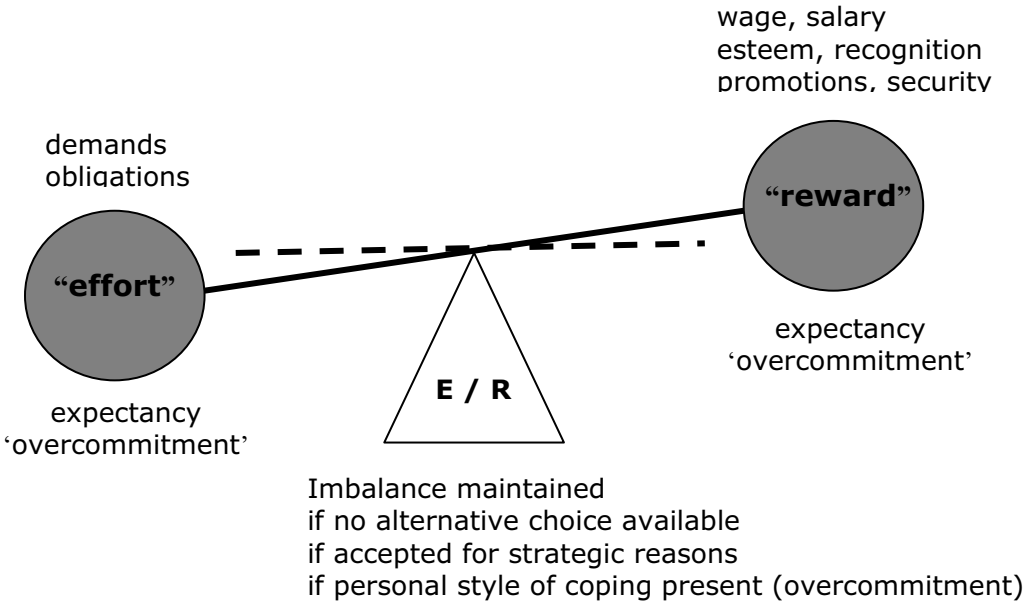

Figure 2.1.1:

The model of effort-reward-imbalance at work, modified from Siegrist, 2002

The job demand-job control model

The job demand-job control model postulates that job strain results from the combined effects of high job demands and low job control. Job control is characterized by two dimensions, namely decision latitude and skill discretion. However, both high demands and low control may also have independent effects on psychological strain and health outcomes. The risk of psychological strain and physical illness are assumed to be especially elevated when the psychological demands of the job are high but the individual's task-specific decision latitude is low (high strain jobs). Finally, coping resources especially the strain-reducing buffering effects of social support have been included in the framework of the revised job demand-job control model (Karasek & Theorell 1990).

Numerous epidemiological and experimental studies have investigated the impact of the demand/control dimension on health outcomes and emphasize the importance of especially low job control for the development of CVD (Schnall et al., 1994; Bosma et al., 1997; Steptoe & Willemsen, 2004). Furthermore, occupational stress defined along the dimensions of demand and control may be particularly relevant to understanding the effects of socioeconomic status (SES) on health and well-being. Examples include the demonstration of an inverse social gradient in mortality from coronary heart disease (Marmot et al., 1984; Marmot et al., 1997) and the differential impact of work stress and SES on the regulation of the hypothalamic-pituitary-adrenal (HPA) axis (Kunz-Ebrecht et al., 2004b).

In a recent cross-sectional study where socioeconomic position was measured by occupational standing and educational achievements, Wege et al. (2008) showed that high demand combined with low control as well as effort-reward-imbalance at work are related to angina pectoris, depression, and poor self-rated health. Although stress at work was related to poorer health in the total study group, the strongest associations were consistently observed in men and women with low educational level or low occupational position.

2.2 Possible psychological consequences of chronic work stress

The two closely related concepts of burnout and exhaustion are discussed as possible consequences of prolonged periods of job-related stress due, for example, to reduced job control or high levels of effort-reward-imbalance or emotional overcommitment.

2.2.1 Burnout

Burnout is a non-psychiatric syndrome characterized by depleted emotional resources, work-related cynicism as well as feelings of work inefficacy or reduced productivity. It has been proposed that these symptoms reflect insufficient recovery from prolonged emotional and interpersonal stress (Maslach et al., 2001). Most researchers have found that job characteristics that provoke chronic job stress, such as high workload, time pressure, lack of job control, insufficient recognition, unfairness, and a lack of social support, are more influential in the etiology of burnout than personality factors such as neuroticism, or demographic factors such as age (Lee & Ashforth, 1996; Maslach, 2007). A recent study of twins concluded that genetic factors did not appear to contribute to the etiology of burnout either. However, familial clustering of burnout has been observed and explains up to 22% of the variance, implicating shared environmental factors as a putative cause (Middeldorp et al., 2005). The psychological symptoms of burnout are often accompanied by various physical symptoms like recurrent headaches, gastro-intestinal discomfort, or disturbed sleep patterns. Burnout has also been positively associated with infectious illnesses, CVD and type 2 diabetes (reviewed in Melamed et al., 2006). Furthermore, burnout is related to measures of job withdrawal, including absenteeism, expression of intentions to leave the job and actual turnover. For people who stay in the job, burnout diminishes productivity and effectiveness due to decreased job satisfaction and a lack of commitment (Maslach, 2007). Cross-time correlations coefficients in longitudinal studies range between 0.50 and 0.60, suggesting that burnout exhibits a remarkable stability

over time (Taris et al., 2005). Though burnout pervades every occupation, it is thought to be more prevalent in service and people-oriented professionals such as teachers, health practitioners, caregivers, fire fighters, and policemen (Maslach et al., 2001; Melamed et al., 2006).

The development of the burnout concept

The psychiatrist Herbert Freudenberger was the first to introduce the term 'burnout', relating it explicitly to physical and emotional exhaustion. Stirred by his experiences as a therapist and social worker he published an article in 1974 with the title *Staff Burn-Out*, in the Journal of Social Issues (Freudenberger, 1974), describing a gradual emotional depletion and a loss of motivation and commitment due to work stress. Interestingly, even at this early conceptual stage, Freudenberger highlighted the majority of symptoms and elements that are still used today to describe the burnout phenomenon. Since many practitioners could identify with this new concept and Freudenbergers very personal memorandum, burnout became increasingly popular. As this article however was mainly based on self-observations and lacked formal definitions and scientific structure, it did not stimulate much research activities (Schaufeli et al., 1993; Hillert & Marwitz, 2006). Burnout research started with Christina Maslach, who coined the empirical term burnout, the way we use it today. As a social psychologist from the University of California, Berkeley, she studied the underlying laws of human behaviour, particularly the question how people cope with emotional arousal on the job. Maslach was especially interested in cognitive strategies like "detached concern", as the postulated ideal tenor in medical professions (Lief & Fox, 1963) as well as the "dehumanization in self-defense", which describes the process of strictly distancing oneself emotionally from others, for reasons of self-protection often accompanied with a cynical attitude (Maslach et al., 2001). She stumbled over the term burnout in a private conversation with a solicitor. He told her that poverty lawyers use the term burnout to refer to a phenomenon similar to her field

of interest (Schaufeli et al., 1993; Hillert & Marwitz, 2006). Maslach adopted the term and set out to define the phenomenon conceptually and scientifically. After interviewing numerous individuals working in different people-oriented professions, it became apparent that burnout seemed to be a complex interplay between physical and emotional exhaustion, a negative self concept in respect to professional efficacy and negative feelings towards work as well as a loss of empathy towards patients or clients. With reference to the findings from these previous interview studies and their own personal perceptions of the burnout phenomenon, Maslach and colleagues then designed a questionnaire in order to study burnout in bigger cohorts (Maslach & Jackson, 1986).

Measuring burnout

The Maslach Burnout Inventory (MBI) is comprised of three subscales, namely emotional exhaustion, depersonalization and lack of personal accomplishment and has now become the most wildly used instrument in burnout research (Maslach & Jackson, 1986). Emotional exhaustion is usually seen as the principle component of burnout and reflects the characteristic lack of energy seen in individuals with burnout. The dimension depersonalization refers to a cynical attitude towards work and was conceptualized as the interpersonal component of burnout. It can also be seen as a dysfunctional coping strategy following exhaustion. The third dimension is lack of personal accomplishment which describes feelings of decline in competence and productivity. This is the self-evaluation component of burnout (Maslach & Jackson, 1986; Maslach et al., 2001). Even though the three-factor structure of the MBI has been broadly confirmed (Schaufeli et al., 2001), the theoretical underpinnings of those three dimensions have been criticized by some researchers as being weak. For example, Kristensen and co-workers (2005) have argued that burnout can be reduced to the dimension of physical and mental fatigue alone and have developed the Copenhagen Burnout Inventory as a new instrument for the assessment of burnout. Similarly, the MBI exhaustion scale has

also been used alone as a measure of burnout (Bekker et al., 2005). However, when equating burnout with fatigue, researchers should weigh the benefit of a parsimonious approach against the drawback of conceptual redundancy, i.e. they risk simply renaming fatigue and thus "serving old wine in a new bottle".

The third dimension of the MBI (lack of accomplishment) has also been criticized on the basis of its relation to the other two dimensions. It has been found to correlate poorly with these (Lee & Ashforth, 1996), suggesting that it may not, in fact describe characteristics that are essential components of the burnout syndrome. However, Schaufeli and co-workers (2005) have argued, that this finding may be explained by differences in the wording of the scales and may, therefore, be an artefact of questionnaire design rather than a conceptual failing of Maslach's definition of burnout. They point out that the accomplishment items are positively worded whilst items in the exhaustion and depersonalization scales are negatively worded.

Finally, there is an unresolved question about whether burnout should be measured continuously or categorically. The MBI measures burnout as a multidimensional continuous phenomenon, providing separate scores for the three different scales. Thus, individuals are described as more, or less, severely burnt-out. The three scales can therefore be interpreted in a time-dependent manner, assuming a sequential process, beginning with exhaustion due to demanding work environments. Leiter and Maslach (1988) originally proposed that then, in order to cope with their feelings of exhaustion, individuals try to gain emotional distance from clients or service recipients. Then, as individuals become increasingly aware of their growing tendency for depersonalization, they perceive themselves as less competent, and lacking in professional efficacy. Golembiewski and co-workers (1999) have postulated a different sequence, starting with depersonalization, leading to reduced accomplishment, which in turn causes emotional exhaustion. Lee and Ashforth (Lee & Ashforth, 1993) examined these two different phase-models of burnout among supervisors

and managers in a public welfare setting. They were able to show that the sequence from emotional exhaustion to depersonalization and lack of personal accomplishment was most consistent with their data, thus supporting the Leiter and Maslach model (Leiter & Maslach, 1988). However, burnout can also be considered as a dichotomous and, therefore, a final state, differentiating those that are burnt-out from those who are not. Clinically validated thresholds for scores from the MBI, allowing the three dimensions to be combined in order to discriminate 'burnout cases' from 'non-cases' have not been provided in the MBI manual but have been developed in The Netherlands (Schaufeli et al., 2001; Brenninkmeijer & VanYperen, 2003; Roelofs et al., 2005).

Other burnout measures

Even though the MBI is the questionnaire most frequently used, various other measures have been developed and implemented. Like the Copenhagen Burnout Inventory (Kristensen et al., 2005), the uni-dimensional Burnout Measure (BM, Pines et al., 1981), for example, focuses strictly on exhaustion and extends the phenomenon beyond the work context. The BM however has also been criticized for confounding the exhaustion of the individual's energetic resources as the core component of the burnout syndrome with depression and anxiety (Melamed et al., 2006). Another well known instrument is the Shirom-Melamed Burnout Measure (SMBM, Lerman et al., 1999; Toker et al., 2005) with its four subscales: emotional exhaustion and physical fatigue, tension, listlessness and cognitive weariness. The Shirom-Melamed Burnout Measure is based on the Conservation of Resources Theory of Hobfoll (1989). In this context, burnout is viewed as an affective reaction to ongoing stress characterized by the gradual depletion of intrinsic energetic resources, leading to emotional exhaustion, physical fatigue and cognitive weariness. Thus the MBI components of depersonalization and lack of accomplishment are seen as consequences of burnout and, therefore, are not included in the assessment. The Teacher Burnout Scale

(TBS, Seidman & Zager, 1987) is an instrument especially targeted at the teaching profession. Its four subscales cover career satisfaction, perceived administrative support, coping with job-related stress and attitudes toward students. Finally the Oldenburg Burnout Inventory (OLBI, Demerouti et al., 2001) is a relatively new and promising instrument focused on two factors (emotional exhaustion and disengagement) that has been repeatedly validated. However, despite this proliferation of instruments designed to detect burnout, no measures have yet made the transition out of the research arena to become tools specifically designed and validated for use in a clinical diagnostic setting.

The diagnosis of burnout

The leading psychiatric classification systems, ICD-10 (International Classification of Diseases, World Health Organisation, 1993) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, 1994) do not provide specific diagnostic criteria for burnout. In the ICD-10 burnout is just briefly mentioned as 'a problem related to life management difficulty' under code Z 73.0. In some European countries burnout patients are currently diagnosed with work-related 'neurasthenia' (ICD-10; code F 48.0), a concept characterized by increased fatigue after mental effort combined with a decrease in occupational performance, thus corresponding to a significant degree with core aspects of the burnout syndrome. Paradoxically, the original definition of 'neurasthenia' excluded burnout by definition. According to the DSM-IV burnout can be included within the categories of 'undifferentiated somatoform disorders' or work-related 'adjustment disorders'.

Prevalence of burnout

Ongoing difficulties with the definition and detection of burnout, together with the lack of clear clinical diagnostic criteria, make it difficult to assess the prevalence of burnout in populations in a comparable manner.

However, studies using questionnaire-based assessments of burnout suggest it to be a relatively common phenomenon. For example, a recent population-based study from Finland that included 3368 working subjects showed that 25.2% of these subjects had mild burnout (defined as experiencing burnout symptoms once a month) and 2.4% suffered from severe burnout (experiencing burnout symptoms at least weekly) as measured with the MBI (Ahola et al., 2005; Honkonen et al., 2006). Burnout appears to be more common in certain at-risk groups. These include individuals, particularly women, with a low level of education and individuals, particularly men, who are single, divorced or widowed (Ahola et al., 2006).

2.2.2 Vital exhaustion

Vital exhaustion (VE) is a concept closely related to burnout. VE is mostly characterized by excess fatigue, accompanied by feelings of increased irritability and demoralization. Individuals are assumed to reach this state when they are no longer able to cope with chronic life stressors such as prolonged work overload, financial problems and associated sleep disturbances. The concept of VE did not arise from a theory formulated a priori, but came instead from clinical
observations of cardiovascular patients (Appels, 2004). Rosenman and Friedman (1975), both American cardiologists, carried out a ground-breaking study in the 1970s that identified a specific behavioural pattern, characterized by impatience, ambition, time pressure and aggressiveness, that more than doubled the risk of a myocardial infarction. However, the association of this so-called Type A behaviour with an increased risk of CVD was not replicated in a later European study (Appels et al., 1987b). Thus, Ad Appels and his colleagues from The Netherlands set out to explain a typical set of symptoms that they had frequently observed in patients with coronary artery disease and myocardial infarction. This set of symptoms was very similar to the Type A behaviour pattern. They asked numerous patients how they had felt in the months preceding their

cardiac event. Patients repeatedly complained about stressful life events, feelings of unusual tiredness and malaise that were not related to physical effort, and often reported chest pain or increased irritability. Based on this data, the novel concept of VE emerged (Appels, 2004).

The final version of the instrument used to assess VE was named the Maastricht Vital Exhaustion Questionnaire and its questions cover unusual fatigue, a disturbed sleeping pattern, general malaise, irritability, energy loss and feelings of discouragement and dejection (Appels et al., 1987a). VE has since been repeatedly identified as a risk factor of coronary artery disease (for reviews see Kop, 1999, 2003) independent of the degree of existing coronary vascular disease. Furthermore, it has been shown that the combination of exhaustion and hostility, an antagonistic and cynical attitude towards other people, significantly increases the risk of restenosis after percutaneous transluminal coronary angioplasty (Mendes de Leon et al., 1996). After establishing the relationship of exhaustion and coronary artery disease in several studies (for reviews see Kop, 1999, 2003), Appels and co-workers set out to demonstrate that this association is plausible from a biological point of view. Since then, subjects with VE have been shown to have lower morning cortisol (Nicolson & van Diest, 2000), higher cytokines, such as tumor-necrosis-factor-alpha (TNF-α) and the interleukins IL1 and IL6 as well as a higher viral load (Appels et al., 2000). Thus, exhausted subjects appear to demonstrate failure of adaptation to social and biological stressors with reduced hypothalamus-pituitary-adrenal (HPA) axis activity which contributes to the activation of immune mediated inflammation (Appels, 2004).

2.2.3 The relationship of burnout, vital exhaustion and depression

There is an undoubted overlap between the symptoms of burnout, VE and depression, leading to an inevitable and ongoing debate about the degree to which these constructs may be treated interchangeably (Iacovides et al., 2003; Appels, 2004; Melamed et al., 2006). It has been suggested that the process of burnout is similar to the process of depression, but

that it occurs in a different context. Whilst depression is a mental disorder characterized by a specific set of clinical symptoms, burnout is coded as 'a problem related to life management difficulty' in the ICD-10, emphasising a definable etiology. Conceptually, the burnout syndrome is closely linked to the social environment at work and therefore the majority of research on burnout originates from the area of work and organisational psychology and occupational medicine. VE and depression, on the other hand, both describe more global states and research originates more from disciplines such as psychiatry, clinical psychology and psychosomatic medicine. For example, Bakker et al. (2000) found that burnout was related to a lack of reciprocity in the occupational domain, whereas lack of reciprocity in intimate relationships was related to depressive symptoms. Importantly, depression is unique in its inclusion of feelings of guilt, hopelessness and worthlessness; this discriminates it from burnout and VE (van Diest & Appels, 1991; Kopp et al., 1998; Suls & Bunde, 2005).

In a meta-analysis of 12 studies, Schaufeli and Enzmann (1998) showed that the MBI subscale of emotional exhaustion shared 26% of its variance with depression, whilst the other two MBI components, depersonalization and lack of personal accomplishment, were less strongly correlated, sharing 13% and 9% of their variance, respectively, with depression. However, the Finnish Health 2000 Study revealed that over 50% of severe burnout cases met DSM-IV criteria for depressive disorders (Ahola et al., 2005) and Kopp et al. (1998) reported a correlation of 0.62 between VE and a depression measure in a large sample of Hungarian adults. However, despite clear conceptual similarities, there are also findings that suggest that these conditions are distinct psychological constructs. For example, Kudielka and co-workers (2004c) have shown in a representative sample of employees of an aircraft manufacturer in Germany, that VE and a common depression scale (depression subscale of the Hospital Anxiety and Depression Scale, HADS-D) loaded on different factors, thereby supporting an earlier study by van Diest and Appels (1991).

A major limitation of previous research is the lack of longitudinal data. One could speculate that burnout and VE can be seen as precursors in the development of a depressive disorder. At the same time, one can hypothesize that a current major depressive episode has a significant impact on the perception of workplace characteristics, such as effort-reward-imbalance, thereby increasing the risk of developing burnout. Furthermore, the relationship between burnout and depression has only been studied using self-report inventories. However, the accurate diagnosis of a mood disorder such as major depression requires further clarification of the duration and clinical validity of symptoms in a clinical interview. Finally, self-report measures may also exaggerate the relationship between the concepts due to common method variance (Lindell & Whitney, 2001). To summarize, the concepts of burnout and depression seem to complement each other and cover partly overlapping phenomena. Thus, in studies on work stress as well as when encountering working patients in clinical practice, it seems beneficial to assess both the occurrence of burnout and of depressive disorders

2.3 The physiology of the stress response

To better understand how psychosocial factors such as chronic work stress or burnout may lead to an increased susceptibility to disease, a detailed understanding of the underlying neuroendocrine physiology is essential. The following section will elaborate the physiology and regulation of two major neuroendocrine systems, the hypothalamus-pituitary-adrenal (HPA) axis and the locus coeruleus-norepinephrine (LC/NE)-autonomic system.

2.3.1 The hypothalamus-pituitary-adrenal (HPA) axis

The HPA axis serves as a central control system of an organism, connecting the central nervous system (CNS) with the endocrine system. The HPA axis is vital for the support of normal physiological functioning and enables organisms to maintain homeostasis under acute stress. Incoming stress signals from higher centres of the brain are integrated in

the hypothalamic paraventricular nucleus of the hypothalamus (PVN) which then coordinates the immediate behavioural, autonomic and neuroendocrine responses to a stressor. In the face of challenge, neural stimulation of the PVN leads to the release of corticotropin-releasing hormone (CRH). After its release into the hypophyseal portal system, CRH then initiates the cleavage of pro-opiomelanocortin (POMC) into adrenocorticotropin (ACTH), beta-endorphin, and other peptides and their subsequent release from the anterior pituitary gland. Whilst CRH directly stimulates ACTH secretion, there are other ACTH secretagogues, like vasopressin, oxytocin, epinehrine and norepinehrine that are known to augment the effects of CRH. The primary target of ACTH is the adrenal cortex, where it triggers the secretion of glucocorticoids (GCs) and adrenal androgens from the zonae fasciculata and reticularis (Chrousos & Gold, 1992). Bioactivity of GCs depends on their interactions with their transport proteins, receptors and activating or deactivating enzymes. In the majority of mammals, including humans, the primary circulating GC is cortisol. In rats and other rodents, it is corticosterone. In humans, the majority of circulating cortisol is bound to plasma proteins, mostly to corticosteroid binding globulin (CBG) (Hammond, 1990). The free hormone hypothesis states that the bound fraction of cortisol is unavailable to tissues and only the free, unbound fraction (about 5-10%) of total cortisol is assumed to be metabolically active (Ekins, 1990). Thus, CBG has an important role in the differential delivery of cortisol to tissues through alteration of binding affinity. Once released from CBG, cortisol passes into the target cells where it binds to intracellular receptors in the cytoplasm.

GCs are amongst the most versatile of hormones, with a wide range of physiological effects. The best studied are those on carbohydrate metabolism and immune function. In order to adapt to the increased metabolic demands under acute stress, GCs enhance circulating levels of energy substrates like glucose, free amino acids and free fatty acids, thereby amplifying catabolic processes whilst simultaneously suppressing

anabolic processes. This is achieved through their action on a number of enzyme systems in the liver, muscles and fat. In the liver for example GCs enhance gluconeogenesis. Additionally, GCs may increase circulating free fatty acids by inhibiting lipoprotein lipase, initiating lipolysis and mobilising free fatty acids from fat depots (Chrousos & Gold, 1992; Ong et al., 1992; McEwen, 2003). Finally, GCs temporarily dampen immune and inflammatory responses, inhibit cytokine synthesis and processes involved in reproduction and cellular growth, thereby ensuring access to resources essential for coping with challenge. However, since an extended bias towards enhanced catabolic processes can take a powerful toll on the organism, GCs also play a key role in the termination of the stress response, preventing it from being pathologically over-activated (Chrousos & Gold, 1992; Herman et al., 2003). Additionally, GCs have important regulatory effects on the cardiovascular system, the regulation of fluid volume and response to haemorrhage as well as on behaviour, appetite control and affective and cognitive processes, like learning and memory (McEwen, 2003). Activity of the HPA axis displays a pronounced circadian rhythm resulting in marked diurnal variation in GC secretion from the adrenal cortex. Peak levels of cortisol and ACTH can be observed shortly after awakening, followed by decreasing concentrations throughout the day, a quiescent period of minimal secretory activity during the night and an abrupt elevation during late sleep (Born et al., 1999; Clow et al., 2004; Wilhelm et al., 2007). This regulation is associated with the light-dark cycle and mediated by the suprachiasmatic nucleus of the hypothalamus (SCN) (Buijs et al., 1997).

Overall functioning of the HPA axis is controlled by several negative feedback loops, acting over three different timescales (fast, intermediate and slow feedback) and through a dual system of nuclear receptors (Chrousos & Gold, 1992; Tsigos & Chrousos, 2002; Dallman, 2007). The mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), which are co-expressed abundantly in neurons of the limbic structure, both bind cortisol but vary significantly in their affinity for cortisol (de

Kloet et al., 2005). The affinity of the MR is about six to tenfold higher than the affinity of the GR. Thus MR activation is maintained even under basal conditions whereas the GR becomes activated under stress and in response to circadian-influenced increases in GC concentrations (Reul et al., 2000). The MR activation is presumed to be involved in the appraisal of stressors and the onset of the stress response, whilst the GR is thought to play a role in the termination of stress responses, including the mobilisation of energy resources required for this purpose. Furthermore, the GR facilitates recovery and promotes memory storage in preparation for future challenges (de Kloet et al., 2005). The mediation of slow genomic actions of GCs through the MR and GR are well studied (de Kloet et al., 2005). There is growing evidence that these receptors also act at the membrane level to mediate rapid non-genomic GC actions. These fast GC effects are assumed to allow for proactive responses, preparing target cells for anticipated perturbations of homeostasis (de Kloet et al., 2007). For example, GC activation of MRs has been shown to cause rapid release of gluatmate in the hippocampus. A rapid increase in high-frequency miniature postsynaptic currents in CA1 neurons in the hippocampus could be demonstrated in response to GCs. Karst and co-workers (2005) were able to demonstrate that GCs increase the glutamate release by increasing release probability of glutamate-containing vesicles. This depends upon 'classical' MRs, which are inserted into the membrane and have a tenfold lower apparent affinity than the nuclear MRs .

Dysfunctional regulation of the HPA axis has been associated with various psychosomatic and stress related pathologies (for reviews see Heim et al., 2000; Raison & Miller, 2003). HPA axis *hyper*activity has repeatedly been related to major depression (for reviews see Holsboer, 2001; Parker et al., 2003) and cardiovascular problems (McEwen, 1998a, 1998b). H*ypo*activity of the HPA axis on the other hand has been associated with autoimmune processes such as lupus erythematosis (Weiner, 1991), multiple sclerosis (Adams & Victor, 1989), atopy and neurodermatitis (Buske-Kirschbaum et al., 1997; Buske-Kirschbaum & Hellhammer, 2003) and psychosomatic

and psychiatric disorders such as post traumatic stress disorder (PTSD) (Yehuda et al., 1993; Rohleder et al., 2004) fibromyalgia (Demitrack & Crofford, 1998) and chronic fatigue syndrome (Cleare et al., 2001; Gaab et al., 2002; Nater et al., 2008).

2.3.2 The locus coeruleus/norepinephrine autonomic system

The locus coeruleus-norepinephrine/autonomic system is located in the brain stem and centrally regulated by the hypothalamus and the locus coeruleus (LC). It functions globally as an alarm system and, when activated, it initiates the discharge of norepinephrine from an extremely dense network of neurons throughout the brain. This results in enhanced arousal, vigilance, and increased anxiety. The sympathetic division of the autonomic nervous system plays an important role in the adaptation to stressful situations, via its peripheral effectors: the sympathetic nerves and the adrenal medulla (Chrousos & Gold, 1992). The parasympathetic division of the autonomic nervous system typically acts to oppose the effects of the sympathetic nervous system. The two systems act in close concert, with the parasympathetic nervous system withdrawing to enhance effects of sympathetic arousal or increasing to reduce them (Tsigos & Chrousos, 2002).

Efferent preganglionic fibres, whose cell bodies are located in the spinal cord, are responsible for the sympathetic innervation of peripheral organs. These nerves synapse in bilateral chains of sympathetic ganglia with postganglionic sympathetic neurons, which innervate the smooth muscle of the vasculature, the heart, skeletal muscles, kidney, gut, fat and many other organs. The primary neurotransmitter of the preganglionic neurons is acetylcholine whereas the postganglionic neurons are mostly noradrenergic. Through the adrenal medulla, the sympathetic nervous system also has a humoral contribution, providing the majority of circulating epinephrine and some of the norepinephrine (Chrousos, 1998). Under resting conditions, only low levels of catecholamines are released from the adrenal medulla into the circulation. However, during stress up

to 35% of the total circulating norepinephrine may be secreted from the adrenal medulla, whilst the remaining proportion is released from sympathetic nerve endings and may enter the blood stream at the side of release. The target organs of catecholamines secreted from the adrenal medulla may be identical to those of the neurotransmitter of postganglionic sympathetic neurons. However, the majority of norepinephrine released from sympathetic nerve endings acts locally with only a small proportion reaching the blood stream (reviewed in Kudielka & Kirschbaum, 2007).

Epinephrine and norepinephrine produce their effects by binding to adrenergic receptors on the surface of target cells. These receptors are exemplary transmembrane proteins that, through coupling with G-proteins, stimulate or inhibit intracellular signalling pathways. In the face of challenge, catecholamine secretion leads to a rapid mobilisation of energy stores (through increased supply of free fatty acids and glucose by glycogenolysis and lipolysis) as well as a down-regulation of less important organ functions (e.g. those of the gastrointestinal tract and reproductive systems). Furthermore, catecholamines have a substantial impact on cardiovascular functioning during stress, increasing heart rate, cardiac output, and blood pressure. Other effects include enhanced respiratory extraction of oxygen via airway dilatation, enhanced platelet aggregation and reduced clotting time (for a recent review see Kudielka & Kirschbaum, 2007). Norepinephrine also activates the amygdala, the principal brain locus for fear-related behaviours, and enhances the long-term storage of emotional memories in the hippocampus and striatum (Tsigos & Chrousos, 2002).

2.4 Assessment of basal HPA axis regulation, feedback mechanisms and HPA axis reactivity

The following section will briefly introduce psychoendocrinological research tools that are commonly used to assess HPA axis regulation.

2.4.1 Measuring basal HPA axis regulation: Cortisol awakening rise and day profiles

There is a considerable body of evidence to show that free salivary cortisol levels and total plasma cortisol levels both show a marked increase (about 50-100%) during the first hour after awakening in the majority of people (Wüst et al., 2000a; Dockray et al., 2008). Pruessner and colleagues (1997) were the first to suggest that the assessment of this rise in cortisol after awakening might represent a useful index of adrenocortical activity. In a highly controlled study under sleep laboratory conditions, Wilhelm and co-workers (2007) recently showed that this cortisol awakening rise (CAR) is a genuine response to awakening, as the transition from sleep to the waking state was found to be a prerequisite for the CAR to occur. The CAR may be simply assessed by taking four saliva samples (directly after awakening, 30, 45, and 60 minutes after awakening), with strict reference to awakening time. A major advantage of this non-invasive measure is its utility in ambulatory settings. Thus, subjects may collect saliva at home or at the workplace. However, compliance with saliva sampling procedures, especially their timing, is crucial to obtain valid data in such settings. Kudielka and co-workers showed that cortisol profiles differ significantly between compliant and non-compliant subjects, with non-compliant subjects showing a significantly lower CAR (Kudielka et al., 2003). Electronic monitoring devices (MEMS® Track Cap; AARDEX, Ltd., Switzerland) can be used to ensure accurate timing of saliva collection. This ambulatory assessment of salivary cortisol measures also benefits from the high temporal stability of salivary cortisol at room temperature, with minimal changes demonstrable over periods of up to one month. Therefore samples can be sent by post and do not require specialized storage which compares favourably to many other biological parameters (Kudielka & Wüst, 2008).

The CAR has been shown to have a medium to high day-to-day stability (Wüst et al., 2000b). However, a recent analysis by Hellhammer and colleagues demonstrated that the CAR on a given day is considerably

influenced by situational factors. Thus, repeated daily measurements are almost certainly necessary in order to obtain reliable trait measures (Hellhammer et al., 2007). The magnitude and time course of the CAR are influenced by a variety of factors. These include genetic factors, age and sex, awakening time, sampling compliance, and day of the week (for a recent review see Kudielka & Wüst, 2008). Peak awakening cortisol responses do not appear to differ by sex. However, women appear to have a slower decrease compared to that of men (Wüst et al., 2000b). Findings regarding the impact of age are not completely consistent. Whilst some studies have reported no associations between the magnitude or the time course of the CAR and age (Pruessner et al., 1997; Wüst et al., 2000b), Kudielka and co-workers have reported small but significant age effects (2003). In their study, cortisol levels immediately after awakening were positively associated with age whereas the following rise of cortisol was less pronounced in older individuals compared to younger participants. Furthermore the CAR appears to be influenced by the awakening time, with early morning awakeners showing a significantly higher CAR compared to late awakeners (Kudielka & Kirschbaum, 2003; Federenko et al., 2004). In line with this, there is data supporting the idea that morning, compared to evening, chronotypes (*'larks'* in comparison to *'owls'*) show higher cortisol levels in the first hour after awakening (Kudielka et al., 2006b, 2007a). It has also been repeatedly demonstrated that the CAR is more pronounced on work compared to weekend days (Kunz-Ebrecht et al., 2004a; Schlotz et al., 2004). In contrast, the impacts of smoking, coffee, the female menstrual cycle phase, and sleep length appear to be minor (Wüst et al., 2000b; Kudielka & Kirschbaum, 2003; Clow et al., 2004; Steptoe & Ussher, 2006; Badrick et al., 2007; Harris et al., 2007).

Altered HPA axis regulation reflected in the CAR has been associated with various health outcomes (reviewed in Kudielka & Wüst, 2008). A higher CAR has been repeatedly shown to be associated with depressive symptomatology (Bhagwagar et al., 2003, 2005; Pruessner et al., 2003),

whereas chronic fatigue syndrome (Roberts et al., 2004; Nater et al., 2008), posttraumatic stress disorder (Rohleder et al., 2004; Wessa et al., 2006; de Kloet et al., 2007) and early loss experience (Meinlschmidt & Heim, 2005) all seem to be associated with a reduced CAR. In patients with various forms of hippocampal damage (Buchanan et al., 2004) as well as in a small sample of patients with global amnesia (Wolf et al., 2005), no CAR could be observed.

Thus, it can be summarized that a range of studies have demonstrated an association between the CAR and psychosocial variables, stress and health. However, the interpretation of individual differences in CAR levels is still under debate and whether positive health outcomes and well-being are consistently associated with a larger or smaller awakening responses remains unclear. Adams and colleagues (2006) suggest that a functional interpretation may help in reconciling the inconsistencies in findings. They examined how day-to-day variations in psychosocial experience are related to daily variations in cortisol. Their results demonstrate that, although there is thought to be a trait component reflected in the CAR, psychosocial and emotional experiences encountered during the previous day had a profound effect on the CAR on the following day. A factor comprised of loneliness, sadness and feeling threatened was associated with a higher next-day CAR, whereas CAR levels measured in the morning did not predict experiences of these states later the same day. Lower wake-up cortisol levels predicted fatigue later that day, which could either be explained by altered metabolic processes or increased immune system activation. Thus, the authors speculate that the CAR is an adaptive response designed to provide the individual with the energy and resources needed to meet the anticipated demands of the upcoming day. The response is based on an evaluation that is influenced, at least in part, by the experiences of the previous day. In the case of chronic stress, this typically adaptive mechanism potentially gets exhausted over time and the CAR is no longer effectively modulated by anticipated daily demands, leading to long-term physiological costs.

An ambulatory cortisol day profile extends the cortisol sampling beyond the CAR and covers the peak waking level, the decrease over the course of the day and low evening levels. However, the health consequences of aberrant day profiles (e.g. typically flattened cortisol rhythms) have not yet been precisely delineated. One the one hand, alterations in rhythmicity of cortisol have been associated with various negative outcomes, including early mortality from cancer (Sephton et al., 2000), obesity and disrupted glucose metabolism (Rosmond et al., 1998). On the other hand aberrant day profiles have also been associated with reduced symptom awareness of upper respiratory illness (URI) and reduced health anxiety (Edwards et al., 2003; Ferguson, 2008). Smyth et al. (1997) assessed the cortisol diurnal cycle in 109 healthy employed and unemployed community residents. Seventeen percent did not show the expected cortisol diurnal profile and those individuals reported fewer URI symptoms. The pattern of the diurnal cycle however was not related to any demographic or psychosocial measures. Edwards and co-workers (2003) also showed that subjects with a less pronounced diurnal decline (flatter profiles) reported fewer URI symptoms. In contrast, in studies on metastatic breast cancer a flatter day profile seems to be related to ill-health and early mortality (Sephton et al., 2000; Bower et al., 2005; Abercrombie et al. 2004; Spiegel et al., 2006).

With regard to stress at work, high levels of job-related stress have previously been associated with a flattening of the diurnal cortisol rhythm (Caplan et al., 1979) and a study by Ockenfels and co-workers (1995) on the relationship between employment and diurnal cortisol activity showed, that unemployed subjects have higher morning levels and lower evening levels than employed subjects. Furthermore, Adam and Gunnar (2001) report that, after controlling for demographic and medical variables, positive relationship functioning was associated with higher morning cortisol levels and a steeper decline in cortisol across the day, whilst greater hours of maternal employment and a greater number of children

in the household were associated with lower morning cortisol values and a less steep decline in cortisol levels across the day.

Finally, Adam et al. (2006) recently showed that not only the CAR, but also the diurnal cortisol slope, changes in systematic ways on a day-to-day basis. Levels of tension and anger each day were related to flatter diurnal cortisol slopes the same day, primarily through the influence of tension and anger on higher evening cortisol levels. Thus, slopes measured on a particular day are likely to reflect a combination of a trait aspect and state variation associated with daily psychosocial experiences. The authors speculate that repeated daily alterations in cortisol slopes over time could become entrained, resulting in a persistent alteration of the trait pattern with consequences on health and physical functioning. One could hypothesize that similar findings would arise with respect to negative emotions due to chronic work stress.

To conclude, studies investigating the influence of an aberrant diurnal cortisol rhythm (i.e. flattened day profiles) on psychosocial variables and health outcomes render inconsistent results and more research is needed to clearly delineate the putative role of the diurnal cortisol rhythm in the regulation of physiological function.

2.4.2 Testing feedback sensitivity of the HPA axis: The Dexamethasone Suppression Test

As described in section 2.3.1, the HPA axis is regulated by the negative feedback action of cortisol on receptors in the hippocampus, hypothalamus and pituitary gland. This feedback loop suppresses the secretion of CRH, ACTH and cortisol itself. The Dexamethasone Suppression Test (DST) is one of several endocrine tests used to measure altered HPA axis regulation. It tests HPA axis negative feedback efficiency by determining the degree to which endogenous cortisol release is suppressed by intake of oral dexamethasone. This synthetic GC acts primarily by binding to GRs in the pituitary gland, mimicking the negative feedback effects of endogenous cortisol such that ACTH and cortisol

release is reduced (de Kloet, 1997, 1998; Cole et al., 2000). Pre-medication with dexamethasone normally takes place the night before cortisol samples are collected. Application of a low dose of dexamethasone with concentrations of 0.5mg or even 0.25mg in adult humans (so-called low-dose DST) is preferable in order to prevent complete suppression of endogenous cortisol production the following day, allowing for hypersuppression (strong suppression) or indications of 'non'-suppression (less suppression) (Yehuda et al., 1993; Huizenga et al., 1998). It has been demonstrated that a high proportion of patients with various affective disorders have elevated cortisol levels after applying the DST (Holsboer, 2000, 2001; Parker et al., 2003), thus escaping the suppressive effect of dexamethasone. In PTSD patients on the other hand enhanced cortisol suppression following dexamethasone has been observed (Yehuda et al., 1993).

2.4.3 Testing HPA axis reactivity under acute stress: The Trier Social Stress Test

After reviewing the literature and finding that situations like final examinations in college students, periods before surgery, combat and novel situations in general had been associated with enhanced levels of 17-hydroxycorticosteroid (17-OHCS) Mason (1968a) assumed that psychological stimuli are among the most potent stimuli to activate the HPA axis. He postulated that HPA axis activation is initiated whenever a stimulus is perceived as novel, uncontrollable, unpredictable, or ambivalent, or if the individual anticipates negative organismic or psychological consequences. Dickerson and Kemeny showed in a recent meta-analysis that acute psychological stress-protocols only elicit solid cortisol responses if they are characterized by uncontrollability, social-evaluative threat or forced failure (Dickerson & Kemeny, 2004). Tasks containing both components (uncontrollability and social-evaluative threat) were associated with the largest HPA axis stress responses and the longest recovery times.

The Trier Social Stress Test (TSST) was introduced more than 15 years ago as a standardized protocol for the experimental induction of moderate psychosocial stress in laboratory settings (Kirschbaum et al., 1993). Its protocol mainly consists of a brief preparation period (3 min) and a test period with two tasks. First, subjects have to deliver a free speech in the form of a job interview (5 min) and secondly they have to perform mental arithmetic (5 min), both in front of a trained audience. The audience is introduced as a team of experts in monitoring nonverbal behaviour and the participants expect to be videotaped for a later analysis of their performance. The audience clothed in white coats and equipped with stopwatches and writing material, is instructed not to respond to the participant with any verbal or facial feedback. At the end of the laboratory appointment the audience members inform the subject about the goal of the study and the nature of the stressor. In about 70–80% of all subjects salivary cortisol levels rise two to threefold in response to the TSST, with peak levels around 10–20 min after cessation of the stress task. Among others, levels of total plasma cortisol, ACTH, epinephrine and norepinephrine, cytokines and blood coagulation parameters have also been shown to rise in response to the TSST. Sampling time points should cover prestress levels, the initial stress response, peak level and recovery, however exact timing always depends on the dynamic of the selected outcome variable (Kudielka et al., 2007c). Repeated exposure to the TSST leads to a rapid habituation of the HPA axis response in the majority of subjects, however Wüst et al. (2005) demonstrated that this habituation is subject to substantial inter-individual variation. Sixteen percent of the participants even showed a sensitization across three test sessions.

Generally, there is a considerable intra- and inter-individual variation in respect to the magnitude of HPA axis responses after psychosocial stress. In numerous studies it could be demonstrated that a variety of factors contribute to this variation in HPA axis reactivity. One consistent finding of studies using the TSST is that men show a significantly larger salivary cortisol and ACTH response than women, whilst this sex difference is

absent in the plasma cortisol response (Kirschbaum et al., 1992; for reviews see Kudielka & Kirschbaum, 2005; Kajantie & Phillips, 2006). Kirschbaum and co-workers (1999) showed, that women in the luteal phase have saliva cortisol stress responses comparable to men, whereas women in the follicular phase or women taking oral contraceptives showed significantly lower free cortisol responses. These findings indicate a possible impact of female sex steroids as potential mediators of HPA axis responses to psychosocial stress. Thus a clear distinction has to be made between the total cortisol secretion and the levels of bio-available free cortisol. Kumsta et al. (2007) recently showed that differences in salivary cortisol levels may at least in part be explained by estradiol-induced changes in corticosteroid binding globulin (CBG) levels.

To investigate the impact of age on HPA axis reactivity to psychosocial stress, Kudielka and colleagues (2004a) compared 102 healthy subjects with an age range from 9 to 76 years. The TSST induced significant HPA axis responses across all age groups. Sex differences were absent in children and young adults, in elderly subjects however gender had significant effects. Elderly men showed larger free salivary cortisol responses compared to women whereas elderly women showed larger total plasma cortisol responses compared to younger women and men. Larger ACTH responses could be observed in younger adults, potentially due to a heightened hypothalamic drive in younger men, which seems to decrease with age. Chronic smoking is an example for a life-style factor with considerable impact on HPA axis stress reactivity. After binding to cholinergic receptors in the locus coeruleus and hypothalamus, nicotine initiates the release of CRH, thereby stimulating the HPA axis. Habitual smokers show blunted cortisol responses to the TSST, possibly reflecting a reduced responsiveness of the HPA axis due to the repeated nicotine exposure (Rohleder & Kirschbaum, 2006). Other factors that contribute to intra- and inter-individual variation include caffeine and alcohol intake, lactation and breast feeding, energy supply, genetic and personality

factors, social support, social hierarchy, interventions as well as cellular mechanisms (for recent reviews see Kudielka et al., 2007b, 2007c).

2.5 HPA axis dysregulation in burnout and vital exhaustion

Studies on HPA axis regulation in burnout and vital exhaustion are still relatively rare and the results that have been published so far seem to render incoherent results. The following section summarizes the existing literature on cortisol regulation under (a) basal and (b) acute stress conditions in burnt-out and (vitally) exhausted subjects and discusses possible explanations for the inconsistencies in findings.

Burnout

To date, evidence on possible relationships between burnout and HPA axis functioning remains somewhat inconsistent. There is data showing either no association between cortisol levels and burnout as well as results suggesting a hyper- as well as a hypoactive HPA axis (for a recent review see Kudielka et al., 2006a).

Two studies by Grossi and co-workers (1999; 2003) examining total cortisol levels in a single blood sample could not reveal associations between cortisol and burnout. Also, in a study by Ekstedt et al. (2004) no differences in morning plasma cortisol levels, a cortisol awakening profile nor the diurnal cortisol profile could be observed in 24 subjects with high versus low burnout scores. Langelaan and co-workers (2006) who compared burnt-out, work-engaged, and healthy managers, also report no differences in the cortisol awakening response (CAR) between groups. In a study of Pruessner and co-workers (1999) however, school teachers with high burnout showed a lower CAR on two sampling days. Furthermore, Morgan et al. (2002) showed in a sample of 41 US soldiers, that higher levels of burnout were associated with lower cortisol levels in the morning and higher cortisol concentrations in the evening. This finding could point to a flattened diurnal secretory cycle in burnt-out military personnel. In contrast, Melamed and co-workers (1999) observed higher salivary

cortisol levels in the morning and afternoon in industrial workers, with non-chronic as well as chronic burnout compared to employees showing no burnout symptoms. Finally, Söderström et al. (2006) examined the diurnal pattern of cortisol, subjective activation, and mental fatigue among workers scoring high and low on burnout. Subjects scoring high on burnout showed higher awakening cortisol during the workday than during the weekend. They also showed higher ratings for activation and mental fatigue during the weekend than the low-burnout group.

Only a few studies investigated basal HPA axis functioning in clinically diagnosed burnout patients. Moch et al. (2003) measured free cortisol secretion in 24/h urine samples before and after a stress management program in 16 female burnout patients (measurements once a month over a four month period) and a healthy untreated control group (measurements at first and fourth month). Relative to the control group, reduced cortisol excretion could be observed in the patient group. This finding seemed to be independent of clinical and psychological improvement due to the intervention. Furthermore, patients had significantly lower morning cortisol serum concentrations (but not ACTH levels) than controls at month four. In a pilot study, Mommersteeg et al. (2006b) found lower salivary cortisol levels after awakening in a group of burnout patients being on sick-leave, compared to a healthy control group. No differences in cortisol levels were observed during the remainder of the day. Even though a psychotherapeutic intervention led to a significant increase in the initially lowered morning cortisol levels, this did not seem to be related to improvements in psychological well-being. In contrast, De Vente and colleagues (2003) observed higher cortisol levels after awakening in a group of 22 clinically diagnosed burnout patients compared to 23 healthy controls, but no differences in cortisol levels at 12 a.m. In addition to the assessment of basal HPA axis activity, a laboratory stress protocol was also applied. However, a close inspection of the reported stress responses reveals that the chosen stress task (i.e. speech, mental arithmetic) did not elicit a task-related cortisol response.

Thus, significant differences in cortisol levels over the course of the test session between burnout patients and controls are due to higher pre-stress cortisol levels in burnout patients. In a recent study by Grossi and co-workers (2005) sex-specific analysis of morning cortisol profiles revealed, that female patients had a significantly higher CAR than subjects with low burnout, whilst cortisol levels of subjects with moderate burnout fall in between. No significant main effect of burnout could be observed in men. Finally, Mommersteeg and colleagues (2006a) showed in a second study, that in a sample of 74 clinically diagnosed burnout patients and 35 healthy controls, clinical burnout was neither reflected in the CAR nor in the diurnal cortisol day curve.

To date, four studies investigated HPA axis feedback sensitivity, all using a 0.5mg DST. Two did not find any associations with burnout (Langelaan et al., 2006; Mommersteeg et al., 2006a) whilst Pruessner et al. (1999) observed greater cortisol suppression after dexamethasone intake in teachers scoring high versus low on burnout. Sonnenschein et al. (2007) also found a positive association between more severe burnout symptoms and stronger cortisol suppression in 42 burnout patients. Interestingly, this effect could only be observed when applying the experience sampling method, but not with retrospectively assessed burnout by questionnaire.

To summarize, there is evidence supporting the idea that burnout is associated with dysregulations of basal HPA axis functioning as well as HPA axis feedback. However, the direction of this relationship still remains unclear and even very well-conducted and highly-controlled studies, such as the one performed by Mommersteeg and colleagues (2006a), could not find any associations between burnout and altered HPA axis function. Only one study examined a possible impact of burnout on HPA axis responses under acute psychosocial stress, although no task-related response could be observed (De Vente et al., 2003). Thus, the reported group differences should be attributed to higher baseline levels in burnout patients. As described above, psychological stress-protocols eliciting solid cortisol responses are characterized by uncontrollability, social-evaluative threat

or forced failure (Dickerson & Kemeny, 2004). Thus, further studies are needed to better elucidate the role of burnout in HPA axis reactivity, applying reserach tools suitable to provoke an acute stress response.

Table 2.1 (A and B) gives a summary of the main studies published so far. The table differentiates between those studies, investigating burnt-out but otherwise healthy subjects and those including patients with a clinical diagnosis.

Actualized Table on the basis of Table 1 from Kudielka, Bellingrath and Hellhammer, 2006

(A) Burnout (BO): Subjects high versus low on BO but without clinical diagnosis			
Ekstedt et al., 2004	◆ single blood sample between 8-9 a.m.: total cortisol ◆ CAR (4 samples): salivary cortisol ◆ diurnal cortisol profile (5 samples): salivary cortisol	◆ no group differences high vs low BO ◆ no group differences high vs low BO ◆ no group differences high vs low BO	ns ns ns
Grossi et al., 1999	◆ single blood sample between 8-10 a.m.: total cortisol	◆ no association BO and cortisol	ns
Grossi et al., 2003	◆ single blood sample between 8-10 a.m.: total cortisol	◆ no group differences high vs low BO	ns
Langelaan et al., 2006	◆ CAR (4 samples): salivary cortisol ◆ low-dose DST (0.5mg DEX) and CAR: salivary cortisol	◆ no group differences high vs low BO ◆ no group differences high vs low BO (after DEX: lower CAR in work engaged managers)	ns ns
Melamed et al., 1999	◆ salivary cortisol 8 a.m. and 4 p.m.	◆ higher 8 a.m. levels in BO ◆ higher 4 p.m. levels in BO	↑ ↑
Morgan et al., 2002	◆ morning and evening samples: salivary cortisol (exact time points not given, p/F statistics not given) ◆ [total cortisol]	◆ lower morning levels in high BO ◆ higher evening levels in high BO [results not reported]	↓ ↑
Pruessner et al., 1999	◆ CAR (4 samples) on 3 consecutive days: salivary cortisol ◆ low-dose DST (0.5mg DEX) and CAR: salivary cortisol	◆ lower CAR in high BO ◆ after DEX lower CAR in high BO	↓ ↓
Söderström et al., 2006	◆ CAR, one workday, one weekend day (4 samples): salivary cortisol ◆ diurnal cortisol profile (5 samples): salivary cortisol	◆ no overall group differences high versus low BO, but higher CAR in high BO on a workday ◆ no group differences high versus low BO	ns ↑ ns

(B) Burnout (BO): Clinically diagnosed BO patients versus controls			
De Vente et al., 2003	◆ CAR (3 samples): salivary cortisol ◆ 12 a.m.: salivary cortisol ◆ laboratory stress test (speech, mental arithmetic): salivary cortisol	◆ higher CAR in BO patients ◆ no group differences ◆ no task-related response (sign. group differences attributable to higher pre-stress ('baseline') levels in BO patients	↑ ns ns
Grossi et al., 2005	◆ CAR (4 samples): salivary cortisol	◆ higher CAR in female BO patients ◆ no group differences in men	♀ ↑ ♂ ns
Moch et al., 2003	◆ 24/h cortisol in urine (before and after intervention) ◆ single blood sample 8 a.m.: total cortisol ◆ single blood sample 8 a.m.: ACTH	◆ lower levels in BO patients ◆ lower 8 a.m. levels in BO patients at month 4 ◆ no group differences	↓ ↓ ns
Mommersteeg et al., 2006a,	◆ CAR (3 samples): salivary cortisol ◆ diurnal cortisol profiles (3 samples): salivary cortisol ◆ CAR (3 samples): salivary cortisol after psychotherapy	◆ lower CAR in BO patients ◆ no group differences (patients vs. controls) ◆ increased CAR in BO patients after psychotherapeutic intervention	↓ ns ↑
Mommersteeg et al., 2006b	◆ CAR (3 samples): salivary cortisol ◆ diurnal cortisol profile (3 samples): salivary cortisol ◆ low-dose DST (0.5mg DEX) and CAR: salivary cortisol	◆ no group differences (patients vs. controls) ◆ no group differences (patients vs. controls) ◆ no group differences (patients vs. controls)	ns ns ns
Sonnenschein et al., 2007	◆ CAR (3 samples): salivary cortisol ◆ low-dose DST (0.5mg DEX) and CAR: salivary cortisol	◆ lower CAR in BO patients ◆ after DEX lower CAR in BO patients	↓ ↓

Vital exhaustion

Regarding VE, the findings from the majority of studies point to a down-regulated HPA axis under basal conditions as well as under acute (laboratory) stress (for a recent review see Kudielka et al., 2006a). Only three studies investigated basal HPA axis regulation in relation to VE. Dahlgren et al. (2004) instructed 34 healthy white collar workers to collect five salivary cortisol samples during one day of a work week with high stress and one day during a week with low stress. Whilst one group of subjects showed higher morning cortisol levels in the high stress week compared to the low stress week, the other group showed an opposite pattern. The latter group was characterized by higher workload, fatigue, and exhaustion during both weeks. Nicolson & van Diest (2000) report that 29 subjects with high levels of VE showed marginally lower basal salivary cortisol levels throughout the day and significantly lower cortisol concentrations in the evening than 30 healthy controls. In contrast, Koertge et al. (2002) found a small but significant positive association between VE and total cortisol measured by a single morning blood sample in a large sample of N=238 female patients with acute coronary syndrome.

In addition to the assessment of basal HPA axis activity, a few studies also investigated the impact of VE on HPA axis reactivity after stress. Data from Nicolson & van Diest (2000) for example point to a subtle HPA axis hyporeactivity in association with VE. The cortisol increases after a laboratory speech task, were generally extremely small with mean increases of 0.79 nmol/l in vitally exhausted subjects and 1.36 nmol/l in controls. Six responders could be observed in a group of 30 controls, showing cortisol increases above 2.76nmol/l. In the VE group however none of the 28 subjects could be classified as responder. Kudielka et al. (2006c) recently applied the TSST three times in 25 healthy middle-aged male employees with test sessions one week apart. Data revealed that mean cortisol responses showed the well-known general habituation effect across test exposures and above that a negative dose-response

relationship between exhaustion and the degree of habituation. Nineteen individuals showed a response habituation whereas six individuals, reporting higher exhaustion scores showed a response sensitization over the three sessions. One could speculate that an existing impact of exhaustion is initially 'masked' by situational or psychological factors since effects of exhaustion became fully apparent only after repeated stress exposure.

In the cross-cultural comparison LiVicordia Study, Lithuanian and Swedish men underwent a standardized laboratory stress battery (i.e. anger recall, mental arithmetic, cold pressure test). Kristenson et al. (2005) reported that the cortisol response to the stress test was positively associated with self-reported health (SRH) and negatively associated with VE. However, after including SRH and VE into the same model, the former was still related to cortisol reactivity but the effect of VE was lost. Finally, the group around Keltikangas-Järvinen, Räikkönnen and Adlercreutz assessed VE in a study examining potential associations between various behavioural and psychological predictors, neuroendocrine responses and insulin-resistance in middle-aged men (Räikkönen et al., 1996; Keltikangas-Järvinen et al., 1997, 1998). VE combined with depression was negatively correlated with mean ACTH levels and positively correlated with the mean cortisol/ACTH ratio during oral glucose tolerance testing. Futhermore, a combined factor of VE and anger-out was associated with an elevated cortisol response to ACTH stimulation with DEX-premedication. Taken together, these findings suggest that VE, in combination with other psychological predictors, has a moderating influence on the hormonal and metabolic parameters studied.

Considering that the only minor positive association between VE and total cortisol was seen in a patient sample with coronary artery syndrome, one can conclude, that the findings regarding VE seem to support the hypothesis of a down-regulated HPA axis under basal conditions as well as after acute stress.

Table 2.1 (C) summarizes the results of the main studies on VE and HPA axis regulation.

(C) Vital Exhaustion (VE)			
Dahlgren et al., 2004	◆ 2 diurnal cortisol profiles (once during each a week with high and low stress levels; 5 samples: +15 min after awakening, 10 a.m., 1 p.m., 4 p.m., bedtime): salivary cortisol	◆ the group with low morning cortisol levels in the high stress week compared to the low stress week had higher workload, fatigue, and exhaustion	↓
Koertge et al., 2002	◆ single blood sample between 8-9 a.m.: total cortisol	◆ small positive association between VE and cortisol in females with coronary stenosis ($r=.13$, $p \leq .05$)	↑
Kudielka et al., 2006	◆ 3 TSST exposures one week apart: salivary cortisol	◆ VE associated with reduced habituation across 3 stress exposures in males ◆ VE marginally associated with lower cortisol responses to first stress exposure ($p=.14$)	↓ (↓)
Nicolson & van Diest, 2000	◆ day 1: evening samples (9:30 p.m., 10:35 p.m.): salivary cortisol ◆ day 2: diurnal cortisol profile (6:55 a.m., 11 a.m., 4 p.m., 5:40 p.m., 7 p.m.): salivary cortisol ◆ laboratory speech task	◆ lower levels in VE patients ◆ marginally lower levels in VE patients ($p=.08$) ◆ significant response less likely in VE patients	↓ (↓) ↓

Possible confounders

How can these inconsistencies in findings regarding the relationship between burnout, VE and HPA axis activity be explained? One could speculate that the contradictory results could at least in part be due to methodological aspects as well as confounding factors of HPA axis regulation. First of all, HPA axis regulation was investigated on different levels, thus comparing results from ACTH measurements, total cortisol in blood or free cortisol in saliva. Furthermore different, sometimes inadequate sampling procedures have been applied, for example a single venipuncture in the morning, in contrast to the assessment of the CAR or cortisol day profiles with varying numbers of saliva samples. Also, different studies used different psychometric scales to measure burnout and generally no accepted and validated clinical diagnostic criteria exist to define a patient group. In the study of Sonnenschein et al. (2007), for example, the association between burnout and stronger cortisol suppression after dexamethasone became only apparent with the experience sampling method, but not with retrospectively assessed burnout by questionnaire.

Furthermore, in most of the past studies, data was only available in either men or women. When data was collected in both men and women, groups were subsequently combined to form one larger study sample. However, possible gender-specific effects might mediate the relationship between burnout/VE and HPA axis regulations, as indicated by the study of Grossi and co-workers (2005). Finally, other factors that are known to influence basal or stress-related cortisol concentrations were not always considered with similar care. Values can be influenced by medication intake or smoking habits (for reviews see Clow et al., 2004; Kudielka et al., 2007b; Kudielka & Wüst, 2008). Time of awakening is an important confounder that needs to be controlled, when measuring the CAR and in the case of ambulant saliva sampling, subjects' compliance significantly explains inter- and intra-individual variation in cortisol levels. In studies investigating HPA axis reactivity to acute stress, different kinds of stress

protocols were applied and furthermore, the female menstrual cycle phase or intake of oral contraceptives were only sometimes controlled for (Kirschbaum et al., 1999; Kudielka et al., 2007b, 2007c).

To conclude, the potential impact of burnout and VE on HPA axis regulation remains elusive. One can only speculate that the underlying effects might either be rather small, or only detectable with highly sensitive research tools (e.g. very low-dose DST, experience sampling method) and through accurate control of various intervening factors that moderate HPA axis activity.

2.6 Allostatic load

McEwen's allostatic load concept, aims to outline a possible biological pathway for how chronic stress can lead to health impairments. The model postulates that an organism responds to challenge by initiating an allostatic response, a complex pathway for adaptation and coping, and shuts off this response when the challenge has passed. The term allostasis was originally introduced by Sterling and Eyer (1988) to describe how the cardiovascular system adjusts to resting and active states of the body. Allostasis depicts a fundamental physiological principle 'maintaining stability through change': In order to maintain stability, an organism must vary all the parameters of its internal milieu and match them appropriately to environmental demands.

As long as these allostatic responses are limited to the period of challenge, adaptation and thus protection is ensured. However if allostatic responses are sustained over months and years, the individual reaches the state of allostatic load (AL). Chronic overactivity or inactivity of physiological systems that are involved in the adaptation to environmental challenge result in a wear-and-tear on the body and brain (McEwen, 1998a, 1998b). Thus, AL captures the cumulative physiological burden exacted on the body through repeated attempts of adaptation. Four scenarios have been proposed, eventually leading to AL. The first is frequent stress. In especially susceptible individuals for example, repeated blood pressure surges can trigger myocardial infarctions. Secondly, AL can be caused by a failure to habituate to repeated challenges, leading to the over-exposure to stress mediators. An example for this type of AL is the finding that a minority of subjects fail to habituate to repeated TSST exposures and continue to show high cortisol responses (Wüst et al., 2005). The third origin of AL is the inability to shut off allostatic responses, which could be reflected in a lack of recovery of blood pressure after a mental stressor, leading to hypertension induced atherosclerosis. The fourth scenario describes inadequate allostatic responses in one allostatic system, that give rise to compensatory increases in other

allostatic systems. An inadequate hormonal stress response for example allows inflammatory cytokines to become overactive (McEwen, 1998b). The initial model proposes that an index quantifying AL should comprise parameters that reflect hypothalamus-pituitary-adrenal (HPA) axis functioning, sympathetic nervous system (SNS) activation, cardiovascular activity, atherosclerosis development, and glucose metabolism. According to McEwen, these parameters can be categorized firstly into primary mediators such as cortisol, epinephrine, norepinephrine and dehydroepiandrosterone-sulfate (DHEA-S). These primary mediators in turn cause primary effects which then lead to six secondary outcomes, namely waist/hip-ratio (WHR), glycosylated haemoglobin (HbA1c), high-density lipoprotein (HDL), total cholesterol/HDL-ratio, and systolic and diastolic blood pressure. Secondary outcomes ultimately result in tertiary outcomes representing actual disease (McEwen & Seeman, 1999). This comprehensive model that incorporates multiple stress sensitive systems was shown to better predict disease susceptibility and future health risks than any single factor on its own (Seeman et al., 1997, 2002; Karlamangla et al., 2002). In the initial MacArthur studies, a first empirical AL composite was introduced based on ten biological measures, coming from an existing database. Theoretically however, AL has been conceptualized as cumulative biological dysregulation across all major regulatory systems of the body. In line with their theoretical reasoning, the original authors therefore suggested to extend the composite to other stress sensitive physiological systems for example the immune system and the blood coagulation system (McEwen & Seeman, 1999; Seeman et al., 2001).

Table 2.2 briefly describes an extended list of 17 AL parameters that were assessed within the Trier Teacher Stress Study.

Table 2.2: Description of AL parameters

Allostatic load (AL) parameters	
cortisol	Cortisol is the principal glucocorticoid produced by the zona fasciculata of the adrenal cortex. It is a vital hormone and glucocorticoid receptors are present in virtually every tissue and organ in the body. Cortisol is essential in the body's physiological response to stress and influences innumerable metabolic and physiological functions. For example, it increases blood pressure, blood sugar levels and has anti-inflammatory and immunosuppressive actions.
epinephrine & norepinephrine	Epinephrine is the main catecholamine produced by the adrenal medulla. Its secretion into the adrenal vein is under the control of sympathetic nerves and is the most important indirect pathway of sympathetic activation. Epinephrine also plays a central role in the short-term stress reaction. When secreted into the bloodstream, it rapidly prepares the body for action in emergency situations. The hormone boosts the supply of oxygen and glucose to the brain and muscles, whilst suppressing other non-emergency bodily processes. The catecholamine norepinephrine also underlies the stress response, directly increasing heart rate, triggering the release of glucose from energy stores, and increasing blood flow to skeletal muscle. Norepinephrine also serves as a neurotransmitter in the sympathetic and central nervous system.
Dehydro-epiandrosterone-sulfate (DHEA-S)	Dehydroepiandrosterone is a natural steroid pro-hormone produced from cholesterol mostly by the adrenal cortex. Thus, blood measurements of DHEA are useful to detect excess adrenal activity. DHEA is a functional antagonist of cortisol and stressful events tend to lower DHEA. DHEA is present in the blood largely as its sulfated derivative (DHEA-S). Its levels decline progressively but variably with age.
systolic blood pressure & diastolic blood pressure	Blood pressure refers to the force exerted by circulating blood on the walls of blood vessels and constitutes one of the principal vital signs. Systolic blood pressure is the peak pressure reached in the arterial system during the heart's contraction phase, whereas diastolic blood pressure is the lowest pressure occurring during cardiac diastole.

	The condition of sustained elevated arterial blood pressure is called hypertension. It typically develops over many years, with blood pressure gradually increasing until it reaches threatening levels. Hypertension can lead to accelerated atherosclerosis as well as insulin resistance. Blood pressure increases acutely in response to a variety of behavioural stressors in humans, however the role of stress in the etiology of hypertension remains controversial.
blood lipids: high-density lipoproteins (HDL) cholesterol/ HDL ratio triglycerides	Lipoproteins are large, complex structures circulating in the blood that contain triglycerides, phospholipids, cholesterol, and proteins. The most important functions of cholesterol are the formation of cholic acid in the liver and the formation and permeability of cell membranes. High circulating concentrations of low-density lipoprotein-cholesterol (LDL) and low circulating concentrations of high-density lipoprotein-cholesterol (HDL) are associated with an increased risk of atherosclerosis and CVD. Triglycerides are synthesised in the liver and adipose tissue, and are utilized as energy sources. Psychosocial stress reliably influences blood concentrations of cholesterol and lipoproteins, potentially through stress-induced hormonal changes that affect lipid metabolism.
fasting glucose & glycosylated haemoglobin (HbA1c)	Glucose levels in the blood are tightly regulated in the human body. Normally, the blood glucose level is maintained between about 70 to 100 mg/dL. Glucose levels rise after meals and are usually lowest in the morning, before the first meal of the day. Failure to maintain blood glucose in the normal range leads to conditions of persistently high (hyperglycemia) or low (hypoglycemia) blood sugar. Diabetes mellitus which is characterized by persistent hyperglycemia is the most prominent disease, related to failure of blood sugar regulation. Glycosylated hemoglobin is a measure used primarily to identify the average plasma glucose concentration over prolonged periods of time. Higher levels of HbA1c are found in people with persistently elevated blood sugar, as in diabetes mellitus. HbA1c levels are indicative of sustained elevations in glucose and insulin resistance that can develop as a result of elevated cortisol and elevated sympathetic nervous system activity.

body-fat & waist/hip ratio (WHR)	Excessive body fat has been shown to predispose to various diseases, particularly CVD, diabetes mellitus, and sleep apnea. The analysis of body composition is used to describe the percentages of fat, bone and muscle in human bodies. Body circumferences and their ratios, such as the WHR indicate the distribution of body fat. The WHR is moderately associated with the amount of abdominal visceral adipose tissue measured by magnetic resonance imaging and has been shown to be a powerful predictor of obesity-related diseases such as CVD, diabetes mellitus, hypertension and hyperlipidemia. Individuals show increased disease risk with greater abdominal fat. Cortisol regulates adipose-tissue differentiation, function and distribution and in excess, it causes central obesity. The WHR can therefore be regarded as one measure of chronic stress exposure.
tumor-necrosis-factor-α (TNF-α)	TNF-α is a pro-inflammatory cytokine and a member of a group of cytokines that all stimulate the acute phase reaction. It is mainly secreted by macrophages and its primary role is the coordination of the local and systemic inflammatory response to pathogens. TNF-α stimulates HPA axis responses by activating CRH and arginine vasopressin neurons in the PVN. High levels of pro-inflammatory cytokines induce sickness behaviour, which is characterized by fatigue, fever, nausea and irritability.
C-reactive protein (CRP)	CRP is a plasma protein and an acute phase protein produced by the liver and adipocytes. It is believed to play an important role in innate immunity, as an early defense system against infections. CRP levels rise dramatically during inflammatory processes and epidemiological studies have demonstrated that CRP and other acute phase reactants predict incident and recurrent CVD.
fibrinogen & D-dimer	Blood clotting is a rapid response to tissue damage. Thrombin converts fibrinogen to fibrin, leading to fibrin deposition and the activation of platelets to form blood clots (coagulation). As damaged tissue is repaired, the fibrin clot must be dissolved in order to maintain the fluidity of blood (fibrinolysis). The break-down of fibrin chains by plasmin yields soluble fibrin fragments such as D-dimer. D-dimer indicates activation of the entire hemostatic system, i.e. coagulation and fibrinolysis.

	Hemostasis factors, like fibrinogen and D-dimer have been shown to predict recurrent cardiac events in patients with CVD but also prospectively predicted diesease risk in individuals with apparently good health at study entry. A procoagulant milieu, as reflected by increased activity of clotting factors (i.e. fibrinogen) and coagulation activation markers (i.e. D-dimer) on the one hand and impaired fibrinolysis on the other hand gradually contributes to atherosclerosis progression.

for overviews see: (Thomas, 1998; Fink, 2007)

Various predictors potentially affecting overall health outcomes have been studied in relation to AL. Factors that seem to be associated with AL are social inequalities and low socioeconomic status, quality of sleep, religious service attendance, sense of coherence (SOC) or chronic caregiving stress, mood disorders and posttraumatic stress disorder (PTSD) (Kubzansky et al., 1999; Evans, 2003; Goodman et al., 2005; Glover et al., 2006; Lindfors et al., 2006; Clark et al., 2007; Maselko et al., 2007).

2.7 Teacher stress

Teaching has often been described as a highly demanding occupation and research on teacher stress has become an area of international research interest (Kyriacou, 1980; Travers & Cooper, 1993, 1996; Guglielmi & Tatrow, 1998). Studies gave evidence that teachers are confronted with a wide range of stressors, including those that are related to teaching itself, those that arise from the relationship of teacher and student and those associated with issues of organisation and administration (Kyriacou, 2001).

Kyriacou defines teacher stress as the experience by a teacher of unpleasant, negative emotions, such as anger, anxiety, tension, frustration or depression, resulting from some aspect of their work as a teacher (Kyriacou, 2001). Teachers have to meet constant deadlines associated with exams and grading. They feel overburdened by excessive paperwork and the lack of preparation time for class, which leaves many with a general perception of being rushed and overworked. Furthermore, teachers have to meet conflicting demands from supervisors, colleagues, students and students' parents; often leaving them unable to satisfy all parties as they would like. Problems with students include disruptive behaviour such as verbal and physical abuse, the heterogeneity in students' abilities in oversized classes, as well as special needs of some of the students. Bauer et al. (2007) for example could recently show that according to the AVEM inventory (Arbeitsbezogene Verhaltens- und Erlebensmuster, Schaarschmidt & Fischer, 1997), a German instrument measuring coping capacity, teachers rated 'destructive and aggressive behaviour of pupils' as the primary stress factor, along with 'size of school class'. Finally, additional stressors are associated with the schools' administration, excluding teachers from decisions that impact directly on their workload as well as their low occupational image (Greenglass, 2007). Is there evidence that these stressors impact on teachers' health and well-being?

Guglielmi & Tatrow conclude in their review (1998), that generally findings seem to support the notion that occupational stress and burnout are associated with poor health in teachers. However, they also criticize the poor quality of many studies that were included in their review. On page 82 it reads: *"The typical teacher stress/burnout and health study can be best characterized as a fishing expedition: a large number of measures is used to assess predictor and criterion variables, at times some individual difference measures are added to the stew, specific predictions are not articulated, the data are analysed by a multitude (sometimes hundreds) of bivariate correlations or t-tests and statistically significant findings are reported. Post hoc explanations of the results are offered without attempting to integrate those findings into a theoretical meaningful framework."* To summarize, the authors state that substantial methodological improvements are needed concerning the research on teacher stress and health outcomes.

The situation of German schools became a topic of public interest in recent years, mainly due to the results of the OECD study 'PISA 2000' (Baumert et al., 2001). In this context, the increasing rates of premature retirement among teachers and with this the rising national pension load initiated a public debate as well as research efforts regarding the occupational burden of German school teachers. Weber and colleagues (2002) for example analysed case reports of teachers, who claimed occupational disability due to health problems. They found that the predominant factors leading to premature retirement in teachers are psychosomatic disorders: The main medical diagnoses, depression and exhaustion/burnout (45%), predominated over muscular/skeletal symptoms (14%) as well as CVD (12%). Furthermore, Bauer et al. (2006) recently assessed occupational coping patterns in a representative sample of 438 grammar school teachers from ten schools in south western Germany. 32.5% of the sample featured signs of burnout, reflected in an exhausted and resigned coping style, whereas an additional 17.7% displayed a tensed coping style. This tensed coping style has also been

associated with negative health outcomes (Schaarschmidt & Fischer, 1997). Applying the Symptom Check List SCL-90R they report that 20.5% of those teachers exhibited psychopathological symptoms, fulfilling the criteria of a clinical disorder. Finally in a second study, Bauer and colleagues (2007) report that 30% of a sample of 949 German teachers suffered from significant mental health problems, measured with the general health questionnaire (GHQ-12).

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Chapter 3

Cortisol dysregulation in school teachers in relation to burnout, vital exhaustion and effort-reward-imbalance

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3.1 Abstract

We analysed whether burnout and vital exhaustion or job-related chronic stress is associated with HPA axis dysregulation in school teachers (N=135; 25-63 yrs.; mean age 46.1±9.20 yrs.). Participants collected seven saliva samples (0, 30, 45, 60 min after awakening, 11am, 3pm, 8pm) on two working days, one leisure day, and after pre-medication with 0.25mg dexamethasone (very low-dose dexamethasone suppression test) to assess basal cortisol day profiles and HPA axis negative feedback sensitivity. No associations were found between basal cortisol activity and burnout (Maslach Burnout Inventory, Teacher Burnout Scale), vital exhaustion (Appels VE Questionnaire), or any component of Siegrist's effort-reward-imbalance model. However, after dexamethasone higher burnout and vital exhaustion and lower reward were significantly related to stronger cortisol suppression, pointing to altered HPA axis negative feedback sensitivity. Though, all teachers were working and in a good health status, burnout/exhaustion as well as facets of the ERI model appear to be associated with subtle dysregulation, manifested as heightened HPA axis negative feedback although not in basal cortisol day profiles.

3.2 Introduction

Early retirement due to chronic work stress is a major problem among German school teachers. Recently, Weber and colleagues (2002) analysed 605 case reports and found that the predominant factors leading to premature retirement in teachers are psychosomatic disorders, with depression and exhaustion (burnout) being the most common amongst them.

Burnout is a non-psychiatric syndrome principally defined by the three core dimensions emotional exhaustion, work-related cynicism, and feelings of work inefficacy or reduced productivity. It has been proposed that burnout is a prolonged response to chronic emotional and interpersonal stress usually accompanied by insufficient recovery (Maslach et al., 2001). Burnout is often accompanied by reports of physical symptoms such as recurrent headaches, gastro-intestinal discomfort, disturbed sleep patterns, or non-specific pain and has been positively associated with various illnesses such as infections, cardiovascular diseases, or type 2 diabetes (reviewed in Melamed et al., 2006). Though burnout pervades every occupation, it is thought to be more prevalent among service and people-oriented professionals such as teachers, health practitioners, caregivers, fire fighters, and policemen (Maslach et al., 2001; Melamed et al., 2006).

Vital exhaustion (VE), a psychological concept that originates from clinical work with cardiovascular patients, is closely related to the burnout syndrome and was originally identified as an independent risk factor for coronary artery disease (for reviews see Kop, 1999; for reviews see Appels, 2004). VE is thought to be a potential consequence of long-term stress or chronic burnout, resulting in excessive fatigue, loss of mental and physical energy, increased irritability, and feelings of demoralization.

The hypothalamic-pituitary-adrenal (HPA) axis, a key stress-responsive endocrine system, may link both burnout and VE to the observed health impairments. The HPA axis regulates the adaptation to increased demands and enables the organism to maintain homeostasis under acute stress.

However, exposed to chronic stress an originally adaptive response can have numerous deleterious consequences. Both hyper- and hypoactivity of the HPA axis have been associated with stress related pathologies (for reviews see Heim et al., 2000; Raison & Miller, 2003). For example, hypercortisolemia is often found in major depression (for reviews see Holsboer, 2001; Parker et al., 2003) whilst hypocortisolemia was found in PTSD (Rohleder et al., 2004), fibromyalgia (Demitrack & Crofford, 1998), and chronic fatigue syndrome (Demitrack, 1997; Gaab et al., 2002).

In ambulatory settings, HPA axis dysregulation is best assessed by investigation of the salivary cortisol awakening response (CAR) and the diurnal secretory activity (Edwards et al., 2001; Kudielka & Wüst, 2008). The cortisol day profile covers the peak waking level, the decrease over the course of the day and low evening levels. An important advantage of salivary cortisol assessment is that repeated saliva collections can be accomplished outside the laboratory, for example in the workplace (Soo-Quee Koh & Choon-Huat Koh, 2007; Kudielka & Wüst, 2008). The dexamethasone suppression test (DST) can be applied for the assessment of negative feedback sensitivity of the HPA axis. The synthetic glucocorticoid dexamethasone binds selectively, and with high affinity to the glucocorticoid receptor (GR). Dexamethasone, acting primarily at the level of the pituitary, inhibits ACTH release and subsequent cortisol release, thereby mimicking the negative feedback effects of endogenous cortisol. Hence, feedback sensitivity is indicated by the extent of cortisol suppression after oral dexamethasone intake (de Kloet et al., 1998; Cole et al., 2000).

To-date, there is a paucity of data on psychophysiological correlates of burnout and even fewer studies report on HPA axis regulation in vitally exhausted though still working employees (Kudielka et al., 2006a; Soo-Quee Koh & Choon-Huat Koh, 2007). Naturally, most ambulatory studies with sampling at the workplace have been constrained in terms of number of volunteers, quantity of samples or assessment days, ranging from single blood draws or urine collections to repeated salivary cortisol

sampling at work and/or non-work days. The DST is however rarely applied in ambulatory assessments of stress at work although it is routinely used in clinical settings.

The existing literature on HPA axis functioning in burnout is rather inconsistent (for a recent review see Kudielka et al., 2006a), with some studies reporting no associations between cortisol levels and burnout (CAR: Langelaan et al., 2006; CAR + diurnal profile: Mommersteeg et al., 2006a), and others reporting on either HPA axis hyperactivity (CAR + 12am salivary sample: De Vente et al., 2003; CAR: Grossi et al., 2005; CAR + diurnal profile: Söderström et al., 2006) or hypoactivity (CAR: Pruessner et al., 1999; CAR + diurnal profile: Mommersteeg et al., 2006b, CAR:). Of the four studies on HPA axis feedback sensitivity (all using 0.5mg dexamethasone), two did not find any associations with burnout (Langelaan et al., 2006 ; Mommersteeg et al., 2006a) whilst Pruessner et al. (1999) observed greater cortisol suppression after dexamethasone intake in teachers scoring high versus low on burnout. Sonnenschein et al. (2007) found a positive association between more severe burnout symptoms and stronger cortisol suppression in 42 burnout patients using the experience sampling method, an effect which could not be observed with retrospectively assessed burnout by questionnaire. Whilst the VE literature is scarce, the majority of studies show a down-regulation of the HPA axis under basal conditions and acute (laboratory) stress (Kristenson et al., 1998; Nicolson & van Diest, 2000; for review see Kudielka et al., 2006a, 2006b).

Psychosocial workplace characteristics have recently been implicated in the genesis of chronic work stress (Siegrist et al., 2004). The effort-reward-imbalance (ERI) model postulates that a lack of reciprocity between personal costs (effort) and personal gains (reward) at the workplace leads to stress and that ERI consequently increases the risk for stress-related disorders. In this model, the inability to withdraw from work obligations is additionally conceptualized as a personality trait called overcommitment (OC). Indeed, ERI and OC have been shown to be

related to self-reported health (Kudielka et al., 2005), VE (Preckel et al., 2005) as well as manifest health problems (for recent review see van Vegchel et al., 2005). To-date, only three studies have investigated the association between ERI/OC and HPA axis regulation. Whilst Hanson et al. (2000) could not find significant associations, the two others report on (minor) positive relationships between cortisol levels and variables derived from the ERI/OC model (Steptoe et al., 2004b; Eller et al., 2006).

The aim of this study was to investigate possible HPA axis dysregulation in either burnout, VE, or ERI/OC using a relatively broad sampling design. Daily cortisol profiles consisting of seven time points were measured across two working days, one leisure day, and after a very low dose DST (0.25mg).

3.3 Methods

3.3.1 Participants and general experimental outline

One hundred and ninety currently employed school teachers were recruited by personal visits to local schools and via newspaper announcements in the region of Trier (Germany) and Luxembourg (Luxembourg). Eligibility, demographics, current health status, and health behaviour (smoking status, medication intake) were assessed by telephone interview. Exclusion criteria for all participants included psychiatric disorders, diabetes, pregnancy, and corticosteroid or psychotropic medication. Eligible volunteers were mailed a package of psychometric assessment questionnaires and invited for a laboratory visit (Bellingrath et al., 2008). Participants received the domestic saliva sampling materials together with both spoken and written instructions, and a prepaid return envelope. The study protocol was approved by the ethics committee of the University of Trier as well as the Rheinland-Pfalz State Medical Association. Written informed consent was provided by all participants. Participants received €50 after completion of the study protocol.

3.3.2 Psychological assessment

Demographics

Demographic variables (gender, age, years of employment, type of school) were recorded based on verbal and written self-reports at the telephone interview and laboratory visit.

Burnout

Burnout was measured using a validated German version (Schwarzer & Jerusalem, 2001) of the Maslach Burnout Inventory (MBI) (Maslach & Jackson, 1986). The MBI is composed of three subscales (MBI-EE: emotional exhaustion; MBI-DP: depersonalization; and MBI-LA: lack of accomplishment) with a total of 22 items. Each item is ranked on a 7-point scale, ranging from "never"=0 to "daily"=6. The MBI-EE scale consists of nine items (e.g., "I feel burned out from my work"). The MBI-DP scale contains five items (e.g., "I do not really care what happens to my students") and the MBI-LA scale has eight items (e.g., "I feel animated when working closely together with my students"; reverse coding). In the present data, the internal consistencies (Cronbach's alpha) of the three subscales were α=.91 (MBI-EE), α=.80 (MBI-DP), and α=.89 (MBI-LA), reflecting good reliability.

Burnout was also measured using the teaching profession specific Teacher Burnout Scale (TBS) (Seidman & Zager, 1987). The TBS is composed of four scales. The first scale, TBS-CS "career satisfaction", consists of five items (e.g., "I look forward to teaching in the future"); the scales TBS-PAS "perceived administrative support" (e.g., "I receive adequate praise from my supervisors for a job done well") and TBS-CJRS "coping with job-related stress" (e.g., "I feel depressed because of my teaching experiences") both have six items; the last scale TBS-ATS "attitudes toward students" (e.g., "The students act like a bunch of animals") is composed of four items. For the TBS, higher scores reflect higher burnout risk. All 21 items are ranked on a 6-point scale with a range from "totally disagree" to "totally agree". For each of the four TBS scales a high reliability in terms of internal consistency (Cronbach's alpha) was

observed in this study sample (TBS-CS: α=.89; TBS-PAS: α=.83; TBS-CJRS: α=.80; TBS-ATS: α=.76).

Vital exhaustion

VE was measured with a German version of the 9-item short form of the original Maastricht Vital Exhaustion Questionnaire (Appels et al., 1987) as used previously (Kudielka et al., 2006b). Questions cover unusual fatigue, a disturbed sleeping pattern, general malaise, irritability, a loss of mental and physical energy, and feelings of demoralization. The short form has been shown to correlate well with the original form ($r=.94$, $p<.001$, $n=452$ Kopp et al., 1998). Scores ranging from 0-18 can be interpreted as: from 0 to 3, no exhaustion; scores from 4 to 10, mild to moderate exhaustion; scores from 11 to 14, substantial exhaustion; and scores >14, severe exhaustion. The high reliability of the short form is reflected by an internal consistency (Cronbach's alpha) of α=.86.

Effort-reward-imbalance and overcommitment

ERI was assessed by its validated German version using the 6-item effort (e.g., "I have a lot of responsibilities in my job") and 11-item reward scale (e.g., "I receive the respect I deserve from my supervisors/colleagues") (Rödel et al., 2004). The ratio of effort to reward expresses the amount of perceived effort-reward-imbalance at work. OC at work was assessed with the 6-item form. On a 4-point rating scale, participants indicate to what extent they personally agree or disagree with the given statements. OC focuses on the "inability to withdraw from work" (five items) and "disproportionate irritability" (one item). For all three scales high internal consistencies (Cronbach's alpha) could be demonstrated for the present study sample (effort: α=.73; reward: α=.80; overcommitment: α=.77).

Hospital anxiety and depression scale

The HADS is a 14-item self-report screening tool originally developed to indicate the possible presence of anxiety and depressive states (Zigmond & Snaith, 1983). Statements referring to symptoms that may have a physical cause (e.g., weight loss, insomnia) are not included to avoid any bias caused by a coexisting general medical condition. Each of the two

subscales, HADS-Anxiety (HADS-A) and HADS-depression (HADS-D), consists of seven items. Answers are coded on a 4-point Likert scale ranging from 0=”not at all” to 3=”mostly”. We applied the validated German version published by Herrmann and co-workers (1995). With α=.80 for the anxiety subscale and α=.83 for the depression subscale, a high reliability in terms of internal consistency could be guaranteed.

3.3.3 Saliva collection

Cortisol levels were assessed on two consecutive working days and one leisure day. Teachers obtained native saliva in 2ml reaction tubes (Sarstedt, Nümbrecht, Germany) since typically-used cotton-based devices artificially reduce free cortisol concentrations (Gröschl & Rauh, 2006). Samples were taken upon awakening (0 min), 30, 45, and 60 minutes after awakening, and at 11am, 3pm, and 8pm on each day. To avoid contamination of saliva with blood, participants were instructed not to brush their teeth before completing the four morning saliva samples. Additionally, smoking, eating, and drinking beverages containing alcohol, caffeine, or fruit juices were not allowed for 60 minutes before sampling. A paper diary was filled out, in which participants reported their individual awakening time, sleep quality (one-item 5-point rating scale), exact sampling times as well as food and drink intake on a daily basis. Besides these restrictions, participants were free to follow their normal daily routines on the sampling days. The night before the fourth sampling day, participants were instructed to take an oral dose of 0.25mg dexamethasone (Jenapharm, Jena, Germany) at 11p.m. The following day, saliva samples were collected as for the previous days. After completion of all four collection days, samples and diaries were returned to the laboratory.

Compliance monitoring

Compliance with saliva sampling procedures, especially the timing, is crucial to obtain valid data in ambulatory settings. In earlier experiments using electronic monitoring devices (MEMS® Track Cap; AARDEX, Ltd.,

Switzerland), we showed that cortisol day profiles differ significantly between compliant and non-compliant subjects, with non-compliant subjects showing significantly lower cortisol awakening responses (Kudielka et al., 2003). In order to control for this compliance bias, participants were both informed in one-on-one interviews about the importance of accurate timing of their saliva collection and that their saliva collection timing would be electronically monitored with the date and time of each sample recorded. In this study, however, every participant received a dummy MEMS® Track Cap since knowledge of monitoring improves subjects' protocol adherence as well as the validity of self-reports (Kudielka et al., 2003). In fact, participants' self-reported diary records of individual awakening and sampling times were used to identify non-compliance. In order to create a dummy variable 'compliant versus non-compliant' a ±15-minutes compliance window was established. For analysis of basal HPA activity, a participant was considered non-compliant if the wake-up sample deviated more than ±15-minutes from the reported awakening time on one of the three days (two working days and one leisure day). For analysis of HPA axis feedback sensitivity (DST), the same applied for the wake-up sample at the fourth sampling day.

3.3.4 Cortisol analysis

Upon arrival, saliva samples were stored at -20°C. Salivary cortisol (nmol/l) was measured by a time-resolved fluorescence immunoassay (DELFIA). The intra- and inter-assay variability was 2.9-7.7% and 6.2-11.5 %, respectively.

3.3.5 Statistical analysis

Statistical analyses were performed using the SPSS statistical software package (Version 13.0.1; Chicago, IL, USA). Unless otherwise stated, results are expressed as mean ± standard deviation (SD). The interrelationships between MBI, TBS, VE, and HADS scores were assessed

using Pearson correlations. Cortisol values were log-transformed before statistical analyses (Figures show untransformed data for illustration reasons).

All subsequent analyses were computed with the command GLM (General Linear Model). First, a repeated-measures analysis of variance (ANOVA) with the 2 within-subject factors *Days* (days 1-3) and *Samples* (seven saliva samples per day) was applied to analyse basal cortisol profiles across days. Second, to test for effects of burnout (MBI and TBS scales), VE, ERI/OC, as well as symptoms of depression and anxiety (HADS scales) on cortisol patterns, separate GLMs with the repeated factors *Days* and *Samples* were calculated entering a questionnaire score as a continuous predictor. Analogous, for the day of the DST, separate GLMs were applied with the repeated factor *Samples* and the questionnaire variables as predictors (MBI, TBS, VE, ERI/OC, HADS scales). All questionnaire scores were entered as continuous variables to avoid any reduction of available information by artificial grouping (Aiken & West, 1991; Royston et al., 2006) as applied earlier (Schlotz et al., 2004; Kudielka et al., 2006b). Gender, age, body-mass-index, waist-hip-ratio, smoking, sleep quality, and awakening time have been discussed as potential sources of between-subject variation in cortisol day profiles (for review see Clow et al., 2004; Steptoe et al., 2004a; Therrien et al., 2007). Therefore, the impact of these variables on cortisol levels was examined first. As gender and smoking status yielded significant effects, these two factors were entered as covariates in subsequent analyses. Finally, in case of significant results concerning burnout (MBI, TBS), VE, or ERI/OC, GLM analyses were repeated entering the respective questionnaire variable (MBI, TBS, VE or ERI/OC) as well as simultaneously the HADS-depression score (see below). F-values and p-levels were corrected according to Greenhouse-Geisser procedure whenever sphericity was violated, though uncorrected degrees of freedom (df) were reported for F-statistics. Greenhouse-Geisser Epsilons were expressed as GG-ε. Effect sizes were calculated for significant results by partial eta squared (η^2), expressing the amount of

variance explained in the dependent variable cortisol by the respective effect.

3.4 Results

3.4.1 Study sample

Of the 190 teachers who volunteered for the lab day, 149 returned the questionnaires and saliva samples. After exclusion of the non-compliant participants, 101 were suitable for analysis of basal HPA activity on the two working days and the leisure day. HPA axis feedback sensitivity (DST) could be analysed in 120 compliant participants. In total, 135 different participants contributed to cortisol data in the analyses (95 females and 40 males, age range 25-63 yrs., mean 46.1±9.20 yrs.). A description of the final study sample is given in Table 3.1.

Table 3.1: Sample description

	N=135	Mean ± SD	Range
Sex			
Male	40		
Female	95		
Age (years)		46.1 ± 9.20	25-63
Years in Job		18.5 ± 10.7	
German School Types			
Elementary/Primary School (Grundschule)	34		
Basic Level Secondary School (Hauptschule)	19		
Secondary School (Realschule)	16		
Grammar School (Gymnasium)	21		
Comprehensive School (Gesamtschule)	6		
Vocational School (Berufsbildende Schule)	18		
Not further specified	20		
Missing	1		
Smoking Status			
Non-smoker	123		
Smoker	12		
MBI Scores			
EE		18.2 ± 12.0	0-54
DP		4.68 ± 5.30	0-24
LA		13.0 ± 9.00	0-36
TBS Scores			
CS		13.1 ± 6.53	5-28
PAS		14.4 ± 6.96	6-33
CJRS		18.6 ± 6.96	6-36
ATS		9.22 ± 4.18	4-21
Vital Exhaustion Scores		9.38 ± 1.06	0-18
0-3 No exhaustion	28		
4-10 Mild/moderate exhaustion	46		
11-14 Substantial exhaustion	31		
>14 Severe exhaustion	30		
ERI Scores			
Effort		16.0 ± 4.53	6-28
Reward		45.2 ± 7.28	21-55
ERI		0.69 ± 0.30	0.20-2.20
OC		16.5 ± 4.11	7-24
HADS-D Scores			
HADS-D		4.85 ± 3.79	0-17
HADS-A		6.88 ± 4.13	0-19

Intercorrelations between MBI, TBS, VE, and HADS scores are presented in Table 3.2. The highest intercorrelations were observed between MBI-EE, TBS-CJRS, and VE.

Table 3.2: Pearson correlation matrix for MBI, TBS, VE, and HADS scores; **p<.01, *p<.05

	MBI-EE	MBI-LA	MBI-DP	TBS-CS	TBS-PAS	TBS-CJRS	TBS-ATS	VE	HADS-D
MBI-LA	.51**								
MBI-DP	.46**	.48**							
TBS-CS	.68**	.65**	.51**						
TBS-PAS	.37**	.21*	.21*	.22*					
TBS-CJRS	.78**	.50**	.40**	.70**	.35**				
TBS-ATS	.38**	.20*	.35**	.42**	.08	.50**			
VE	.70**	.43**	.32**	.56**	.35**	.73**	.28**		
HADS-D	.54**	.58**	.41**	.61**	.31**	.62**	.30**	.65**	
HADS-A	.55**	.43**	.26**	.48**	.25**	.60**	.35**	.60**	.63**

3.4.2 Basal HPA axis activity: Cortisol day profiles on work and leisure days

An initial ANOVA with repeated measures *Days* (days 1-3) and *Samples* (seven saliva samples per day) resulted in a significant main effect of sampling time (main effect *Samples*: GG-ε=.72, $F_{6,588}$=137.3, p<.001, η^2=.58) showing the typical circadian pattern of cortisol with high levels after awakening and a significant decline over the remainder of the day (Fig. 3.1). Furthermore, a difference in the course of the cortisol levels across days was observed (interaction *Samples by Days*: GG-ε=.72, $F_{12,1176}$=3.1, p<.001, η^2 =.03). Post-hoc, we broke this initial ANOVA down into three subsequent ANOVAs comparing two days, respectively. Significant interactions emerged comparing the first working day with the leisure day (GG-ε=.72, $F_{6,618}$=3.9, p=.003, η^2=.04; higher cortisol levels at the first working day, effect mainly driven by differences in the morning samples) and the second working day with the leisure day (GG-ε=.80, $F_{6,600}$=4.3, p<.001, η^2 =.04; higher cortisol levels at the second working day, effect mainly driven by differences in the morning samples), but not comparing the two working days (GG-ε=.81, $F_{6,630}$=.36, p=.87).

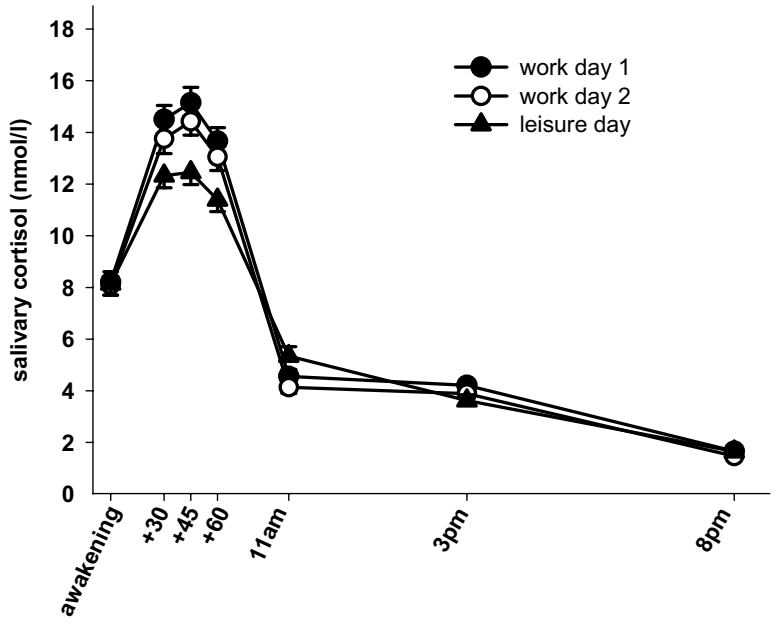

Figure 3.1: Cortisol profiles (untransformed data; nmol/l) in N=101 participants across two working days and one leisure day; data are expressed as mean ± SEM (standard error of mean)

We then added each questionnaire variable (MBI, TBS, VE, ERI and HADS scores) to separate GLMs to test for their effects on basal cortisol levels. None of these GLMs, however, revealed a significant association between cortisol levels and any of these variables over the three days (all $F<2.86$, all $p>.13$).

3.4.3 HPA axis feedback sensitivity: The Dexamethasone Suppression Test

After pre-medication with 0.25mg dexamethasone, cortisol levels were considerably reduced (Fig. 3.2). In contrast to basal HPA axis activity, significant associations between dexamethasone-suppressed cortisol levels and burnout, exhaustion, and ERI-reward could be found. Separate GLMs with repeated measures and the different burnout subscales as independent variables showed that cortisol suppression varied depending on the extent of burnout. Significant associations were found for the subscales MBI-EE (Fig. 3.2.A; main effect MBI-EE: $F_{1,116}=3.9$, $p=.05$, $\eta^2=.03$; higher emotional exhaustion related to lower cortisol levels, effect

driven by differences in the morning samples) and MBI-LA (interaction MBI-LA: GG-ε=.47, $F_{6,696}$=3.4, p=.02, η^2=.03; higher lack of accomplishment related to lower cortisol, effect mainly driven by differences in the morning samples).

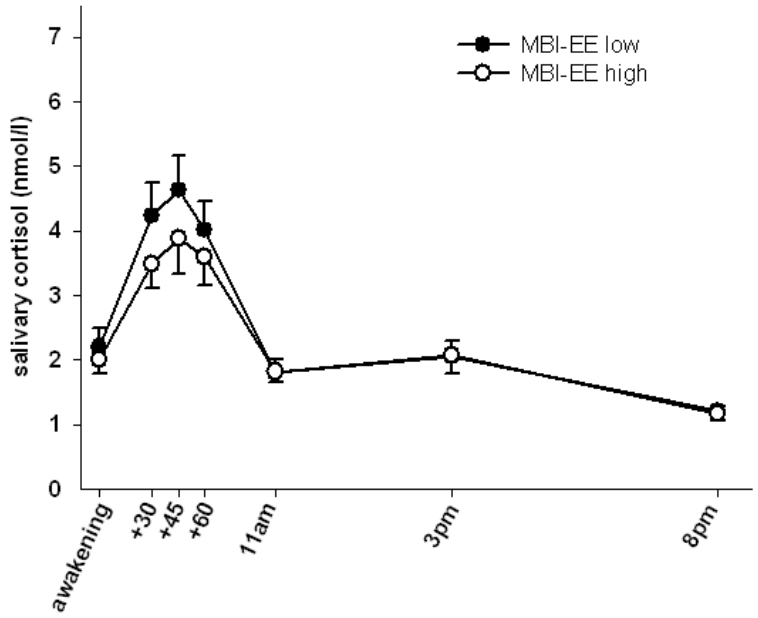

Figure 3.2.A: Cortisol profiles (untransformed data; nmol/l) after dexamethasone intake in N=120 participants high versus low on MBI-EE,; for illustration reasons the sample was artificially divided by median split into groups high versus low on MBI-EE; statistics are based on continuous questionnaire scores; data are expressed as mean ± SEM (standard error of mean)

For the TBS, two of the four subscales yielded significant effects (main effect TBS-CS: $F_{1,116}$=5.8, p=.018, η^2=.05; interaction TBS-CS: GG-ε=.49, $F_{6,696}$=5.5, p=.001, η^2=.05; lower career satisfaction indicated by higher TBS-CS scores related to lower cortisol levels; interaction TBS-PAS: GG-ε=.47, $F_{6,678}$=2.8, p=.046, η^2=.02; lower perceived administrative support indicated by higher TBS-PAS scores related to lower cortisol levels, effect mainly driven by differences in the morning samples). Furthermore the degree of VE (Fig. 3.2.B; interaction VE: GG-ε=.48, $F_{6,696}$=3.3, p=.025, η^2=.03; higher VE related to lower cortisol levels, effect mainly driven by differences in the morning samples), and reward from work (Fig. 3.2.C; interaction reward: GG-ε=.47, $F_{6,696}$=2.8, p=.045, η^2=.02; lower reward related to lower cortisol levels, effect mainly driven by differences in the morning samples) were significantly associated with suppression of cortisol after dexamethasone.

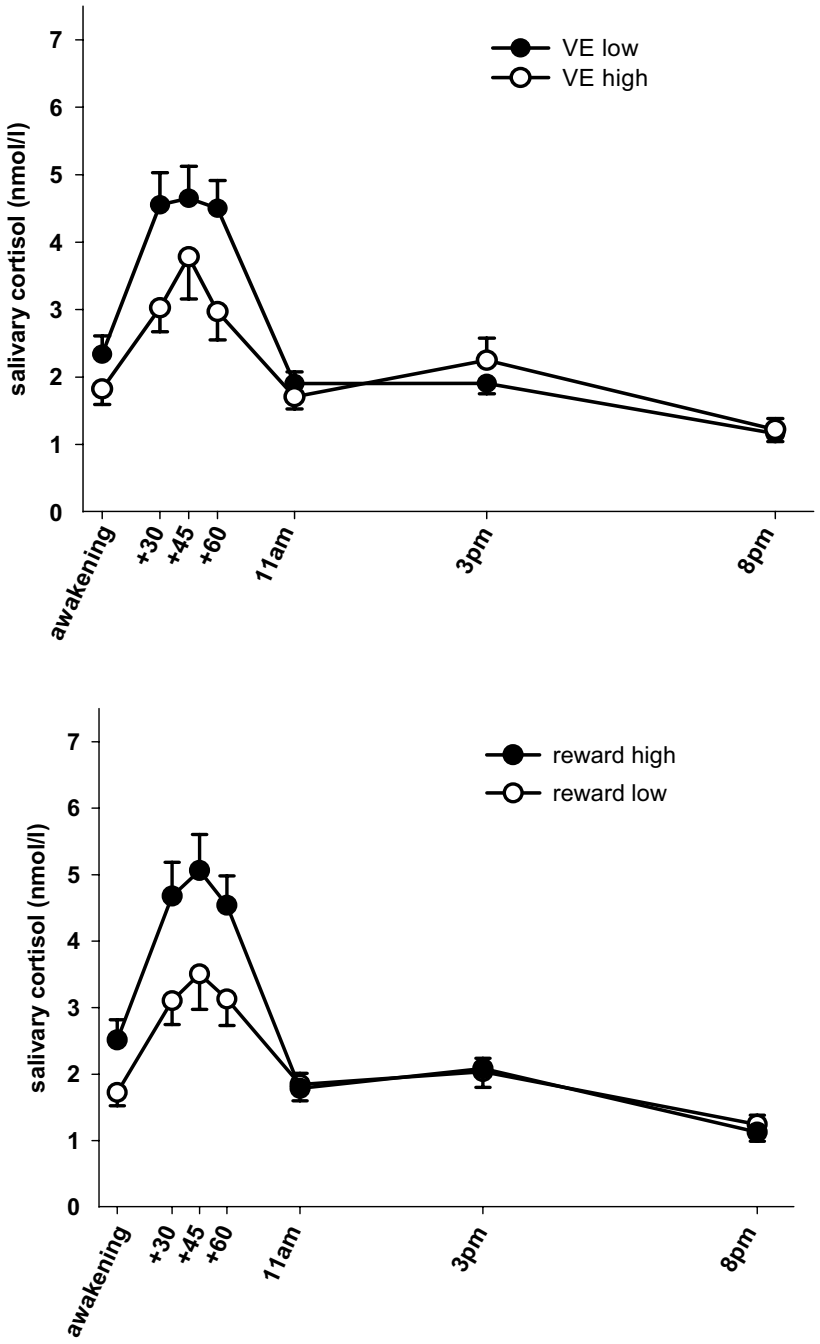

Figure 3.2.B and 3.2.C: Cortisol profiles (untransformed data; nmol/l) after dexamethasone intake in N=120 participants high versus low on (b) VE, and (c) ERI-reward; for illustration reasons the sample was artificially divided into groups high versus low on the respective variable (according to cut-off scores for VE; by median split for the ERI-reward scale); statistics are based on continuous questionnaire scores; data are expressed as mean ± SEM (standard error of mean)

Whilst no significant effects emerged for HADS-Anxiety, the degree of HADS-depression was significantly associated with suppression of cortisol after dexamethasone (main effect HADS-D: $F_{1,116}$=4.1, p=.045, η^2=.03; interaction HADS-D: GG-ε=.48, $F_{6,696}$=3.1, p=.027, η^2=.03; higher depression scores related to lower cortisol levels, effect mainly driven by differences in the morning samples). In a final set of analyses, we repeated GLMs for all burnout, exhaustion, and ERI variables that previously had rendered significant relationships with cortisol levels after dexamethasone, now simultaneously entering HADS-depression scores. In these models, the previously observed effects of burnout, exhaustion, and ERI did not remain significant concurrently entering HADS-D.

3.5 Discussion

Overall, the results of this study suggest that subtle dysregulation can be found in school teachers with high levels of burnout, VE, and a low reward from work. The association of cortisol levels and such work-related questionnaire scores could be observed, however, only after application of the DST. In the DST, teachers with high levels of burnout, VE, or low reward from work showed a significantly stronger cortisol suppression indicating an increased negative feedback activity of the HPA axis. In contrast, analysis of basal cortisol profiles revealed no association with burnout, VE, or ERI/OC on either the working days or leisure day. However, differences between the working days and leisure day could be observed. This observation is in line with earlier reports of higher cortisol awakening responses on working days compared to non-working days (Kunz-Ebrecht et al., 2004; Schlotz et al., 2004; Langelaan et al., 2006).

Previous inconsistent findings on HPA axis regulation in burnout and VE (Kudielka et al., 2006a) might be, at least in part, ascribed to methodological differences between studies (e.g., sampling designs/times, sampling in blood vs. urine vs. saliva, non-clinical populations vs. burnout-patients, in-/exclusion or control of potentially confounding factors, invalidation by sampling non-compliance, etc.). For example, Pruessner and colleagues (1999) found blunted salivary cortisol levels in the first

hour after awakening on two consecutive days in 66 teachers scoring high versus low on a composite burnout score whilst Mommersteeg et al. (2006b) observed lower salivary cortisol levels in the morning in 22 burnout patients compared to 21 healthy controls. Our results are in accordance with the findings of both Mommersteeg et al. (2006a) and Langelaan et al. (2006) who recently reported that burnout was not reflected in salivary cortisol levels after awakening and over the course of the day in comparably large study samples. It is very unlikely that our null findings regarding basal HPA axis regulation are compromised by participants' adherence to the ambulatory saliva sampling procedure since non-compliant participants were excluded from our analyses.

In respect to the DST, our findings are in line with the results of the Pruessner et al. (1999) and Sonnenschein et al. (2007) studies but in contrast to the results of the studies by Mommersteeg et al. (2006a) and Langelaan et al. (2006), which both did not find an association between burnout and cortisol suppression after dexamethasone. Interestingly, the Sonnenschein et al. study showed a positive relationship between burnout symptoms and cortisol suppression in the DST using entries from an electronic symptom diary (experience sampling methodology) whilst this effect could not be shown by retrospectively derived burnout scores. Another important methodological difference between these earlier studies and our present data was the dosage of dexamethasone. We have, for the first time, applied a very low-dose DST using 0.25mg instead of 0.5mg to enhance test sensitivity (Huizenga et al., 1998). We would suggest that this very low-dose DST is a very sensitive tool, detecting differences in feedback sensitivity which are not (yet) reflected in basal HPA activity. Changes in receptor number or binding affinity can alter the effectiveness of cortisol feedback. It can be hypothesized that in individuals with high levels of burnout/exhaustion, chronically elevated cortisol levels or repeated cortisol peaks due to ongoing acute stress may have increased the sensitivity of the GR, which in turn leads to an especially sensitive regulation of the negative feedback loop. Pruessner and colleagues, who

reported a stronger suppression after the DST in burnout subjects using 0.5mg also found blunted cortisol levels in the first hour after awakening on normal work days. In this case, the lower levels of cortisol after the DST might reflect an already overall lowered basal HPA activity in their sample.

Beside burnout, the concept of work-engagement was also investigated in the study of Langelaan et al. (2006) in order to elucidate two opposite poles of work-related well-being. Surprisingly, enhanced cortisol suppression in work-engaged managers was observed in response to the DST compared to a burnout and control group. In respect to the ERI/OC model, to the best of our knowledge, our study is the first investigation into associations between the model components and cortisol suppression after dexamethasone. To-date, there is a paucity of data on the relationship between basal cortisol levels and variables derived from the ERI/OC model (Hanson et al., 2000; Steptoe et al., 2004b; Eller et al., 2006). Whilst no significant relationships emerged in our study between basal HPA axis regulation over three days on the one hand and effort, reward, ERI, or overcommitment on the other, we found that enhanced work stress in terms of low reward from work was associated with stronger cortisol suppression in a very low-dose DST. Overall, these results appear to fit to our burnout findings, however, they contrast the findings of Langelaan and co-workers, if the concept of work engagement is understood as the opposite pole of work stress on a unipolar dimension. This could indicate, however, that work engagement does not simply reflect the opposite or positive pole of chronic work stress.

Interestingly, our stronger cortisol suppression in the DST in participants with higher burnout/exhaustion or depressive symptomatology bears a stronger resemblance with cortisol profiles after dexamethasone pre-treatment in patients with posttraumatic stress disorder (PTSD) (Yehuda et al., 1993) or chronic fatigue syndrome (CFS) (Demitrack, 1997; Demitrack & Crofford, 1998; Gaab et al., 2002) compared to patients with

major depression (MD) who repeatedly showed less post-dexamethasone cortisol suppression (Holsboer, 2001; Parker et al., 2003).

The question to which degree burnout or VE and depression are essentially interchangeable constructs is often discussed in the burnout literature (Iacovides et al., 2003; Appels, 2004; Melamed et al., 2006). In line with this discussion, recent findings from the Finnish Health 2000 Study also revealed that over 50% of severe burnout cases as measured by the MBI met DSM-IV criteria for depressive disorders (Ahola et al., 2005). Furthermore, we know from previous studies that burnout, VE, depression, and anxiety show moderate to high interrelationships. Despite a clear overlap between symptoms, earlier research clearly suggests distinct psychological constructs. In a previous sample of 822 employees, we recently showed that VE and depressive symptomatology are significantly interrelated concepts but reflect distinct psychological constructs (Kudielka et al., 2004b). To-date, most researchers agree that despite substantial overlap of symptoms, there are certain aspects which need to be distinguished. Burnout has a greater conceptual link to the social environment at work, whereas VE and depression both describe more global states. Unique to the conceptualisation of depression however are feelings of guilt, hopelessness, and worthlessness which discriminates it from burnout and VE (van Diest & Appels, 1991; Kopp et al., 1998; Suls & Bunde, 2005). Accordingly, in the present sample of healthy teachers, free of any psychiatric diagnosis (including depression), all burnout-related scales showed moderate to high intercorrelations with depressive symptomatology as measured by HADS-D (see Table 3.2). Due to this considerable amount of shared symptomatology, it is not surprising that the effects of the work stress variables and the HADS-D effect on cortisol profiles after dexamethasone became non-significant "controlling" simultaneously one for the other. The effects appeared to cancel each other out. However, since major depression is more often related to reduced HPA axis negative feedback functioning, the present finding of heightened HPA axis negative feedback functioning in burnout might

underline the idea of different constructs, especially considering the positive correlation between burnout and depressive symptomatology as measured by HADS-D (see Table 3.2). In sum, future research on burnout/exhaustion and HPA axis regulation should definitely expand into the investigation of the interplay between burnout, exhaustion, and depressive symptoms. For example, based on our results it may be speculated that certain sub-sets of individuals might respond differentially to chronic work stress. In some individuals work stress could lead to burnout and VE whereas in others it might manifest in work-induced depression.

The aim of this exploratory study was to investigate possible HPA axis dysregulation in either burnout (MBI, TBS), VE, or ERI/OC. With this, one has to bear in mind that multiple testing increases the risk for chance findings due to potential alpha error accumulation. So, our results have to be interpreted with adequate caution. Interestingly, the present findings are quite consistent across the different tests and questionnaires supporting the view that the reported results are probably no pure chance findings.

One further limitation of our study might be the overrepresentation of women. As in other teacher samples, the ratio of women to men was about 2:1 reflecting the general situation of teachers in German schools (Pruessner et al., 1999; Unterbrink et al., 2007). Furthermore, we cannot rule out that our sample might, at least in part, reflect a selection of somewhat less burdened teachers since among the more heavily burdened faculty fewer volunteered to participate in the somewhat time-consuming study. However, a large range of possible burnout and VE scores was covered in the study sample. Compared to a normative (healthy) Dutch sample comprised of N=3,892 subjects, our teacher sample reported mean MBI-EE scores ranking at the higher end of the medium tertile (Schaufeli & Van Dierendonck, 1995) and about half of our sample reported substantial to severe VE. As for ERI/OC, our sample had scores comparable with a cohort of 709 workers in a highly competitive industrial

sector (Kudielka et al., 2004a) and only slightly lower levels than another German sample of 949 teachers (Unterbrink et al., 2007). However, as we did not study a patient sample, we cannot draw conclusions regarding HPA alterations in clinical cases of burnout and VE. It is noteworthy that significant associations between job-related stress and altered HPA axis functioning could even be observed in chronically stressed but otherwise healthy and fully functioning participants (no sick-leave) with high burnout and VE scores. Due to its cross-sectional design, complex interactions between complaints and symptoms of work stress and physiological outcome parameters or any temporal ordering cannot be determined and therefore no conclusions about "cause and effect" can be drawn.

Credits to the present study are its relatively large sample size, the homogeneity of the sample regarding educational and socioeconomic status, and the control of non-compliance by exclusion of non-compliant profiles from statistical analyses in order to avoid invalidation of cortisol data. Furthermore, the sampling design was relatively broad. Hellhammer and co-workers (2007) recently showed that at least two assessment days are necessary to obtain reliable trait measures of basal pituitary-adrenal activity, as different state and trait factors affect the course of the cortisol profiles over the day. Finally, four different questionnaires were used to assess burnout, VE, and ERI/OC to cover various aspects of job-related stress or possible consequences of chronic stress at work.

In summary, burnout/exhaustion and ERI-reward appear to be associated with subtle HPA axis dysregulation in healthy working teachers, which manifested in heightened negative feedback functioning but not in basal cortisol day profiles on either working or leisure days. Since studies on HPA axis regulation in individuals with higher levels of burnout and VE are rather inconsistent we speculate that the underlying effects might either be rather small, only detectable when various intervening factors moderating HPA axis activity are controlled for (e.g., compliance), or when highly sensitive research tools are applied (e.g., very low-dose DST, experience sampling method).

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Chapter 4

Chronic work stress and exhaustion are associated with higher allostatic load in female school teachers

Stress, in press.

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4.1 Abstract

Epidemiological studies have shown that chronic work stress or unfavourable psychosocial work conditions are prospectively associated with different adverse health outcomes. The aim of the present cross-sectional study was to investigate the relationship between work-related chronic stress as well as exhaustion and a cumulative measure of physiological wear-and-tear called allostatic load (AL). AL could be a possible biological pathway how chronic work stress and exhaustion lead to health impairments in the long run. As the teaching profession has been proposed to be a potentially high stressful occupation, chronic work stress (effort-reward-imbalance) and exhaustion were assessed in 104 female school teachers. Allostatic load was first analysed according to McEwen's classical model comprised of ten parameters including cortisol, epinephrine and norepinephrine, dehydroepiandrosterone-sulfate (DHEA-S), waist/hip-ratio (WHR), glycosylated haemoglobin (HbA1c), high-density lipoprotein (HDL), total cholesterol/HDL-ratio, and systolic and diastolic blood pressure. Additionally it was extended by tumor-necrosis-factor-alpha (TNF-α), C-reactive protein (CRP), fibrinogen, D-dimer, percent-body-fat, triglycerides, and glucose levels. A substantial proportion of our sample was highly exhausted whereas relatively few teachers showed high effort-reward-imbalance. AL scores were significantly higher in women high on effort-reward-imbalance or suffering from exhaustion. Although all teachers have been in a good health status, chronic work stress as well as exhaustion appears to be associated with changes in a multisystem summary indicator of physiological risk.

4.2 Introduction

An increasing number of epidemiological studies report a prospective association between unfavourable psychosocial work conditions (e.g., in terms of high job demands and low job control or effort-reward-imbalance) and different adverse health outcomes (Bosma et al., 1998; Hemingway & Marmot, 1999; Kuper et al., 2002; Siegrist, 2004; Rozanski et al., 2005). Exhaustion, the core dimension of the burnout syndrome, has also been shown to predict poor health (Falger & Schouten, 1992; Appels et al., 1993; Kop et al., 1994, 1999, 2003; Gidron et al., 2002; Koertge et al., 2002; Melamed et al., 2006b). McEwen's allostatic load (AL) model could be a possible biological pathway how chronic work stress in terms of effort-reward-imbalance and exhaustion can lead to health impairments (McEwen & Stellar, 1993; McEwen, 1998b, 1998a). The AL index is conceptualized as a summary measure capturing the cumulative physiological burden exacted on the body through attempts to adapt to life's demands. It is thought to reflect the wear-and-tear on the body and brain resulting either from chronic overactivity or inactivity of physiological systems that are involved in the adaptation to environmental challenge (McEwen, 1998b). A composite AL index reflecting hypothalamus-pituitary-adrenal (HPA) axis functioning, sympathetic nervous system (SNS) activation, cardiovascular activity, atherosclerosis development, and glucose metabolism has been shown to increase with age and has proven useful in predicting various physiological changes that precede disease manifestation (Seeman et al., 2002; Crimmins et al., 2003). Instead of focusing on individual parameters in single biological systems, the AL concept incorporates multiple stress sensitive systems, as this comprehensive measure was shown to better predict future health risks than any single factor on its own (Seeman et al., 1997a, 2002; Karlamangla et al., 2002). The initial model proposes that parameters quantifying AL can be categorised into primary mediators such as cortisol, epinephrine, norepinephrine and dehydroepiandrosterone-sulfate (DHEA-S) causing primary effects which in turn lead to six secondary

outcomes, namely waist/hip-ratio (WHR), glycosylated haemoglobin (HbA1c), high-density lipoprotein (HDL), total cholesterol/HDL-ratio, and systolic and diastolic blood pressure, that ultimately result in tertiary outcomes representing actual disease (McEwen & Seeman, 1999). Theoretically, AL has been conceptualised as cumulative biological dysregulation across all major regulatory systems of the body. In the initial MacArthur studies, a first empirical AL composite was introduced based on a set of ten biological measures in an existing database. In line with their theoretical reasoning, the original authors suggested to extend this first operationalisation to other stress sensitive physiological systems (Kudielka & Kirschbaum, 2007) such as the immune system and the blood coagulation system (McEwen & Seeman, 1999; Seeman et al., 2001). Meanwhile, the originally introduced AL index was successfully expanded by further factors like tumor-necrosis-factor-alpha (TNF-α), C-reactive protein (CRP), fibrinogen, insulin, glucose, low-density lipoprotein (LDL), triglycerides, albumin, and body-mass-index (BMI) (Schnorpfeil et al., 2003; Hellhammer et al., 2004; Goodman et al., 2005). In the last decade, the AL concept has triggered cumulative research activities and was studied in relation to various predictors such as social inequalities and socioeconomic status, quality of sleep, religious service attendance, sense of coherence or chronic caregiving stress, mood disorders and posttraumatic stress disorder (PTSD) that could potentially affect overall health outcomes (Kubzansky et al., 1999; Evans, 2003; McEwen, 2003; Goodman et al., 2005; Glover et al., 2006; Lindfors et al., 2006; McEwen, 2006; Clark et al., 2007; Maselko et al., 2007). Currently, data on the relationship between work-related stress and AL is still extremely rare. Schnorpfeil and colleagues (2003) were the first to investigate the association between AL and psychosocial work characteristics. They found a weak but significant association between an extended AL score based on 14 parameters and job demands in industrial workers. Others investigated whether repetitive work is associated with endocrinological indicators of stress though did not refer to the AL model (Hansen et al., 2003). The

teaching profession has been repeatedly described as a potentially stressful occupation (Guglielmi & Tatrow, 1998) reflected in alarmingly high rates of early retirement in German school teachers (Weber et al., 2002). Our aim was therefore to contribute to the question whether long-term job-related stress in apparently healthy school teachers manifests in this cumulative health outcome measure prior to the onset of a manifest clinical disease.

Chronic work stress was assessed in terms of effort-reward-imbalance (ERI) postulating that a lack of reciprocity between personal costs (effort) and personal gains (reward) at the workplace leads to stress and consequently to an increased risk for stress-related disorders. Indeed, high effort-reward-imbalance has been found to be related to increased risk for cardiovascular disease, type 2 diabetes, depression, alcohol dependence, and sleep problems (Tsutsumi et al., 2001; Kivimäki et al., 2002; Kudielka et al., 2004a; Kumari et al., 2004; Kouvonen et al., 2006). Exhaustion is a core symptom of the burnout syndrome. Burnout develops when demands at the workplace (e.g., high work load and continuous time-pressure) exceed an individual's capacity to cope over a long period of time. In the present study, exhaustion was measured by the emotional exhaustion subscale of the Maslach Burnout Inventory (MBI-EE) (Maslach & Jackson, 1986; Brenninkmeijer & VanYperen, 2003) and the Maastricht Vital Exhaustion Questionnaire (VE) (Appels et al., 1987). Vital exhaustion is characterized by excessive fatigue, a loss of mental and physical energy, increased irritability, and feelings of demoralization. Whilst burnout is positively associated with various physical symptoms (e.g., recurrent headaches, disturbed sleep patterns) as well as manifest diseases (e.g., cardiovascular diseases, or type 2 diabetes) (Mohren et al., 2001; Melamed et al., 2006b), the closely related concept of vital exhaustion has been primarily established as an independent risk factor for coronary artery disease (Falger & Schouten, 1992; Appels et al., 1993; Kop et al., 1994, 1999, 2003; Gidron et al., 2002; Koertge et al., 2002).

In sum, the aim of the present cross-sectional study was to investigate the association between chronic work stress, reflected in effort-reward-imbalance and exhaustion, and a cumulative measure of physiological wear-and-tear (allostatic load, AL). As a high AL is assumed to be a possible biological mechanism explaining how the costs of chronic work stress can lead to health impairments, we hypothesized that AL is higher in teachers with high chronic work-related stress in terms of effort-reward-imbalance or suffering from exhaustion.

4.3 Methods

4.3.1 Participants and general experimental outline

Teachers were recruited by personal visits to local schools as well as via newspaper announcements in the region of Trier (Germany) and Luxembourg (Luxembourg). The analysis is based on 104 healthy currently working women. Volunteers with psychiatric disorders, medicated with corticosteroids or psychotropic drugs, a history of cancer, artery disease or heart failure, serious endocrine diseases (including diabetes, polycystic ovarian syndrome, etc.), or pregnant women were not included. Demographics and current health status were assessed during a telephone screening in eligible subjects. After the telephone screening, the remaining volunteers received a package of questionnaires via mail for psychometric assessment and were invited to an early morning lab visit after overnight fasting (before school, between 6:30 and 9:00 a.m.). As the lab appointment included anthropometric measurements and blood withdrawals for the assessment of allostatic load parameters (itemized below) participants were instructed to refrain from any medication, coffee or substance use for 12 hours prior to the sample collection.

Blood pressure as well as body composition was measured after a ten minutes rest period whilst lying down. For the estimation of percent-body-fat, bioelectrical impedance analysis (B.I.A.; Nutri Plus, Data Input GmbH, Darmstadt, Germany) was applied. Waist/hip-ratio was calculated based on the waist circumference (measured at its narrowest point between the

ribs and iliac crest) and the hip circumference (measured at the maximal buttocks). The night before their lab appointment, subjects were requested to complete an overnight urine collection, including the first void after awakening the next morning. Subjects were instructed to add hydrochloric acid diluted to 12.5% to the urine sample for the purpose of conservation. The ethic committees of the State Medical Association of Rheinland Pfalz and the University of Trier approved the study protocol. All participants provided written informed consent and were paid 50 Euros as an incentive after completion of the study.

4.3.2 Psychological assessment

Effort-reward-imbalance

Effort-reward-imbalance (ERI) was assessed by its validated German version using the 6-item effort and 11-item reward scale (Rödel et al., 2004; Siegrist et al., 2004). For both scales, high internal consistencies (Cronbach's alpha) could be demonstrated for the present study sample (effort: α=0.74; reward: α=0.82). The ratio of effort to reward expresses the amount of perceived effort-reward-imbalance at work and was computed according to the formula given by the authors. A value close to zero indicates relatively low effort and relatively high reward whereas values above 1.0 indicate a high amount of effort spent not matched by appropriate rewards. According to Siegrist and coworker`s specification, the ratio was transformed into a binary variable with values ≤1.0 indicating low risk and values >1.0 indicating high risk (Siegrist et al., 2004).

Exhaustion

Vital Exhaustion (VE) was measured with a German version of the 9-item short form of the original Maastricht Vital Exhaustion Questionnaire (Appels et al., 1987) as used previously (Kudielka et al., 2006b). To compare teachers with low versus high levels of VE, a binary measure was used contrasting "no to moderate exhaustion" (scores 0-10) with "substantial to severe exhaustion" (scores 11-18). The high reliability of

the short form is reflected by an internal consistency (Cronbach's alpha) of α=0.89.

Emotional exhaustion was measured using a validated German version (Schwarzer & Jerusalem, 2001) of the Maslach Burnout Inventory (MBI-EE) (Maslach & Jackson, 1986). This scale consists of nine items and is often described as the superordinate scale of the burnout concept (Brenninkmeijer & VanYperen, 2003). Each item is ranked on a 7-point scale, ranging from "never"=0 to "daily"=6. According to the cut-off scores described by Schaufeli and Van Dierendonck (1995) based on a normative sample, high (as opposed to low) emotional exhaustion was defined by MBI-EE scores ≥20. In the present data, the internal consistency (Cronbach's alpha) of the MBI-EE subscale was α=0.92, reflecting good reliability.

Hospital anxiety and depression scale-depression

The HADS-D is a self-report screening tool indicating the possible presence of depressive states (Zigmond & Snaith, 1983). The subscale HADS-depression (HADS-D) consists of seven items, which are coded on a 4-point Likert scale ranging from 0="not at all" to 3="mostly". We applied the validated German version published by Herrmann and co-workers (1995). With α=0.83 a high reliability in terms of internal consistency could be guaranteed.

4.3.3 Allostatic load

According to the classical description of AL, the original score is based on ten parameters namely cortisol, epinephrine and norepinephrine, dehydroepiandrosterone-sulfate (DHEA-S), waist/hip-ratio (WHR), glycosylated haemoglobin (HbA1c), high-density lipoprotein (HDL), total cholesterol/HDL-ratio, and systolic and diastolic blood pressure (Seeman et al., 1997b). For an extended AL concept, we added C-reactive protein (CRP), tumor-necrosis-factor-alpha (TNF-α), fibrinogen, D-dimer, percent-body-fat, triglycerides, and fasting glucose levels to additionally account for immunological, blood coagulation, and metabolic processes as was

previously suggested by the original authors (McEwen & Seeman, 1999; Seeman et al., 2001). A composite AL measure composed of the sum of risk factors was computed based on the number of parameters on which each subject scored in the highest quartile of risk for the total sample (except for HDL and DHEA-S where inclusion in the lowest quartile constitutes risk) as introduced by Seeman and co-workers (1997b). AL values can therefore range from 0-10 for the classical AL score and from 0-17 for the extended AL score with higher scores reflecting greater cumulative physiological burden.

One conceptual issue concerning the predictive value of AL composites which still needs further clarification is the direction of risk for cortisol as both hyper- and hypoactivity of the HPA axis have been associated with stress-related pathologies (for reviews see Heim et al., 2000; Raison & Miller, 2003). The existing literature on HPA axis functioning in exhaustion is rather inconsistent with some studies reporting no associations between cortisol levels and exhaustion and others reporting on either HPA axis hyperactivity or hypoactivity (for a recent review see Kudielka et al., 2006a). Therefore, in a complementary analysis risk for cortisol was calculated including extreme cortisol scores on either end of the continuum (highest and lowest 12.5%) as was previously done by Glover and colleagues (2006) who investigated AL in PTSD which is often associated with reduced cortisol levels.

4.3.4 Biochemical analysis

All biological data were determined by a commercial laboratory (Synlab, Trier, Germany: total cholesterol, HDL, triglycerides, glucose, HbA1c, fibrinogen, D-dimer) or by the Psychobiological Research Laboratory of the University of Trier, Germany (cortisol, epinephrine, norepinephrine, DHEA-S, CRP, TNF-α). After overnight fasting, venous blood was collected using Monovettes (Sarstedt, Nümbrecht, Germany) for DHEA-S, blood lipids, glucose and CRP (serum-Monovettes), HbA1c and TNF-α (EDTA-Monovettes) as well as fibrinogen and D-dimer (citrate-Monovettes). Blood

samples were instantaneously stored on ice and centrifuged at 4ºC for 15 minutes at 2000g in an adjacent room and plasma or serum was pipetted into aliquots. Within 60 minutes, aliquots were transferred to the core lab (Synlab) and processed right away or frozen at -20ºC (DHEA-S, CRP) or -80ºC (TNF-α) until further analysis. All samples were processed according to standard laboratory procedures.

Plasma levels of TNF-α and D-dimer and serum levels of DHEA-S and CRP were determined using high-sensitivity enzyme-linked immunosorbent assays (ELISA) (TNF-α: Quantikine HS, R&D Systems Europe, Abington, United Kingdom; intra- and inter-assay variation ≤5.8%; D-dimer: VIDAS® D-dimer ExclusionTM, bioMérieux, Marcy-l´Etoile, France; intra- and inter-assay variation ≤6.2%; DHEA-S and CRP: IBL, Hamburg, Germany; intra- and inter-assay variation DHEA-S ≤7.5% and intra- and inter-assay variation CRP ≤12.9%). Plasma fibrinogen levels were determined by a routine clotting assay following the Clauss method (Clauss, 1957) (intra- and inter-assay variation ≤4.4%). Serum levels of total cholesterol, HDL and triglycerides were analysed by an enzymatic color-UV-assay using autoanalyser (Olympus AU 640, Olympus, Hamburg, Germany; intra- and inter-assay variation total cholesterol ≤1.6%; intra- and inter-assay variation HDL ≤3.0%; intra- and inter-assay variation triglycerides ≤0.9%). Serum levels of glucose were analysed by the hexokinase method using autoanalyser (Olympus AU 2700, Olympus, Hamburg, Germany; intra- and inter-assay variation ≤1.3%). Plasma levels of HbA1c as well as urinary cortisol, epinephrine and norepinephrine were determined from high performance liquid chromatography (HPLC) preparation (intra- and inter-assay variation HbA1c ≤1.5%; intra- and inter-assay variation catecholamines ≤7.0%; intra- and inter-assay variation cortisol ≤10.0%). The values for cortisol, epinephrine and norepinephrine were adjusted for renal function using the 12-hours creatinine excretion rate as per standard procedure.

4.3.5 Statistical analysis

Statistical analyses were performed using the SPSS statistical software package (Version 14.0.1; Chicago, IL, USA). Unless otherwise stated, results are expressed as mean ± standard deviation (SD). Interrelationships between questionnaire scores (ERI, VE, MBI-EE), allostatic load and age as well as between single AL parameters were assessed using Pearson correlations. Interrelationships between questionnaire scores (ERI, VE, MBI-EE) and single AL parameters were assessed by partial correlation controlling for age. Student's t-test were applied to test for possible age effects and to compare the AL indices (dependent variable) in groups scoring low versus high on effort-reward-imbalance (ERI) or exhaustion (VE and MBI-EE). Despite clear unidirectional hypotheses, the presented significance level was set at $p \leq 0.05$ according to two-tailed testing. Empirical effect sizes were calculated as standardized mean difference (Cohen´s d; d=0.20 small effect, d=0.50 moderate effect, d=0.80 strong effect) (Cohen, 1988). A curve estimation analysis was applied to test for possible quadratic associations between the AL parameter cortisol and the questionnaire scores.

4.4 Results

4.4.1 Study sample

In sum, 104 eligible healthy women from 25 to 61 years of age (mean age ± SD: 45.0±9.75 yrs.) participated in the lab assessment and returned the questionnaires and urine samples. All participants were currently working as a school teacher in one of the major German school types, thus our sample is characterized by very high homogeneity regarding educational and socioeconomic status. A substantial proportion of our sample was highly exhausted (47% for VE and 40% for MBI-EE) whereas only 14% qualified for the ERI high risk group (see Table 4.1).

Table 4.1: Description of the grouping variables

	N	Mean	Range
ERI			
ERI ≤1	87		
ERI >1	15	0.74 ± 0.46	0.24-4.43
Missing	2		
VE			
"No to mild exhaustion"	54		
"Substantial to severe exhaustion"	49	9.85 ± 5.39	0-18
Missing	1		
MBI-EE			
MBI-EE <20	61		
MBI-EE ≥20	42	18.0 ± 11.2	1-46
Missing	1		
AL Scores			
Classical	104	3.4 ± 1.8	0-9
Extended	97	5.0 ± 3.0	0-14

As expected, high intercorrelations were observed between the two AL indices and both AL indices showed moderate correlations with age. The two exhaustion measures (VE and MBI-EE) showed high intercorrelations and both correlated moderately with ERI. No intercorrelations however could be observed between ERI or exhaustion and age (see Table 4.2). HADS-D scores were highly correlated with exhaustion (VE: $r=0.64$ $p<0.001$ and MBI-EE: $r=0.48$ $p<0.001$) and moderately associated with effort-reward-imbalance (ERI: $r=0.40$ $p<0.001$).

Table 4.2:
Pearson correlation matrix for ERI, VE, MBI-EE, age and allostatic load (AL); **p<0.01, *p<0.05

	ERI	VE	MBI-EE	Age	AL Classical
VE	0.44**				
MBI-EE	0.44**	0.69**			
Age	0.14	0.15	0.05		
AL Classical	0.26**	0.14	0.10	0.54**	
AL Extended	0.22*	0.13	0.09	0.45**	0.87**

No significant differences in age could be found for the respective groups scoring low versus high on ERI or exhaustion (all t<-1.65 all p>0.1; low ERI risk: 44.7±9.82 yrs. versus high ERI risk: 48.1±9.82 yrs.; low VE: 43.5±10.83 yrs. versus high VE: 46.7±8.17 yrs.; low MBI-EE: 44.4±10.59 yrs. versus high MBI-EE: 45.9±8.39 yrs.).

4.4.2 Allostatic load

Table 4.3 presents the distribution of all AL parameters and the respective cut-off values used to calculate the AL indices. AL scores ranged from 0 to 9 for the classical AL index and from 0 to 14 for the extended AL index.

Table 4.3: Distribution of allostatic load (AL) parameters and cut-off values

	Mean	SD	Range	Cut-off	Normal Range
Parameters with high values (within highest quartile) indicating possible risk					
Cortisol in urine (µg/g creatinine)	22.4	26.7	0.0 - 216.7	> 25.6	not applicable
Norepinephrine in urine (µg/g creatinine)	53.1	29.5	6.81 - 229.2	> 64.0	not applicable
Epinephrine in urine (µg/g creatinine)	4.23	2.82	0.17 - 17.0	> 5.55	not applicable
Waist/hip-ratio	0.82	0.08	0.68 - 1.33	> 0.86	< 0.85
Glycosylated haemoglobin in plasma (%)	5.26	0.39	4.00 - 7.20	> 5.41	< 6
Cholesterol/high-density lipoprotein-ratio in serum (mg/dl)	3.24	0.85	1.47 - 7.83	> 3.58	< 4 - 6
Systolic blood pressure (mm Hg)	124.7	16.9	99.0 - 175.0	> 134	< 140
Diastolic blood pressure (mm Hg)	81.3	10.7	57.0 - 109.0	> 89.0	< 90
Tumor-necrosis-factor-α in plasma (pg/ml)	1.30	1.72	0.02 - 12.2	> 1.44	not applicable
C-reactive protein in serum (mg/l)	2.45	3.76	0.05 - 31.1	> 2.77	0.07 - 8.2
Fibrinogen in plasma (g/l)	3.14	0.81	1.99 - 6.00	> 3.63	1.80 - 3.6
D-dimer in plasma (µg/ml)	0.29	0.18	0.06 - 1.36	> 0.38	0.00 - 0.5
Body-fat in %	32.8	6.93	16.4 - 52.2	> 37.3	20 - 31
Triglycerides in serum (mg/dl)	96.2	40.5	33.0 - 218.0	> 120.0	< 200
Fasting glucose in serum (mg/dl)	94.1	10.7	71.0 - 143.0	> 100.0	74 - 106
Parameters with low values (within lowest quartile) indicating possible risk					
Dehydroepiandrosterone-sulfate in serum (µg/ml)	1.03	0.58	0.20-3.34	< 1.33	1-3
High-density lipoprotein in serum (mg/dl)	66.9	14.4	35.0-120.0	< 76.0	> 60

Table 4.4 shows intercorrelations between single AL parameters and Table 4.5 illustrates and how they relate to ERI and exhaustion. No significant associations between single AL parameters and ERI or exhaustion could be observed.

Table 4.4: Pearson correlations between single allostatic load parameters; **p<0.01, *p<0.05

	Cort	Norepi	Epi	WHR	HbA1c	Chol/ HDL	Syst. BP	Diast. BP	TNF-α	CRP	Fibr	D-dim	Body-fat	Triglyc	Gluc	DHEA-S
Norepi	0.27**															
Epi	0.08	0.08														
WHR	0.05	0.07	-0.23*													
HbA1c	0.04	0.16	-0.13	-0.00												
Chol/HDL	0.04	0.19	-0.11	0.26**	0.26**											
Syst. BP	0.02	0.21*	0.04	0.16	0.37**	0.28**										
Diast. BP	0.01	0.19	0.03	0.12	0.40**	0.31**	0.86**									
TNF-α	-0.08	0.06	-0.08	0.10	-0.02	0.19	-0.05	-0.06								
CRP	0.02	0.18	-0.19	-0.00	0.22*	0.10	0.02	0.11	0.08							
Fibr	-0.02	0.17	-0.10	0.05	0.27**	0.14	0.28**	0.26**	0.20*	0.51**						
D-dim	0.02	0.19	-0.16	0.03	0.22*	0.13	0.14	0.20*	-0.06	0.23*	0.26**					
Body-fat	-0.02	0.19	-0.33**	0.17	0.42**	0.35**	0.22*	0.32**	0.08	-0.46**	0.49**	0.34**				
Triglyc	0.00	0.18	-0.16	0.10	0.22*	0.45**	0.32**	0.36**	0.15	0.15	0.24*	0.19	0.20			
Gluc	0.01	0.19	-0.09	0.20*	0.34**	0.35**	0.29**	0.33**	0.06	0.13	0.06	0.21*	0.34**	0.21*		
DHEA-S	-0.13	-0.20*	-0.14	0.09	-0.18	-0.05	-0.20*	-0.08	-0.05	-0.14	-0.18	-0.07	-0.01	-0.28**	0.09	
HDL	0.02	-0.03	0.08	-0.22*	-0.16	-0.62*	0.02	-0.02	-0.09	-0.11	-0.13	-0.04	-0.30**	-0.15	-0.25*	-0.15

Table 4.5: Partial correlations between ERI, VE and MBI-EE and single allostatic load parameters controlling for age

	ERI	VE	MBI-EE
Cort	0.11	0.18	0.05
Norepi	0.15	0.11	-0.06
Epi	-0.04	0.18	0.20
WHR	0.06	-0.08	-0.13
HbA1c	0.12	0.09	0.19
Chol/HDL	0.06	-0.13	-0.08
Syst. BP	-0.08	0.03	-0.03
Diast. BP	0.02	0.07	0.08
TNF-α	-0.05	-0.13	-0.08
CRP	0.24	0.14	0.23
Fibr	0.02	-0.05	0.01
D-dim	0.13	-0.04	0.02
Body-fat %	0.19	0.06	0.11
Triglyc	0.09	-0.01	-0.08
Gluc	0.23	0.10	0.10
DHEA-S	-0.08	-0.09	-0.02
HDL	0.01	0.21	0.15

Cort: Cortisol; **Norepi:** Norepinephrine; **Epi:** Epinephrine; **WHR:** Waist/hip-ratio; **HbA1c:** Glycosylated haemoglobin; **Chol/HDL:** Cholesterol/high-density lipoprotein-ratio; **Syst. BP:** Systolic blood pressure; **Diast. BP:** Diastolic blood pressure; **TNF-α** Tumor-necrosis-factor-alpha; **CRP:** C-reactive protein; **Fibr:** Fibrinogen; D-dim: D-dimer; **Body-fat %:** Percent-body-fat; **Trigclyc:** Triglycerides; **Gluc:** Glucose; **DHEA-S:** Dehydroepiandrosterone-sulfate; **HDL:** High-density lipoprotein

Using the AL composite measure, however, significant differences in AL emerged between teachers scoring low versus high on ERI and exhaustion. In more detail, women in the high ERI risk group showed significantly higher AL compared to women in the low ERI risk group as reflected in the classical ($t(100)=-2.00$ $p=0.048$ $d=0.52$) and extended AL index ($t(93)=-2.26$ $p=0.026$ $d=0.59$). Women high on VE showed significantly higher AL scores than women low on VE (classical AL: $t(101)=-2.29$ $p=0.024$ $d=0.45$; extended AL: $t(94)=-2.21$ $p=0.029$ $d=0.45$) and finally, women high on emotional exhaustion (MBI-EE) had marginally higher AL scores compared to women low on emotional exhaustion (classical AL: $t(101)=-1.95$ $p=0.055$; extended AL: $t(94)=-1.72$ $p=0.088$).

Furthermore, differences in AL scores became more substantial contrasting individuals with a high risk on all three questionnaires (ERI + VE + MBI-EE) versus individuals with no risk in any of the questionnaires

(classical AL: t(57)=-3.13 p=0.003 d=0.98; extended AL: t(52)=-3.02 p=0.004 d=0.97; ERI + VE + MBI-EE risk group: N=12 for classical AL, N=11 for extended AL; no risk group: N=47 for classical AL, N=43 for extended AL). Although smoking was not considered as an exclusion criterion in the first instance, a possible impact of regular smoking on AL parameters should be considered. After excluding five smokers from the analyses, the differences in AL between the above described groups became even more apparent (see Figure 4 A-F; low versus high ERI risk: classical AL t(95)=-2.16 p=0.033 d=0.56; extended AL t(88)=-2.47 p=0.015 d=0.64; low versus high VE: classical AL t(96)=-2.23 p=0.028 d=0.45; extended AL t(89)=-2.31 p=0.023 d=0.48; low versus high MBI-EE: classical AL t(96)=-2.03 p=0.045 d=0.42; extended AL t(89)=-2.06 p=0.043 d=0.43; combined ERI + VE + MBI-EE risk versus no risk: classical AL t(54)=-3.17 p=0.002 d=1.00; extended AL: t(49)=-3.19 p=0.002 d=1.02).

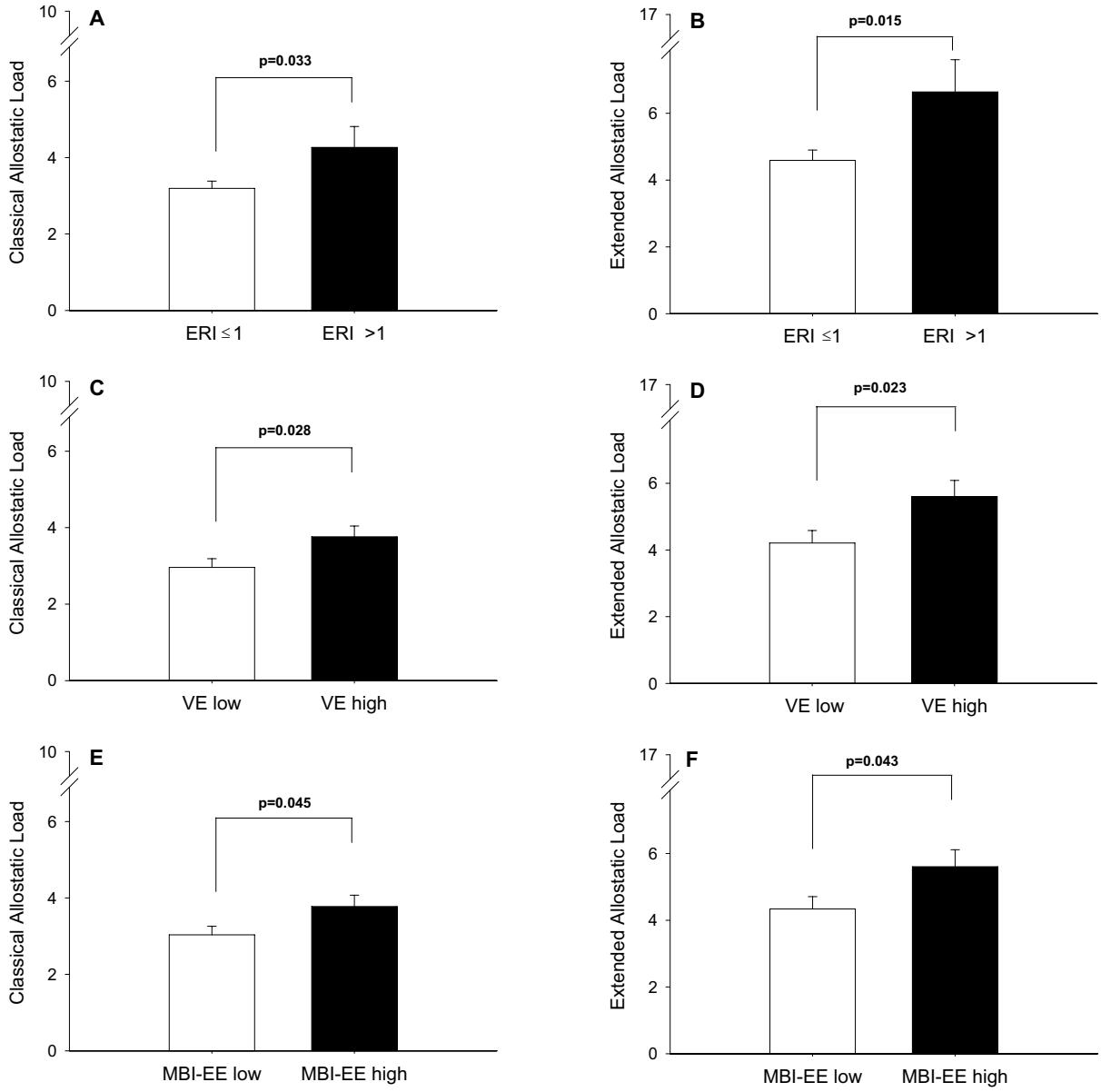

Figure 4.A-F:

4.A: Classical AL Scores in low (N=82) versus high (N=15) ERI risk **4.B:** Extended AL Scores in low (N=76) versus high (N=14) ERI risk; ERI cut-off according to Siegrist et al. (2004) **4.C:** Classical AL Scores in low (N=52) versus high (N=46) VE **4.D:** Extended AL Scores in low (N=48) versus high (N=43) VE; VE cut-off according to questionnaire categories **4.E:** Classical AL Scores in low (N=58) versus high (N=40) MBI-EE **4.F:** Extended AL Scores in low (N=53) versus high (N=38) MBI-EE, MBI-EE cut-off according to Schaufeli and van Dierendonck (1995); Student's t-tests based on non-smokers with complete sets of AL-parameters per score (subjects with missings excluded); data are expressed as mean ± SEM (standard error of mean)

As outlined above, there is an ongoing discussion on the direction of risk for cortisol. Therefore, in a complementary analysis risk for cortisol was alternatively defined as any value in the highest or lowest 12.5% of the total sample. For both, ERI (classical AL: $t(95)=-2.26$ $p=0.026$ $d=0.59$; extended AL: $t(88)=-2.56$ $p=0.012$ $d=0.68$) and VE (extended AL: $t(89)=-2.04$ $p=0.044$ $d=0.43$) significant differences between the groups were also observed using this alternative composite in respect to cortisol (analyses based on non-smokers). For VE, group differences for the classical AL approached the level of significance ($t(96)=-1.67$ $p=0.098$). For the MBI-EE risk groups, however, the differences missed significance or showed marginal significance (classical AL: $t(96)=-1.48$ $p=0.14$; extended AL: $t(89)=-1.79$ $p=0.076$). To additionally test whether the relationship between cortisol and ERI or exhaustion is better described in quadratic than linear terms, a curve estimation analysis was performed. However, no significant quadratic associations could be found (all $F<1.94$ all $p>0.15$).

4.5 Discussion

The purpose of this study was to elucidate whether chronic work stress or unfavourable psychosocial work conditions are associated with a cumulative measure of physiological wear-and-tear called allostatic load (AL). We assessed work-related stress in terms of effort-reward-imbalance (ERI) and the extent of exhaustion (VE and MBI-EE) in 104 female school teachers since especially the teaching profession is characterized by potentially high stressful psychosocial workplace characteristics (Guglielmi & Tatrow, 1998).

Overall, our findings showed that slightly but significantly higher AL scores can be found in female school teachers with high levels of effort-reward-imbalance and exhaustion, reflecting subtle dysregulation across multiple stress-sensitive systems. It is noteworthy that compared to other studies on AL, the subjects participating in our study were relatively young, currently working, and in a good health status. Nevertheless, high chronic

work stress as well as exhaustion was associated with signs of cumulative physiological burden in this sample. These observations underline the idea that the AL composite might have high predictive power for onset or progression of a variety of stress-related health problems in apparently healthy individuals or in individuals in sub-clinical states. The hypothesis that a composite measure across multiple stress-sensitive systems is more sensitive for the detection of early signs of dysregulation that could lead to later disease manifestation (Seeman et al., 1997b) is strengthened by the fact that no significant associations could be observed between single AL parameters and ERI or exhaustion (see Table 4b). From a practical point of view, an AL summary measure may play an important role in monitoring health states over time or in the prevention of stress-related health impairments in the future.

The initial operationalisation of AL included ten biological variables, reflecting HPA axis functioning, sympathetic nervous system (SNS) activation, cardiovascular activity, atherosclerosis development, and glucose metabolism. As already suggested by the original authors, we expanded the original score to additionally account for immunological, blood coagulation, and metabolic processes because the AL index has been theoretically conceptualized as a comprehensive marker of cumulative dysregulation across stress-sensitive physiological systems (McEwen & Seeman, 1999; Seeman et al., 2001; Schnorpfeil et al., 2003; Hellhammer et al., 2004; Goodman et al., 2005). Hence, for an extended AL composite, we additionally analysed CRP, TNF-α, fibrinogen, D-dimer, percent-body-fat, triglycerides, and fasting glucose levels. Interestingly, teachers high versus low on ERI or exhaustion showed significant differences for both, the classical as well as the extended AL composite, with only very minor increases in effect sizes for the extended AL sum score. With this, one could be tempted to conclude that the original index is the more parsimonious approach. Though, we would advise against premature conclusions, since findings depend on the specifics of a particular cohort under investigation with the present sample consisting of

highly functioning healthy female teachers. Our results are in line with an earlier report from Schnorpfeil and colleagues (2003) who were the first to apply the AL concept to psychosocial work characteristics. Their study revealed a weak but significant association between an extended AL score based on 14 parameters and job-demands in industrial workers. This association however was dependent on age with an increasing effect of job-demands on AL in older subjects. In our study sample, AL was also moderately correlated with age, a finding which is already known from the MacArthur Studies of Successful Aging (Seeman et al., 1997b). Such an association may point to the importance of other factors that contribute to the cumulative burden of an individual across the life span like protective or damaging factors encoded in one´s genetic make-up. However, none of our work stress variables was related to age and there was also no significant difference in age between ERI and exhaustion risk groups suggesting an independent effect of work stress and exhaustion on AL over and above age-related factors.

A second extension of the original conception of the AL composite which was also applied in our study relates to the parameter cortisol. The direction of risk for cortisol is still a controversial issue in the ongoing discussion regarding the predictive value of AL composites since studies report both on hyper- as well as hypoactivity of the HPA axis in association with different stress-related pathologies (for reviews see Heim et al., 2000; Raison & Miller, 2003). Likewise, the existing literature on HPA axis regulation in exhaustion does not render a consistent picture. To-date, HPA axis hyperactivity, hypoactivity or no associations between cortisol levels and exhaustion have been described (for a recent review see Kudielka et al., 2006a). In our own teacher cohort, no association of ERI or exhaustion and basal HPA activity could be found recently in an analysis of salivary cortisol day profiles across several work and leisure days (Bellingrath et al., 2008). Though, after dexamethasone pre-treatment, stronger cortisol suppression was observed in relation to exhaustion pointing to an increased HPA axis negative feedback

sensitivity. In sum, based on such findings there was no strong argument in favour for one or the other direction of risk for cortisol in work stress and exhaustion. Therefore, we conducted a complementary analysis where risk for cortisol was calculated including extreme cortisol scores on both ends of the continuum (highest and lowest 12.5%) as was previously described by Glover and colleagues (2006) in a sample of PTSD patients. Using this alternative composite, the respective picture of results changed somewhat. Effect sizes for differences between the ERI risk groups were slightly larger. In contrast, the differences between the groups scoring high versus low on exhaustion were less apparent, henceforth yielding only one clearly significant group difference for the extended AL in VE whilst the other comparisons only showed marginally significant effects (classical AL for VE and extended AL for MBI-EE) or no significant effect (classical AL for MBI-EE). Furthermore, curve estimation rendered non-significant effects for quadratic relationships between cortisol and ERI or exhaustion. Overall it appears that more distinct group differences emerge, at least for exhaustion, if the classical linear approach is applied for cortisol (risk defined as highest quartile) compared to the alternative computation (risk defined as highest plus lowest 12.5%).

It is well established that burnout, vital exhaustion and symptoms of depression show substantial interrelationships (Iacovides et al., 2003; Appels, 2004; Ahola et al., 2005; Melamed et al., 2006a). Despite a clear overlap between symptoms, earlier research still suggests distinct underlying psychological constructs (Kudielka et al., 2004b). In the present sample of healthy teachers (free of any psychiatric diagnosis including depression), effort-reward-imbalance and exhaustion showed moderate to high correlations with depressive symptomatology as measured by the HADS-D. Due to this considerable amount of shared symptomatology, it is not surprising that the effects of effort-reward-imbalance and exhaustion on AL become non-significant if controlling for HADS-D (results not shown in detail), suggesting that they cancel each other out. A similar effect has also been observed in a recent analysis on

HPA axis feedback regulation in stressed teachers (Bellingrath et al., 2008). In view of such observations, future studies should definitely expand into the investigation of the interplay between work-related exhaustion and depressive symptoms.

An important limitation of the present study is its still relatively small sample size, especially in comparison to the large cohort studies which first gave insight into the predictive value of the AL model measuring latent risk for poor health outcomes in the absence of disease manifestation (Seeman et al., 1997b; Karlamangla et al., 2002). Furthermore, investigating only women limits the generalisation of our results. Though, we restricted the analysis to a solely female data set because some of the parameters which constitute the AL sum score show significantly different distributions across men and women (e.g., DHEA-S, Orentreich et al., 1984) and, in general, there is still a paucity of data focusing directly on women's health. Surprisingly, a gender-specific approach in studies implementing AL composites however is rarely seen in the literature. Furthermore, the cross-sectional nature of our data does not permit any inferences about temporal ordering and complex interactions between symptoms of work stress, exhaustion and physiological outcome parameters, reflected in the AL composite. For example, individuals with compromised physical health as reflected in elevated AL could be at greater risk for exhaustion due to work stress. Thus, prospective studies are required to evaluate the predictive value of AL composites in the area of work stress. Furthermore, a longitudinal perspective would offer the opportunity to test the hypothesis whether the association of work stress with AL is mediated by exhaustion, to investigate different subgroups (e.g., chronic work stress with exhaustion versus chronic work stress without exhaustion versus no chronic work stress but exhaustion) and whether such groups might benefit differentially from, e.g., social support. Finally, future studies should additionally evaluate the role of non-occupational strain.

Credits to the present study are the high homogeneity of the sample regarding educational and socioeconomic status as well as the integration of additional stress-sensitive systems in the AL composite expanding the classical operationalisation according to its theoretical conceptualisation (McEwen & Seeman, 1999).

In sum, this is the first study investigating allostatic load (AL) in female school teachers in respect to effort-reward-imbalance and exhaustion. We found that high levels of effort-reward-imbalance (ERI) at the workplace as well as high levels of exhaustion (VE and MBI-EE) are associated with higher AL sum scores, reflecting the cumulative wear-and-tear that results from repeated efforts to adapt to stressors over time. It is noteworthy that small but significant associations between work stress as well as exhaustion and AL could even be uncovered in a sample comprised of relatively young and fully functioning subjects (no sick-leave). Despite limitations (see above), these findings may further underline the potential advantage of a composite AL score in quantifying future disease risk in a non-geriatric, apparently healthy and working sample with symptoms of work stress and exhaustion compared to a confined investigation of single biological risk factors.

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Chapter 5

Effort-reward-imbalance and overcommitment are associated with hypothalamus-pituitary-adrenal (HPA) axis responses to acute psychosocial stress in healthy working school teachers

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5.1 Abstract

In this study, we examined HPA axis responses to acute psychosocial stress in relation to effort-reward-imbalance (ERI) and overcommitment (OC) to test whether chronic stress at work is accompanied by altered HPA axis stress responses in teachers. According to Siegrist's work stress model, ERI reflects stress due to a lack of reciprocity between personal costs and gains at work whereas OC is conceptualized as a personality trait mainly characterized by the inability to withdraw from work obligations.

Fifty-three medication-free, non-smoking, healthy teachers (33 women, 20 men, 29-63 yrs., mean age 49.9±8.58 yrs.) were confronted with the Trier Social Stress Test (TSST), a widely-used standardized stress protocol to induce acute psychosocial stress in the laboratory. ACTH (five samples), total plasma (six samples) and free salivary cortisol (eight samples) were repeatedly measured before and after challenge. In the total group, ERI and OC were only marginally associated with HPA axis responses to acute stress. However, in the subgroup of responders (N=30) high levels of OC were significantly associated with lower ACTH ($p=0.03$) as well as plasma ($p=0.02$) and salivary cortisol ($p<0.001$) responses and results remained significant controlling for depressive symptoms. When additionally controlling for acute perceived stressfulness of the TSST, significant associations between OC and HPA axis responses emerged in responders as well as the total study sample. In respect to ERI, higher stress levels were solely related to significantly stronger plasma cortisol increases after TSST exposure, but this effect became non-significant controlling for depressive symptomatology. In sum, our findings support the notion of HPA axis hyporeactivity in highly overcommitted school teachers.

5.2 Introduction

Psychosocial workplace characteristics have recently been implicated in the genesis of chronic work stress (Siegrist et al., 2004). The model of effort-reward-imbalance (ERI) suggested by Siegrist and co-workers is rooted in the notions of reciprocity and fairness as the basic grammar of social exchange. It provides a conceptual framework for possible associations between chronic work stress and adverse health outcomes by postulating that personal self-regulation, which is assumed to impact on health and well-being, is dependent on distributive justice. Threats to successful social exchange, for example a lack of reciprocity between personal costs (effort) and personal gains (reward) at the workplace are assumed to elicit stress, consequently increasing the risk for stress-related disorders (Siegrist, 2002). Efforts represent job demands and obligations imposed on the employee, whereas rewards are conceptualized as three distinct categories, namely financial reward, esteem and security/career opportunities. Thus a working individual not receiving the adequate appreciation for her or his efforts at the work place, potentially experiences stress as reflected in effort-reward-imbalance. Furthermore, in this model the inability to withdraw from work obligations combined with a high need for approval was conceptualized as a personality trait called overcommitment (OC). OC reflects a cognitive-motivational pattern of coping with demands based on elements of Type A behavior that reflect an extreme ambition in combination with a special need for control and approval (see van Vegchel et al., 2005). Thus, overcommited individuals tend to repeatedly exaggerate their efforts at work while at the same time overtaxing their resources. This consequently diminishes their potential to recover from job demands which eventually results in exhaustion and poor health (Siegrist, 2001; Preckel et al., 2005).

Numerous studies have applied the ERI/OC model to different health outcomes. High ERI has been found to be related to increased risk for cardiovascular disease, type 2 diabetes, depression, alcohol dependence, and sleep problems (Tsutsumi et al., 2001; Kivimäki et al., 2002; Kudielka

et al., 2004b; Kumari et al., 2004; Kouvonen et al., 2006). Whereas OC has been shown to be associated with musculoskeletal pain (Joksimovic et al., 2002), incidence of cardiovascular disease (Bosma et al., 1998; Kivimäki et al., 2002) as well as cardiovascular risk factors like elevated blood lipids and blood coagulation factors (Vrijkotte et al., 1999). According to Siegrist´s conceptualization (Siegrist, 2002) ERI leads to a state of distress, thereby activating the two major stress axes, the sympathetic-adrenomedullary system (SAM) and the hypothalamic-pituitary-adrenal (HPA) axis. These neuroendocrine systems regulate the adaptation to increased demands and enable the organism to maintain homeostasis under acute stress. Under chronic stress however, this originally adaptive response can have numerous deleterious consequences. Thus, impaired functioning of HPA axis regulation has been associated with several stress-related diseases and psycho-pathologies (for reviews see Heim et al., 2000; Raison & Miller, 2003; Miller et al., 2007).

To-date, there is a paucity of data on the relationship between HPA axis regulation and ERI or OC. So far, only four studies have investigated the association between model components (namely ERI and OC) and basal HPA axis regulation. A first study by Hanson et al. (2000) could not find significant associations between ERI/OC and salivary cortisol levels using the experience sampling method. Seventy-seven subjects (health professionals and office clerks) collected saliva samples and simultaneously answered diary questions at semirandom intervals up to ten times over the course of a day. In this study, neither ERI/OC nor a momentary demand-satisfaction-ratio was significantly associated with salivary cortisol levels. Steptoe and co-workers (2004) investigated whether ERI/OC are related to the free cortisol increase after awakening as well as salivary cortisol profiles over a working day in 86 men and 79 women from the Whitehall II cohort. They could show that OC is positively associated with the increase in salivary cortisol after awakening in men but not in women. Furthermore, they report a main effect of OC on free cortisol day profiles in men, an effect which is mainly driven by higher cortisol values at a single time point

(14h-1430h). Eller and colleagues (2006) measured free cortisol responses to awakening and two additional salivary cortisol samples over the remainder of the day in 83 healthy subjects. In women, they observed a higher cortisol awakening rise (CAR) with higher ERI. In men, effort, ERI and OC were associated with a higher CAR as well as higher free cortisol levels throughout the day. In a recent analysis of salivary cortisol day profiles across two working days and one leisure day, we could not find an association between ERI/OC and basal HPA activity in an own cohort of healthy teachers (Bellingrath et al., 2008b). However, applying a low dose dexamethasone suppression test (0.25 mg) in 120 teachers we observed a stronger cortisol suppression in teachers with low reward from work suggesting an increased HPA axis negative feedback sensitivity. Finally, Wirtz et al. (2008) were the first to investigate the relationship between the model component OC and salivary cortisol responses to acute psychosocial stress in 50 healthy men. Applying the Trier Social Stress Test (TSST), they showed that higher OC scores were associated with lower levels of salivary cortisol.

To the best of our knowledge, there is yet no study available that analyzed whether the different components of the ERI/OC model (namely the subscales effort and reward, effort-reward-imbalance ratio and OC) are associated with HPA axis regulation in men and women under acute psychosocial stress in terms of adrenocoticotropin (ACTH), total plasma cortisol as well as free salivary cortisol responses. To answer this question, we therefore recruited working healthy male and female school teachers. Teachers have been chosen since the teaching profession has been repeatedly described as a potentially stressful occupation (Guglielmi & Tatrow, 1998), as reflected in alarmingly high rates of early retirement among German school teachers (Weber et al., 2001). Thus, the aim of the present study was to investigate possible associations between all scales of the ERI/OC model and HPA axis responses to acute psychosocial stress in male and female teachers.

5.3 Methods

5.3.1 Participants and general experimental outline

Sixty-two currently employed school teachers from the region of Trier (Germany) and Luxembourg (Luxembourg) consented to participate in this laboratory stress study. We initially approached subjects who already participated in the first part of the Trier Teacher Stress Study (Bellingrath et al., 2008b, 2008a; Kudielka et al., 2008; von Känel et al., 2008). In order to capture the whole continuum of work stress, we admitted either teachers who self-reported a high subjective level of work-related stress as well as teachers who reported not to be stressed by their job. All subjects were told that they participate in a larger project investigating the physiological correlates of chronic work stress in school teachers and that, in this particular study, they will be confronted with a brief laboratory stress task that consists of a speaking and a mental arithmetic part to induce moderate psychosocial stress. First, we ascertained eligibility, demographics, the current health status and health behaviour (smoking status, medication intake) in a telephone interview. The same exclusion criteria were applied as in the first study including psychiatric disorders, diabetes, pregnancy, and corticosteroid or psychotropic medication. To avoid the well-known habituation effects on endocrine stress responses to the TSST, it was ensured that no participant had previously participated in a TSST study or a study with a similar design (Wüst et al., 2005; Kudielka et al., 2006b). The study protocol was approved by the ethics committee of the University of Trier as well as the Rheinland-Pfalz State Medical Association. Written informed consent was provided by all participants. Participants received €70 after completion of the study protocol.

5.3.2 Experimental protocol

Participants were instructed to refrain from physical exercise, a heavy lunch and alcoholic beverages on test days. In order to prevent effects due to time of testing, test sessions were only run in the afternoon and started between 15h and 16h (Kudielka et al., 2004a). Premenopausal women not

taking oral contraceptives were invited during the luteal phase of the menstrual cycle, as verified by self-reports (Kirschbaum et al., 1999). In the laboratory, at first an intravenous catheter was inserted in the antecubital vein of the dominant arm for later blood draws. After a rest period of 50 min after canula insertion, the subject was informed about the nature of the stress protocol and directly exposed to the Trier Social Stress Test (TSST, Kirschbaum et al., 1993). The TSST consists of a three min preparation phase followed by a five min free speech phase (job interview) and a five min mental arithmetic task in front of a panel (for recent reviews and a detailed description see Kudielka et al., 2007a, 2007b). The panel members were graduate students well trained for this task and the panel always comprised one female and one male member. A recent meta-analysis showed that the components of social evaluative threat and uncontrollability render the TSST a reliable tool to elicit robust physiological stress responses (Dickerson & Kemeny, 2004).

5.3.3 Blood and saliva sampling

Blood samples for the assessment of ACTH and total plasma cortisol were collected in EDTA containing monovettes (Sarstedt, Nümbrecht, Germany) 1 min before as well as 1, 10, 20, 30 and 90 min after cessation of the TSST. In parallel, subjects obtained native saliva in 2 ml reaction tubes (Sarstedt, Nümbrecht, Germany) for later assessment of salivary free cortisol. Additional saliva samples were obtained at 45 and 60 min after cessation of the TSST.

5.3.4 Hormonal analysis

Blood samples were instantaneously stored on ice and centrifuged at 4ºC for 15 min at 2000 g in an adjacent room and pipetted into aliquots. Aliquots for the analysis of plasma cortisol as well as saliva samples were stored at -20°C and aliquots for the analysis of ACTH were stored at -80°C until assayed. ACTH and total plasma cortisol were measured by enzyme-linked immunosorbent assays (ELISA) (plasma cortisol: IBL Hamburg,

Germany, intra- and inter-assay variation ≤6.9%; ACTH: Biomerica Newport Beach, USA, intra- and inter-assay variation ≤6.0%). Salivary cortisol (nmol/l) was measured by an inhouse time-resolved fluorescence immunoassay (DELFIA, intra- and inter-assay variation ≤11.5%).

5.3.5 Psychological assessment

Demographics

Demographic variables (sex, age, years of employment, type of school) were recorded based on verbal and written self-reports during the telephone interview and at laboratory visits.

Effort-reward-imbalance and overcommitment

Effort-reward-imbalance (ERI) was assessed by its validated German version using the 6-item effort scale (e.g., "I have a lot of responsibilities in my job") and 11-item reward scale (e.g., "I receive the respect I deserve from my supervisors/colleagues") (Rödel et al., 2004). The ratio of effort to reward expresses the amount of perceived effort-reward-imbalance at work. Overcommitment (OC) at work was assessed with the 6-item form. On a 4-point rating scale, participants indicate to what extent they personally agree or disagree with the given statements. OC focuses on the "inability to withdraw from work" (five items) and "disproportionate irritability" (one item). For all three scales high internal consistencies (Cronbach's alpha) could be demonstrated (effort: α ranging from 0.61-0.78; reward: α ranging from 0.70-0.88; overcommitment: α ranging from 0.64-0.82) (Siegrist et al., 2004).

Hospital anxiety and depression scale-depression subscale

The HADS-D is a self-report screening tool indicating the possible presence of depressive states (Zigmond & Snaith, 1983). The subscale HADS-depression (HADS-D) consists of seven items, which are coded on a 4-point Likert scale ranging from 0="not at all" to 3="mostly". We applied the validated German version published by Herrmann and co-workers (1995) for which a high reliability of α=0.81 (internal consistency) was demonstrated in a normative population.

Perceived Stressfulness of the TSST

Nine items were employed to assess the subjective stressfulness of the TSST. Items are coded on a 7-point rating scale where subjects indicate to what extent they personally agree or disagree with the given statements. After cessation of the stress protocol subjects rated the extent of their personal involvement, how strenuous the task was, how stressful, difficult, new, challenging, threatening, controllable and whether they performed well.

5.4 Statistical analysis

Statistical analyses were performed using the SPSS statistical software package (Version 14.0.1; Chicago, IL, USA). Unless otherwise stated, results are expressed as mean ± standard deviation (SD). Cortisol and ACTH values were log-transformed before statistical analyses (Figures show untransformed data for illustration reasons).

A factor analysis (principal component, varimax with Kaiser-normalization) was employed to create a superordinate scale 'perceived stressfulness of the TSST' based on the nine single subjective stress ratings assessed directly after cessation of the TSST. Differences between groups were analyzed by Student's t-tests (two-tailed testing). All subsequent analyses were computed with the command GLM (General Linear Model). Since sex, menstrual cycle phase or intake of oral contraceptives, age, and BMI have been described as potential intervening variables, we assessed their impact on HPA axis stress responses (for recent reviews see Kudielka et al., 2007a; 2007b). As described in more detail below (see results), very few smokers and women taking oral contraceptives or sex steroids we excluded from all analyses to eliminate further potential confounding factors. The two variables sex and menstrual cycle phase/postmenopausal status yielded significant effects for ACTH as well as salivary and plasma cortisol. Therefore, a respective grouping factor was introduced coding for men versus premenopausal women in the luteal phase of the menstrual cycle

versus postmenopausal women. This control variable was entered as a covariate in all analyses.

First, a repeated-measures analysis of variance (ANCOVA) with the within-subject factor *Samples* was applied to analyze hormonal profiles in response to the TSST. Second, to test for effects of ERI/OC on cortisol response patterns, separate GLMs with the repeated factor *Samples* were calculated entering a respective questionnaire score as a continuous predictor (effort, reward, ERI, OC). Questionnaire scores were entered as continuous variables to avoid any reduction of available information by artificial grouping (Aiken & West, 1991; Royston et al., 2006) as applied earlier (Schlotz et al., 2004; Kudielka et al., 2006c). In a further set of GLMs, analyses were rerun including only responders. Subjects were defined as responders if their TSST-induced salivary cortisol response reached at least 2.5 nmol/l over the individual baseline level, an elevation which is thought to reflect a cortisol secretory episode (Van Cauter & Refetoff, 1985; Schommer et al., 2003).

In a further step, we added the HADS-D score to the respective GLMs in order to additionally control for possible effects of depressive symptomatology. Finally, we forced pre-stress baseline values into the GLMs to additionally control for differences in pre-stress hormone concentrations. In a secondary analysis, we simultaneously controlled for HADS-D as well as the 'perceived stressfulness of the TSST' to further elucidate the role of the acute processing of the stressor. F-values and p-levels were corrected according to Greenhouse-Geisser procedure whenever sphericity was violated. Effect sizes were calculated for significant results by partial eta squared (η^2), expressing the amount of variance explained in the dependent variable by the respective effect.

5.5 Results

5.5.1 Study sample

A total of 62 teachers underwent the stress protocol. Because of the well-known intervening effects of habitual smoking (Rohleder & Kirschbaum, 2006) and the intake of oral contraceptives or sex steroids (Kirschbaum et al., 1999; Kudielka et al., 1999) on acute HPA axis stress responses, we excluded two smokers and five women taking oral contraceptives or receiving hormonal replacement therapy from all analyses as indicated above. Two further subjects had missing data in their endocrine measures due to technical problems. This rendered a final study sample of 53 subjects. All participants were currently working as a school teacher in one of the major school types in Germany or Luxembourg, thus our sample is characterized by very high homogeneity regarding educational and socioeconomic status. Socio-demographic and psychological characteristics are detailed in Table 5.1.

Table 5.1: Sample description

	N=53	Mean ± SD	Range
Sex			
Men	20		
Women	33		
Premenopausal Women in Luteal Phase	10		
Postmenopausal Women	23		
Age (years)		49.9 ± 8.58	29-63
Years of Employment		22.6 ± 10.8	4-40
German School Types			
Elementary/Primary School (Grundschule)	12		
Basic Level Secondary School (Hauptschule)	7		
Secondary School (Realschule)	7		
Grammar School (Gymnasium)	8		
Comprehensive School (Gesamtschule)	1		
Vocational School (Berufsbildende Schule)	10		
Not further specified	7		
Missing	1		
ERI Scores			
Effort		15.6 ± 4.55	6-24
Reward		45.5 ± 7.71	24-55
Effort-Reward-Imbalance		0.67 ± 0.30	0.27-1.45
Overcommitment		15.1 ± 4.25	7-23
HADS-Depression Score		4.7 ± 3.68	0-15

5.5.2 Analysis in the total study sample

An initial ANCOVA with repeated measures resulted in a significant main effect of sampling time for salivary cortisol (main effect *Samples*: $F_{2.82,140.77}$=43.5, p<0.001, η^2=.47), plasma cortisol (main effect *Samples:* $F_{1.80,89.96}$=101.9, p<0.001, η^2=.67) and ACTH (main effect *Samples*: $F_{1.67,83.6}$=74.1, p<0.001, η^2=.60), reflecting the significant TSST-related response in all three HPA axis measures.

In subsequent analyses, we then added a respective continuous questionnaire variable (effort, reward, ERI, OC) one by one to the GLMs to test for their effects on the stress hormone responses. Neither effort nor reward were significantly related to salivary cortisol, plasma cortisol or ACTH responses to acute psychosocial stress (all F<1.94, all p>0.16). Also, the ratio between effort and reward (ERI) was not associated with salivary cortisol or ACTH responses to the TSST (all F<0.87, all p>0.45). However, for total plasma cortisol the interaction ERI by *Samples* approached the level of significance ($F_{1.73,84.7}$=2.58, p=0.09). This effect was driven by higher increases of plasma cortisol after the TSST with higher ERI.

Furthermore, marginally significant effects were rendered for associations between OC and cortisol responses to the TSST (salivary cortisol: main effect *Samples*: $F_{1,49}$=3.20, p=0.08; plasma cortisol: interaction OC by *Samples*: $F_{1.8,87.5}$=2.87, p=0.07), with higher levels of OC being related to lower cortisol responses. Though, OC was not significantly related to the ACTH response to the TSST (both F<1.38, both p>0.26).

5.5.3 Analysis in the subsample of responders

Even though the stress protocol elicited significant neuroendocrine responses in the total study sample (see above), the mean increase in salivary cortisol in the total sample was relatively low (mean: 3.97±4.08 nmol/l; range: -2.2 to 13.76 nmol/l). Because endocrine stress reactivity can only validly be assessed in responders, we rerun all analysis in the subsample of responders as defined by an individual salivary cortisol increase of at least 2.5 nmol/l (see above). The subgroup of responders

was comprised of 30 subjects with five women in the luteal phase of their menstrual cycle, eleven menopausal women and 14 men and showed a mean salivary cortisol increase of 6.71±3.34 nmol/l (range: 2.64 to 13.76 nmol/l). A factor analysis clustered six out of the nine single subjective stress ratings to a combined factor termed 'perceived stressfulness of the TSST', inquiring about how strenuous, controllable, difficult, stressful, threatening the task was and whether the subjects performed well. A comparison of the responders and non-responders subjective reports revealed that responders perceived the TSST as significantly more stressful ($t_{32.92}$=-2.50, p=0.02).

In line with the GLM results in the total study sample, no significant associations could be found for effort and reward (all F<2.33, all p>0.10). Furthermore, ERI was not related to the salivary cortisol or ACTH responses to the TSST (all F<1.38, all p>0.25). The marginally significant effect observed for plasma cortisol in the total sample, however, reached the level of significance within the group of responders (interaction ERI by *Samples*: $F_{2.15,55.91}$=3.03, p=0.05, η^2=.10). Also, in the subsample of responders, OC was significantly associated with all HPA measures (see Figure 1), with higher levels of OC being related to a lower neuroendocrine stress response (salivary cortisol: main effect OC: $F_{1,26}$=13.3, p<0.001, η^2=.34; plasma cortisol: main effect OC: $F_{1,26}$=6.65, p=0.02, η^2=.20; ACTH: interaction OC by *Samples*: $F_{1.73,44.93}$=3.94, p=0.03, η^2=.13).

We observed relatively high intercorrelations between ERI/OC and HADS-Depression scores (ERI and HADS-D: r=0.51, p<0.001; OC and HADS-D: r=0.48, p<0.001) in the total study sample. Therefore, to control for a possible influence of depressive symptomatology on the described associations between ERI/OC and the neuroendocrine response to the TSST in the subgroup of responders, we repeated those GLMs that had previously rendered significant relationships with neuroendocrine measures, now simultaneously controlling for depressive symptomatology. While the association between ERI and plasma cortisol responses became non-significant controlling for depressive symptomatology (interaction ERI

by *Samples*: $F_{2.14,53.55}$=0.75, p=0.48), the associations between OC and HPA axis responses stayed significant even after adding the HADS-D scores as additional control variable (salivary cortisol: main effect OC: $F_{1,25}$=9.34, p=0.005, η^2=.27; plasma cortisol: main effect OC: $F_{1,25}$=4.53, p=0.04, η^2=.15; ACTH: interaction OC by *Samples*: $F_{1.73,43.28}$=3.36, p=0.05, η^2=.12).

In a final set of analysis, we additionally forced the pre-stress hormone levels into the respective GLMs in order to control for any differences in pre-stress levels. The picture of results remained practically unchanged (salivary cortisol: main effect OC: $F_{1,24}$=4.63, p=0.04, η^2=.16; plasma cortisol: main effect OC: $F_{1,24}$=3.60, p=0.07, η^2=.13; ACTH: interaction OC by *Samples*: $F_{1.28,30.73}$=5.85, p=0.02, η^2=.20).

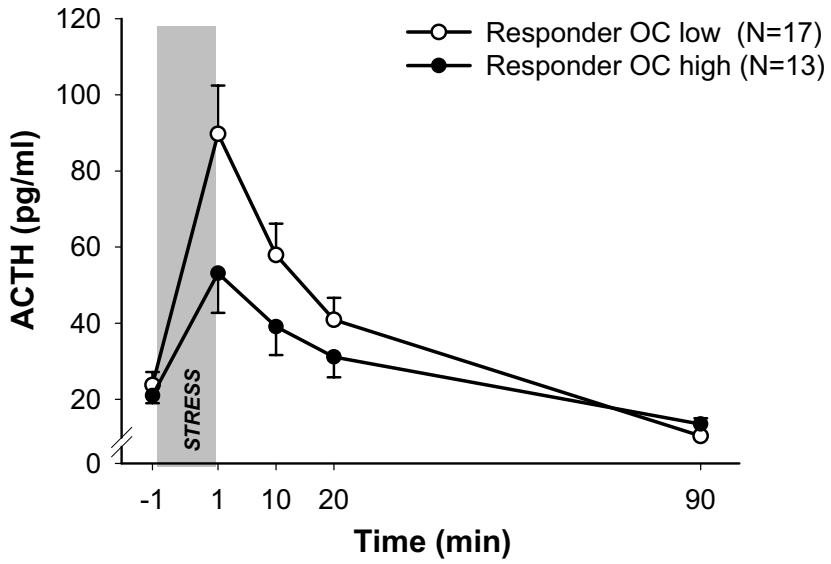
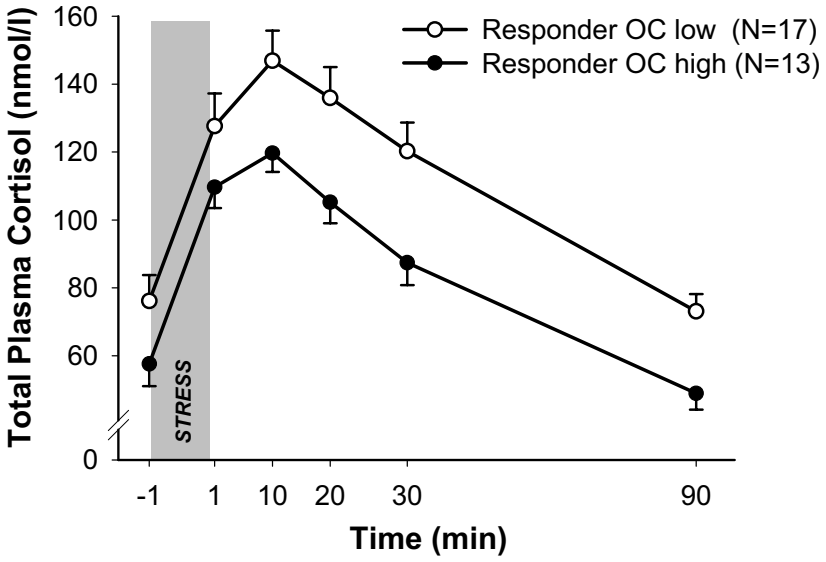


Figure 5.A: ACTH responses to psychosocial stress (TSST) in N=30 responders high versus low on overcommitment (OC); for illustration reasons the sample was artificially divided by median split into groups with high versus low OC; statistics are based on continuous OC questionnaire scores; data are expressed as mean ± SEM (standard error of mean)



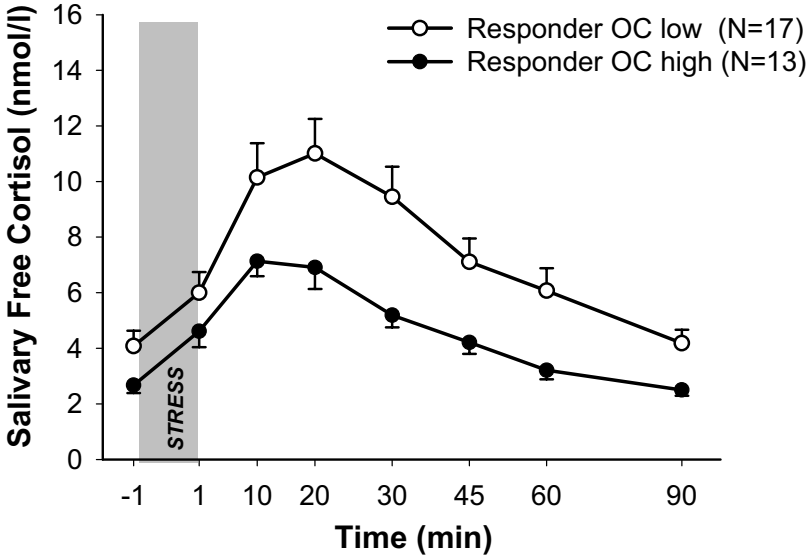


Figure 5.B and 5.C: total plasma cortisol (**5.B**) and salivary free cortisol (**5.C**) responses to psychosocial stress (TSST) in N=30 responders high versus low on overcommitment (OC); for illustration reasons the sample was artificially divided by median split into groups with high versus low OC; statistics are based on continuous OC questionnaire scores; data are expressed as mean ± SEM (standard error of mean)

5.5.4 Analysis of the role of acute perceived stressfulness

In a secondary analysis we investigated whether the acute processing of the stressor, as reflected by the 'acute perceived stressfulness of the TSST', differed in subjects scoring above versus below the median in ERI or OC. We found that subjects scoring above the median in OC reported significantly more perceived stressfulness when confronted to the TSST ($t_{50.98}$=-3.52, p<0.001) whereas no such difference was found in respect to ERI (t_{51}=-.23, p=0.82).

When the factor 'perceived stressfulness of the TSST' is additionally included into the GLM as a second covariate (besides HADS-D), the OC effects observed for the responders become even more apparent (salivary cortisol: main effect: OC $F_{1,24}$=11.61, p=0.002, η^2=.33; plasma cortisol: main effect OC: $F_{1,24}$=4.81, p=0.04, η^2=.17; ACTH: interaction OC by *Samples*: $F_{1.78,42.64}$=4.06, p=0.03, η^2=.15). Even in the total study sample the association between OC and HPA axis reactivity becomes significant when simultaneously controlling for depressive symptomatology as well as acute perceived stressfulness of the TSST for salivary as well as plasma cortisol and approaches the significance for ACTH (salivary cortisol: main effect OC: $F_{1,47}$=4.52, p=0.04, η^2=.09; plasma cortisol: main effect OC: $F_{1,47}$=5.91, p=0.02, η^2=.11; ACTH: interaction OC by *Samples*: $F_{1.77,82.98}$=2.33, p<0.11, η^2=.05).

5.6 Discussion

In sum, in this study we observed associations between effort-reward-imbalance (ERI) or overcommitment (OC) and HPA axis responses to acute psychosocial stress. While these effects reached the level of significance in the subsample of responders, results at least approached the level of significance in the total study sample. In more detail, in our sample highly overcommitted teachers showed lower HPA axis responses after an acute challenge compared to teachers with low levels of OC. This relationship emerged for salivary and plasma cortisol as well as ACTH levels and stayed significant even after controlling for depressive

symptomatology. Furthermore, a higher level of ERI was related to a higher increase in plasma cortisol concentrations after the TSST. This association, however, did not remain significant after controlling for depressive symptomatology as measured by HADS-D scores. Importantly, the observed HPA axis hyporeactivity in relation to OC cannot be attributed to a significantly larger proportion of subjects scoring high on OC in the subgroup of cortisol non-responders as shown by cross tabulation (χ^2_1=1.68, p=0.19). In the group of non-responders, 17 subjects had OC scores below and 6 above the median. In the responder group, 17 subjects had lower and 13 higher OC scores. With this, it becomes obvious that even more subjects scoring high on OC belong to the subsample of responders. However, when additionally accounting for differences in the 'acute perceived stressfulness of the TSST' significant associations of OC and HPA axis responses could be observed in the subgroups of responders as well as in the total study sample. This finding provides evidence that the observed hypocortisolemic stress responses can be explained by differences in OC even and especially when altered acute processing of the TSST is controlled for.

Interestingly, we see more robust findings for the subscale OC than the ERI subscale. Such a finding could be due to the fact that OC is conceptualized as a personality trait. Thus, OC should be more stable over time and therefore more resistant to situational changes and less likely to be influenced by momentary affect, whereas ERI is probably more state-dependent reflecting a dynamic work environment. One could speculate that most employees re-evaluate their investments and rewards at work on a regular basis whereas OC is a much more stable underlying motivational pattern.

Our results are in line with two other reports. In an earlier study, Siegrist et al. (1997) observed reduced maximal cortisol responses in stressed middle managers in terms of ERI, applying the Stroop colour-word conflict task providing preliminary evidence for attenuated neuroendocrine stress responses. More recently, Wirtz and colleagues (2008) reported a

significant association between higher OC scores and lower salivary cortisol as well as norepinephrine responses after the TSST in a sample of male adults. Our study expands these initial findings in several ways. Firstly, our study is comprised of men as well as women allowing for inferences across sex. Secondly, beyond salivary cortisol we additionally analyzed ACTH and plasma cortisol responses in order to describe HPA axis responses to acute stress. Thirdly, we investigated whether these endocrine stress responses are related to all subscales of the ERI/OC model, namely effort, reward, effort-reward-imbalance and overcommitment.

It can be speculated that reduced ACTH and cortisol responses in individuals high on OC might be the consequence of a chronic state of stress. As suggested earlier, hypocortisolism or a hyporeactive HPA axis may develop under prolonged stress (or trauma) and there may be a time course in the development of such neuroendocrine abnormalities (Fries et al., 2005; Kudielka et al., 2006a). A first stage is assumed to be characterized by a recurrent high hormonal responsiveness to acute challenges. In the long run, however, this initially heightened hormonal response may result in attenuated neuroendocrine stress responses due to a functional adaptation to repeated stimulation triggered by high levels of work stress and an unfavourable style of coping with demands (OC). According to McEwen's model of allostatic load not only chronic overactivity but also chronic (and inadequate) hypoactivity of physiological systems that are involved in the adaptation to environmental challenge results in wear-and-tear of the body and brain (McEwen, 1998a, 1998b). McEwen coined the term allostatic load to capture the cumulative physiological burden exacted on the body through repeated attempts of adaptation, depicting a biological pathway for how chronic stress can lead to health impairments in the long run. The development and persistence of hypocortisolism over time may be due to reduced biosynthesis or depletion at several levels of HPA axis (CRH, ACTH, cortisol), CRH hypersecretion and adaptive down-regulation of pituitary CRH receptors or

change in receptor sensitivity, increased feedback sensitivity of the HPA axis, and finally morphological changes (Heim et al., 2000; Melamed et al., 2006).

Interestingly, in the present data the association between OC and a respective endocrine response to stress is apparent for ACTH as well as for total and free cortisol, pointing to a suprapituitary level of change. Though, prestress baseline levels are slightly higher for free as well as total cortisol but not for ACTH (indicated by GLM main effects for free and total cortisol responses and an interactional effect for the ACTH response; see results), possibly reflecting further effects of chronic work stress at the level of the adrenal cortex.

In the present study, we observed a surprisingly high percentage of 43% non-responders (23 out of 53 subjects). Normally, we see a responder rate of 70 to 80% in our laboratory applying the TSST (Kirschbaum et al., 1993; Kudielka et al., 2007a, 2007b). This fact cannot be attributed to any change in the standard procedure of the stress protocol, as the TSST was originally developed in Trier and used by our group in numerous studies in the past decades. In a recent comprehensive meta-analysis, Dickerson and Kemeny showed that acute psychological stress protocols reliably elicit solid ACTH and cortisol responses if they are characterized by uncontrollability, social-evaluative threat or forced failure and concluded that such criteria are fulfilled by the TSST protocol (Dickerson & Kemeny, 2004). A more likely explanation for the high percentage of non-responders could be that the TSST might not be a suitable stressor for school teachers. The teacher population was originally selected because the teaching profession is assumed to be an especially stressful occupation with high and enduring psychosocial demands at the workplace (Guglielmi & Tatrow, 1998; Weber et al., 2001, 2004). Regarding the relatively high percentage of non-responders in the present teacher cohort, it could be speculated that school teachers perceive a TSST-like situation, particularly a free speech in front of an audience, as less threatening compared to other professionals. Over the years, teachers

might have habituated to such kinds of psychosocial challenges in everyday working life. Furthermore, in Germany, the teaching profession is still largely characterized by high job stability and job changes are relatively rare. Therefore, the standard cover story (applying for a new job) might have appeared somewhat artificial to our teachers. Finally, our panel members are specially trained graduate students and their appearance might possibly be very close to high school seniors. In an upcoming study, we therefore want to compare a teacher versus non-teacher population in order to further investigate possible differences between vocations in endocrine as well as subjective stress responses to the TSST.

One important restriction of the present study is obviously the reduced sample size by the large number of non-responders limiting the statistical power in the subgroup of responders. Our results in the subsample of 30 responders should therefore be interpreted with adequate precaution. Furthermore, the cross-sectional nature of this study does not allow any inferences about temporal ordering between ERI/OC and HPA axis regulation. In respect to OC however, it seems unlikely that OC is influenced by alterations in neuroendocrine stress responses as OC is conceptualized as a psychological trait with high intraindividual stability over time (Siegrist, 2002).

Credits to the present study are the high homogeneity of the sample regarding educational and socioeconomic status as well as a broad characterisation of HPA axis responses to stress, including ACTH, total plasma cortisol as well as free salivary cortisol. Finally, all components of the ERI/OC model were considered as possible predictors of HPA axis regulation.

In sum, the results of the present study suggest an impact of overcommittment on HPA axis stress responses in male and female school teachers, an effect which is most apparent in those subjects that responded to the TSST. High levels of overcommittment were associated with a blunted ACTH as well as total and free cortisol response following

psychosocial stress, possibly reflecting an adaptation of the HPA axis to prolonged or repeated stimulation due to chronic work stress.

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Chapter 6

Summary and general discussion

The primary objective of this section is to summarise and integrate the findings presented in the previous chapters. General limitations of the study, implications of the results for health and disease risk in respect to workplace characteristics, and an outlook on future research questions will be discussed.

The present thesis seeks to enhance our understanding of the association between chronic work stress in terms of effort-reward-imbalance and overcommitment, burnout, exhaustion and negative health outcomes. To shed more light on possible underlying mechanisms, I assessed basal HPA axis regulation, HPA axis feedback regulation, HPA axis reactivity after acute psychosocial stress, as well as a cumulative marker for physiological wear-and-tear called allostatic load in a sample of healthy working teachers. Teachers have been chosen as subjects due to the alarmingly high rates of early retirement among German school teachers, suggesting that this profession is extremely stressful (Weber et al., 2001).

Taken together, I can conclude from my findings that already in these otherwise healthy subjects, chronic work stress as well as high burnout and exhaustion scores seem to be reflected in subtle changes in psychobiological stress markers before a potential disease manifestation.

In the first study, we conducted a comprehensive assessment of basal HPA axis activity on two work days and one leisure day. Furthermore, we tested HPA axis feedback functioning by application of a very low-dose dexamethasone suppression test (DST). No associations could be found between basal cortisol activity and burnout, vital exhaustion (VE), or any component of Siegrist's effort-reward-imbalance/overcommitment (ERI/OC) model (Maslach & Jackson, 1986; Appels et al., 1987; Seidman & Zager, 1987; Rödel et al., 2004). However, after the administration of dexamethasone higher burnout and VE as well as lower reward from work were significantly related to stronger cortisol suppression. This finding suggests that chronic work stress appears to be associated with altered HPA axis negative feedback sensitivity. One could hypothesize that, in individuals with high levels of burnout or exhaustion, the GR may have

become more sensitive due to chronically elevated cortisol levels or repeated cortisol peaks caused by recurring episodes of acute stress. In contrast to previous studies, a very low-dose DST (using 0.25mg instead of 0.5mg) was applied in this study, to enhance test sensitivity (Huizenga et al., 1998). It could be speculated that this very low-dose DST is more sensitive in detecting differences in feedback sensitivity which are probably not yet reflected in basal HPA axis activity. Despite the fact that we studied a sample of healthy teachers free of any psychiatric diagnosis, we observed moderate to high intercorrelations between all burnout-related scales and depressive symptomatology as measured by the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D, Zigmond & Snaith, 1983). Thus, we also tested for a possible impact of depression on HPA axis feedback functioning. Major depression has mostly been shown to manifest in reduced HPA axis negative feedback sensitivity. However, in our sample the degree of HADS-depression was related to a stronger suppression of cortisol after dexamethasone, in the same way as burnout, exhaustion and low reward from work. When these work stress variables that previously had rendered significant results were entered into the analysis simultaneously with HADS-depression scores, the effects appeared to cancel each other out. A possible explanation for this finding might be found in the considerable conceptual overlap between burnout and depression, both sharing the major symptom of extreme fatigue and exhaustion. The chronic fatigue syndrome and atypical depression, also being mainly characterized by extreme fatigue, have repeatedly been associated with a hypoactive HPA axis (Cleare et al., 2001, 2003; Gaab et al., 2002; Gold & Chrousos, 2002; Gold et al., 2002; Nater et al., 2008). One could therefore speculate that the fatigue component of depression is driving this effect. Consequently, more studies are needed that explicitly investigate the complex interplay between burnout, exhaustion and different forms of depression in respect to HPA axis functioning.

We then proceeded to investigate the relationship between chronic work stress and exhaustion with physiological dysregulation in a broader sense.

Instead of focusing on a particular biological system like the HPA axis, we decided to measure allostatic load (AL) as a multi-system summary indicator of physiological risk. Results showed that AL scores were significantly higher in women high on effort-reward-imbalance and exhaustion, indicating a higher cumulative burden. The initial operationalisation of AL included ten biological variables, reflecting HPA axis functioning, sympathetic nervous system (SNS) activation, cardiovascular activity, atherosclerosis development, and glucose metabolism. For an extended AL composite, we also analysed CRP, TNF-α, fibrinogen, D-dimer, percent-body-fat, triglycerides, and fasting glucose levels to additionally account for immunological, blood coagulation and further metabolic processes. Interestingly, teachers high versus low on ERI and exhaustion showed significant differences for both, the classical as well as the extended AL composite, with only very minor increases in effect sizes for the extended AL sum score. No significant associations however could be observed between single AL parameters and ERI or exhaustion. This observation underlines the necessity of a composite score to detect early and subtle signs of dysregulation across multiple stress-sensitive systems that could lead to later disease manifestation, especially in a young and healthy sample.

For the second part of the Trier Teacher Stress Study, 53 medication-free, non-smoking, healthy teachers who already took part in the first part of the study were re-invited to examine HPA axis responses to acute psychosocial stress. In order to test whether chronic stress at work in terms of effort-reward-imbalance and overcommitment is accompanied by altered HPA axis stress reactivity, our subjects were confronted with the Trier Social Stress Test (TSST Kirschbaum et al., 1993). ACTH, total plasma cortisol and salivary free cortisol were repeatedly measured before and after challenge. Overall, effort-reward-imbalance and overcommitment were only marginally associated with HPA axis responses to acute stress. However, in the subgroup of responders we observed a HPA axis hyporeactivity in highly overcommitted school teachers,

expressed in lower ACTH as well as plasma and salivary cortisol responses. This hyporeactive HPA axis in individuals high on OC might be the consequence of a chronic state of stress, reflecting a functional adaptation to repeated stimulation triggered by high levels of work stress and an unfavourable style of coping with demands (OC). Compared to the responder rates of 70% to 80% we normally expect when applying the TSST (Kirschbaum et al., 1993; Kudielka et al., 2007a, 2007b), the high percentage of non-responders (43%) in the present study was surprising. This finding can most likely be explained by a natural habituation effect in everyday working life. One can easily assume that particularly the free speech in front of the panel is less threatening for a teacher compared to individuals working in other professions. Thus, replications in a larger cohort are needed as well as further investigations scrutinising possible differences between vocations in endocrine as well as subjective stress responses to the TSST. In an upcoming study, we therefore want to repeat a protocol similar to the study presented in Chapter 5 and contrast a teacher versus non-teacher population.

The data presented in this thesis must be interpreted within the specific limitations of the study design. One general limitation which applies to all three of the studies might be the overrepresentation of women. The ratio of women to men was about 2:1 in our study sample, reflecting the general situation of teachers in German schools (Pruessner et al., 1999; Unterbrink et al., 2007). When investigating the impact of work stress and exhaustion on AL, we chose to analyse a solely female data set. We decided that a gender-specific approach was required because some of the parameters which constitute the AL sum score show significantly different distributions across men and women (e.g., DHEA-S, Orentreich et al., 1984). This however clearly limits the generalisation of the findings presented in Chapter 4 and only a replication of our results in a male sample would allow tentative conclusions regarding the relationship of ERI, exhaustion and AL. Langelaan et al. (2007) recently examined 290 healthy male Dutch managers to explore whether AL mediates the

relationship between burnout and physical health. No association was found between burnout or the exhaustion component of the MBI and AL. The AL sum score in this study however has to be interpreted as a proxy measure of AL. It did not include primary mediators but was restricted to secondary outcomes (BMI, systolic and diastolic blood pressure, CRP, HDL, HbA1C and glucose).

Also, we explicitly chose not to study a patient sample suffering clinical burnout. This allowed us to examine possible alterations in stress-sensitive physiological systems before actual disease manifestation, considering that such findings may have important implications for the prevention of stress-related disorders. However, the heavily burdened teachers were not as likely to volunteer for this relatively time-consuming study or they had to be excluded due to medication with antidepressants. We cannot rule out that our teacher sample might reflect a specific selection of less burdened teachers, so that the associations we found might therefore underestimate the true population effect. Thus, it is noteworthy that significant associations between job-related stress and altered HPA axis functioning as well as AL could even be observed in chronically stressed but otherwise healthy, currently working participants. This is remarkable, especially in respect to the AL findings, because the subjects participating in our study were relatively young, compared to other studies on AL, which often investigated geriatric samples (Seeman et al., 1997, 2001). The cross-sectional design of the studies presented in this thesis is another limitation because it made it impossible to adequately analyse the causal relations that exist between various determinants of chronic work stress, specific complaints associated with the burnout syndrome and physiological outcome parameters. Only a longitudinal analysis would enlarge our knowledge about the temporal ordering of the variables involved and might therefore enable us to draw conclusions about 'cause and effect' relations. Finally, one can criticize that chronic work stress, burnout and exhaustion were solely assessed by self-report questionnaires, which have reduced reliability due to a well-

documented retrospection bias (Stone et al., 2004, 2005). Indeed, Sonnenschein and colleagues (2007) very recently showed that general burnout symptom severity assessed by questionnaires was not related to endocrine measures, whilst general burnout symptom severity assessed with the electronic diary method was. The electronic diary measures symptoms within the context of everyday life, taking into account intra-individual variability in symptoms as well as avoiding retrospection bias. Therefore, the aggregated individual mean of the diary records is a more reliable and ecologically valid index of symptom severity than a simple questionnaire score (Bolger et al., 2003).

A noteable strength of the Trier Teacher Stress Study is the high homogeneity of the sample regarding educational and socioeconomic status. Credits to the assessment of basal HPA axis activity are a broad sampling design including measurements of CAR and day profiles on two work days and a leisure day as well as the control of non-compliance by exclusion of non-compliant profiles from statistical analyses in order to avoid invalidation of cortisol data. In respect to the analysis of AL, it is noteworthy that we expanded the classical operationalisation according to its theoretical conceptualisation (McEwen & Seeman, 1999) by integrating additional stress-sensitive systems in the AL composite. Also, we conducted a complementary analysis where risk for cortisol was calculated including extreme cortisol scores on both ends of the continuum (highest and lowest 12.5%), taking into account that both a hyper- as well as hypoactive HPA axis is known to be associated with negative health outcomes (for reviews see Heim et al., 2000; Raison & Miller, 2003). A strong point of the last study presented in Chapter 5 is first of all the broad characterisation of HPA axis reactivity including measures of ACTH, total plasma and salivary free cortisol. Furthermore, this is the first study to consider all aspects of the ERI/OC model in respect to HPA axis responses to a standardized psychosocial stress test.

Outlook and future research directions:

As the results presented in this thesis are preliminary and converging evidence is needed to support our findings, I would like to raise some ideas for future research.

Failing to habituate to repeated stress exposures has been proposed to be one of the four scenarios, eventually leading to AL. Kudielka et al. (2006) recently observed a negative dose-response relationship between exhaustion and the degree of habituation of the cortisol response across three TSST exposures. Considering our results of higher AL in highly exhausted female teachers, the investigation of potential alterations in habituation patterns due to chronic work stress, burnout and exhaustion will be of great interest in this sample.

Burnout has recently been associated with an increased risk of cardiovascular disease (CVD) (Toppinen-Tanner et al., 2005; Honkonen et al., 2006; Melamed et al., 2006a) although the physiological mechanisms that could link burnout with CVD are not yet fully understood. It is known, that low-grade systemic inflammation promotes atherosclerosis. Thus, one can hypothesize that enhanced inflammation activity, reflected in increased levels of pro-inflammatory and decreased levels of anti-inflammatory cytokines might contribute to the increased CVD risk in burnt-out individuals by initiating atherosclerosis (Kilic et al., 2006; Tziakas et al., 2007). We recently demonstrated that higher levels of total burnout symptoms independently predicted higher levels of the pro-inflammatory cytokine TNF-α, lower levels of the anti-inflammatory cytokine IL4, and a higher TNF-α/IL4 ratio. Higher levels of the subscale 'lack of accomplishment' predicted decreased IL-4 levels and a higher TNF-α/IL4 ratio (von Känel et al., 2008). Thus, based on these findings, which strengthen the assumption that burnout is associated with increased systemic inflammation, it would be interesting to study whether burnout is also associated with alterations in immune parameters during acute psychosocial stress. To date, few studies have investigated immune parameters in relation to burnout and the findings published so far have

been restricted to measurements of immune parameters of subjects at rest. For example, Mommersteeg et al. (2006) recently investigated immune functioning in 56 subjects with severe burnout and in 38 healthy control subjects. The burnout group showed an increased production of the anti-inflammatory cytokine IL10 by monocytes after lipopolysaccharide (LPS) stimulation. No differences were observed in IL10 release induced by the T-cell mitogen phytohemagglutinin (PHA) nor in the pro-inflammatory cytokines gamma interferon and TNF-α. Moreover, the capacity of dexamethasone to regulate cytokine release did not differ between the groups as well as the blood lymphocyte subset counts. Thus, despite the wide range of parameters investigated, no evident changes in overall immune functioning related to burnout were observed. The authors speculate that the finding of a higher IL10 release of LPS-stimulated monocytes in burnt-out subjects may point to a subclinical viral infection, which may have contributed to the exhaustion symptoms. Thus, evidence on relationships between work stress, burnout and immune functioning remains unclear and to the best of my knowledge no study has yet been published that examined possible alterations in immune parameters in relation to burnout before and after the TSST. Therefore, we plan to measure changes in blood lymphocyte subset counts as well as cytokine production of peripheral blood mononuclear cells (PBMCs) after PHA stimulation before and after the TSST in our teacher population. Moreover, Wirtz et al. (2003) demonstrated that more dexamethasone was required to suppress IL-6 production by monocytes in vitally exhausted men, pointing to a decrease in monocyte glucocorticoid receptor sensitivity. Therefore, in an additional analysis we want to expand this investigation and examine whether chronic work stress in terms of ERI/OC, VE or burnout are related to the glucocorticoid sensitivity of circulating leukocytes in men and women and whether this relationship is influenced by acute stress.

Furthermore, meta-analyses have established that elevated levels of the blood coagulation parameters fibrinogen and D-dimer in the circulation are

biological risk factors for the development and progression of coronary artery diesease (Ernst & Resch, 1993; Lip, 1995; Danesh et al., 2001; Hackam & Anand, 2003). As VE is a known psychosocial risk factor for coronary artery diesease, we have recently investigated whether plasma levels of these two blood coagulation markers are associated with VE in 150 school teachers (Kudielka et al., 2008). Gender-specific analyses revealed an association between fibrinogen and exhaustion in men. In a next step, it is planned to analyse whether alterations due to chronic work stress are not only reflected in the basal plasma levels but also in the reactivity of blood coagulation parameters in response to the TSST.

Another aspect that could contribute to the reported association of burnout and increased risk for CVD is a repeated activation of the autonomic nervous system. In this context, cardiac autonomic control is another interesting marker relevant to the conceptualisation of AL. Disordered baroreflex function and depressed heart rate variability (HRV) can indicate a dysfunctional regulation of the autonomic nervous system and have been shown to be independent predictors of CVD and cardiovascular mortality (Kristal-Boneh et al., 1995; Tsuji et al., 1996; Schwartz & La Rovere, 1998). However, not many studies have investigated the impact of exhaustion and burnout on cardiac autonomic control. Watanabe and co-workers (2002) report a reduced amplitude of the high-frequency HRV component in middle-aged exhausted workers, but no differences between exhausted and not-exhausted workers in the low frequency component. Vrijkotte et al. (2000) observed a higher heart rate during and directly after work, a higher systolic blood pressure during work and leisure time and a lower 24h-hour vagal tone in male office employees with high ERI. Hintsanen and colleagues (2007) also recently investigated parameters of the ERI/OC model. In their sample of young and healthy Finnish adults, higher ERI was associated with indices of lowered high-frequency HRV components among women, suggesting decreased vagal tone. Lower reward was associated with a higher heart rate (HR) in women. High HR, in conjunction with simultaneously low

vagal tone, is likely to reflect sympathetic activation. No significant associations of ERI or its components with HR and HRV were found in men. The authors concluded that this combination of low parasympathetic and high sympathetic activation among women reflects a state of chronic stress due to unfavourable workplace characteristics. This may be associated with deteriorating cardiovascular health already in early adulthood prior to the manifestation of actual symptoms of CVD.

Thus, in addition to the singular measures of systolic and diastolic blood pressure which were part of the AL sum score, measures of ambulatory blood pressure, combined with electrocardiogram (ECG) recordings to investigate measures of baroreflex sensitivity, blood pressure variability and HRV at rest as well as during acute mental stress could significantly enlarge our knowledge regarding alterations in regulation of the autonomic nervous system due to chronic work stress, burnout and exhaustion.

Finally, Melamed and co-workers (2006b) showed in a prospective epidemiological study that chronic burnout might be a risk factor for the onset of type 2 diabetes in apparently healthy individuals. To study the mechanisms that could potentially explain this association, it would be interesting to measure metabolic markers related to glucose-insulin function in an experimental setting. Keltikangas-Järvinen et al. (1998) for example report associations of VE and measures of ACTH, cortisol, insulin and glucose during an oral glucose tolerance test (OGTT). In a study of Agardh and colleagues (2003) low decision latitude and a low sense of coherence (SOC), interpreted as a low ability to cope with stressors, were associated with type 2 diabetes. Homeostasis model assessment (HOMA), an equation used to quantify insulin-resistance and β-cell function, revealed that low SOC was also associated with insulin resistance. Based on these findings, one could speculate that signs of insulin-resistance and low β-cell function could also be detected in individuals with burnout and high levels of ERI and overcommitment, potentially before actual disease manifestation.

To conclude, the present work tried to integrate different approaches and research tools from work psychology, health psychology, psychosomatic medicine and psychoneuroendocrinology to study how chronic work stress affects health outcomes in school teachers. We are convinced that a psychobiological perspective may significantly enlarge our understanding of the relationship between stress at work and negative health outcomes, with important implications for the prevention and treatment of work-related ill health. In order to be able to apply suitable preventive measures targeted to the specific strains of the teaching profession, further research is needed that aims to analyse how stressors relevant for teachers impact on stress physiology. It is becoming apparent that in order to antagonize this global trend towards stress-related health impairments, organisations as well as society as a whole, need to put a greater emphasis on a work-life balance and fairness at work, including a more understanding attitude towards people who develop somatic symptoms due to stressful work conditions. Precise knowledge about psychobiological pathways could help to develop specific diagnostic tools that allow an early identification of risk factors and could be an incentive to implement structural and organisational changes, so that workers are better protected from mental and physical disorders due to chronic work stress. Taking an individual perspective, knowledge about physiological mechanisms could also help stressed and burnt-out workers to better understand their own health problems.

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