

The psychophysiology of burnout

De psychofysiologie van burnout

Paula M.C. Mommersteeg 2006

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The psychophysiology of burnout

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Chapter 1

Introduction

INTRODUCTION

The main aim of this thesis is to investigate whether severe burnout is associated with physiological disturbances. We assume that their stress-response system has become dysregulated, which is translated into an adverse adaptation of an otherwise normal response to the increased demands of the environment.

Burnout is the ultimate product of a chronic process in which work stress is assumed to play a decisive role. People with burnout feel extremely fatigued, have become alienated from their work, experience reduced competence, and report a whole range of complaints such as a depressed mood, increased irritability, an inability to relax, disrupted sleep, somatic complaints such as aching muscles, headaches, gastro-intestinal problems, and concentration and memory problems (Hoogduin, Schaap et al. 2001; Maslach, Schaufeli et al. 2001). In general, these health complaints have gradually increased over a period of at least half a year to a year, sometimes much longer. Although burnout is generally not preceded by psychopathology, the best predictor for a future burnout is having reported burnout symptoms in the past (Schaufeli and Enzmann 1998). Burnout leads not only to deteriorated health, but also to personal, social and economic costs (Schaufeli 2003).

When we assume burnout to be a stress-related syndrome, one might expect to find signs of dysregulation in the stress-response systems of the body. It is one of the goals of this thesis to explore this possibility. Establishing changes in the stress-response system in burnout could contribute to a more fine-grained diagnosis of burnout, and might be used to distinguish burnout from other stress-related disorders. In addition, any observed change in physiological functioning could give clues for the type of treatment (e.g. medication use) to be applied.

In order to understand how stress can lead to such dysregulation, it is necessary to understand how the stress response works. The paragraph on 'stress' deals with the stress-response, and how stress can lead to a deteriorated health. Next, we focus on the components of the stress response, which may have become disturbed in burnout. Most attention is paid to the stress-regulatory hypothalamus pituitary adrenal (HPA)-axis with its hormones cortisol and dehydroepiandrosterone-sulphate (DHEAS). As burned-out persons report a deteriorated health, the immune system may have been affected as well. Moreover, the immune system communicates with the neuro-endocrine system. Changes in neuro-endocrine function may therefore affect immune responsivity. The potential dysregulations in immune function are described in more detail in the paragraph on 'stress and the immune system'.

Our research population consists of burned-out persons who are currently on sick leave, having received a clinical diagnosis, and about to be receiving treatment for their complaints. This 'clinical' burnout group is at the 'sick' end of their complaints, in comparison to a still working population of people with high burnout scores. Physiological dysregulation is expected to be more pronounced in this group, which increases the

likelihood of finding a disturbance. Investigation of a clinical burnout group receiving treatment provides the opportunity to study the relationship between changes in complaints (hopefully improvement) in relation to changes in physiological functioning. Physiological dysregulation that is resistant to treatment may reflect an underlying vulnerability for developing burnout. In that case, healthy people with a similar dysregulation could be more prone to develop burnout under similar stressful circumstances.

To put the development of burnout as a chronic stress syndrome in a broader perspective the following paragraphs deal with the predictors of burnout, the epidemiology in society, personality correlates and the overlap with other stress-related disorders.

BURNOUT

Work-stress is defined as ‘a state of incapability of the employee to meet the demands of the work environment’. There are several theoretical models on work-stress, which predict a negative health effect. The best known are the demand-control (support) model of Karasek (1979), and the effort-reward imbalance model (ERI-model) of Siegrist & Weber (1986) (De Jonge, Le Blanc et al. 2003). The first model predicts that high workload, lack of control and insufficient social support can lead to an elevated stress level. The second model predicts stress responses when there is an imbalance of high effort combined with low reward. It is predicted in the ERI-model that persons who show over-commitment towards work are especially at risk (De Jonge, Le Blanc et al. 2003).

Indeed job demands and lack of control correlate high with burnout and job dissatisfaction (Schaufeli and Enzmann 1998), which in turn can lead to sick leave and work disability (Geurts 2003; Houtman and De Jonge 2003). High workload and time-pressure show strong relation with burnout. These work characteristics are more strongly related to burnout than personality characteristics. Interference of work-home is related to burnout as well. The relation of gender, age and fulltime versus part-time working with burnout is overall weak and dependent on the sample. The above models show that indeed work-stress, mainly a high workload, time-pressure and lack of control, are predictors of burnout and consequent sick leave.

EPIDEMIOLOGY OF BURNOUT

About 30% of the working population reports working under a high workload on a regular basis. An estimated 9% of the working population in the Netherlands could be labeled as ‘burnout’, as defined by the cut-off point of the exhaustion subscale of the Dutch version

of the Maslach Burnout Inventory¹ (www.statline.nl). This group is still at work and can therefore be labeled as relatively healthy. A high work-load and the central complaint of burnout ‘emotional exhaustion’ are good predictors for sickness absence (Bekker, Croon et al. 2005; Toppinen-Tanner, Ojajärvi et al. 2005). After a year of sick leave the phase of disability pension begins. Though the relation with work is not automatically reported, research shows that 50% of the persons with disability pension claim that their complaints are work-related (Houtman and De Jonge 2003). A gradual increasing percentage of people, from 31% in 1999 to 37% in 2004, receive disability pension due to psychological complaints (www.statline.nl). Of this group the majority (34%) has been diagnosed with mood disorders (any form of depression), adaptation disorder (28%) and response to severe stress (9%). It is clear that burnout and consequent sick leave put a burden on society in terms of loss of effective work force and financial costs.

BURNOUT AND PERSONALITY

Why one person is susceptible to developing a burnout while their colleagues in the same stressful work setting are not, is subject to much debate. Differences in vulnerability, due to certain personality characteristics, may predispose a person to experience stress and stress-related health problems. Studies have looked at personality traits as locus of control, hardiness, optimism and type A behavior in relation to burnout (van der Zee 2003). Personality traits are often aggregated into models with multiple dimensions, such as the classical ‘Big Five Model²’ of personality. Especially neuroticism, the tendency to see things in a negative perspective, is related to burnout, whereas hardiness and extraversion seem to be protective (Schaufeli and Bakker 2003). More recently the temperament model of Cloninger, describing temperament in three dimensions Psychoticism (impulsivity, aggression), Extraversion (novelty seeking, positive affect) and Neuroticism (avoidance, depression) (PEN-model) has come into view. Interestingly these temperament types are hypothesized to be related to underlying differences in physiological functioning (Cloninger, Bayon et al. 1998; Depue and Collins 1999; Dickerson and Kemeny 2004; Korte, Koolhaas et al. 2005). Therefore, different personality or temperament types related to burnout may represent differences in physiological profile. We did not explicitly look at temperament or personality differences in relation to the physiological changes in burnout. However, throughout this thesis the total score on the symptom checklist ‘SCL90’ is used as an indication for the reported psychoneuroticism or general psychopathology.

¹ In the period of 1997-2004: 8 - 11%. The cut-off point of > 2.21 is based on the Dutch version of the Maslach Burnout Inventory, subscale ‘exhaustion’ which consists of 5 items, ranging from 0 (never) to 6 (every day).

² Five dimensions: extraversion, agreeableness, conscientiousness, emotional stability, intellect/openness

PSYCHOSOMATIC COMPLAINTS

Burnout shows overlap in symptoms with other stress-related health outcomes like depression (major depression disorder; MDD), fatigue (Chronic fatigue syndrome; CFS, vital exhaustion), anxiety (posttraumatic stress disorder; PTSD), and sleep disorders. Other unexplained chronic psychosomatic syndromes are mentioned in relation to burnout as well; whiplash, repetitive strain injury (RSI), irritable bowel syndrome (IBS), multiple chemical sensitivity, and fibromyalgia (Ursin and Eriksen 2001). Despite the overlap in symptoms, the work-related character distinguishes burnout from syndromes with a resembling appearance (Schaufeli and Enzmann 1998; Shirom 2005). The overlap between MDD, CFS and burnout is used throughout this thesis as a theoretical starting point to speculate about the potential physiological disturbances to be observed in burnout. What can be expected in burnout, considering the observed changes in CFS and MDD?

STRESS

If work-stress can lead to burnout, the question arises what the mediating mechanisms might be. For understanding this issue, it is crucial to study the physiological stress-response as a potential mediator. Under stressful conditions, the body becomes activated to meet the increased demands of the environment. During acute stress the ‘fight-flight response’ is turned on. The sympathetic (activating) pathways of the body elevate heart rate, blood pressure, respiration, and glucose synthesis. Simultaneously the parasympathetic pathways (rest & recover) involved in feeding, sleep, and sexual drive are decreased. This whole system can be activated by external and internal cues, and since organisms learn from their experiences, can become sensitized for cues related to a potential stressor (Ursin and Eriksen 2001). A person with burnout may experience a full-blown stress response at the sight of his companies’ logo on a coffee mug.

In the long run, the inability to properly terminate a stress response, or chronic exposure to stress can lead to pathological changes. The first to acknowledge this was Hans Selye. In the 1930’s he described this process as the ‘General Adaptation Syndrome’, which consists of three stages; the alarm reaction, the stage of resistance, and the stage of exhaustion. More recently the term allostatis, or ‘stability through change’ was introduced by Sterling & Eyer (1988). Allostatis is the adaptation of a set point (homeostasis) to meet the changing demands of the environment. This concept can be portrayed as the constant heating of a room with an open window, which is not a problem during a sunny autumn’s day, but will be a burden during a freezing winter’s eve. The set point for room temperature needs to be adjusted to be able to maintain a constant temperature under these different conditions. In the long run the ‘allostatic load’, or the price that is paid for the change in set point, can lead to wear and tear (McEwen 1998). The equivalent in burnout, the recurrent activation of the stress response system, leads to an allostatic change in the set point. This could initially result in a state of hyperarousal, in which the system becomes activated too soon

(at the sight of a coffee mug). In this case the allostatic load is the energetically costly activation of the stress-response, while at the same time inhibiting, and thus neglecting, the pathways involved in rest and recovery. In the long run the allostatic load on both the stress-regulatory system and the system involved in rest and recovery may have adapted in a way we consider maladaptive; burnout. In this thesis we assume that chronic work-stress has led to wear and tear. A potential candidate for the mechanism underlying the complaints observed in burnout is the HPA-axis.

H P A - A X I S

The HPA-axis, the Hypothalamus Pituitary Adrenal-axis (Figure 1; HPA-axis, page 14) is the response system involved in maintenance, mediation and recovery from a stress response. At the onset of an acute stress response, signals from the brain (mainly the limbic system) activate the hypothalamus, to secrete corticotrophin-releasing hormone (CRH). Whether or not a situation is labeled as stressful is under control of the limbic system. Input from amygdala (emotional flavoring), hippocampus (recollection and consolidation of memory), and the prefrontal cortex (working memory) is processed, estimating a potential stressful situation. When estimating a situation, CRH influences these systems, working together with other brain hormones like serotonin (mood), dopamine (reward, motivation), epinephrine (acute stress response), and oxytocine (social behavior). Clearly whether or not a situation is perceived as stressful is a complex process. Released CRH travels via the portal vein to the pituitary gland to induce the release of ACTH to the bloodstream. In turn ACTH in the blood initiates the synthesis and release of cortisol from the adrenal gland. Cortisol is the major glucocorticoid of the body. Its main action is to control the available energy by increasing the blood glucose level, via gluconeogenesis (glucose synthesis) and glycogenolysis (glucose release from storage). The release of glucose may act to replenish the depleted energy levels of the acute phase of the stress response, and the synthesis continues to produce energy for the long-term demands. At the same time cortisol mediates the shut down of processes that take up energy and are not critically involved in the stress-response, such as food intake and digestion, inhibits the immune response, sleep, and reproduction. As the HPA-axis and its components are critically involved in the functioning of these systems, prolonged activation of the HPA-axis could affect the other regulatory pathways (figure 2, page 15). Dysregulation of this system is assumed in this thesis to give rise to the pattern of complaints as seen in burnout.

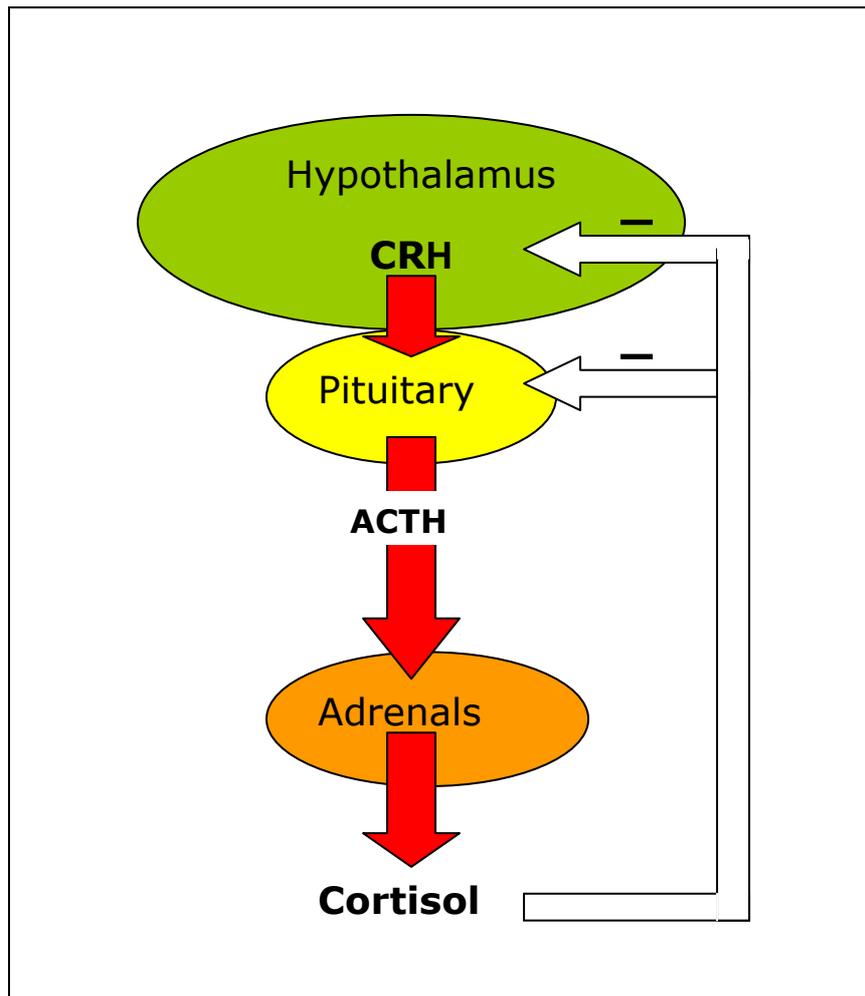


FIGURE 1: HPA-AXIS

Upon stimulation CRH is released by neurones in the hypothalamus. CRH stimulates the release of ACTH by the pituitary. Subsequent increased ACTH levels release cortisol from the adrenal cortex. Cortisol inhibits CRH and ACTH release and thus reduces its own release by negative feedback.

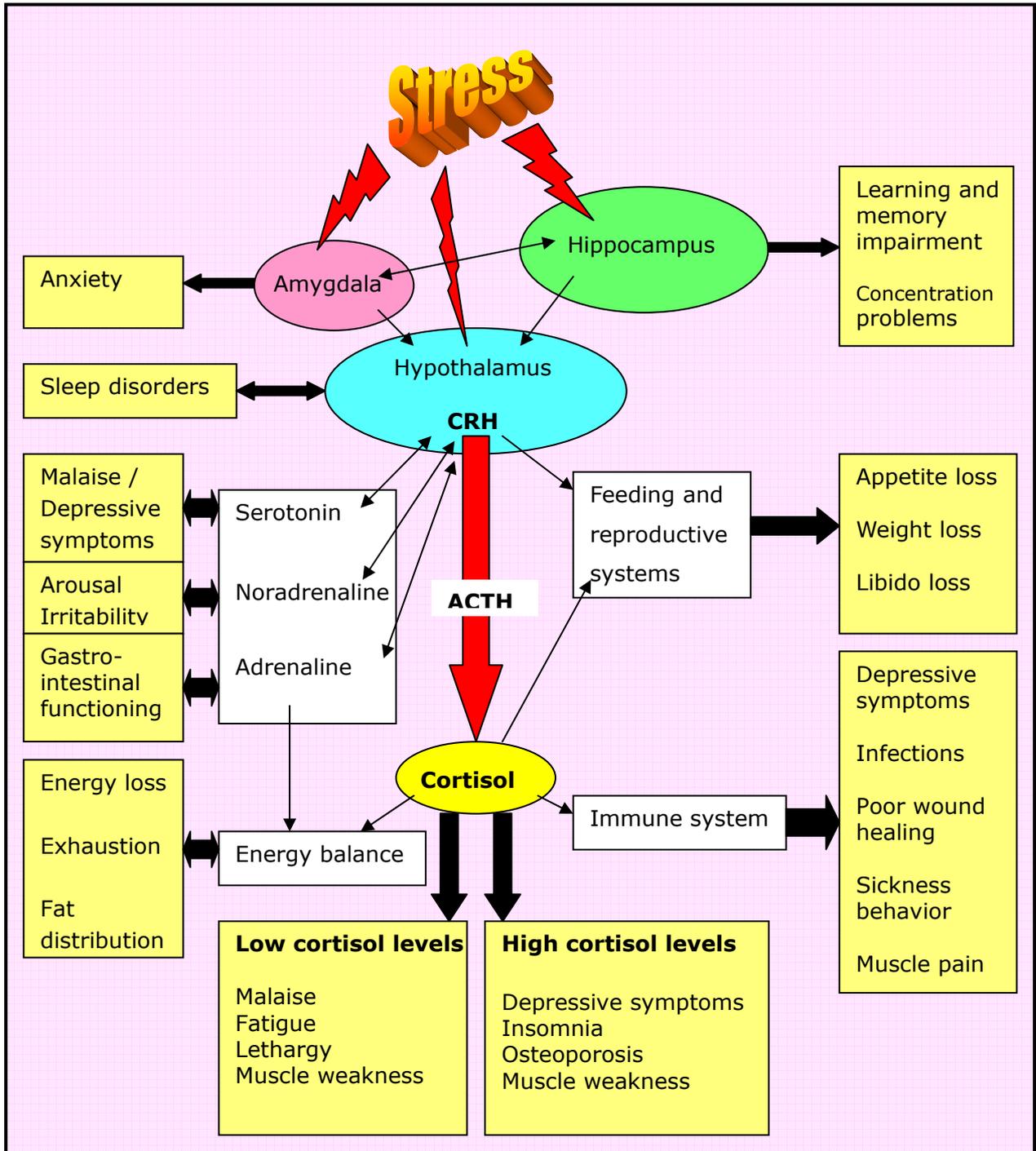


FIGURE 2 PHYSIOLOGY OF BURNOUT SYMPTOMS

The central stress regulatory axis of the body is the HPA-axis. Every part of this axis is connected with other regulatory systems involved in action and rest, in order to maintain balance in the body. Disturbance of the central HPA-axis due to chronic stress can therefore lead to imbalance in coupled subsystems. This could explain a variety of symptoms found in burnout such as exhaustion, sleep problems, depressive symptoms, irritability, concentration problems, backpain and gastro-intestinal problems.

RECEPTORS & FEEDBACK

Cortisol is synthesized from cholesterol in the adrenal cortex, a gland adjacent to the kidneys. About 10% of the circulating cortisol is biologically active free cortisol, the major part is bound by corticosteroid binding globulin (CBG). This transporter molecule acts as a buffer system. Cortisol binds to its receptor in the cell cytoplasm, and is then transported to the nucleus where the complex binds to the promoter region of various genes, leading to activation or inhibition of the transcription of genes (Berne and Levy 1993). Cortisol acts upon two types of receptors; one is the high-affinity mineral-corticoid receptor (MR), involved in homeostasis, maintenance of cortisol levels (the diurnal cycle), and controlling the threshold of a stress-response. The other is the low-affinity glucocorticoid-receptor (GR), which becomes activated with increased amounts of cortisol, e.g. during the stress-response and after awakening. The GR receptor is present in many cell types, e.g. all cells of the immune system. In the hippocampus the MR and GR receptor are differentially involved in information processing (De Kloet, Oitzl et al. 1999). Occupation of the GR receptor in the hippocampus, mainly under high circulating cortisol levels, e.g. under stressful conditions, is involved in memory consolidation dependent on the context. Once again the example of the burned-out employee panicking at the sight of the company's coffee mug is fitting. Another important feature of the GR-receptor is controlling the stress response by negative feedback and mobilizing energy resources (De Kloet 2003). Cortisol binding to the GR-receptor in the hypothalamus and pituitary leads to an inhibition of the release of CRH and ACTH, thereby terminating a stress response. This negative feedback system is dependent on the number of receptors and their sensitivity for cortisol. Thus termination of a stress response is in part under control of the state of the GR-receptor. It becomes apparent that changes in receptor functioning can be part of the change in the allostatic 'set-point', which may be the central mechanism for disturbance of HPA-axis functioning.

A subtle way of investigating HPA-axis functioning is by mimicking the negative feedback response with dexamethasone (Kirschbaum and Hellhammer 1994). Dexamethasone is a synthetic glucocorticoid with actions similar to cortisol. It selectively binds with high affinity to the GR receptor, inhibiting the release of ACTH and subsequent cortisol (De Kloet, Meijer et al. 1998). The dexamethasone suppression test (DST) comprises of a low oral dose (0.25-1 mg) of dexamethasone ingested in the evening, the following morning the release of cortisol is partially inhibited. The strength of the inhibition, as compared to a control group, could show whether the negative feedback pathway in burnout is more sensitive to dexamethasone, resulting in more suppressed cortisol levels, or rather insensitive, with less suppressed cortisol levels. In a similar way the inhibitory action of dexamethasone on immune functioning is investigated, which is discussed below.

DIURNAL COURSE AND AWAKENING RESPONSE

The HPA-axis shows a diurnal cycle under control of the suprachiasmatic nuclei (SCN), the *zeitgeber* of the body. As a result, cortisol shows a gradual decline during the day with the lowest level being in the first hours of sleep. During the second half of the night the cortisol level starts to rise again. Immediately after awakening the cortisol level increases dramatically, and peaks at about 30 minutes after awakening, the so called ‘Cortisol Awakening Response’ (CAR) (Pruessner, Wolf et al. 1997; Edwards, Clow et al. 2000; Wust, Wolf et al. 2000). The awakening response is rather stable over days (Wust, Wolf et al. 2000), and even after prolonged periods of time (Huizenga, Koper et al. 1998). In Box 1 (page 19) possible confounders of cortisol and the awakening response are described. The cortisol level during the awakening response is within the range of cortisol levels observed under stress conditions. The awakening response is shown to vary with level of (chronic) stress (Schulz, Kirschbaum et al. 1998; Pruessner, Hellhammer et al. 2003; Schlotz, Hellhammer et al. 2004). The potential candidates for finding a dysregulation in the HPA-axis of persons with burnout are the cortisol awakening response, the diurnal course of cortisol and the cortisol awakening response after dexamethasone intake. The types of dysregulation are hypothesized in the following paragraph.

HYPER- AND HYPOCORTISOLAEMIA

In the long run, under chronic stress conditions, the HPA-axis may have been activated too long and too often, and in combination with insufficient recovery, allostatic load might be increased. A change in the allostatic set point of the HPA-axis could result in a change in availability of cortisol. At the same time, the number or sensitivity of the GR may have changed. As cortisol affects a number of other regulatory systems involved in activation and rest, e.g. cortisol prevents glucose uptake by the liver, suppresses immune functioning, and affects hippocampus-mediated memory, these systems can become affected by the change in circulating glucocorticoid levels (McEwen 2000; Sapolsky, Romero et al. 2000; Raison and Miller 2003; De Kloet, Joels et al. 2005). Some possible dysregulations in related systems are depicted in Figure 2.

As an outcome of chronic stress paradoxically two pathways are suggested: either a hypoactive HPA-axis, or a hyperactive HPA-axis (Raison and Miller 2003). The *hypocortisolemic* state is characterized by lower circulating cortisol levels and an up-regulation of GR, resulting in increased feedback sensitivity (Heim, Ehlert et al. 2000). This has been observed in PTSD trauma survivors (Stein, Yehuda et al. 1997; Yehuda, Halligan et al. 2004), chronic fatigue syndrome and fibromyalgia (Clauw and Chrousos 1997; Parker, Wessely et al. 2001; Gaab, Huster et al. 2002). In contrast, the *hypercortisolemic* state, characteristic of major depressive disorder, shows higher circulating cortisol levels and decreased glucocorticoid responsiveness (e.g. dexamethasone non-suppression) (Holsboer 2000; Pariante and Miller 2001).

In burnout, repeated stress and subsequent bursts of cortisol may have increased the sensitivity of the GR to increase the recovery phase of the stress response. As a result the negative feedback pathway could have become extra sensitive towards cortisol. In that case the dexamethasone suppression test (DST) would show an increased suppression of cortisol, indicating a more sensitive system, accompanied by lower circulating cortisol levels; the hypoactive HPA-axis.

The depression component in burnout on the contrary predicts a hyperactive HPA-axis. The higher circulating levels of cortisol and non-suppression of the DST could represent an inability to efficiently shut down a stress response. The HPA-axis has become non-responsive to the negative feedback of the higher circulating cortisol levels (Pariante 2004). The hypo- and hypercortisolemic pathways are opposite to one another. As burnout is characterized by both fatigue and depressive symptoms we can predict either dysregulation to have occurred. It is also likely that within the burnout group different persons show counteracting pathways, which may be related to the individual differences in reported complaints, dependent on the level of fatigue or depression. The presence of opposite dysregulations in individuals within the burnout group reduces the chance of finding an overall difference with healthy subjects. This brings about the need to compare subgroups of individuals within the burnout group, in addition to the traditional between group comparison of burnout vs. a healthy control group.

Overall we expect the effects of the fatigue component in burnout to be dominant, first of all because exhaustion is the core component of burnout, and second because it is questionable that a negative mood characteristic for burnout is indicative for a real major depression in clinical terms. Hence we hypothesize a hypofunctioning of the HPA-axis, with lower awakening levels, lower levels throughout the day, and an increased sensitivity for dexamethasone (lowered levels after dexamethasone intake). Nevertheless, we speculate that within the burnout group a subgroup with high scores on depression will show a hyperactive HPA-axis and the subgroup with high fatigue a hypoactive HPA-axis.

D H E A S

Another endocrine parameter that was investigated is dehydroepiandrosterone-sulphate (DHEAS). DHEA(S) is a precursor for the production of sex hormones, and the levels decline with age (Kroboth, Salek et al. 1999). In addition, DHEA(S) shows actions opposite to the regulatory effects of cortisol; it is involved in the improvement of immune functioning, muscle restoration and bone mass recovery, and decrease of cholesterol levels (Chen and Parker 2004). Cortisol and DHEA(S) are both synthesized from cholesterol in the adrenal gland and released in response to ACTH. A change in either hormone could result in a shift in balance between the two, and is hypothesized to change in stress-related syndromes. Indeed in CFS, PTSD and Major depression disorder changes in DHEA(S) levels or a shift in balance between cortisol and DHEA(S) were observed, though the

results are contradictory (Scott, Salahuddin et al. 1999; Kanter, Wilkinson et al. 2001; Young, Gallagher et al. 2002; Assies, Visser et al. 2004; Cleare, O'Keane et al. 2004). Circulating DHEAS levels are more abundant, more stable and serve as a buffer for the DHEA levels. Therefore in our burnout group DHEAS levels were measured from saliva rather than the DHEA level. The hypothesized lower circulating cortisol levels in burnout may have favored the release of increasing DHEAS levels, or a shift in balance between cortisol and DHEAS towards DHEAS. Though based on the above-mentioned studies, we cannot be sure what to expect in burnout.

BOX 1: CORTISOL CONFOUNDERS

Some studies have described an effect of awakening time on the awakening response (Edwards, Evans et al. 2001; Kudielka and Kirschbaum 2003; Federenko, Wust et al. 2004), whereas others did not (Pruessner, Wolf et al. 1997; Wust, Wolf et al. 2000). The same can be concluded for gender, weekday vs. weekend day, age and smoking (Clow, Thorn et al. 2004). The awakening response is more pronounced under the influence of light (Scheer and Buijs 1999; Leproult, Colecchia et al. 2001). It appears to be independent of sleep quality, sleep duration, disrupted sleep, or waking by an alarm clock. Body mass index (BMI), alcohol consumption, blood glucose levels and shift in body posture did not show to affect the awakening level as well (Hucklebridge, Clow et al. 1999; Gerra, Zaimovic et al. 2000; Wust, Wolf et al. 2000; Hucklebridge, Mellins et al. 2002; Clow, Thorn et al. 2004). The awakening response is in part (30-60%) influenced by genetic factors, whereas the decline of cortisol during the day is predominantly affected by environmental influences (Scott, Salahuddin et al. 1999; Wust, Federenko et al. 2000; Kanter, Wilkinson et al. 2001; Bartels, De Geus et al. 2003; Assies, Visser et al. 2004; Kupper, de Geus et al. 2005). Recent studies show that the lack of an awakening response could be due to non-compliance (Kudielka, Broderick et al. 2003; Broderick, Arnold et al. 2004; Kupper, de Geus et al. 2005). Still it is possible that the flat curves are a physiological feature of a person rather than an indicator of non-compliance.

Salivary cortisol maintains stability within a week of storage at room temperature or under varying temperatures, which makes it suitable for postal collection (Clements and Parker 1998; Groschl, Wagner et al. 2001). Repeated freeze-thawing does not significantly decline cortisol levels in saliva. The effect of eating, drinking or dental care during collection is not significant either (Groschl, Wagner et al. 2001). Still most studies recommend absence of eating, drinking (except water) and dental care in the 30 minutes period before taking a sample.

BOX 2: IMMUNOLOGY

Immune cells, or leukocytes, can be divided into granulocytes, monocytes and lymphocytes. Granulocytes are cells with large granules in the cytoplasm, e.g. basophylic granulocytes. Monocytes e.g. macrophages are phagocytosing -eating-cells, and play a central role in the innate immunesystem. T-cells, B-cells and NK-cells are all lymphocytes. T-cells are named T-cells as they matured in the thymus , and B-cells have matured in the bone-marrow. Leukocytes can be recognized based on the 'cluster of differentiation' or CD on the outside, e.g. all T-cells are CD3 positive, or CD3+, and dependent on the subtype they express CD4+ or CD8+. NK-cells express CD16+ and CD65+, B cells show CD19+.

The first phase of an immune response is the non-specific mobilisation of cells as natural killer cells, macrophages and the release of inflammatory cytokines. Natural killer cells recognize and kill virus infected cells and tumor cells. Macrophages engulf, 'eat' invading pathogens and present parts of the pathogen (antigen) on the outside of the cell, as antigen presenting cell (APC). The APC's connect to T-cells and B-cells. This process is part of the aquired immunity, which is slower and antigen-specific. Every T-cell or B-cell responds to a single antigen via expression of a specific antigen receptor. The first step for activation of the specific immune response is proliferation (cell division or mitosis), expanding the number of cells. T and B-cells develop into memory cells, which become quickly activated in a secondary encounter with a pathogen. This mechanism encompasses the therapeutic basis of vaccination (Roitt 1994). This response is called 'cell mediated immunity'

T-cells can be roughly divided into T-helper/ inducer cells (CD4+) and T cytotoxic/ suppressor cells (CD8+). T-helper cells activate B-cells to produce antibodies (immunoglobulines, or Ig) against an antigen. This response is named the 'humoral immunity'. Cytokines (messenger molecules) that mediate this response are interleukin 4 (Il-4), Il-0 and Il-13, or anti-inflammatory cytokines. On the other hand, T-helper/ inducer cells release a host of cytokines called the pro-inflammatory cytokines e.g. interferon gamma (IFN- γ), Il-2 and TNF- α . The pro and anti-inflammatory cytokines are mutually inhibitory and also represent a balance between the cell mediated and humoral immunity, sometimes named the Th1/ Th2 balance. A disturbed cellular immunity (Th1) is associated with auto-immune diseases as rheumatoid arthritis, multipel sclerosis, type 1 diabetes and Crohn's disease, whereas a disturbance of humoral immunity (Th2) is linked to allergic reactions as asthma, seasonal allergic rhinitis, IgE mediated allergies and eczema (Elenkov and Chrousos 2002; Elenkov, Iezzoni et al. 2005). However, is is important to keep in mind that monocytes/macrophages also secrete pro-and anti-inflammatory cytokines. This important subset plays therefore a pivotal role in determining the final cytokine balance.

STRESS AND THE IMMUNE SYSTEM

Stress affects immune functioning. Box 2 (page 20) provides a more detailed description of the immune system and its components. In the acute phase of a stress response there is an augmented immune reaction, with elevated circulating lymphocytes in the bloodstream and increased levels and functioning of macrophages (monocytes) and NK-cells. After about an hour the increased circulating levels of glucocorticoids will have shut down the increase and instead an inhibition of the immune response is present. In situations of chronic stress, recurrent circulating cortisol levels may increase the allostatic load on the immune system. The prolonged inhibition of the immune response, could increase the likelihood of sickness; the reduced ability to respond to an invading pathogen. Cohen et al. showed a connection between chronic stress and increased sensitivity for a common cold virus (Cohen, Frank et al. 1998). On the other side, chronic stress, and possible lower circulating cortisol levels are also connected with a shift towards pro-inflammatory Th2 type responses [box 2], which increases the activation of allergic reactions. Some studies have found a shift towards pro-inflammatory Th2 type responses in Chronic fatigue syndrome (Patarca 2001; Skowera, Cleare et al. 2004; Gaab, Rohleder et al. 2005).

Cytokines have been suggested as the mediators for the stress-related changes in mood and susceptibility to disease. Cytokines can make you feel sick (Maier and Watkins 1998; Dantzer 1999; Dantzer 2001; Johnson 2002). Pro-inflammatory cytokines as IL-1, IL-6 and TNF-alpha are pyrogenic; they increase the set point for body temperature, inducing fever. In addition, behavioral changes as reduced food intake, reduced explorative behavior, sleep disturbances, decreased physical, social and sexual activity were observed. These changes are referred to as Sickness Behavior. Sickness behavior resembles depressive symptoms, and as IL-1, IL-6 and TNF-alpha are potent inducers of CRH release and can induce GR resistance it was suggested that these cytokines may be involved in depression as well (Raison and Miller 2003; O'Brien, Scott et al. 2004; Pariante 2004). Fatigue is a component of the sickness behavior concept as well which favors investigation of the pro-and anti-inflammatory cytokines in burnout.

In this thesis cytokines are measured *in vitro* in response to a potent stimulator, because circulating levels of cytokines in plasma are usually below the detection limit. The pro-inflammatory cytokines TNF- α and IFN- γ were selected as they are produced predominantly by monocytes after LPS stimulation (TNF- α) or by T cells after T-cell-mitogenic stimulation (IFN- γ) (Box 2, page 20). IL-10 was selected as the anti-inflammatory cytokine produced by monocytes after LPS, and predominantly by T cells after PHA stimulation.

Glucocorticoids are important inhibitors of immune functioning. The actions of glucocorticoids on the immune system have been investigated *in vitro*. Dexamethasone binds to the GR-receptor in the immune cells, inhibiting the release of cytokines. The change in cytokine release in response to increasing concentrations of dexamethasone is an indication for the potential of GR in leukocytes. When selecting the cytokines, we took

into consideration that TNF- α and IFN- γ are highly sensitive to regulation by dexamethasone, whereas e.g. IL-6 is relatively resistant to regulation by glucocorticoids. We selected IL-10, since we knew that this cytokine would provide us with the opportunity to also determine the stimulatory effect of glucocorticoid agonists on this anti-inflammatory cytokine. The IFN- γ /IL-10 ratio was used as an indicator of the pro/anti-inflammatory cytokine ratio. We did not conduct a classical Th1/Th2-ratio calculation using IFN- γ and IL-4 because PHA is a very poor inducer of IL-4.

Once again it is hard to predict what changes will be apparent in burnout. Based on the central complaint in burnout; exhaustion, we expect a change which resembles the shift towards pro-inflammatory cytokine production observed in CFS, and changes in the glucocorticoid sensitivity of T-cells and monocytes.

STUDY AIMS AND OUTLINE OF THIS THESIS

The main aim of this project is to search for physiological disturbances in persons with severe burnout complaints. These obviously may show up by comparing them with a healthy control group. Equally important is the analysis of individual differences in the burnout group. There may be opposite types of dysregulation, the hyper- and hypo-active HPA-axis. These types are presumably related to differences in the reported complaints; depression and fatigue respectively. The burnout group consists of persons who show individual differences in the fatigue and depression complaints. Therefore the hypothesized opposite dysregulations could obscure findings in the burnout group as a whole. Our studied population are burned-out persons who are currently on sick leave and who are at the onset of treatment. The recovery of the burnout complaints shows variation between persons, which may be related to the individual differences in physiological functioning. Longitudinal measurements could reveal the correlation between the initial complaints, and the change in complaints with the physiological functioning.

In this thesis we investigated functioning of the HPA-axis in the cortisol awakening response (CAR), the diurnal course during the day (DAY-curve), and the negative feedback of glucocorticoids by the dexamethasone suppression test (DST). These parameters were studied in a longitudinal setting after treatment and at follow-up. Additionally the assessment of physiological (dys)functioning was extended with the measurement of DHEAS as a potential counterpart for cortisol functioning. The immune system may show changes in burnout as well. The release of pro- and anti-inflammatory cytokines involved in sickness-behavior was also investigated, and as cortisol inhibits immune functioning, the effect of glucocorticoids on the release of these cytokines was studied.

In the pilot study described in **chapter 2**, 22 burnout persons who had received a clinical diagnosis and 21 controls were compared for burnout related complaints (burnout, fatigue, depression, cognitive functioning, SCL90) and salivary cortisol after awakening (for

analysis of the CAR) and the DAY curve. After 14 treatment sessions the cortisol levels and the complaints were measured again in the burnout group ($n = 19$).

Project A was a larger and more detailed version of the pilot study. A new group of burnout persons, who were mostly on sick leave for their complaints, had received a clinical diagnosis, and were at the onset of treatment, were measured before treatment, after a treatment period and at follow-up. In **chapter 3** the cross-sectional part of this study is dealt with; 74 burnout persons and 35 controls were compared with respect to reported burnout complaints, cortisol CAR, DAY-curve and the Dexamethasone Suppression test (DST). The differential effect of fatigue (potential hypoactivity) and depressive symptoms (possible hyperactivity) on HPA-axis functioning was investigated as well.

The longitudinal part is **chapter 4**, the burnout group, but not the control group, was measured after treatment ($n = 62$) and at follow-up ($n = 53$). Multilevel regression analysis was used to estimate the effect of the initially reported complaints and the change in complaints as well as confounding variables on the cortisol CAR, DAY-curve and DST over the three measurements.

Project B focussed on immune functioning in burnout persons ($n = 56$), and the results are presented in **Chapter 5**. Endocrine variables in this study were the cortisol CAR, DST, and the hormone DHEAS. Immune cell count, number of T-cells (T-helper/ inducer and T suppressor/ cytotoxic), B-cells and NK-cells were determined and in vitro stimulation of pro- and anti-inflammatory cytokine release was measured. The capacity of dexamethasone to regulate cytokine release was compared between the groups.

Finally in **Chapter 6** the results are summarized, discussed and conclusions are drawn.

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Chapter 2

Cortisol Deviations in People with Burnout Before and After Psychotherapy; a Pilot Study.

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A B S T R A C T

Burnout is characterized by exhaustion, cynicism and feelings of reduced competence. These complaints may be reflected in disturbances in the main stress regulatory endocrine system: the HPA-axis. In this study the HPA-axis hormone cortisol was sampled after awakening and during the day in 22 participants with clinical burnout and in 21 healthy controls. The cortisol level after awakening was shown to be significantly lower in the burnout group as compared to the control group. Cortisol levels during the day did not differ. The same sampling procedure was repeated after 14 sessions of psychotherapeutic intervention. The intervention led to a significant reduction in complaints and to an increase of the initially lowered morning cortisol levels. No consistent correlations, however, between the changes in subjective complaints and the change in cortisol parameters were found.

Keywords: burnout, cortisol, cortisol awakening response, follow-up

INTRODUCTION

Burnout is a state of persistent exhaustion, which is work-related and characterized by *emotional* exhaustion (a feeling of being ‘empty’ or ‘worn out’), cynicism or depersonalisation and reduced competence (Maslach, Schaufeli et al. 2001). These symptoms result from prolonged periods of high workload or persistent or recurrent stress without sufficient recovery. Chronic stress leads to changes in the adaptive state (‘allostasis’) of the body which may lead to wear and tear, and to an ‘allostatic load’ in the long run (McEwen 2000). From a psycho-physiological point of view the symptoms of burnout reflect disturbances of neural and hormonal stress-regulatory systems. The central neuroendocrine system involved in long term adaptation to stress is the hypothalamus pituitary adrenal (HPA)-axis, with cortisol as its major regulatory hormone (Sapolsky, Romero et al. 2000; Cook 2002). The HPA-axis is interconnected with other regulatory systems which are involved in regulating the energy balance, mood states, sleep, and cognition. A disturbed HPA-axis could therefore have an impact on these systems (Raison and Miller 2003), causing the array of symptoms as observed in burned out individuals. Disturbances in the HPA-system are also evident in other stress-related pathologies such as chronic fatigue syndrome (CFS), depression and posttraumatic stress disorder (Ehlert, Gaab et al. 2001; Parker, Wessely et al. 2001). Higher cortisol levels are a characteristic of major depression (Holsboer 2001; Pruessner, Hellhammer et al. 2003). PTSD and CFS, however, if anything, rather show a *hypo*-function of the HPA-axis (Demitrack 1997; Heim, Ehlert et al. 2000; Parker, Wessely et al. 2001; Roberts, Wessely et al. 2004). Because the clinical symptoms of these illnesses are overlapping with burnout, a deviation of the HPA-axis may be associated with burnout as well.

Cortisol secretion shows a circadian rhythm, it peaks in the morning and then gradually declines during the day. Another aspect of cortisol secretion is the so called ‘cortisol awakening response’ (CAR). This acute rise, superposed on the normal cycle, reaches its peak about 30 minutes after awakening. The CAR is found to be altered in situations of stress and high job strain, showing higher awakening levels and a steeper increase (Schulz, Kirschbaum et al. 1998; Steptoe, Cropley et al. 2000; Wust, Federenko et al. 2000). To date studies on the relationship between burnout and HPA-axis functioning are contradictory. Several studies used ratings on a burnout scale as an indication of burnout. Participants who reported high scores were found to have both higher and lower salivary cortisol levels after awakening (Pruessner, Hellhammer et al. 1999, respectively; Grossi, Perski et al. 2004), higher morning and afternoon salivary cortisol levels (Melamed, Ugarten et al. 1999), and no difference in plasma cortisol (Grossi, Perski et al. 2003). In these studies, despite their high ratings, all participants were still at work and had not received a clinical diagnosis for their complaints. Two studies in which burnout was clinically diagnosed showed lower urinary, but not plasma, cortisol levels (Moch, Panz et al. 2003), and increased levels of salivary cortisol after awakening. The present study focuses on persons

who have received a clinical diagnosis of burnout and who are for the greater part on sick leave as well.

Whatever the HPA-axis deviation in burnout may be, not much is known about the changes in time, and whether they covary with severity of the symptoms. Moch et al. (2003) found no change in (reduced) urinary cortisol levels of burnout persons after four months of stress management intervention. In the present study we sampled saliva of burnout participants before and after receiving psychotherapeutic treatment for their complaints. If changes in cortisol are the result of the current burnout symptoms, one might expect that the HPA-axis function will normalise when the clinical signs of burnout decrease after therapy. Therefore the aim of this pilot study is twofold: first to establish a possible deviation in HPA-axis functioning in burnout participants, and second to assess the co-variation of symptom recovery and cortisol parameters.

METHODS

PARTICIPANTS AND PROCEDURE

A total of 22 burned-out persons (7 males and 15 females; $M = 45$ years, $SD = 8$ years), were included in the study. Burnout was diagnosed on the basis of an intake procedure which included a checklist with ICD-10 criteria (World Health Organisation: WHO 1994) for work-related neurasthenia. Persons suffering from other primary DSM-IV (American Psychological Association: APA 1994) axis 1 disorders, such as mood or anxiety disorders were excluded. To be included they had to be on sick leave for at least 50% for at least three months, and not be using oral corticosteroid medication. The mean duration of symptoms at the onset of the study varied between 4 and 48 months ($M = 26$ months, $SD = 37$ months). Participants in the burnout group were either on partial ($n = 6$) or total sick leave ($n = 16$) and had either a part-time ($P = 50\%$) or a full-time job ($P = 50\%$). Control persons, $n = 21$ (7 male and 14 female; $M = 50$ years, $SD = 7$ years), were included via age- and sex matched -relatives of participants and via acquaintances of the researchers. Before participation in the study all participants gave written informed consent. Burnout participants received a manual-based cognitive-behavioural treatment (Schaap, Keijsers et al. 2001). Treatment focussed on reduction of complaints, cognitive therapy, work resumption, work-related interventions and relapse prevention. After the standard treatment period of 14 sessions ($M = 6$ months, $SD = 1,3$ months) 19 burnout participants were measured for a second time. At this stage, 5 participants had resumed work, 7 participants were on partial sick leave and another 7 were on total sick leave. The control group was not measured again.

CORTISOL SAMPLING

Saliva for cortisol analysis was collected by a salivette; a plastic tube with a cotton role (Sarstedt, Etten-Leur, the Netherlands). All participants received questionnaires and salivettes at home. Saliva was collected on two consecutive week days at 0, 15, 30 minutes after awakening for the CAR analysis, and at noon, 6 pm and 10 pm for the day-curve. Collection time was registered by paper diary. Possible cortisol influencing parameters as smoking, the use of oral contraceptives and prescribed medication were registered. The same procedure was repeated after about 6 months for the burnout group, but not for the control group. The samples were kept in the refrigerator after collection and sent at room temperature to the institute where the samples were stored at -20°C . Samples were analysed in a lab in Dusseldorf (Germany), by a time-resolved immunoassay with fluorescence detection as described elsewhere (Dressendorfer, Kirschbaum et al. 1992).

QUESTIONNAIRES

A questionnaire was filled out on demographic data, duration of complaints and work status. Burnout was measured with the Dutch version of the Maslach burnout inventory (UBOS), with subscales exhaustion, depersonalisation, and of (reduced) competence (Schaufeli and Van Dierendonck 2000). Fatigue was measured by the 'Checklist Individual Strength' 20 item version (CIS-20R) (Vercoulen, Alberts et al. 1999), Depression with the Beck Depression Inventory (BDI) (Bouman, Luteijn et al. 1985), psychoneuroticism with the Symptom Checklist (SCL-90) (Arrindel and Ettema 1981) and cognitive complaints with the Cognitive Failure Questionnaire (CFQ) (Broadbent 1982). Sleep-quality in the past month was assessed with the Dutch State and Trait sleep assessment scale (GSKS; 4 weeks) (Meijman, Thunnissen et al. 1990). All scales are well validated Dutch versions that have shown reasonable to good reliability.

STATISTICS

Outliers in the cortisol samples with z scores greater than three standard deviations ($P = 1.7\%$ of the data) were excluded from analysis. Two samples (0.3%) were missing in the total dataset. The cortisol values did not differ significantly between days and the two-day averaged values were used for analyses. If a sample was missing, then the value of the other day was used. Repeated measures analysis of variance was used for analysis of the CAR, the three cortisol samples after awakening as the within factor and (burnout and control) group as the between factor. The three cortisol samples taken during the remainder of the day (noon, 6 pm and 10 pm) were analysed in a separate repeated measures analysis of variance, with sample time as within factor and group as between factor. After treatment 'treatment' was introduced as a within variable in the repeated measures analysis of the CAR and the day-curve. Greenhouse-Geisser correction was applied whenever sphericity

was violated. The questionnaire scores of the burnout vs. the control group were compared using one-way ANOVA's. Paired samples t tests were used to compare the questionnaire scores pre- vs. post-therapy. The CAR samples was recalculated into Area Under the Curve (AUC) measurements according to J.C. Pruessner et al. (2003a) for Spearman rank correlation with the questionnaire scores (Pruessner, Kirschbaum et al. 2003).

RESULTS

BURNOUT VERSUS CONTROL GROUP

The burnout group and the control group were not different in sex composition, $\chi^2 (1, N = 43) = .01, p = .92$, employment status (part-time vs. full-time), physical activity, smoking or use of oral contraceptives (data not shown). The burnout group was somewhat younger than the control group ($M = 43$ year vs. $M = 50$ year), $t (41) = -2.8, p = .008$, and the burnout group used more prescribed medication, $\chi^2 (1, N = 43) = 4.7, p = .03$. The burnout group did not differ in time of awakening ($M = 8:04$ AM, $SD = 52$ min.) from the control group ($M = 7:52$ AM, $SD = 53$ min.), $t (35) = .73, p = .47$. As shown in table 1, the burnout group reported more fatigue, depression, cognitive complaints, sleep problems and had a higher level of psychoneuroticism.

Figure 1 shows the CAR (on the left), and the cortisol levels during the day (on the right), for the burnout and the control group. There is a significant rise in cortisol after awakening (main effect of CAR; $F (2, 67) = 15, p < .001$, effect size (partial eta squared) $\eta_p^2 = .27$). The burnout group had significant lower cortisol levels after awakening (main effect of group; $F (1,39) = 15, p < .001, \eta_p^2 = .28$). There was, however, no difference between the burnout and the control group in the *rise* after awakening (group x CAR; $F (2,67) = .41, p < .66, \eta_p^2 < .01$). Cortisol shows a significant decline during the day (main effect of time; $F (1,55) = 58, p < .001, \eta_p^2 = .60$), but there was no difference between the burnout and control group in cortisol level during the day (main effect group; $F (1,38) = .07, p = .79, \eta_p^2 < .01$), nor in cortisol decline between the groups during the remainder of the day (group x time; $F (1,55) = .47, p = .79, \eta_p^2 = .01$). Introducing sex and age as covariates did not change the results. Exclusion of participants using medication from the analyses did not affect the results either. No consistent pattern of correlations within the burnout or control group were observed between the cortisol parameters and the questionnaire scores.

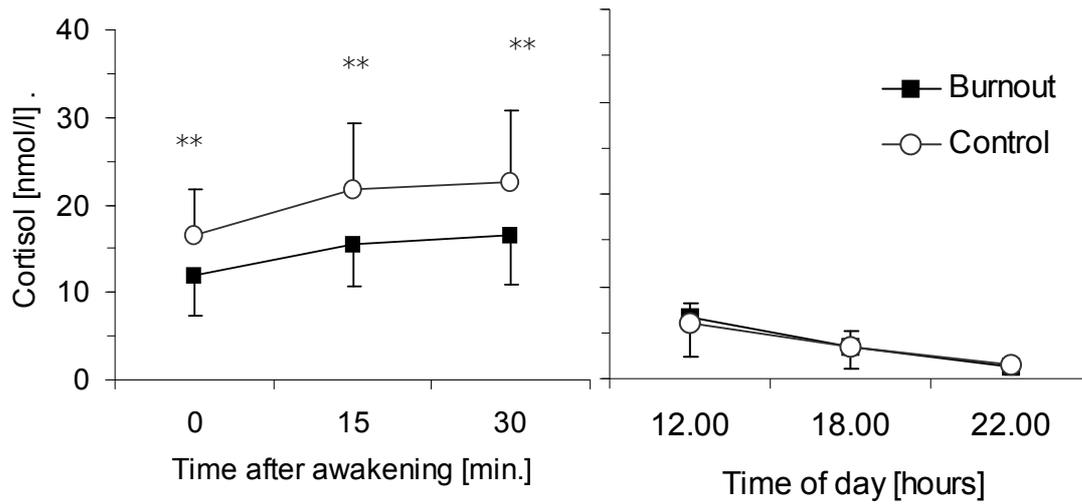


Figure 1. The Cortisol Awakening Response (CAR) and day-curve in the burnout and the control group. Mean values of 2 days and SD are shown. ** $p < .01$

Table 1. Questionnaire scores of the burnout and the control group

Questionnaire	Burnout		Control		$F_{(1, 43)}$ value
	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)	
Burnout (UBOS)					
Exhaustion	4.6	(1.0)	0.9	(0.6)	200.3***
Depersonalisation	3.5	(1.3)	0.7	(0.6)	72.0***
Competence	3.8	(1.1)	5.1	(0.6)	24.4***
Fatigue (CIS20R)	106.6	(21.4)	37.6	(17.8)	135.2***
Depression (BDI)	16.1	(6.0)	3.1	(3.4)	78.1***
Cognitive Functioning (CFQ)	68.3	(19.6)	45.9	(13.8)	19.2***
Sleep quality 4 weeks (GSKS)	6.8	(2.8)	1.6	(1.5)	57.5***
Psychoneuroticism (SCL90)	174.6	(38.8)	98.4	(6.8)	71.0***

$n = 22$ in the burnout group and $n = 21$ in the control group

*** $p < .001$

BEFORE AND AFTER THERAPY

Table 2 shows questionnaire scores of the burnout group ($n = 19$) before and after treatment. The burnout group showed significant improvement with respect to exhaustion (UBOS exhaustion), fatigue (CIS20), level of depressive symptoms (BDI), sleep quality (GSKS-4 weeks), cognitive functioning (CFQ), and psychoneuroticism (SCL90). No change occurred in depersonalisation, (UBOS depersonalisation), or perceived competence (UBOS competence).

Figure 2 displays the CAR (on the left) and the cortisol day level (on the right) of the 19 burnout participants before and after treatment. There is a significant rise in cortisol after awakening (main effect of CAR; $F(2, 36) = 31.5, p < .001, \eta_p^2 = .64$). After treatment the CAR level had increased significantly as compared to the CAR level before treatment (main effect of treatment; $F(1, 18) = 11.3, p = .003, \eta_p^2 = .39$). The rise in cortisol after awakening did not change from before to after treatment (treatment \times CAR; $F(2, 36) = 1.1, p = .35, \eta_p^2 = .06$). Cortisol during the day shows a significant decline (main effect of time; $F(1, 26) = 63.8, p < .001, \eta_p^2 = .78$). The cortisol level during the day had not changed from pre- to post- treatment (main effect of treatment; $F(1, 18) = .16, p = .70, \eta_p^2 < .01$), except for a higher level of cortisol at 22.00 hrs, as compared to the pre-therapy sample at 22.00 hrs, $t(18) = 2.4, p = .03$. The decline in cortisol during the day is not different before and after treatment (treatment \times time; $F(1, 27) = 1.2, p = .30, \eta_p^2 = .06$). Although both the symptoms and the cortisol level after awakening showed a change from pre- to post-treatment, there were no significant correlations between the change in CAR and the change in questionnaire scores. In addition, the reported complaint duration at the onset of the study was not related to the increase in cortisol after treatment. In other words there does not seem to be a dose-response relation between the change in symptoms and the change in cortisol parameters.

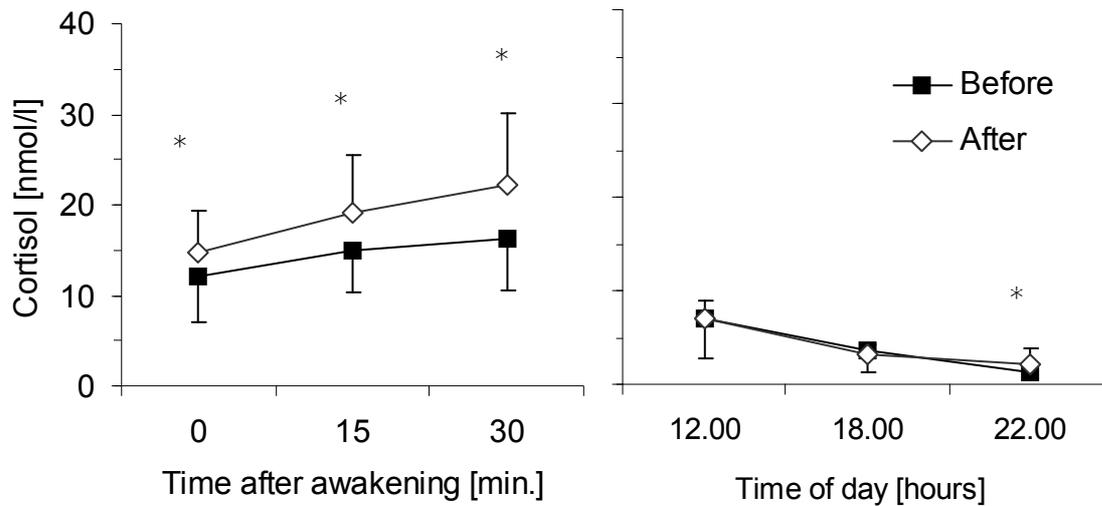


Figure 2. Cortisol levels in the burnout group before and after 14 treatment sessions. Mean cortisol levels of 2 days and *SD* are shown. * $p < .05$

Table 2. Questionnaire scores in the burnout group before and after treatment

Questionnaire	<i>n</i>	Before		After		<i>t</i> _(<i>n</i>-1) value
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Burnout (UBOS) ¹						
Exhaustion	11	3.9	(0.9)	2.8	(1.4)	2.8*
Depersonalisation	11	3.1	(0.3)	3.1	(0.5)	0.2
Competence	11	4.1	(0.9)	4.3	(0.9)	-1.0
Fatigue (CIS20R)	19	102.2	(19.5)	69.0	(26.4)	7.2***
Depression (BDI)	19	15.1	(5.9)	7.1	(4.7)	6.0***
Cognitive Functioning (CFQ)	19	65.2	(18.8)	54.5	(22.6)	3.1**
Sleep quality 4 weeks (GSKS)	18	6.7	(3.0)	3.6	(3.1)	4.5***
Psychoneuroticism (SCL90)	19	167.5	(35.9)	139.8	(39.9)	3.3**

Values are means with standard deviation (*SD*)

¹Because of long-term sick leave or loss of work, 8 persons were unable to fill out the UBOS questionnaire after treatment

* $p < .05$; ** $p < .01$, *** $p < .001$

DISCUSSION

We showed that clinically diagnosed burnout is associated with lower cortisol levels shortly after awakening. The slope, however, did not differ from the control group. The cortisol levels on the other sampling moments during the day were not different between the groups either. The lower awakening levels of cortisol in the burnout group had increased after 14 treatment sessions, while the level of subjective complaints decreased.

The lower awakening levels in the burnout group before treatment are in line with the findings of Pruessner et al. (1999), but opposite to those of Melamed et al. (1999); and also opposite to the recent study in clinical burnout persons by de Vente (2003). who observed *higher* salivary cortisol levels after awakening. Our study and the study of de Vente agree with respect to a normal cortisol secretion of persons with burnout during the rest of the day. Neither Grossi et al. (2003) nor Moch et al. (2003) observed any differences in plasma cortisol either (although the latter result was based on a single blood sample taken between 8 and 10 am).

One of the factors that may contribute to the inconsistency of these findings is that a major part of these studies have included persons who were selected on the basis of questionnaire ratings, and were still able to work and thus probably had a relative moderate level of complaints. Our group certainly had the more severe complaints of 'clinical burnout' and the majority was unable to work. This, however, was also the case in the burnout group of de Vente's study, and the in- and exclusion criteria were quite parallel. A credit to our design is the sampling on two days to obtain a more reliable estimate of the CAR and day-curve. It thus remains difficult to explain why we, with respect to the CAR, found the opposite.

Assuming the reliability of our finding: how to interpret the lower CAR level in the burnout group? Schmidt-Reinwald et al. (1999) have suggested that the cortisol increase after awakening represents the *capacity* of the adrenal cortex to produce cortisol. This suggests lower adrenal capacity in the post awakening period in our burnout persons, or a state of inability to acutely mobilize the system. In chronic fatigue syndrome (CFS) severe fatigue is correlated with hypo-activity of the HPA-axis and lower levels after awakening. This is also interpreted as a sign of adrenal exhaustion (Strickland, Morriss et al. 1998; Heim, Ehlert et al. 2000; Parker, Wessely et al. 2001; Roberts, Wessely et al. 2004). In burnout, both fatigue and depression-like aspects are present (Huibers, Beurskens et al. 2003). If anything, depression is often characterized by a relatively more hyperactive HPA-axis (Scott and Dinan 1998; Holsboer 2001; Pruessner, Hellhammer et al. 2003). Our finding of lower cortisol levels after awakening points to a hypo-activity of the HPA-axis rather than to a hyperactive system. This suggests that burnout might be associated with fatigue/exhaustion rather than with depressive mood. Within the burnout group, however, we observed no correlations of the cortisol parameters with the fatigue or depression scales. A larger group of participants could provide the opportunity to assess the relative influence of fatigue- and depression-like symptoms on cortisol in a burnout group.

One of the aims of this study was to investigate whether symptom improvement would coincide with a change in cortisol parameters. Though the burnout group improved in their subjective complaints and showed an increase in CAR levels after treatment, there was no quantitative relationship between these changes. Similar to these findings Theorell et al. did not find a relation either between the psychological changes and changes in plasma cortisol in a one year follow-up study in a group of healthy managers (Theorell, Emdad et al. 2001). Moch et al. (2003) found a decrease in complaints in a burnout group, but no significant changes were observed in cortisol levels after 4 months of intervention. Altogether these data suggest a relative independence of the course of stress hormones and of subjective complaints.

A limitation of our design is the absence of a repeated measure after 6 months in the control group. Therefore one could label the observed cortisol increase after treatment as a chance observation in absence of a reference group re-measured after the same time interval. Our measures, however, were based on the average of two sampling days, which adds to their reliability. Moreover, the change observed in the burnout group showed an even moderate effect size, implying a low probability of being due to chance. Moreover the CAR has shown to have a moderate to high test-retest stability over time (Pruessner, Wolf et al. 1997; Wust, Wolf et al. 2000). Nevertheless, to definitely exclude the influence of chance, the re-measurement of a control group is desirable in replications of these findings. In conclusion, this pilot study shows a reduction in morning cortisol levels of persons suffering from burnout complaints, possibly pointing to a state of exhaustion. These morning cortisol levels were increased after 14 treatment sessions. This increase, however, bore no quantitative relation to the improvement in symptoms of burnout.

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Chapter 3

Clinical burnout is not reflected in the cortisol awakening response, the day-curve or the response to a low-dose dexamethasone suppression test.

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SUMMARY

Burnout is presumed to be the result of chronic stress, and chronic stress is known to affect the HPA-axis. To date, studies on HPA-axis functioning in burnout have showed inconsistent results. In the present study a large sample ($n = 74$) of clinically diagnosed burnout individuals, mostly on sick-leave, were included and compared with 35 healthy controls. Salivary cortisol was sampled on two days to determine the cortisol awakening response (CAR) and the day-curve. In addition the dexamethasone suppression test (DST) was applied to assess the feedback efficacy of the HPA-axis.

There were no differences observed in the CAR, day-curve or CAR after DST in the burnout group as compared to a healthy control group. Burnout shows overlap in symptoms with chronic fatigue syndrome (CFS) and depression. Therefore, differential changes in HPA-axis functioning that resemble the hypo-functioning of the HPA-axis in CFS, or rather the hyper-functioning of the HPA-axis in depression, might have obscured the findings. However, no effect of fatigue or depressive mood on HPA-axis functioning was found in the burnout group. We concluded that HPA-axis functioning in clinically diagnosed burnout participants as tested in the present study, seems to be normal.

Keywords (6): Burnout; Salivary Cortisol; Cortisol Awakening Response; Dexamethasone Suppression Test; Fatigue; Depression

INTRODUCTION

The burnout syndrome is characterized by excessive exhaustion, a cynical work attitude and feelings of reduced competence (Maslach, Schaufeli et al. 2001). In addition, increased irritability, muscular aches and pain, dizziness, tension headaches, inability to relax, dyspepsia, disrupted sleep, and concentration and memory problems have been reported. Burnout is supposed to be the outcome of persistent chronic work stress and insufficient recovery. Physiologically the hypothalamus pituitary adrenal axis (HPA-axis) is the central mechanism regulating the long term adaptation of an organism to stress. The HPA-axis hormone cortisol supports the stress response and at the same time has a stress inhibitory function. Changes in HPA-axis functioning have been observed in many stress-related disorders (Raison and Miller 2003). It is therefore not unlikely to assume disturbances in HPA-axis functioning in burnout as well.

HPA-axis functioning can be assessed in several ways: basal level of circulating cortisol, circadian variation, or the more recently explored parameter: the cortisol awakening response (CAR), which is the immediate increase of cortisol in the 30 minutes after awakening. The CAR is supposed to represent the capacity of the adrenal cortex to produce cortisol (Schmidt-Reinwald, Pruessner et al. 1999). Changes in the CAR have been associated with measures of chronic work stress (Schulz, Kirschbaum et al. 1998; Lundberg and Hellström 2002; Kunz-Ebrecht, Kirschbaum et al. 2004). The feedback sensitivity of the HPA-axis can be determined by using the Dexamethasone Suppression Test (DST). Cortisol mediates its actions centrally by binding to the glucocorticoid receptor, preventing the release of ACTH, and, in turn, suppressing the release of cortisol in the adrenal gland. Changes in receptor number or binding affinity alter the effectivity of cortisol feedback. Dexamethasone, a synthetic glucocorticoid, mimics the negative feedback effect of cortisol; it binds with high affinity to the glucocorticoid receptor in the pituitary gland, inhibiting the peripheral release of cortisol (De Kloet, Meijer et al. 1998). A low dose of dexamethasone, 0.5 mg, does not completely suppress the cortisol response, which allows variance to remain. At this dosage both a stronger suppression (hypersuppression), and less suppression, indicative of non-suppression, of cortisol should be observable. The extent to which cortisol release is inhibited after dexamethasone intake indicates central feedback sensitivity (Cole, Kim et al. 2000).

Several studies have focused on a possible HPA-axis disturbance in burnout. However, the results are inconclusive; Melamed et al. (1999) found elevated (salivary) cortisol levels during the working day. In contrast Pruessner et al. (1999) found *lower* levels after awakening. These studies included relatively healthy participants from a working population divided into subgroups according to their score on a burnout questionnaire. Only a few studies included participants with more severe symptoms and with a clinical diagnosis of burnout. A pilot study performed by our group (Mommersteeg et al., in press) included individuals who had received a clinical diagnosis for burnout, and who were either

on partial or full sick-leave. This group of 22 burnout participants showed *lower* salivary cortisol levels after awakening than a healthy control group, but the groups did not differ in cortisol during the remainder of the day. Remarkably, in a similar study De Vente et al. (2003) showed, in a group of 22 clinically diagnosed burnout persons, *higher* cortisol levels after awakening, and also no differences during the remainder of the day. These two studies were comparable with respect to diagnostic criteria, symptom severity of the participants, sampling methods and percentage on sick leave. In addition Grossi et al. (2004) observed elevated cortisol levels after awakening in a group of 22 burnout patients, compared with participants with low scores on a burnout questionnaire. A limitation to these studies, however, was the small number of participants. The discrepancy in findings thus may be due to chance. Therefore, it was decided to undertake a study with a much larger number of participants and extending the standard cortisol measurement repertoire of the CAR and day variables, with the DST.

It is hard to predict what deviations may be expected in burnout persons on theoretical grounds. The symptoms which characterize clinical burnout to some extent show a resemblance to those of depression, chronic fatigue syndrome (CFS), and post-traumatic stress disorder (PTSD) (Brenninkmeyer, Yperen et al. 2001; Huibers, Beurskens et al. 2003), i.e. persistent fatigue, anhedonia, melancholy, sleep disorder, concentration problems, worrying, restlessness and irritability (Schaufeli and Enzmann 1998). These disorders, however, show contrasting HPA-axis disturbances (Ehlert, Gaab et al. 2001). In major depression higher circulating levels of cortisol have been found, together with an impaired negative feedback inhibition of the HPA-axis, i.e.: non-suppression in response to the DST, at least in part of the patients (Holsboer 2001; Pariante and Miller 2001; Pruessner, Hellhammer et al. 2003). Chronic fatigue syndrome and PTSD are often, though not consistently, associated with reduced cortisol levels and stronger suppression in response to the DST (Demitrack 1997; Strickland, Morriss et al. 1998; Heim, Ehlert et al. 2000; Parker, Wessely et al. 2001; Gaab, Huster et al. 2002; Roberts, Wessely et al. 2004; Yehuda, Halligan et al. 2004). The HPA-axis deviations associated with severe fatigue (a *hypo* function) may be opposite to the HPA-axis deviations associated with depressive symptoms (a *hyper* function) in a burnout group. The use of a larger sample will allow analysis of the relative contribution of these symptoms associated with the variance in cortisol variables and provide more unequivocal conclusions about the nature of the HPA-axis deviations in individuals diagnosed as burnout.

METHODS

PARTICIPANTS

The burnout group consisted of 74 participants, mean age 43.9 years ($SD = 8.7$, 24-61 years), 53 men and 21 women. The control group included 35 participants, mean age 44.9 years ($SD = 10.5$, 27-61 years), 25 men and 10 women. Clients of a private health care institute were asked to participate after having received a diagnosis. The diagnosis was based on a clinical interview checking ICD-10 adapted criteria for work-related neurasthenia (WHO 1994), and semi-structured interviews using Dutch versions of the Anxiety Disorder Interview Schedule for DSM-IV (original version: DiNardo and Barlow 1988; DSM-IV: APA 1994), and sections of the Structured Clinical Interview for DSM-IV (SCID) on undifferentiated somatoform disorder and the adaptation disorder (First, Spitzer et al. 1997; Groenestijn, Akkerhuis et al. 1999). Of the burnout participants included, according to the ICD-10 adapted criteria for work-related neurasthenia, 95% ($n = 70$) were (in terms of DSM-IV) primarily diagnosed with 'somatoform undifferentiated disorder', 1 subject was diagnosed with adaptation disorder, 1 subject met the criteria for general anxiety disorder, and 2 subjects did not receive a primary diagnosis. In addition, 15 participants (20%) received a secondary diagnosis of comorbidity for either depressive ($n = 8$), anxiety ($n = 5$) or pain disorder ($n = 2$). These comorbid participants did not differ from the rest of the burnout group on demographic variables, or symptoms severity. Age- and gender- matched control subjects were included via the burnout participants, of whom 10 spouses, filled-up with co-workers of the researchers. All participants gave written informed consent. The study was approved of by the local ethics committee.

PROCEDURE

Participants received instructions, filled out questionnaires and collected saliva at home. Saliva was collected via a plastic tube with a cotton role (Sarstedt, Etten-Leur, the Netherlands). Saliva was collected on two consecutive weekdays upon awakening (0 min), 15 and 30 minutes after awakening, and at 1200h (before lunch), 1800h (before dinner) and at 2230h. Participants were instructed to take an oral dose of dexamethasone (0.5 mg, PO) on the second evening at 2230h, after taking the saliva sample. On the consecutive morning three saliva samples were collected at 0, 15 and 30 minutes after awakening, to determine the dexamethasone-suppressed cortisol levels. Two participants in the burnout group and one in the control group refrained from dexamethasone intake. There is no information on dexamethasone bioavailability in the participants. Participants were instructed not to brush their teeth, eat or drink coffee or alcohol 30 minutes before taking a sample. A paper diary was filled out during saliva collection, in which participants reported time, perceived and expected stress, and food and drink intake.

Furthermore sleep-quality, perceived daily stress (reported as less than usual, normal or more than usual), and physical complaints were reported on a daily basis.

Collected samples were kept at 4 °C during the collection period. Upon non-cooled postal return the saliva samples were stored at – 20 °C. Cortisol was analyzed using an immunoassay (DELFA), as described elsewhere (Dressendorfer, Kirschbaum et al. 1992). For the used technique the precision of the intra- and interassay variability is 2.9 – 7.7% and 6.2- 11.5% respectively.

MEASURES

The participants filled out questionnaires on demographic data, duration of complaints and work status. Factors with a potential influence on cortisol, such as smoking, the use of oral contraceptives and medication were registered (Canals, Teresa Colomina et al. 1997; Pruessner, Wolf et al. 1997; Kirschbaum, Kudielka et al. 1999). The burnout symptoms exhaustion, cynicism and feelings of reduced competence were measured with the Dutch version of the Maslach burnout inventory (UBOS), 15 item version (Schaufeli and Van Dierendonck 2000). Fatigue was assessed with the 20 item version of the Dutch fatigue scale ‘Checklist Individual Strength’(CIS-20R, Vercoulen, Alberts et al. 1999). Sleep-quality of the past night was assessed with the Dutch State and Trait sleep assessment scale, 14 items version (GSKS, Meijman, Thunnissen et al. 1990). Level of depressive symptoms were assessed with the Dutch version of the CES-D, 20 items (Bouma, Ranchor et al. 1995). Finally, the Dutch version of the Symptom Checklist (SCL-90) was used to assess (psycho)somatic complaints (Arrindel and Ettema 1981). All questionnaires are well validated Dutch versions that have shown reasonable to good reliability.

STATISTICAL ANALYSIS

Per sample point, cortisol data that deviated over three standard deviations of the mean were excluded from further analysis. Missing data and outliers made up 4,5% of the dataset. Paired samples *t*-tests of the cortisol data per sample point did not show any significant differences between day 1 and day 2. Therefore, cortisol samples were pooled over the two sampling days and the mean data of the two days were used for further analysis. The demographic variables and questionnaire scores of the burnout and the control group were compared using Pearson’s Chi-square test and one-way ANOVA. Repeated measures analysis was used for the analysis of the cortisol data, with the “within factors” time; CAR (0, 15 and 30 minutes after awakening), or day-curve (1200h, 1800h and 2230h) and group (burnout or control) as “between factor”. Greenhouse-Geisser correction was applied whenever sphericity was violated.

The CAR was recalculated into two ‘area under the curve’ (AUC) measures: the cortisol amount (the AUC ground), and the AUC increase (slope), according to Pruessner et al. (2003). These AUC measurements were also recalculated corrected for the reported

sampling time. The AUC measures were used to test the associations with the questionnaire scores.

To check for the possibly contrasting effects of fatigue and depressive symptoms on cortisol in the burnout group, the burnout group was split into 4 subgroups based on the quartiles of the fatigue scores [CIS20R], and separately into quartiles of the depression scores [CES-D]. These resulting subgroups were the “between” factor in repeated measured analysis of variance with the CAR or day-curve as repeated “within” factors.

RESULTS

Table 1. Demographic variables of the burnout and the control group

		Burnout	Control	Test variable
		<i>n</i> = 74	<i>n</i> = 35	
Gender	Male : Female (<i>n</i>)	53:21	25:10	$\chi^2 = 0.00$
Age	Years	43.9 (8.7)	44.9 (10.5)	$F = .266$
BMI	kg/m ²	25.1 (3.5)	24.2 (3.3)	$F = 1.43$
Education	Secondary	35%	23%	$\chi^2 = 1.6$
	College education	62%	74%	
Job	Full-time	76%	43%	$\chi^2 = 6.13^*$
	Part-time	23%	40%	
Medication	None	68%	80%	$\chi^2 = 4.22$
	Other	17%	8%	
	Potential influencing of which:	15%	12 %	
	Antidepressants	4%	3%	
	Glucocorticoids	4%	9%	
	Beta-blockers	7%	--	
Sick leave	Full	62%	3 %	$\chi^2 = 81.1^{***}$
	Partial	30%	--	
	Not	8%	97%	
Complaint duration	Months	16.3 (12.1)	--	--
	< 3	5,6 %		
	3-6	19,4 %		
	6-12	27,8 %		
	12-24	31,9 %		
	24-36	11,1 %		
	>36	4,2 %		

Means (and standarddeviations) or percentages

* $p < .05$, *** $p < .001$

DEMOGRAPHICS

Table 1 shows the demographic characteristics of the burnout and the control group. The groups did not differ in age, sex composition, BMI, smoking or education level. Medication use, and medication potentially of influence on cortisol were not different between the burnout and the control group. Participants in the burnout group had more fulltime jobs and were either on full or partial sick-leave. The self-reported mean duration of complaints in the burnout group was 16 months (SD = 12 months). Fifty percent of the burnout participants reported a former history of work-related health problems.

LEVEL OF COMPLAINTS

The burnout group, as expected, reported significantly higher levels of exhaustion and depersonalization and lower competence on the burnout questionnaire compared with the control group (table 2). The burnout group felt significantly more fatigued (CIS20R), and depressed (CES-D), and reported a worse sleep quality (GSKS). The burnout group also scored higher on all subscales of the symptom checklist (SCL-90).

Table 2. Test variables in the burnout and control group

		Burnout <i>n</i> = 74	Control <i>n</i> = 35	Test value <i>F</i>
Burnout UBOS	Exhaustion	4.8 (0.9)	1.3 (0.9)	349.7***
	Cynicism	3.4 (1.4)	1.3 (1.1)	65.81***
	Competence	3.8 (1.0)	4.6 (0.8)	13.97***
Fatigue	CIS20R	105.6 (18)	39.5 (12)	363.0***
Depression	CES-D	23.1 (8.3)	4.0 (3.7)	161.9***
Sleep quality	GSKS last night	5.5 (3.3)	2.8 (3.0)	36.61***
Subscales SCL90	Fear	18.8 (5.7)	11.2 (2.2)	58.86***
	Agorafobia	9.0 (2.9)	7.3 (0.9)	11.16 **
	Depression	35.5 (9.0)	18.4 (2.8)	119.6***
	Somatisation	24.4 (7.8)	13.5 (1.1)	66.28***
	Insufficiency	24.2 (6.6)	11.4 (2.2)	123.3***
	Sensitivity and distrust	32.3 (9.4)	21.1 (4.0)	45.12***
	Hostility	10.1 (2.8)	6.6 (0.9)	51.34***
	Sleep problems	8.1 (3.6)	4 (1.5)	42.15***
Total score SCL90	Psychoneuroticism	176.2 (39)	103.3 (11)	119.3***

Means (and standarddeviations)

p* < .01, *p* < .001

CORTISOL AWAKENING RESPONSE AND DAY-LEVEL

In figure 1 the cortisol levels of the burnout and the control group are shown, immediately after awakening (left) and during the day (right). Both the burnout and the control group show a significant rise in cortisol in the 30 minutes after awakening (main effect of time, $F = 36.4$, $df = 1.5, 159$, $p < .001$, partial eta squared $\eta^2 = .26$), and a significant decline of cortisol during the day (main effect of time, $F = 169.6$, $df = 1.4, 149$, $p < .001$, $\eta^2 = .62$). There was, however, no difference between the burnout and the control group in cortisol level (group, $F = .07$, $df = 1, 105$, $p = .79$, $\eta^2 < .01$) or rise after awakening (group x time, $F = .12$, $df = 1.5, 159$, $p = .89$, $\eta^2 < .01$), or in level (group, $F = .12$, $df = 1, 104$, $p = .73$, $\eta^2 < .01$) or decline during the day (group x time, $F = .09$, $df = 1.4, 149$, $p = .86$, $\eta^2 < .01$). Excluding participants with possible influencing medication and comorbidity of diagnosis did not alter the results. The burnout ($M = 0724$ h, $SD = 53$ min) and the control group ($M = 0720$ h, $SD = 45$ min) did not differ in mean time of awakening, $t(107) = .37$, $p = .72$.

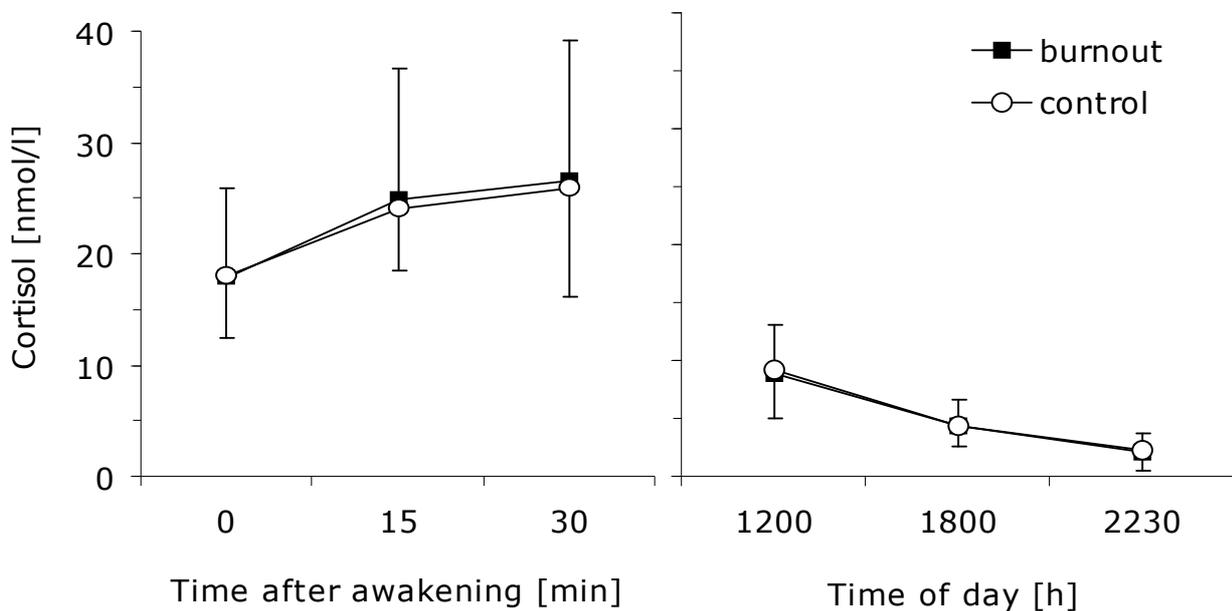


Figure 1. Cortisol awakening response (CAR) and day-curve in the burnout and control group. There is no difference in the CAR or day-curve between the burnout and the control group. Mean values of 2 days and SD are shown.

CORTISOL AWAKENING RESPONSE AFTER DEXAMETHASONE SUPPRESSION

Figure 2 shows the CAR after intake of 0.5 mg dexamethasone. The CAR was significantly reduced after dexamethasone intake, but still showed a significant rise in the 30 minute post-awakening period, (main effect time; $F = 5.9$, $df = 1.5, 137$, $p = .003$, $\eta^2 = .06$). There was no difference between the burnout ($n = 64$) and the control group ($n = 31$) in the rise (group x time; $F = .06$, $df = 1.5, 137$, $p = .89$, $\eta^2 < .01$), nor in the mean level after awakening (group; $F = .002$, $df = 1, 93$, $p = .97$, $\eta^2 < .01$). Excluding participants with possible influencing medication and comorbidity of diagnosis did not alter the results.

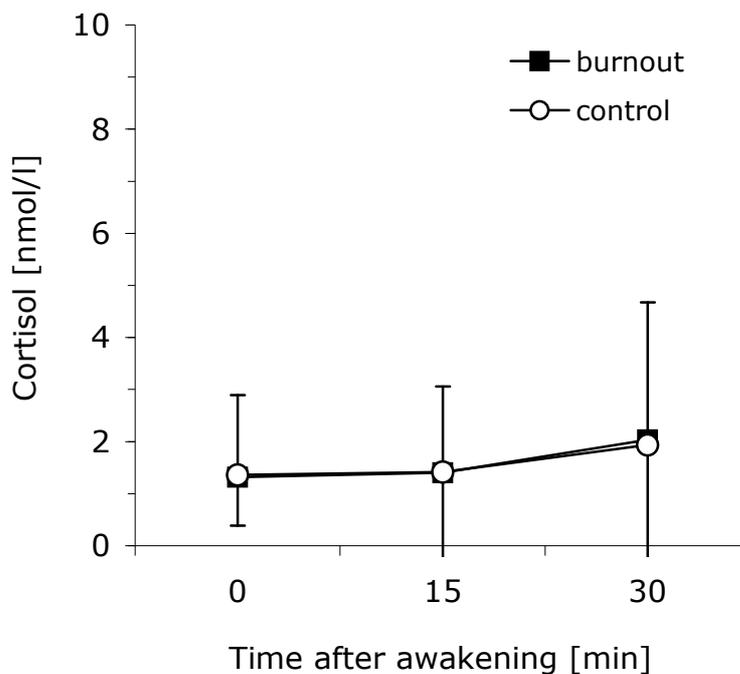


Figure 2. Cortisol awakening response (CAR) after dexamethasone intake in the burnout and control group. There is no difference in the CAR between the burnout and the control group. Mean values and *SD* are shown.

PSYCHOLOGICAL VARIABLES AND CORTISOL

No significant correlations were observed between the cortisol AUC measurements (level and slope), with or without dexamethasone intake and the level of complaints in neither the burnout nor the control group (data not shown).

EFFECTS OF FATIGUE AND DEPRESSIVE SYMPTOMS ON CORTISOL

To examine further the effects of fatigue and depressive symptoms on cortisol, the burnout group was subdivided into four quartiles of fatigue scores and separately into four quartiles of depression scores (subgroups $n=18$). These subgroups were not different in gender composition, age, BMI, complaint duration, previous history of work-related complaints, UBOS scores and mean sleep quality. The fatigue or depressive quartiles were introduced as a between factor in the repeated measures analysis. There were no main or interaction effects for the fatigue or depressive subgroups in the analyses of the CAR, day-curve and CAR after dexamethasone-intake (data not shown).

ADDITIONAL ANALYSIS

In addition to the previous analyses we rechecked all of them for the potential confounding effects of gender, age, BMI, oral contraceptive use, smoking, sick-leave, work-status, seasonal effect, activity and perceived stress during the day, coffee/alcohol/food intake per measurement, time of awakening and sampling time, flat CAR (exclusion of AUC increase < 0 , controls 18%, burnout 19%), hours of sleep and sleep quality. In the burnout group we additionally checked for the possible influence of complaint duration, partial vs. full sick-leave, and history of work-related health problems. None of the main findings as mentioned were significantly influenced by any of these variables, though some incidental significant effects emerged, which were hard to interpret and may well be chance findings.

DISCUSSION

This study shows that there are no clear disturbances in HPA-axis functioning in individuals clinically diagnosed with burnout, as evidenced by a normal cortisol awakening response, diurnal course and normal DST.

The burnout group reported quite severe burnout-related complaints such as fatigue, depressive symptoms, sleep problems and psychosomatic complaints. Within the burnout group there was no association between the cortisol parameters and any of the indicators of severity of complaints. In addition, the analysis of possible contrasting effects of fatigue or depressive complaints on the cortisol parameters was not significant either.

The CAR results are in contrast with the findings of our earlier pilot study, in which the burnout group showed a lower CAR level after awakening, and also with the studies of De Vente and Grossi, in which a higher awakening cortisol level in burnout subjects were observed. These previous studies have a similar design as the present one, and these studies included clinically diagnosed individuals. A direct comparison of the data of our pilot and the present study revealed differences in sex composition and mean time of awakening; the pilot study included more women (68% vs. 28% respectively), and the participants in the pilot group took their first saliva sample on average about 15 minutes later. These factors, however, could not explain the difference in the CAR between these studies: in each study gender composition and time of awakening were matched for by a control group. As an extra check we introduced gender and time of awakening as covariates in a between-studies repeated measures analysis of the CAR in both burnout groups. The difference in CAR between studies remained.

The day curve of cortisol was not different between the burnout and the control group, which is in line with most earlier studies (De Vente, Olff et al. 2003; Moch, Panz et al. 2003; Mommersteeg, Keijsers et al., in press).

Studies which used ratings on a burnout questionnaire in a relatively healthy working population have shown contradictory findings, both with respect to awakening levels, and levels during the remainder of the day. Groups with a high-score on a burnout questionnaire showed either lower, higher or unchanged salivary cortisol levels after awakening (Melamed, Ugarten et al. 1999; Pruessner, Hellhammer et al. 1999; Grossi, Perski et al. 2003), and higher levels during the day (Melamed, Ugarten et al. 1999).

The overall picture so far is that there is no consistency in the type of dysregulation of the HPA-axis in burnout, irrespective the way it is measured. A credit to the present study is its large sample size which adds to the reliability of the findings. In addition the burnout participants received a clinical diagnosis. There may be a bias in our recruitment procedure towards selection of severe cases, but this allows a robust test of the hypotheses.

This is the first study to date to apply the DST in a clinically diagnosed burnout group. No evidence for a disturbed feedback function was found. In the study of Pruessner et al. 0.5 mg DST resulted in lower cortisol levels in a group participants who scored high on a

burnout questionnaire. The suggested hyper suppression must be reconsidered by the fact that the burnout group already showed lowered cortisol levels before dexamethasone intake, which equals the lowered level after dexamethasone intake (Pruessner, Hellhammer et al. 1999). Since there is a close relationship between basal cortisol levels and the feedback sensitivity of the HPA axis to a low dose of dexamethasone (Huizenga, Koper et al. 1998), it is plausible that the lower cortisol levels after dexamethasone intake in the study of Pruessner et al. reflect a lowered general cortisol level rather than a hyper-suppression.

We suggested that the HPA-axis deviations as a result of severe fatigue (*a hypo* function of the HPA-axis and hyper suppression in the DST) may be opposite to the effect of depressive symptoms (*a hyper* function and non-suppression in the DST) and thus may obscure a difference with a healthy control group (Holsboer 2000; Rief and Auer 2000; Gaab, Huster et al. 2002). The analyses, however, did not reveal an association of fatigue or depressive symptoms with cortisol parameters in the burnout group. It might be that the reported complaints of fatigue and depressive symptoms were not severe enough to affect the HPA-axis? The burnout group on average reported lower fatigue scores (CIS20R) than a group with established Chronic Fatigue Syndrome ($n = 298$, $M = 113.1$, $SD = 14.6$) (Vercoulen, Alberts et al. 1999), and also lower depressive (CES-D) scores than a group of patients with major depressive disorder (MDD) ($n = 21$, $M = 30.9$, $SD = 2.7$) (Natelson, Denny et al. 1999). When dividing, however, the burnout group into quartiles, the highest quartiles had fatigue and depression scores comparable to CFS and MDD groups. The effects of severe fatigue or depression on cortisol are not as clear-cut as sometimes suggested. Cleare (2003) concluded in his review that there is no obvious HPA-axis disturbance in CFS, though a low cortisol may act as a maintaining factor. Studies on major depression disorder seem to be more consistent; 40-60 % of drug-free depressed patients show hypercortisolism (Parker, Schatzberg et al. 2003), which implies however that a similar 40-60 % of drug-free depressed patients do *not* show hypercortisolism (Brown, Varghese et al. 2004). Moreover, hypercortisolism is not a core characteristic of MDD in outpatients and community samples (Peeters, Nicolson et al. 2004). The relation between stress-related mental disorders and HPA-axis disturbance indeed is not as obvious as often assumed.

In our study a whole range of variables might potentially have affected cortisol. Most of them (gender, age, BMI, medication use, seasonal effect, sampling time, activity level and observed stress during the day, coffee/ alcohol/ food intake, time of awakening, hours of sleep and sleep quality) were introduced as covariates in the analyses, or excluded. In an additional analysis persons with a flat CAR (AUC increase < 0), a possible indication of non-compliance (Kudielka, Broderick et al. 2003; Broderick, Arnold et al. 2004), have been excluded, as were subjects taking medication that may influence cortisol and those with comorbidity (having an additional diagnosis besides undifferentiated somatoform disorder). These exclusions did not affect the main results. Complaint duration, part-time

vs. full-time sick leave, and history of work-related health problems in the burnout group did not affect the main results either. Thus there is no obvious reason to assume a major influence of any of these variables on the results. The absence of any correlations between symptom severity, as indicated by the burnout questionnaire (UBOS), (subscales of) the symptom checklist SCL-90, and the cortisol parameters adds to the solidity of the conclusion that there is no change in HPA-axis functioning in burnout.

Perceived control, social evaluation and shame (Levine 2000; Dickerson, Gruenewald et al. 2004; Dickerson and Kemeny 2004) are modulators of the HPA-axis. These factors may have contributed to the development of burnout but have waned in the period after the diagnosis. So a HPA-axis influence for *developing* burnout can not be excluded. Only a longitudinal study can provide clarity on the role of the HPA-axis in the development of burnout symptoms.

Our negative results do not refute a role of the HPA-axis in the long-term effects of stress, but if there is, the picture is much more complex than initially thought. As stated, in other research areas like CFS and MDD the picture is confusing as well (Heim, Ehlert et al. 2000; Peeters, Nicolson et al. 2004). Maybe the approach of just taking saliva samples or a low-dose DST is not sensitive enough to reveal subtle dysregulations in the HPA-axis. The HPA-axis is a complex regulatory system with all types of compensations that can take place on several levels in the axis. Discovering more subtle disturbances would require more sensitive measurement techniques like the combined DEX/CRH-test or the effects of CRH and ACTH infusion (Holsboer 2000). Whatever this may reveal, our results suggest that the more feasible techniques as we used in the present study do not hold promise as diagnostic tools, and are not useful to uncover the origins of the symptoms of the burnout syndrome.

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Chapter 4

A longitudinal study on cortisol and complaint reduction in burnout

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SUMMARY

Several studies have investigated the association between burnout and HPA-axis functioning, but the results are far from consistent. This does not preclude the possibility that within a group of burnout patients a recovery of symptoms in a longitudinal course corresponds to (changes in) cortisol parameters. The latter possibility is tested in the present study before and after treatment, and at follow-up.

HPA-axis functioning and burnout complaints were assessed in burned-out participants at baseline ($n = 74$), post-treatment ($n = 62$) and at follow-up ($n = 53$). Multilevel regression analysis was used to test the hypothesis. Burnout complaints were significantly reduced at 8.5 months post-treatment, but there was no further reduction in complaints at follow-up 6.3 months later. Cortisol after awakening, and after dexamethasone intake showed no changes from baseline to post-treatment and follow-up. There was a small decline in cortisol during the day over the longitudinal course. The cortisol level after awakening in the longitudinal course showed significant positive association with the initial exhaustion level, a negative association with the change in the burnout exhaustion score, and a positive association with the change in depression. Although these associations are statistically significant, they only explain a small fraction of the variance in cortisol after awakening between and within persons. This implies that changes at symptom level are hardly related to changes in cortisol functioning, therefore the clinical implications of this finding are limited.

Keywords: burnout; longitudinal; cortisol; dexamethasone suppression test; multilevel; treatment

INTRODUCTION

Burnout is the result of chronic work stress and insufficient recovery. The central complaint in burnout is extreme exhaustion, other dimensions are cynicism or depersonalization, and feelings of reduced competence (Maslach, Schaufeli et al. 2001). Its symptoms are depressed mood, increased irritability, inability to relax, disrupted sleep, somatic complaints as aching muscles, headaches, gastro-intestinal problems, and concentration and memory problems.

Psychological treatment to reduce burnout complaints is effective to a certain extent, but individuals differ widely in the rate of recovery. Van Rhenen et al. reported a reduction of burnout complaints over a six-months period towards the normal range in 30-50 % of a working population after physical and cognitive intervention (van Rhenen, Blonk et al. 2005). Huibers et al. showed that in a group of fatigued employees on sick leave, at 12 months 43% had returned to the normal range of fatigue, and 62% had resumed work (Huibers, Bleijenbergh et al. 2004). Could it be that individual differences in stress physiological functioning would account for these observed differences in recovery? Several studies have tried to find stress physiological correlates of burnout. The focus has mainly been on possible deviations in HPA axis functioning, this in line with parallel efforts in the areas of depression, chronic fatigue syndrome (CFS) and post-traumatic stress disorder (PTSD) (Ehlert, Gaab et al. 2001; Parker, Wessely et al. 2001; Parker, Schatzberg et al. 2003). The HPA-axis is interconnected with other regulatory systems which are involved in regulating the energy balance, mood states, sleep, and cognition. A disturbed HPA-axis could therefore have an impact on these systems (Raison and Miller 2003), causing the array of symptoms as observed in burned out individuals. Studies which have included working subjects with high scores on a burnout questionnaire showed contradictory results (Melamed, Ugarten et al. 1999; Pruessner, Hellhammer et al. 1999; Grossi, Perski et al. 2003). Studies in a more severe burnout population, who have received a clinical diagnosis and who are on sick-leave, show inconsistent results as well. Both lower, higher and unchanged levels after awakening, and higher and unchanged levels during the day were reported (De Vente, Olf et al. 2003; Moch, Panz et al. 2003; Grossi, Perski et al. 2005; Mommersteeg, Keijsers et al. 2006).

Recently our group has shown that in a clinical burnout group on sick-leave, the cortisol awakening response (CAR), diurnal course and the CAR after a low-dose dexamethasone suppression test were not different from a healthy control group, even accounting for the potentially counteracting influences of depressive symptoms and fatigue (Mommersteeg, Heijnen et al. 2006). In the present study the same group of burnout participants were measured again after having received treatment and once more at follow-up, about six months later. Cortisol after awakening, during the day and after dexamethasone intake was compared between the three succeeding time-points. Based on the previous study it becomes unlikely that the burnout group shows cortisol changes longitudinally.

Follow-up data on the recovery phase of burnout in relation to cortisol are scarce. In a previously performed pilot study, which included a post-treatment measurement, a group of 22 burnout participants showed a lowered CAR as compared with a healthy control group before treatment, and the disappearance of this difference after treatment. No quantitative relationship however, existed between the reduction in complaints and the changes in cortisol (Mommersteeg, Keijsers et al. 2006). Moch et al. (2003) did not find any differences in serum cortisol levels at baseline, but, after an intervention of 4 months, a lower cortisol level was observed in 16 persons with burnout as compared to a control group. In the present study, the larger sample size enables us to focus more reliably on the relation between burnout complaints and cortisol longitudinally.

It is known that cortisol functioning shows large inter-individual variability whereas intra-individual characteristics are more stable (Pruessner, Wolf et al. 1997; Huizenga, Koper et al. 1998; Wust, Wolf et al. 2000). Perhaps the inter-individual variability obscures any changes in cortisol functioning within persons, that could be observed when measured in a longitudinal setting. Besides that repeated measurements in the same group increases power, and may hence be able to reveal interactions between cortisol and the reported complaints. The assumption of the present study therefore is that, though the burnout group does not show differences in HPA-axis functioning before treatment, it is possible for individual differences in cortisol functioning in the burnout group to be related to the rate of recovery of symptoms. We hypothesize that individual differences in cortisol functioning in the burnout subjects are related to the initially reported complaints, and with the changes in level of complaints.

In order to test the hypotheses we used Multilevel Regression Analysis (MLRA) (also known as hierarchical linear models, mixed-effects models, or random coefficient models) (Schwartz and Stone 1998; Goldstein, Browne et al. 2002; Hox 2002). With MLRA multiple regression analysis can be done for repeated measurements, and the explained variance is assigned to different *levels* between and within persons.

In short, the outline of this study is to examine whether cortisol parameters in a group of burnout persons are related to the extent of complaint reduction in a longitudinal setting.

METHODS

PARTICIPANTS

The burnout group consisted of 74 participants, mean age 43.9 years ($SD = 8.7$, 24-61 years), 53 men (mean age = 46 years, $SD = 8$) and 21 women (mean age = 39 years, $SD = 9$). Clients of a Dutch psychotherapy outpatient clinic were asked to participate after having received a diagnosis. The diagnosis was based on a clinical interview as described in the cross-sectional part of this study (Mommersteeg, Heijnen et al. 2006). There is no overlap in participants between this (cross-sectional and longitudinal) study and the aforementioned follow-up pilot-study of 22 burnout participants. All participants gave written informed consent. The study was approved of by the medical ethical committee of the University Medical Center Utrecht.

LONGITUDINAL MEASUREMENTS

Sampling occurred at three time-points: before treatment (baseline), 8.5 months later, after treatment (post-treatment) ($SD = 2.6$) and at follow-up 6.3 months after post-treatment ($SD = 1.0$). The participants received a manual-based cognitive-behavioral treatment aimed specifically at reducing burnout complaints and factors maintaining the complaints (Keijsers, Schaap et al. 1997). At post-treatment and at the follow-up the participants reported their progress compared with the last measurement and the number of treatment sessions they had received. The post-treatment measurement was taken after completion of treatment, with a minimum of 3 months between baseline and post-treatment, or after a maximum of 20 treatment sessions. Follow-up was scheduled 6 months after the post-treatment measurement. The data collection period stretched out from April 2002 till September 2004.

CORTISOL MEASUREMENT PROTOCOL

The participants received instructions, filled out questionnaires and collected saliva at home, which were returned by post after completion (Clements and Parker 1998). Participants were instructed not to brush their teeth, eat or drink coffee or alcohol 30 minutes before taking a saliva sample. Per time-point salivary cortisol was sampled on three consecutive weekdays. Several aspects of basic HPA-axis functioning were assessed; the acute increase of cortisol in the 30 minutes after awakening -the so called cortisol awakening response (CAR)-, the diurnal decline of cortisol during the day (day-curve), and the suppressed awakening response after a low-dose dexamethasone intake (dexamethasone suppression test, DST). The synthetic glucocorticoid dexamethasone

inhibits the production of cortisol, which is an indication of negative feedback functioning (Cole, Kim et al. 2000).

During the first two days saliva was collected upon awakening (0 min), 15 and 30 minutes after awakening, and at 1200h (before lunch), 1800h (before dinner) and at 2230h.

Participants were instructed to take an oral dose of dexamethasone (0.5 mg, PO) on the second evening at 2230h, after taking the saliva sample. On the morning of day 3 the dexamethasone-suppressed cortisol levels were determined at 0, 15 and 30 minutes after awakening. A low-dose DST does not completely block the cortisol release, thus variance remains. Two participants in the burnout group refrained from dexamethasone intake. Collected samples were kept at 4 °C during the collection period. Upon return the saliva samples were stored at – 20 °C. Cortisol was analyzed using a luminescence immunoassay (LIA), as described elsewhere (www.ibl-hamburg.com). The precision of the intra- and inter-assay variability for the used technique is less than 10%.

QUESTIONNAIRES

At each time-point the burnout symptoms exhaustion, cynicism and feelings of reduced competence were measured with the Dutch version of the Maslach burnout inventory general survey (MBI-GS), 15 item version scored from 0 (never) to 6 (always) (Schaufeli and Van Dierendonck 2000). Fatigue was assessed with the 20 item version of the Dutch fatigue scale ‘Checklist Individual Strength’, the item responses ranged from 1 (I agree) to 7 (I disagree) (CIS-20R, Vercoulen, Alberts et al. 1999). Sleep-quality of the past night was assessed with the Dutch State and Trait sleep assessment scale 14 items version, with item responses 0 (true) and 1 (false), a higher score indicating more sleep problems (GSKS, Meijman, Thunnissen et al. 1990). Level of depressive symptoms was assessed with the Dutch version of the CES-D, 20 items ranging from 0 (least) to 3 (most complaints) (Bouma, Ranchor et al. 1995). Finally, the Dutch version of the Symptom Checklist (SCL-90) was used to assess (psycho)somatic complaints (Arrindel and Ettema 1981). It consists of 90 items ranging from 1 (not at all) to 5 (a lot), a higher score indicating more complaints. All questionnaires are well validated Dutch versions that have shown reasonable to good reliability.

POTENTIAL CONFOUNDERS

The participants reported demographic variables age, gender, BMI, education and information about their complaints; complaint duration at the onset of the study and if they had previously experienced work-related health problems. Every time a saliva sample was taken, time, activity level, perceived stress (Smyth, Ockenfels et al. 1998), and food, smoking and drink intake was kept in a paper diary (Canals, Teresa Colomina et al. 1997). In the same diary the participants reported daily sleep quality, hours spent in bed during the night, perceived daily stress and physical complaints. Per time-point variables as

medication use, the use of oral contraceptives, smoking, job circumstances and sick leave were reported (Pruessner, Wolf et al. 1997; Kirschbaum, Kudielka et al. 1999).

STATISTICAL ANALYSIS

The questionnaire scores, demographic variables and cortisol at baseline, post-treatment and at follow-up were compared using a paired sample t-test, comparison was done for baseline – post-treatment and post-treatment – follow-up. The demographic variables and questionnaire scores of the burnout participants who had dropped out at post-treatment and follow-up were compared with the completers using Pearson's Chi-square test and one-way ANOVA. The demographic variables of the completers at the different time-points were compared with the Wilcoxon signed rank test. Per sample point, cortisol data that deviated over three standard deviations of the mean were excluded from further analysis. Missing data and outliers within the group who completed the study made up 1.5% of the dataset.

MULTILEVEL REGRESSION ANALYSIS

In order to analyze this dataset multilevel regression analysis (MlwiN version 1.10, Centre for Multilevel Modeling, London, UK) was used (Goldstein, Browne et al. 2002), using cortisol as the dependent variable (Hruschka, Kohrt et al. 2005). With this statistical method a model is built from the explanatory variables which are nested within different hierarchical *levels*. Momentary cortisol measurements (sample-level) are nested within two weekdays (weekday-level) which are nested within longitudinal measurements at three time-points (time-point-level), which are nested within persons (person level). We refer to these levels as sample-level, weekday-level, time-point-level, and person-level.

Longitudinal data collection is often subject to missing data due to drop-out of participants. Unlike repeated measures analysis, multilevel regression analysis (MLRA) does not require listwise deletion of missing data. In the basic model the total error variance is assigned to the four levels with time as the explanatory variable. The relative proportion of variation at each level is represented by the intraclass correlation coefficient (ICC). The basic model is subsequently compared with models in which the explanatory variables are introduced per level, starting with the lowest, or sample level. Variables that do not significantly contribute to the model are excluded and new variables of the higher level are introduced. Eventually the final model contains all significant variables. Per variable the reported estimate with the standard error was used in significance testing by computing the test statistic Z . In addition the calculated standardized coefficient ' β ' (standardized for the particular scale of a variable) is reported for comparison between the explanatory variables.

CAR, DAY AND DST-MODEL

The cortisol samples were analyzed in three *separate* multilevel models; the CAR-model, the DAY-model and the DST-model. The first model includes the cortisol samples, taken at 0, 15 and 30 minutes after awakening, on two consecutive days. The second model, the DAY-model, contains the daily cortisol samples, taken at 1200h (noon), 1800h and 2230h, on two consecutive days. In the third model, the suppressed cortisol levels after dexamethasone intake are sampled at 0, 15 and 30 minutes after awakening. We refer to this model as the ‘Dexamethasone Suppression Test’-model, or DST-model. In order to approach a normal distribution of the cortisol data a square root transformation was performed on the cortisol measurements for analysis of the CAR and DAY-model, and log transformation was used for the DST model.

EXPLANATORY VARIABLES AND CONFOUNDERS

Fixed effects estimated at the *sample-level* included a number of potential confounders. First, the reported time of taking a sample. Second, food, coffee or alcohol intake and nicotine use consumed in the 30 minute period before taking a sample were all coded ‘1’ if taken and ‘0’ if not taken. Third; activity level in the 30 minute period before taking a sample was coded ‘0’ light, ‘1’ average and ‘2’ heavy. Finally, perceived stress was reported as ‘0’ not present and ‘1’ present if a stressful event occurred before taking a sample, or if a stressful event was expected the following hour.

At the *weekday-level* the included variables were: sleep-quality of the past night, hours spent in bed, physical complaints during the day and perceived daily stress; ‘-1’, less than normal, ‘0’ normal and ‘1’ more than normal. At *time-point - level*, six different categories of medication were introduced as dummy variables; glucocorticoids, beta-blockers, antidepressants, anti-hypertensives (affecting the renine/angiotensine system), benzodiazepines (sleep medication) and other medication. Time between the different time-points (months), number of treatment sessions (categorized into 0-10, 11-20 or > 20 sessions), subjective change in complaints between time-points (coded as; ‘0’ recovered, ‘1’ improved, ‘2’ slightly improved, ‘3’ no change, ‘4’ worse). Smoking, oral contraceptive use, work situation; no job, part-time or fulltime job, and sick-leave (not, partial or fully) were introduced. Finally the season in which the samples were taken was introduced to control for possible seasonal effects (King, Rosal et al. 2000). At *person-level* the explanatory variables of the reported complaints (exhaustion, fatigue, depression, sleep and psychoneuroticism) at baseline and the *change* (Δ) in the reported complaints were introduced. The change (Δ) in reported complaints was calculated as the reported complaints at baseline minus the mean level of the reported complaints at post-treatment and at follow-up. The mean level of complaints at post-treatment and follow-up was chosen as there was no significant difference between the reported complaints at post-treatment and follow-up. Finally demographic variables as gender, age, BMI, education; ‘1’

college education and '0' other, complaint duration at onset of the study, former history of work-related complaints; '0' no and '1' yes.

All explanatory variables were centered; the overall mean of a variable was subtracted from all values of the variable, which is called 'grand mean centering'. Dichotomous variables as gender and smoking (yes/ no) were centered around zero as well. In this way the intercept in the regression equation is always interpretable as the expected value of the outcome variable, when all explanatory variables have their mean value.

RESULTS

LONGITUDINAL GROUP CHARACTERISTICS

Table 1 displays the characteristics of the burnout group at baseline, post-treatment and at follow-up. The post-treatment measurement was on average 8.5 months ($SD = 2.6$, range = 5-15 months) after baseline, the group consisted of 62 burnout participants. At follow up, 6.3 months after post-treatment ($SD = 1.0$, range = 4-9 months), the group consisted of 53 participants.

There was no significant difference in the burnout group between the consecutive time-points in smoking or medication use. At post-treatment the group reported less full-time jobs and more loss of work. There was no significant change in work between the post-treatment and the follow-up measurement. There was a significant decrease in reported sick leave at post-treatment and again at the follow-up measurement. Fewer persons received treatment and more persons reported to have finished their treatment between the post-treatment and follow-up measurement.

There were no significant differences between the dropouts at post-treatment and at follow-up and the completers for age, gender, BMI, smoking, oral contraceptive use, medication use, complaint duration at onset, work, sick-leave, previous history of work-related problems, any of the burnout-related complaints, nor cortisol outcome variables (data not shown).

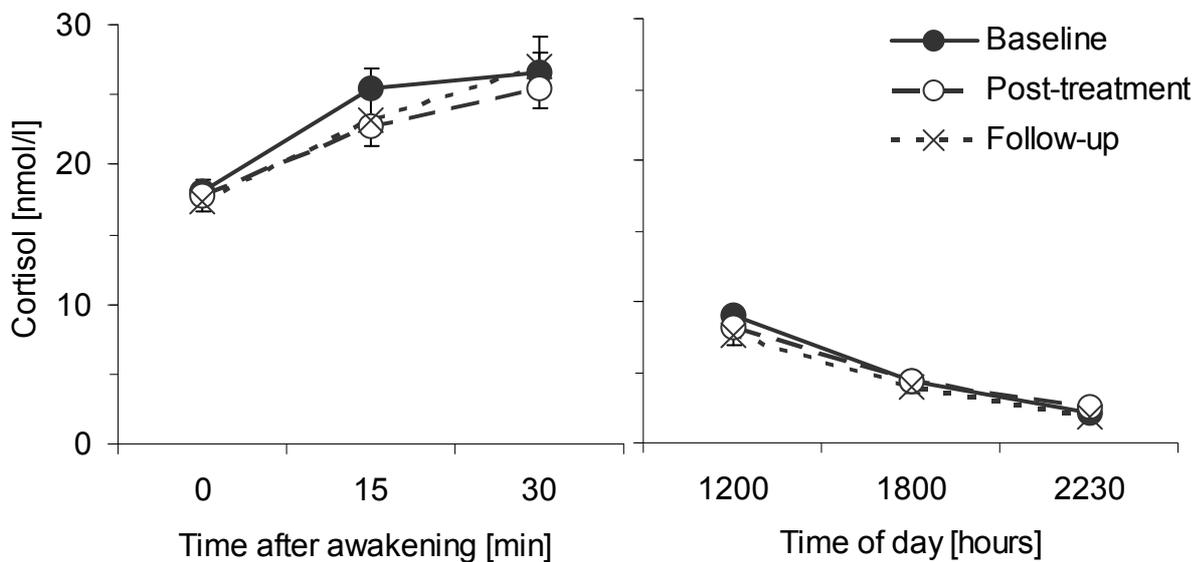


Figure 1. Cortisol after awakening (CAR) (left) and cortisol day-curve (DAY) (right) at baseline, post-treatment and at follow-up. Mean data of 2 days and SEM are shown.

Table 1. Characteristics of the burnout group at baseline, post-treatment and at follow-up.

		Baseline <i>n</i> = 74	Post-treatment <i>n</i> = 62	Follow-up <i>n</i> = 53
Gender	Male	53 (72%)	44 (71%)	36 (68%)
Age	Years	43.9 (8.7)	44.8 (8.6)	44.7 (9.0)
BMI	kg/m ²	25.1 (3.5)	25.2 (3.7)	25.1 (3.8)
College education		46 (62%)	39 (63%)	34 (64%)
Smoking ^a		23 (31%)	17 (27%)	18 (34%)
Medication ^a	None	49 (66%)	35 (57%)	31 (59%)
	Other	25 (34%)	25 (40%)	21 (40%)
	of which:			
	Antidepressants	3 (4%)	7 (11%)	7 (13%)
	Glucocorticoids	3 (4%)	2 (3%)	-
	Beta-blockers	5 (7%)	4 (7%)	1 (2%)
	Benzodiazepines	2 (3%)	3 (5%)	3 (6%)
	Anti-hypertensive	1 (1%)	3 (5%)	3 (6%)
Job ^a	Full-time	56 (76%)	35 (57%)*	33 (62%)
	Part-time	17 (23%)	16 (26%)	10 (19%)
	No job	1 (1%)	8 (13%)	10 (19%)
Sick leave ^a	Full	46 (62%)	15 (24%)*	5 (9%)*
	Partial	22 (30%)	15 (24%)	6 (11%)
	Not	6 (8%)	29 (47%)	40 (76%)
Received treatment ^a		-	59 (95%)	24 (45%)*
Finished treatment ^a		-	31 (50%)	50 (94%)*

* $p < .05$, ** $p < .01$, *** $p < .001$

Means (*SD*) or number (%)

^aWilcoxon signed rank test of baseline – post-treatment and post-treatment – follow-up.

QUESTIONNAIRE SCORES

In table 2 the mean questionnaire scores are shown at baseline, post-treatment and at follow-up. All questionnaire scores showed significant differences between baseline and post-treatment; the participants reported less complaints. There were no significant differences in questionnaire scores between post-treatment and follow-up, except for the depression score (CESD) which was significantly lower at follow-up.

Table 2. Questionnaire scores at baseline, post-treatment and follow-up

	Baseline	Post-treatment	Follow-up
Burnout [MBI-GS] ^a			
Exhaustion	4.83 (0.93)	3.06 (1.38) ^{***}	2.86 (0.99)
Depersonalisation	3.44 (1.37)	2.48 (1.44) ^{***}	2.36 (1.41)
Competence	3.83 (1.01)	4.18 (0.99) ^{***}	4.22 (0.90)
Fatigue [CIS20R]	105.58 (18.4)	75.39 (27.3) ^{***}	78.97 (26.6)
Depression [CES-D]	23.05 (8.34)	15.03 (10.04) ^{***}	12.85 (10.13) [*]
Sleep quality past night [GSKS]	5.45 (2.32)	3.82 (2.73) ^{***}	4.06 (2.47)
Symptom checklist [SCL90]			
Depression	35.35 (9.05)	24.74 (7.89) ^{***}	23.88 (8.32)
Somatisation	24.21 (7.86)	17.75 (5.25) ^{***}	18.27 (5.93)
Insufficiency in thinking	23.97 (6.60)	16.41 (6.10) ^{***}	16.83 (6.49)
Sleep problems	7.99 (3.54)	5.68 (2.90) ^{***}	5.71 (2.79)
Psychoneuroticism	175.27 (38.77)	131.13 (30.24) ^{***}	129.29 (30.24)

* $p < .05$, ** $p < .01$, *** $p < .001$

Mean (*SD*)

^aData at post-treatment $n = 53$ and at follow-up $n = 41$. Due to sick leave or loss of work some participants were unable to fill out the MBI-GS questionnaire.

BASIC CORTISOL ANALYSIS

Figure 1 (page 76) shows the mean cortisol values at baseline, post-treatment and at follow-up, for the cortisol awakening response (CAR), and the day-curve. Figure 2 (below) shows the feedback efficiency of dexamethasone on the cortisol awakening response at the three time-points. Paired samples analysis revealed no differences in mean cortisol levels for the CAR, or the suppressed cortisol level after dex-intake between the consecutive measurements. There is no difference between the mean cortisol levels during the day at baseline, post-treatment and follow-up except for one point. Paired samples analysis of the evening cortisol sample taken at 2230h showed a lower cortisol level at the follow-up measurement as compared with the post-treatment sample. All other cortisol analyses were performed with multilevel regression analysis as reported below. This multilevel regression analysis tests the hypothesis for the whole distribution of values. In addition we checked for potential effects when comparing extreme groups (quartiles) of cortisol. This analysis did not show significant effects.

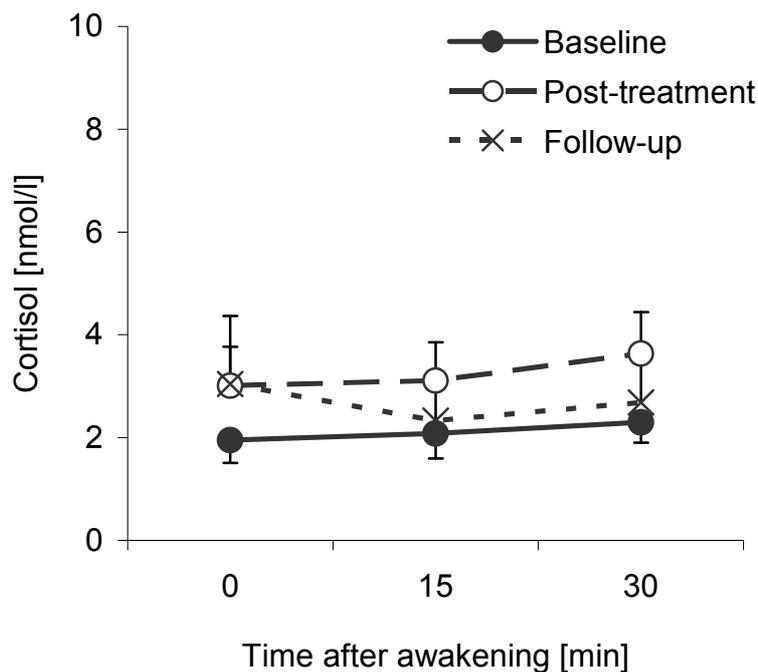


Figure 2. Cortisol awakening response after dexamethasone intake (DST) at baseline, post-treatment and at follow-up. Mean data and *SEM* are shown.

MULTILEVEL REGRESSION ANALYSIS ZERO-MODEL

The three different analyses, i.e.: cortisol CAR, cortisol DAY and cortisol DST, all showed significant variance at the person, time-point and sample levels. Cortisol CAR, but not cortisol DAY showed a significant variance component on the weekday-level. The main effect of time, either sample number (centered as $-1, 0$ and 1) or the actual reported time per sample (centered hours after midnight), was introduced to fit the CAR, DAY and DST model. There was a significant increase in cortisol after awakening and a significant decrease in cortisol during the day. The suppressed CAR after dexamethasone intake showed a flat curve; no significant increase or decrease was observed. Time accounted for 21.0% (CAR), 53.6% (DAY) and 0% (DST) respectively of the variance at sample-level. The model with time included was considered the reference-, or ‘zero’ model.

Table 3. Multilevel estimates for the curve and main effects of complaints on cortisol after awakening (CAR), the day-curve (DAY) and the CAR after dex-intake (DST).

	CAR		DAY	DST
	estimate (<i>s.e.</i>)	β^b	estimate (<i>s.e.</i>)	estimate (<i>s.e.</i>)
<i>Basic model:</i> ^a				
Intercept	3.402 (.235)***		4.348 (.085)***	-.123 (.053)*
Slope	.406 (.035)***		-.132 (.004)***	-.014 (.017)
<i>Main effects:</i>				
Time-point	.022 (.083)		-.071 (.034)*	-.030 (.042)
Exhaustion baseline	.241 (.116)*	.169		
Δ Exhaustion ^c	-.340 (.108)**	-.350		
Depression baseline	-.015 (.013)	-		
Δ Depression ^c	.037 (.014)**	.283		

* $p < .05$, ** $p < .01$, *** $p < .001$

The table shows the basic model and main effects. Significant confounders are summarized in the tekst.

^a Basic model: Cortisol (CAR/DAY/DST) = intercept + slope of CAR/DAY/DST.

^b Standardized coefficient β = unstandardized coefficient (estimate) * SD explanatory variable / SD outcome variable

^c Change in variables (Δ) = variable at baseline – mean (variable post-treatment and variable follow-up)

CAR-MODEL

The outcome variable cortisol CAR showed significant variance on each of the four levels (sample, weekday, time-point and person). The intraclass correlation coefficient (ICC) in the zero model was 0.13 at person-level, 0.25 at time-point level, 0.20 at weekday-level and 0.42 at sample level. Thus the maximal variance to be explained after introducing the explanatory variables is 42% of the cortisol samples after awakening, 20% between the two sampling weekdays, 25% between the three measurement occasions and finally 13% between persons.

Table 3 shows the intercept, slope (time) and main explanatory variables of the CAR model (left column). There is a significant intercept, indicating that the average cortisol level is significantly deviant from zero. The significant slope was discussed above; there is a significant rise in cortisol after awakening, which is visualized in figure 1, the left graph. There was no significant effect of time-point (baseline, post-treatment and follow-up) on the cortisol response after awakening, there is no overall difference between baseline, post-treatment and follow-up.

The reported complaints at the onset of the study and the change in complaints (depicted by Δ) were introduced as the main explanatory variables. There was a significant effect for Δ exhaustion (MBI: $M = 1.82$, $SD = 1.4$, 95% confidence interval; 1.73-1.90) and Δ depression (CESD: $M = 8.7$, $SD = 9.8$, 95% confidence interval; 8.1-9.3). A higher level of exhaustion at baseline is associated with an overall higher awakening cortisol level. The reduction of exhaustion complaints is associated with a decrease in awakening cortisol level. There is no effect of baseline depression, but a decrease in depressive symptoms is significantly correlated with an increase in awakening cortisol level. The reported standardized coefficients (β) show that the effect of exhaustion is larger than the effect of depression.

The main findings as presented in table 3 were corrected for a number of significant confounders. There was a significant effect on the CAR for the confounding variables gender (men = 0, women = 1) ($estimate = -.302$, $s.e. = .084$, $p < .001$, $\beta = .205$), smoking ($estimate = -.243$, $s.e. = .081$, $p = .003$, $\beta = .169$), antidepressant use ($estimate = -.556$, $s.e. = .115$, $p < .001$, $\beta = .242$) and anti-hypertensive medication ($estimate = -.587$, $s.e. = .200$, $p = .003$, $\beta = .169$). Thus the cortisol CAR is lower for women, smokers, antidepressant users and anti-hypertensive medication users.

Compared to the 'zero'-model the final model explained in total -3.9% variance at the sample level, 5.1% at day level, 15.6% at time-point level, and finally 87.8 % at person-level. The variance at time-point level can be further divided; 12.3% is due to the (change in) exhaustion and depression variables. As the maximal explained variance at time-point level is 25%, exhaustion at baseline and the decrease in exhaustion and depression account in total for 3% variance *within* persons. Similar calculation of the variance at person level shows that 30.7% is due to the exhaustion and depression variables, which accounts in total for 4% of the variance *between* persons.

DAY-MODEL

The outcome variable cortisol DAY showed significant variance at three levels. There was significant variance at person level (ICC = 0.10), at the time-point level; ICC = 0.16, and ICC = 0.74 at sample-level. Thus 74% of the variance to be explained is between the cortisol samples during the day, 16% between the three measurement occasions, and 10% at person level. In table 3 the intercept, slope (time) and time-point of the DAY model (middle column) is reported. There is a significant intercept and slope, indicating that the average cortisol level is significantly deviant from zero, and there is a significant decline of cortisol during the day.

There is a small, but significant, effect of time-point; there is a somewhat lower cortisol level during the day at post-treatment and at follow-up. The day-curve of the three time-points is shown in figure 1, the right graph. There is no main effect for any of the reported complaints at baseline, nor for the improvement of complaints after treatment. None of the potential confounding variables introduced in this model proved to be significant. The introduction of the time-point variable explained 7.9% at time-point level. As the maximum variance to be explained at the time-point level was 16%, the introduction of the time-point variable explained 1.3% in total.

DST-MODEL

The outcome variable cortisol after awakening after dexamethasone intake, or cortisol DST, showed significant variance at sample-level (ICC = .27), time-point – level (ICC = .49) and at person-level (ICC = .24). A maximum of 24% of the variance to be explained is at the person level, 49% at time-point level and 27% at sample level. Table 3 reports the intercept, slope and time-point of the awakening response after dexamethasone intake (DST-model, right column). The intercept is significantly different from zero, there is no significant slope nor is there a difference between the time-points in the cortisol DST. (A negative intercept is possible as the data are log transformed). Figure 2 shows the DST curves at baseline, post-treatment and at follow-up. The following confounders had a significant effect: gender (*estimate* = -.171, *s.e.* = .050, $p < .001$, $\beta = .257$), and smoking (*estimate* = -.108, *s.e.* = .046, $p = .02$, $\beta = .167$). Cortisol after dexamethasone intake was significantly lower for women and smokers. The final model explained 20.2 % of the variance at person level, 7.4 % at time-point level and 0 % at sample level.

DISCUSSION

In this study a group of clinically diagnosed burnout participants was measured before and after treatment and again at follow-up. There were no changes between baseline, post-treatment and follow-up in cortisol after awakening, or after a low-dose dexamethasone intake, and a small decrease in the cortisol day level over the time-points. The reported complaints were significantly reduced after treatment, which had stabilized at follow-up. Cortisol after awakening was positively associated with exhaustion at the onset of the study, and the decrease in exhaustion was associated with a decrease in the overall awakening cortisol level. A decrease in depressive complaints was associated with an increase in the overall awakening cortisol level. There were no associations between the complaints at baseline (or the change in complaints) and the cortisol during the day or after dexamethasone intake.

COMPLAINT REDUCTION

This study is not a randomised controlled trial to evaluate the effect of the intervention. In fact our only interest is the variance in the changes of symptoms over time, whether due to the intervention or even to spontaneous changes. The reported reduction in complaints, which stabilizes at follow-up, is in concordance with the intervention study of Moch et al. (2003) in a clinical burnout group who received treatment and medication in the first month of the study, the study of van Rhenen et al. (2005) in a highly stressed working population, and the study of Huibers et al. (2004) in a group of employees with severe fatigue on sick-leave.

At post-treatment and at follow-up the burnout group, despite the significant decrease in complaints, reported more exhaustion, fatigue, depression and psychoneuroticism compared with a normal population (Arrindel and Ettema 1981; Bouma, Ranchor et al. 1995; Bultmann, de Vries et al. 2000; Schaufeli, Bakker et al. 2001). The decrease in complaints was rather strong in the first 8 months after treatment, and levels at 6 months follow-up. This raises doubts whether further spontaneous decrease will occur in the years to come. This ultimate level reached might as well reflect a premorbid state reflecting a vulnerability to develop burnout.

LONGITUDINAL CORTISOL

The cortisol data show a stable pattern. There was no difference in the slope of the cortisol response over the three time-points. As is generally reported there was a significant increase in cortisol after awakening, a decline during the day and a decreased response with a flat curve after dexamethasone intake. The intraclass coefficients (ICC) of the cortisol samples in each model show moderate to high reliability of the samples (CAR = 0.42, DAY = 0.74, DST = 0.27). The overall cortisol level during the day showed a small but significant decrease over the baseline, post-treatment and follow-up measurements. These data are different from the follow-up studies on cortisol in burnout so far. In a previously performed pilot study we showed that the initial lower cortisol awakening level in a clinical burnout group had increased after treatment, while there was no difference in the cortisol day level (Mommersteeg, Keijsers et al. 2006). Moch et al. (2003) showed that morning plasma cortisol levels were significantly reduced after an intervention compared with a healthy control group, while the initial levels were not different from the control group. The urinary free-cortisol level, which was lower at baseline, was still reduced after treatment compared with the control group. The present study was done with a much larger sample of burned-out individuals and with a more intensive treatment period, which is a credit to the reliability of the present findings.

The intraclass correlation coefficients at person level showed that 13% of the variation in cortisol after awakening, 10% during the day and 24% after dexamethasone intake is attributable to differences between persons. The remainder of the variance to be explained is thus due to factors within persons and error variance. This implies that the variability of cortisol within persons is larger than the variability of cortisol between persons, which is different from the conclusions of previous studies (Pruessner, Wolf et al. 1997; Huizenga, Koper et al. 1998; Wust, Wolf et al. 2000). There were no differences in cortisol production in a longitudinal course, but there is variance to be explained in cortisol functioning within persons and unexplained variance to differentiate between persons. This finding should be taken into account when comparing differences between groups of persons; differences between persons will never account for major changes in cortisol production simply because the largest cortisol effect is due to differences within persons. Indeed the cortisol response after awakening shows a significant genetic component (Wust, Federenko et al. 2000; Kupper, de Geus et al. 2005), though the major part of the influence on the cortisol changes after awakening and during the day remain to be unraveled. In retrospect this observation leans credit to our idea to investigate the intra-individual covariation between cortisol and complaints, despite the finding that inter-individual differences at baseline (between burnout and healthy controls) are absent.

MULTILEVEL REGRESSION ANALYSIS

We hypothesized that changes in burnout complaints could be associated with differences in cortisol functioning. A higher level of exhaustion at baseline was correlated with an overall higher level of cortisol after awakening. A decrease in exhaustion after treatment and at follow-up was correlated with a decrease in the awakening cortisol level. There was no effect of baseline depression, but a decrease in depressive symptoms was significantly correlated with an increase in the awakening cortisol level. Overall the burnout group improves in exhaustion and depressive symptoms and the effect of the change in depression and fatigue on cortisol are opposite to one another. There was no association of the burnout complaints at baseline, or the change in complaints with the cortisol day-curve or the cortisol awakening response after dexamethasone intake.

Moch et al. (2003) showed that the decrease in exhaustion, psychiatric symptoms and depression was not accompanied by a rise in urinary unbound cortisol levels. We did not observe consistent correlations between the change in the CAR and the change in burnout complaints in the pilot study (Mommersteeg, Keijsers et al. 2006). Moreover, as we previously reported, there was no relation at baseline between exhaustion or depression in the burnout group and the cortisol awakening response, day-curve or DST (Mommersteeg, Heijnen et al. 2006). Compared with the above mentioned studies multilevel regression analysis made a more subtle analysis of the cortisol data possible and numerous potential confounders were controlled for, which favors the present study. However, of the total variance to be explained in cortisol after awakening, in total only 4% of the variance at person level and 3% of the variance at time-point level could be explained by the exhaustion at baseline, and the change in exhaustion and depressive complaints in time. The standardized coefficients show that the effect is the largest for the change in exhaustion and depression. In contrast to what we expected little variance was explained *within* the persons, at the different time-points. This makes it difficult to attribute the effect of the change in reported complaints to either differences between persons or individual changes within persons. The implications of these findings are therefore limited. It must be noticed that though an effect for the MBI exhaustion on cortisol was observed, there was no significant effect for the reported fatigue [CIS20]. The MBI exhaustion and the CIS20R fatigue score correlated $r = 0.3$, 0.8 , and 0.7 respectively for the consecutive time-points. Apparently exhaustion as reported on the MBI provides different information than the CIS20 score. Moreover, there was a loss of 13% of the MBI data post-treatment and at follow-up for persons who were unable to fill out the MBI due to work-loss or enduring sick leave.

POTENTIAL CONFOUNDERS

The cortisol awakening level was significantly lower for women, smokers, use of antidepressants and anti-hypertensive medication. The reduced cortisol awakening level after dexamethasone intake was significantly lower for women and smokers. There were no significant confounders found for the cortisol level during the day. The effects of smoking and gender on the cortisol level after awakening have been studied before, overall these studies do not show differences in the awakening level for gender or smoking (Kirschbaum, Kudielka et al. 1999; Kudielka and Kirschbaum 2003; Kunz-Ebrecht, Kirschbaum et al. 2004). Though there is no information available on menstrual cycle phase, it is not likely that that this could have accounted for the observed differences in gender (Kirschbaum, Kudielka et al. 1999). The use of medication, gender and smoking account for the majority of the differences between persons ($11.4\% - 4\% = 7.4\%$), still, as mentioned before, variability between persons is not large and it may only be due to the repeated measurement over a longitudinal course that the effects become apparent. Various potential confounders were introduced at each level. We found no effect for activity, reported stress, or intake of food, coffee, alcohol or nicotine in the 30 minute period before taking a sample. There were no differences between the different sampling days for sleep-quality, hours spent in bed, daily physical complaints or reported stress. The time-lap between the different time-points did not affect the results and neither did the number of treatment sessions, oral contraceptive use, work situation or sick-leave. In addition we did not find evidence for a seasonal effect of cortisol sampling.

CONCLUSION

Burned-out participants show decreased complaints after treatment, which remains stable at follow-up. Cortisol does not change over the course of time. Multilevel regression analysis provides a useful tool to unravel the effect of explanatory variables on cortisol functioning between and within persons while controlling for potential confounders. We had anticipated that a solid relation between burnout and cortisol should have been manifest in the worse period just before treatment and in a correlation between cortisol and the rather strong decrement of complaints after treatment. However, the reduction in exhaustion and depressive complaints explained some variance of the differences between and within persons in the cortisol functioning over time, but the effects are too modest to represent any clinical or diagnostic value. We conclude that the recovery from burnout complaints and basal cortisol production are hardly related to each other, therefore the clinical implications of this finding are limited.

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Immune and Endocrine Function in Burnout Syndrome

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Objective: Burnout is a stress-induced work-related syndrome. It is associated with a higher incidence of infections possibly pointing to a compromised immune system. In the present study, endocrine and ex vivo immune function of severe cases of burnout were investigated. **Methods:** Endocrine and immune variables were compared in 56 persons with burnout and 38 healthy control subjects. Cortisol after awakening, after a low-dose dexamethasone, and dehydroepiandrosterone-sulphate (DHEAS) were analyzed from saliva. Peripheral blood was analyzed for T, B, and NK cell number and in vitro mitogen-induced pro- and antiinflammatory cytokine release. The capacity of dexamethasone to regulate cytokine release was compared between the groups. **Results:** The burnout group showed an increased production of the antiinflammatory cytokine interleukin-10 (IL-10) by monocytes after lipopolysaccharide stimulation. No differences were observed in IL-10 release induced by the T-cell mitogen PHA nor in the proinflammatory cytokines gamma interferon and tumor necrosis factor alpha. The capacity of dexamethasone to regulate cytokine release did not differ between the groups. The number of peripheral blood T cells, B cells, or NK cells was not different either. The burnout group showed higher DHEAS levels but no difference in cortisol levels after awakening or after dexamethasone intake in comparison to controls. **Conclusion:** Production of the antiinflammatory cytokine IL-10 by monocytes was increased in individuals with burnout syndrome. It seems unlikely that glucocorticoids or changes in glucocorticoid receptor function play a role in this higher IL-10 production. **Key words:** burnout, cytokines, IL-10, monocyte, glucocorticoids, DHEAS.

AUC = area under the curve; **BMI** = body mass index; **CAR** = cortisol awakening response; **CIS20R** = checklist individual strength; **CFS** = chronic fatigue syndrome; **DHEAS** = dehydroepiandrosterone-sulphate; **DST** = dexamethasone suppression test; **IFN- γ** = gamma interferon; **IL** = interleukin; **LPS** = lipopolysaccharide; **MBI-GS** = Maslach Burnout Inventory General Survey; **NK-cell** = natural killer cell; **PHA** = phytohemagglutinin; **SCL90** = symptom checklist; **TNF- α** = tumor necrosis factor alpha.

INTRODUCTION

Burnout is an adverse work-related syndrome characterized by persistent exhaustion, a cynical work attitude, and feelings of reduced competence (1). Additionally, people experiencing burnout report tension headaches, an inability to relax, gastrointestinal problems, muscle aches, disrupted sleep, concentration and memory problems, and depressive symptoms (2,3). There is considerable overlap of these symptoms in related syndromes like chronic fatigue syndrome (CFS) (4) and vital exhaustion (5). The core component of all of these syndromes is exhaustion, but the three components that characterize burnout are by definition work stress-related (2). Moreover, CFS is additionally defined by symptoms reflecting pain (4), whereas pain is not a central component of burnout. The vital exhaustion questionnaire score is used as a risk-factor for cardiovascular disease (5). Persons experiencing burnout report depressive symptoms, but the constructs of depression and burnout are not synonymous (2,6). In The Netherlands, a stable 9% of the working population report emotional exhaustion in the clinical burnout range. Emotional

exhaustion predicts sickness absence, and over one third of the long-term sickness compensation claims are the result of psychological complaints (www.statline.nl).

Burnout is associated with an increased incidence of self-reported illnesses such as common cold, flu-like illness, and gastroenteritis (7). The core symptom of burnout, exhaustion, was shown to be the strongest predictor of infections, although the other aspects of burnout, cynicism (or depersonalization) and reduced competence (or personal accomplishment), also contributed to the prediction of infections. Whether this increased risk of common infections in persons with burnout is the result of dysregulation of immune function is the topic of the present study.

It is now widely accepted that chronic stress can lead to downregulation of immune function, which may impair an effective immune response to infectious challenges and thereby increase the risk of infectious diseases (8). Because burnout is the result of chronic work-related stress, it may thus be associated with decreased immune functioning as well. This study focuses on severe cases of burnout seeking psychological treatment for their complaints.

Few studies have examined immune function in relation to burnout symptoms. Nakamura et al. reported an association of a higher score on the burnout subscale depersonalization with lower natural killer cell activity (9). Bargellini et al. found that low personal accomplishment was associated with reduced numbers of total lymphocytes, T cells (CD3+), including the subsets of T cells CD4+ (T helper/inducer cells), and T suppressor/cytotoxic cells (CD8+) (10). Taken together, these studies demonstrate a reduced lymphocyte number and activity in relation to burnout, although it is remarkable that no relation was found with the core symptom of burnout, i.e., exhaustion. All of these studies, however, focused on individuals with burnout complaints in a working population who can be considered relatively healthy. To date, no studies on immune function in burnout have examined more severe cases of individuals with burnout.

In the present study, in addition to immune cell numbers, the capacity to produce cytokines by immune cells after in

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vitro stimulation was determined. Cytokines are soluble communicators between components of the immune system and the brain. They are involved in stress-induced behavioral and cognitive changes known as “sickness behavior” that resemble the side symptoms of burnout (11). Cytokines can be divided into proinflammatory cytokines such as interleukin (IL)-2, tumor necrosis factor alpha (TNF- α), and gamma interferon (IFN)- γ and antiinflammatory cytokines like IL-4 and IL-10. T helper (Th) cells are categorized on the basis of their pro- or antiinflammatory cytokine production into T helper type 1 (Th1) and T helper type 2 (Th2) cells, respectively (12). Monocytes produce both proinflammatory and antiinflammatory cytokines. A disturbed balance between pro- and antiinflammatory cytokines has been found to be related to several infectious, autoimmune/inflammatory, and allergic diseases (12). Several stressors have been associated with a shift in cytokine production toward an antiinflammatory pattern with glucocorticoids and/or catecholamines as the proposed mediators of this shift (12). Because persons with burnout report more infections (7), which may be the result of an inadequate response to invading pathogens, one could hypothesize a shift toward antiinflammatory cytokine production to exist in those with burnout.

Some earlier studies have investigated cytokine release in persons with burnout and in related syndromes like CFS and vital exhaustion. Gaab et al. observed a positive correlation between reported fatigue and stimulated monocyte release of IL-6 and TNF- α in a group of patients diagnosed with CFS (13). Visser et al. observed higher IL-10 production by monocytes in patients with CFS (14). Considering exhaustion as the core component of burnout, we hypothesized to find higher antiinflammatory cytokine production by monocytes and T cells in persons with severe burnout.

The glucocorticoid cortisol and its synthetic analog dexamethasone are potent modulators of the immune system with immunosuppressive effects (12). We recently showed that there are no changes in salivary cortisol levels after awakening, during the day, or after the dexamethasone suppression test (DST) in a clinical burnout group compared with a healthy control group (15). Irrespective of whether the negative findings could be replicated in the present sample, we considered it worthwhile to measure cortisol parameters again to investigate their potential role in the immune function. The DST is an indication for glucocorticoid receptor sensitivity and subsequent negative feedback functioning of the hypothalamic–pituitary–adrenal axis (16). The steroid dehydroepiandrosterone-sulfate (DHEAS) also shows an immunomodulatory function but opposite from cortisol (17). Low DHEAS levels seem to be associated with poorer health (18), although Grossi et al. and Moch et al. found no differences in serum or plasma DHEAS in participants with burnout (19,20). A shift in the cortisol/DHEA(S) ratio toward cortisol has been associated with mood disorders and perceived stress (21).

The immune-modulating effect of cortisol not only depends on circulating cortisol levels, but also on receptor sensitivity of immune cells for glucocorticoids. Immune cells express

glucocorticoid receptors, and in vitro exposure of peripheral blood lymphocytes to dexamethasone results in immunosuppression. Wirtz et al. found 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 (22). Visser et al. observed an increased sensitivity to dexamethasone in patients with CFS (23), whereas Kavelaars et al. found a significant reduction in the maximal effect of dexamethasone on phytohemagglutinin (PHA)-induced T cell proliferation (24). In the present study, we investigated the inhibiting effect of increasing dexamethasone concentrations on PHA-stimulated IFN- γ and IL-10 cytokine release in persons with burnout as well as the dexamethasone effect on lipopolysaccharide (LPS)-stimulated TNF- α and IL-10 production by monocytes. In line with the studies in CFS, we expected to find an altered glucocorticoid sensitivity of T cells and monocytes in persons with burnout.

In summary, the goal of the present study is to identify potential changes in immune and endocrine function in burnout individuals, focusing on lymphocyte subset numbers, cortisol parameters, DHEAS, pro- and antiinflammatory cytokines, and the sensitivity of the immune cells to glucocorticoids.

METHODS

Participants

The burnout group consisted of 56 participants (25 men and 31 women), mean age 43.0 years (standard deviation [SD] = 9.3, range = 27–65 years). The control group included 38 participants (19 men and 19 women), mean age 44.8 years (SD = 8.6, range = 30–60 years). Seven persons were excluded from blood sampling as a result of medication use ($n = 5$) or refrained from having their blood sample taken ($n = 2$). There was no difference in age, gender, body mass index (BMI), or complaints in these persons compared with the rest of the burnout group.

Enrollment of the burnout group took place through different healthcare institutions, where the participants experiencing burnout had applied for treatment. In addition, information about the research project was posted on several burnout-related web sites. Interested participants received a screening questionnaire by mail or e-mail. Selection of the participants was based on cutoff scores indicating clinical burnout as reported by the Dutch version of the Maslach Burnout Inventory General Survey (MBI-GS) (exhaustion ≥ 2.20 and depersonalization ≥ 2.00 or competence ≤ 3.66) (25), severe fatigue (checklist individual strength; CIS20R) ≥ 76 (26), and exclusion of symptom check list (SCL90) scores within the psychopathological range (total score > 214) (27). After selection, 52 participants with burnout received a clinical diagnostic interview by a qualified psychologist; details are described in more detail elsewhere (15). According to the diagnostic interview, 45 persons (87%) were diagnosed with the International Classification of Diseases, 10th Revision criteria for “work-related neurasthenia” and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for “undifferentiated somatoform disorder” (3,28). Participants with burnout had to be at the initial stage of treatment for their complaints and to report full or partial sickness absence. Medication use for asthma, rheumatoid arthritis, or diabetes and use of antidepressants were exclusion factors. Control participants were selected through a local newspaper advertisement and coworkers of the researchers. The data collection period of blood and saliva sampling was between August 2003 and December 2004. The participants in this study are a fresh selected sample; there is no overlap in participants between this study and our previously described studies (15,29). All participants gave written informed consent. Approval was obtained by the medical ethical committee of the University Medical Center Utrecht.

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Questionnaires

The participants filled out questionnaires on demographic data, duration of complaints, stressful life events in the past 3 months (yes/no), and work status. Factors with a potential influence on cortisol such as smoking, menstrual cycle, the use of oral contraceptives, and medication were registered (30–32). In addition to the burnout inventory, several questionnaires were included that focused on complaints such as fatigue, poor sleep quality, depressive symptoms, and general psychopathology. The burnout symptoms exhaustion, cynicism, and feelings of reduced competence were measured with the Dutch version of the MBI-GS, 15-item version (33). Fatigue was assessed with the 20-item version of the Dutch fatigue scale CIS20R (34). Sleep quality of the past month was assessed with the Dutch State and Trait sleep assessment scale, 14-item version (GSKS (35)). Level of depressive symptoms was assessed with the Dutch version of the CES-D, 20 items (36). Finally, the Dutch version of the symptom checklist SCL90 was used as an indication for general psychopathology (27). All questionnaires are well-validated Dutch versions that have shown reasonable to good reliability.

Endocrine Measures

Saliva was collected at home for cortisol and DHEAS assessment. Samples were kept in the refrigerator and on return they were stored at -20°C . Saliva for cortisol analysis was sampled by a Salivette with a cotton roll (Sarstedt, Etten-Leur, The Netherlands) on 3 consecutive weekdays at 0, 15, and 30 minutes after awakening. The second evening, participants were instructed to take an oral dose of 0.5 mg dexamethasone. One person in the burnout group and three persons in the control group refrained from dexamethasone intake.

On the first 2 days of cortisol sampling, participants were instructed to collect an extra saliva sample at 30 minutes after awakening for DHEAS analysis by passive drool rather than by a cotton role (37). The samples were analyzed using a chemiluminescence assay (LIA) as described elsewhere (www.ibl-hamburg.com).

Immune Variables

Blood Collection Procedure

Participants were instructed to take a light meal on the morning of blood sampling and refrain from coffee, chocolate, and fruit intake. Blood was collected in 10-mL heparinized Vacu-tubes between 9:00 AM and 1:00 PM at the University Medical Center. The fatigue questionnaire (CIS20R) and the sleep quality scale (GSKS) were filled out. Questions on flu-like symptoms and common cold at the moment and in the past week, medication intake, and menstrual cycle date were reported.

Leukocyte Subpopulations

Circulating numbers of monocytes, T cell subsets, B cells, and natural killer (NK) cells were assessed in heparinized whole blood using dual-color fluorescence analysis with a Becton Dickinson Calibur flow cytometer. Whole blood was stained using monoclonal antibodies labeled with either fluorescein isothiocyanate (FITC) or phycoerythrin (PE) to quantify CD14⁺ (monocytes), CD3⁺ (total T), CD4⁺ (T helper), CD8⁺ (suppressor/cytotoxic-T), CD19⁺ (B), CD16⁺CD56⁺ (NK), and CD3⁺/CD16⁺CD56⁺ (NK-T) cells. Absolute numbers of cells were calculated from a total leukocyte blood count.

Cytokine Production

Whole blood diluted 1:10 with RPMI-1641 (Gibco, Grand Island, NY), 100 U/mL penicillin, 100 $\mu\text{g}/\text{mL}$ streptomycin, and 2 mmol/L L-glutamine was stimulated with the T cell mitogen PHA (Remel Europe Ltd., final concentration 25 $\mu\text{g}/\text{mL}$) at $37^{\circ}\text{C}/5\%$ CO_2 in 96-well round-bottom plates in the presence of 0, 1, 3, 10, 20, 50, 100, and 300 nmol/L dexamethasone. For IL-10 and IFN- γ determination, supernatants were collected after 72 hours of culture. Cytokine production was measured in culture supernatants using standard enzyme-linked immunosorbent assay (ELISA) kits (CLB, Amsterdam, The Netherlands).

To stimulate monocyte cytokine production, 1:10 diluted whole blood (with RPMI-1641 supplemented with antibiotics) was stimulated with LPS

(*Escherichia coli* 0127: B8, Sigma, final concentration 2 ng/mL) at $37^{\circ}\text{C}/5\%$ CO_2 in 96-well flat-bottom plates. The effect of dexamethasone on cytokine production was assessed in the presence of the following dexamethasone concentrations: 0, 1, 3, 10, 20, 50, 100, and 300 nmol/L. Supernatants were collected after 24 hours of culture and IL-10 and TNF- α cytokine levels were measured using standard ELISA kits (CLB).

Statistical Analysis

The demographics and questionnaire scores of the burnout and the control group were compared using χ^2 test and one-way analysis of variance (ANOVA). One-way ANOVA was used to test for differences in endocrine and immune parameters. Positively skewed variables of the immune and endocrine data set were log transformed for the analysis, although the untransformed values are presented. A repeated-measures analysis was applied for analysis of the cortisol awakening response (CAR) with time after awakening as the within factor and group as the between factor. The cortisol (in nanomoles per liter) and DHEAS (in nanograms per milliliter) measurements on day 1 were significantly correlated with the measurements at day 2 (DHEAS: $r = 0.236$, $p = .029$, cortisol: 0 minutes; $r = 0.347$, $p = .001$, 15 minutes; $r = 0.553$, $p < .001$, 30 minutes; $r = 0.494$, $p < .001$). The data of the 2 days were pooled for further analysis. The CAR was recalculated into two area under the curve (AUC) measures: the AUC level, the amount of cortisol after awakening, and the AUC slope, the shape of the curve after awakening (38). Exclusion of persons with a negative slope (AUC slope < 0 ; burnout group 16%, control group 18%), which is considered to be an indication of noncompliance (39), did not affect the results. The cortisol/DHEAS ratio was calculated by dividing the cortisol AUC level by the DHEAS level. The IFN- γ /IL-10 ratio was calculated using the PHA-induced cytokine levels. Dexamethasone-inhibited cytokine production curves were analyzed using repeated-measures analysis with “dexamethasone concentration” as the within-subject factor and “group” as the between factor. Greenhouse-Geisser correction was applied. Logistic transformation of the positively skewed data set did not lead to different outcomes in the repeated-measures analysis; therefore, the nontransformed data set was used. Effect sizes are reported as partial eta squared (η_p^2) for the repeated-measures analysis and eta squared (η^2) for the one-way ANOVAs, 0.01 = small, 0.06 = moderate, and 0.14 = large (40). Eta squared is the proportion of the total variance that is attributed to an effect. An alpha level of 0.05 was used for all statistical tests.

RESULTS

Table 1 shows that there were no differences in gender, age, BMI, smoking, or oral contraceptive use between the burnout and the control group. The groups did not differ in reported common cold or flu-like symptoms, menstrual cycle phase during blood sampling, or the occurrence of a stressful life event in the past 3 months (data not shown). The control group reported more weekly strenuous exercise, more alcohol intake (data not shown), and a higher percentage of women in menopause (Table 1). From these potential confounders, only menopause showed an association with the outcome variables. The menopause group showed a lower number of monocytes and granulocytes. However, controlling for menopause status did not affect the results and therefore the noncorrected results are reported.

The burnout participants reported partial or complete sickness absence, the mean complaint duration at the intake of the study was 31.6 months (SD = 30.6), and 46% reported to have had work-related complaints before. The moment of cortisol sampling was on average 2 weeks apart from the blood sampling, but there was no difference between the burnout (mean = 0.47 months, SD = 1.3) and the control group (mean = 0.54 months, SD = 0.34) in this time interval ($F_{1,86} = 0.17$, $p = .68$).

TABLE 1. Demographic Variables and Complaints

	Burnout	Control	Test Value
Gender (male)	25 (45%)	19 (50%)	$\chi^2=0.261$
Age, mean (SD)	43.0 (9.3)	44.8 (8.6)	$F=0.95$
Body mass index, mean (SD)	24.4 (4.0)	24.5 (3.2)	$F=0.001$
Smoker	13 (23%)	5 (13%)	$\chi^2=1.48$
Women			
Contraceptive use	6 (19%)	7 (37%)	$\chi^2=1.87$
Menopausal	3 (10%)	6 (32%)	$\chi^2=3.83^b$
Sickness absence			
Not	5 (9%)	38 (100%)	$\chi^2=75.65^c$
Partial	26 (46%)	—	
Fully	25 (45%)	—	
Medication use			
None	32 (57%)	27 (71%)	$\chi^2=1.87$
Beta-blockers ^a	4 (7%)	0	
Benzodiazepines ^a	6 (11%)	0	
Hypertensive	2 (4%)	2 (5%)	
Antihistamine	2 (4%)	0	
Nonsteroidal antiinflammatory drugs	0	1 (3%)	
Other	10 (18%)	8 (21%)	

Burnout $n = 56$, control $n = 38$.

Data given as number (percentage) unless otherwise noted.

^a In the blood sampling, two participants who used beta-blockers and one person who used benzodiazepines were excluded.

^b $p < .05$; ^c $p < .001$.

Table 2 shows the questionnaire scores of the burnout and the control group. The burnout group reported more fatigue, depressive symptoms, lower sleep quality, and scored higher on general psychopathology compared with the control group. Fatigue and sleep quality were filled out twice, once during the intake and once more on the day of blood sampling. The reported complaints and the main physiological outcome variables were unrelated within the groups.

Endocrine Parameters

Table 3 shows the mean scores of the endocrine variables. Repeated-measures analyses showed a significant increase in

cortisol after awakening (time: $F_{2,146} = 37, p < .001$, partial eta squared (η_p^2) = 0.29), but no difference between the groups (groups: $F_{1,92} = 0.16, p = .69, \eta_p^2 < 0.01$) nor a difference between the groups in the increase (slope) after awakening (group \times time: $F_{2,146} = 0.58, p = .52, \eta_p^2 < 0.01$). Cortisol levels after dexamethasone showed a small, but significant increase after awakening (time: $F_{2,137} = 3.7, p = .04, \eta_p^2 = 0.04$), but no difference between the groups (groups: $F_{1,87} = 1.3, p = .26, \eta_p^2 = 0.02$) nor a group difference in the increase after awakening (group \times time: $F_{2,137} = 0.54, p = .54, \eta_p^2 < 0.01$). The burnout group showed significantly higher DHEAS levels compared with the control group, but the cortisol/DHEAS ratio

TABLE 2. Test Variables in the Burnout and the Control Group

	Burnout ($n = 56$)	Control ($n = 38$)	F^a
Burnout (Maslach Burnout Inventory General Survey)			
Exhaustion	4.76 (0.97)	1.17 (0.53)	430.10
Depersonalization	3.51 (1.50)	1.08 (0.64)	88.69
Competence	3.55 (1.32)	4.70 (0.84)	22.79
Fatigue (checklist individual strength)			
At inclusion	106.48 (16.26)	43.18 (13.10)	399.42
At blood sampling	93.63 (19.34)	38.61 (12.12)	235.52
Sleep quality (Dutch State and Trait sleep assessment scale, 14-item version)			
At inclusion	7.05 (3.85)	2.31 (2.83)	42.15
At blood sampling	6.21 (3.84)	2.29 (2.78)	28.20
Depressive symptoms (Center for Epidemiologic Studies–Depression)	25.58 (9.19)	4.32 (3.63)	182.92
General psychopathology (symptom checklist)	181.36 (32.75)	104.20 (10.29)	197.13

Data given as means (standard deviation).

^a All F values are significant at the $p < .001$ level and $\eta^2 > 0.20$.

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TABLE 3. Endocrine Parameters in the Burnout and the Control Group

	Burnout (<i>n</i> = 56)	Control (<i>n</i> = 38)	F	η^2
Cortisol				
0 min	15.26 (5.69)	15.53 (6.19)	0.05	0.001
15 min	19.70 (7.51)	18.68 (7.37)	0.43	0.005
30 min	21.18 (8.11)	20.40 (6.9)	0.23	0.003
Area under the curve level	37.92 (13.04)	36.65 (12.29)	0.23	0.002
Area under the curve slope	7.41 (8.97)	5.58 (9.16)	0.93	0.010
Cortisol after dexamethasone suppression test ^a				
0 min ^b	1.10 (1.38)	1.40 (1.60)	1.53	0.017
15 min ^b	1.01 (1.59)	1.72 (2.87)	2.65	0.029
30 min ^b	1.53 (2.44)	1.98 (3.10)	0.67	0.007
DHEAS (ng/mL) ^b	3.49 (2.77)	2.30 (1.83)	5.50 ^c	0.056
Cortisol/DHEAS ratio ^b	19.30 (19.95)	26.98 (22.05)	2.95	0.032

Cortisol (nmol/L), DHEAS (ng/mL).

Data given as mean (standard deviation).

^a Dexamethasone suppression test in burnout group *n* = 55, control group *n* = 35.

^b Analysis of variance on log-transformed data.

^c *p* < .05.

DHEAS = dehydroepiandrosterone-sulphate.

was not different. The difference in DHEAS level remained after introducing gender, age, and BMI as covariates in the analysis.

Leukocyte Cell Count

The number of leukocytes was not different between the burnout (10.0×10^6 cells/mL blood, SD = 2.9) and the control group (9.6×10^6 cells/mL blood, SD = 2.8) ($F_{1,85} = 0.43, p = .51, \eta^2 < 0.01$). Moreover, there was no difference in mean erythrocyte sedimentation rate between the burnout group (7.0 mm/hour, SD = 6.1) and the control group (7.7 mm/hour, SD = 7.4) ($F_{1,84} = 0.194, p = .67, \eta^2 < 0.01$). There were no differences between the groups in mean granulocyte, monocyte or lymphocyte number, nor in numbers of B cells (CD19+), NK cells (CD16+ 56+), T cells (CD3+), T helper/inducer cells (CD4+), T suppressor/cytotoxic cells (CD8+), or CD4+/CD8+ratio (data not shown). There was a significant difference in a subset of T cells expressing CD16/ 56 determinants (NK-T cells) (log NK-T; $F_{1,86} = 4.13, p = .045, \eta^2 = 0.046$), i.e., the burnout group (mean = 0.08, SD = 0.07) had fewer NK-T cells compared with the control group (mean = 0.14, SD = 0.20).

Phytohemagglutinin and Lipopolysaccharide-Induced Cytokine Secretion

Table 4 shows the mean cytokine levels in the supernatants of PHA-stimulated T cells and LPS-stimulated monocytes. Interestingly, the burnout group shows a significantly higher LPS-induced IL-10 production by monocytes compared with the control group with a medium to large effect size. No other differences were observed between the groups in monocyte TNF- α , T cell IFN- γ , T cell IL-10 release, nor in the T cell IFN- γ / IL-10 ratio. *Within* the burnout group, the IL-10 levels showed no dose-response relationship with any of the psychological complaints.

Regulation of Cytokine Secretion by Dexamethasone

Figure 1 shows the dexamethasone inhibition of cytokine release in PHA-stimulated T cell cultures. Increasing dexamethasone concentrations significantly inhibited IFN- γ (Fig. 1A) and IL-10 production (Fig. 1B) (dexamethasone concentration: $F_{2,567} = 42, 53, p < .001, \eta_p^2 = 0.34, 0.40$, respectively), but no group differences were apparent.

TABLE 4. Mitogen-Induced Cytokine Release in the Burnout and the Control Group

	Burnout	Control	F	η^2
T cell				
Gamma interferon ($\times 1000$) ^a	16.3 (28.3)	13.0 (13.4)	0.21	0.003
Interleukin-10 ^a	298.3 (286.2)	308.4 (344.7)	0.11	0.001
Gamma interferon/interleukin-10 ratio ^a	69.3 (128.9)	50.2 (42.7)	0.07	0.001
Monocyte				
Tumor necrosis factor alpha	881.5 (343.9)	855.0 (253.9)	0.15	0.002
Interleukin-10 ^a	52.5 (38.0)	33.6 (24.9)	9.01 ^b	0.100

Burnout *n* = 49, control *n* = 38.

Nontransformed means (pg/mL) and (standard deviation).

^a Analysis of variance on log-transformed data.

^b *p* < .01.

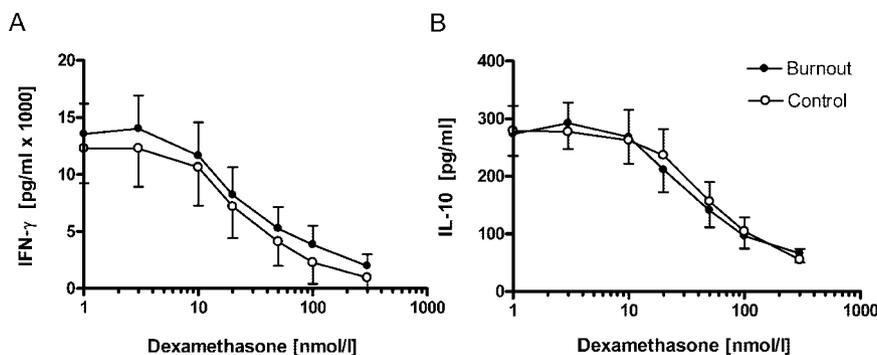


Figure 1. Dexamethasone inhibition of T cell cytokine release. Whole blood samples were cultured in the presence of T cell mitogen phytohemagglutinin and increasing dexamethasone concentrations. Graphs show the mean and standard error of the burnout (●) and the control group (○) for (A) gamma interferon and (B) interleukin-10. Basal cytokine release in the absence of dexamethasone is shown in Table 4.

Figure 2 shows the dexamethasone effect on LPS-stimulated monocytes. Dexamethasone significantly inhibited TNF- α release (Fig. 2A; dexamethasone concentration: $F_{2,567} = 403, p < .001, \eta_p^2 = 0.83$), but the inhibitory effect was not different between the groups. LPS-induced IL-10 release (Fig. 2B) increased at low dexamethasone concentrations with a peak at 50 nmol/L and decreased at higher dexamethasone levels (dexamethasone concentration: $F_{7,574} = 9.9, p < .001, \eta_p^2 = 0.11$). The overall IL-10 level was significantly higher in the burnout group compared with the control group (groups: $F_{1,82} = 6.0, p = .017, \eta_p^2 = 0.07$). The significant interaction of the groups with the dexamethasone concentration (group \times dexamethasone: $F_{2,152} = 3.2, p = .05, \eta_p^2 = 0.04$) became nonsignificant after controlling for the initial IL-10 level.

DISCUSSION

This is the first study that focuses on possible immune changes in severe cases of burnout on sick leave. Despite the wide range of parameters investigated, no evident changes in most endocrine, receptor, and immune functioning were observed. There was an increased release of the antiinflammatory cytokine IL-10 by monocytes (but not T cells) in the burnout group compared with the control group. The burnout group showed a higher level of DHEAS but no difference in the cortisol/DHEAS ratio.

Results of studies in CFS, a syndrome with analogous symptoms, may serve as a reference for our results. In the review of Lyall et al., the results of several studies on immune function in CFS are summarized. Their main conclusion was that there are no clear differences between patients with CFS and normal control subjects with respect to T, B, or NK cell numbers and function or cytokine levels (41). A similar review by Patarca concluded that there is a predominance of T cells producing proinflammatory cytokines in CFS, but that no other clear interpretable patterns emerge (42). A credit to the present study is that only few studies differentiated between the antiinflammatory IL-10 release by T cells and monocytes. The observed higher IL-10 release by monocytes is in concordance with Visser et al. who reported higher LPS-induced IL-10 levels in CFS (14). In contrast, Gupta et al. did not observe a difference in LPS-activated monocyte IL-10 release in six patients with CFS compared with six healthy control subjects, although there was a decrease in PHA-induced IL-10 and spontaneously produced IL-10 (43).

What could be the significance of a higher IL-10 release in burnout? As mentioned before, persons with burnout report more common cold, flu-like infections, and gastroenteritis (7). Vital exhaustion is associated with an increased pathogen burden (i.e., response to antibodies for herpes simplex virus, varicella zoster virus, Epstein-Barr virus, and cytomegalovi-

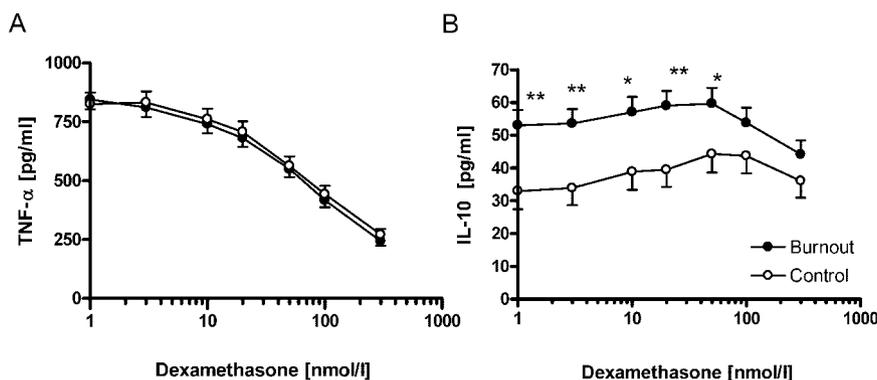


Figure 2. Dexamethasone regulation of monocyte cytokine release. Whole blood samples were incubated in the presence of lipopolysaccharide to stimulate monocyte cytokine release and increasing dexamethasone concentrations. Graphs show the mean and standard error of the burnout (●) and the control group (○) for (A) tumor necrosis factor alpha and (B) interleukin-10. Basal cytokine release in the absence of dexamethasone is shown in Table 4. * $p < .05$, ** $p < .01$.

IMMUNE AND ENDOCRINE FUNCTION IN BURNOUT

rus) and with higher serum levels of IL-10 (44). Moreover, psychosocial stress, a longer duration of stressful life events, and enduring problems related to work are associated with increased risk of developing a cold after exposure to the common cold virus (45). The observed immune dysregulations in our study show peculiar similarity with a study on a viral common cold infection (46). The rhinovirus is the most important common cold virus (47). In vitro exposure of immune cells to rhinovirus causes an inhibition of T cell proliferation mediated by a virus-dependent increase in monocyte IL-10 release. The amounts of IL-10 and the number of monocytes producing this cytokine on stimulation with the rhinovirus were comparable with those seen after LPS stimulation (46). These data suggest that the higher IL-10 release in burnout like we observed might be causally related to a common cold virus infection. IL-10 exerts its antiinflammatory effect through inhibition of macrophage activation, T cell proliferation, and proinflammatory cytokine production, i.e., inhibition of the antiviral cytokine IFN- γ (12), thus promoting the increased viral load. However, the burnout and the control group in our study did not differ in the reported cold or flu-like symptoms at the time of blood sampling or the week before. The duration of common cold symptoms is typically 1 week, whereas 25% of the persons infected with a common cold do not show signs of the infection (47). Our finding may point to a subclinical viral infection, which may have contributed to the exhaustion symptoms. Glaser et al. underlined the importance of latent virus reactivation or subclinical viral infections in CFS. Different types of psychological stressors can reactivate latent Epstein-Barr virus, which in turn upregulate IL-10 production in monocytes (48). The possibility that the changes in immune parameters in burnout as observed are the result of subclinical infections is worth further investigation.

The burnout and the control group were not different in the effect of dexamethasone on the cytokine release or in the level of cortisol in saliva. The effect of dexamethasone is an indicator of glucocorticoid receptor functioning. These data imply that glucocorticoids and the glucocorticoid receptor are not critically involved in the observed changes in IL-10 release by stimulated monocytes in the burnout group. The absence of a difference in salivary cortisol levels between the groups is in accordance with the findings in our previous study (15). The burnout group showed a higher level of DHEAS. The observed higher DHEAS level contradicts studies suggesting a role of lower DHEAS in deteriorated health (18,49). So far studies in burnout found no changes in plasma DHEAS levels (19,20). Although DHEAS is considered to be stable (49,50), the correlation between the DHEAS levels on the 2 days in our study was significant but small. DHEAS has been associated with increased IL-10 production (51), and DHEA, the nonsulfatized form of DHEAS, has been found to reduce susceptibility to viral, bacterial, and protozoan infections (17). However, DHEA and DHEAS can also have immunostimulatory effects (17). Therefore, the relevance of the increased DHEAS level in burnout for immune function remains to be determined.

In conclusion, we showed that burnout is associated with changes in monocyte antiinflammatory immune function, which may point to some role of (subclinical) infection. A possible role for DHEA(S) remains to be elucidated.

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Chapter 6

Discussion

SUMMARY OF THE RESULTS

The main question of this thesis was whether people with burnout would show deviations in physiological functioning. In each chapter the HPA-axis was studied. In the pilot study (chapter 2) the burnout group showed a lower cortisol awakening level compared to the control group, and an increase of this level after treatment. However neither the *rise* after awakening nor the cortisol curve throughout the day was different from the control group. There were no relevant correlations between the CAR and the reported complaints. The lower cortisol level after awakening as observed in the pilot was not found in a larger group despite the similarities in inclusion criteria and complaints of the burnout groups (Chapter 3). The cortisol DAY level and the cortisol level after dexamethasone intake were not different between the burnout and the control group either. Fatigue or depression complaints in the burnout group were not related to the cortisol CAR, DAY curve or DST. Thus there was no indication for a differential hypo- or hyperfunction by either fatigue or depressive symptoms respectively on the HPA-axis functioning in burnout. In the longitudinal part of project A (chapter 4) cortisol after awakening, and after dexamethasone intake showed no changes between the longitudinal measurements. The reported burnout complaints were significantly reduced after a treatment period, but there was no further reduction of the complaints at follow-up and the complaints were still higher than norm scores for a healthy population. The CAR over the three measurements was significantly correlated to the initial exhaustion level. A decrease in depressive symptoms was correlated with an increased CAR, whereas a decrease in fatigue was correlated with a decreased CAR over the three measurements. These findings are contradictory to the supposed hyper- and hypo-active state of the HPA-axis in MDD and CFS respectively. These findings, despite their significance, explained only a minor part of the variance within (3%) and between (4%) the burnout individuals. Finally the burnout group in Project B, described in Chapter 5, showed no deviations in the cortisol CAR, nor the DST. The DHEAS level, but not the cortisol/ DHEAS-ratio, was significantly elevated in the burnout group. The burnout group had significantly higher levels of the anti-inflammatory cytokine IL-10 produced by LPS stimulated monocytes. The IL-10 production of stimulated T-cells was not different from a control group, and neither were there differences in the pro-inflammatory cytokine release of TNF- α or IFN- γ . The effect of dexamethasone on pro- and anti-inflammatory cytokine release in vitro was not different between the burnout and the control group, nor was there a change in number of whole blood counts of T-cells, B-cells and NK-cells.

What do these results show about the psychophysiology of burnout? First of all that the results are not as clear-cut as we had initially hypothesized. The idea that either hypo- or hyperactivity of the HPA-axis would be present in burnout, or a mix between those two, dependent on individual differences in complaints, was not confirmed. The initial lower cortisol level after awakening in the pilot study was contradicted by the negative results of Project A and B. Due to the larger sample sizes more significance should be attributed to the latter findings. The individual differences in reported depressive or fatigue complaints, did not explain the absence of a difference between the groups. However in the longitudinal study there was a slight correlation of exhaustion and depressive symptoms with the awakening cortisol level over the three measurements.

HPA - AXIS ; CAR , DAY - CURVE AND DST

Based on previous studies on the CAR in burnout (Pruessner, Hellhammer et al. 1999; De Vente, Olf et al. 2003; Grossi, Perski et al. 2004; Grossi, Perski et al. 2005; Mommersteeg, Keijsers et al. 2006), it was expected that the CAR was the most promising candidate for dysregulation. Measurement of the DST for feedback functioning seemed promising as well (Pruessner, Hellhammer et al. 1999). The increase after awakening is in the range of the increase of cortisol levels during stress, hence we can assume the GR-receptor to be the main receptor involved in the actions of the awakening response, and the consequent termination of the awakening response. However, Schmidt-Reinwald et al. (1999) showed that cortisol levels after awakening are not correlated with the acute increase in cortisol in response to a laboratory stress challenge, the Trier Social Stress Task (TSST). Instead the awakening level was directly related to the increased basal ACTH level (Schmidt-Reinwald, Pruessner et al. 1999). Thus the awakening response and the cortisol response to a stressor are not the same, and provide different information. We did not investigate the TSST in our study, but a study on the effect of the TSST in a clinical burnout group by De Vente et al. showed negative results (De Vente, Olf et al. 2003, de Vente et al. personal communication). Therefore having added the TSST to our repertoire of possible HPA-axis dysregulations probably would not have added much to our findings.

Despite the relation with stress-related syndromes that is found in some studies, the *significance* of the awakening response is far from clear (Clow, Thorn et al. 2004). More fundamental research is needed to investigate the origin of the CAR and its significance. A better understanding of the CAR might reveal why similar studies on stress-related disorders like burnout differ widely in the observed dysregulation of the CAR.

The diurnal level is mainly controlled by environmental cues whereas the awakening response is for a large part controlled genetically (Wust, Federenko et al. 2000; Bartels, De Geus et al. 2003; Kupper, de Geus et al. 2005). Despite their different origin the diurnal level is related to the awakening level, a lower initial level after awakening correlates with a lower diurnal level (Edwards, Evans et al. 2001). Recently a large epidemiological study on

twins, their families and spouses, showed that burnout does not appear to be influenced by genetic factors (Middeldorp, Stubbe et al. 2005). Rather environmental factors shared by family members explained 22% of the variance, and the remaining 78% was due to unique environmental factors (Middeldorp, Stubbe et al. 2005). This is consistent with the finding that a high work-load, an environmental factor, is a better predictor of burnout than personality traits, which have a genetic component (Schaufeli and Bakker 2003). The personality trait ‘neuroticism’, which is a core characteristic of people with burnout (van der Zee 2003; Langelaan, Bakker et al. 2006), is rather strongly (about 50%) influenced by genetic factors (Middeldorp, Cath et al. 2005). High neuroticism is related to an increased cortisol response after awakening (Portella, Harmer et al. 2005). The total score “psychoneuroticism” as general indicator for neurotic distress (Bech 2004), in this thesis was not related to the cortisol parameters. The burnout group improves significantly on the psychoneuroticism score after treatment, while ‘neuroticism’ is considered to be a stable personality trait. Therefore the high score of psychoneuroticism in burnout may have evolved as a consequence of the high work-load environment, rather than being a reflection of a genetic predisposition to neuroticism. Consequently our findings point to an environmental effect of high work-load as the major contributor to burnout, rather than a genetic effect of neuroticism.

DAY - CURVE

If the environmental effect of work-load is the major cause of burnout, we would predict a disturbance of the day-curve rather than of the awakening response, as the awakening response is for a large part under genetic control whereas the day-curve is not (Wust, Federenko et al. 2000; Bartels, De Geus et al. 2003; Kupper, de Geus et al. 2005). We did not find a deviation in the day-curve of the burnout group (chapter 2 and 4). The evening sample of the pilot (chapter 2), however showed a significant rise after 14 treatment sessions. In contrast, in the longitudinal study (chapter 4) the cortisol day curve showed a small, but significant decline over the three measurements (chapter 3). The decline of cortisol after a treatment period is consistent with an intervention study of McKinney et al. (1997) and a study by Theorell et al. (2001) in a healthy working group; morning serum cortisol levels were significantly decreased after an intervention in a 4,5 month and one year follow-up study respectively. Additionally the burned-out group of Moch et al. had a reduction in serum cortisol levels after an intervention of 4 months when compared to a control group. The initial cortisol level was not different between the intervened and the control group in either study. It must be noted that this decline after treatment was apparent only when compared to the control group. The burnout group did not appear to have changed compared to their initial level (Moch, Panz et al. 2003). The longitudinal decline in our studied burnout group was rather small; 1.3% of the variance in the cortisol over the day was explained by the decline over the three measurements. Additionally there

was no correlation with the complaints or the change in complaints. Considering the absence of a cross-sectional disturbance in the day-curve, the absence of a relation with the complaints, the contradictory findings longitudinally and the small amount of variance explained, we conclude that the day-curve is not notably dysregulated in burnout.

DEXAMETHASONE SUPPRESSION TEST

The suppressed cortisol level of the DST showed the intended reduction of cortisol, and there was variation in the dataset to be able to either observe a hyper-suppression hypothesized for the fatigue component of burnout or non-suppression, an indicator for the depression component. There were no consistent non-suppressors among the burnout group. The few persons (< 10%) who showed a sign of non-suppressed cortisol levels (e.g. 70% suppression or less, the median of the group was 95% suppression), did not show this 'non-suppression' consistently across all measurements, and moreover there was no relation with depressive symptoms. Neither the DST used in project A or B (chapter 3-5) showed a relation with the complaints, nor was there a relation with the improvement of complaints. The dexamethasone suppression test does not point to a disturbed negative feedback in burnout.

The absence of a disturbed feedback as measured *in vivo* is supported by the absence of a change in receptor sensitivity for dexamethasone on lymphocytes *in vitro* (chapter 5). Neither the cytokine release induced by dexamethasone in PHA-stimulated T-cells nor LPS stimulated monocytes were significantly different between the burnout and the control group. The DST and the dexamethasone effect on lymphocytes are both indicators of the negative feedback effect of glucocorticoids, mediated via the GR-receptor. The DST acts via GR-receptors in the pituitary, whereas the *in vitro* effect of dexamethasone is mediated via peripheral GR-receptors on lymphocytes. The study of Ebrecht et al., however, failed to observe a correlation between dexamethasone inhibition on lymphocytes *in vitro* and the dexamethasone suppression test *in vivo*. This suggests that the sensitivity of the glucocorticoid receptor for glucocorticoids is tissue dependent (Ebrecht, Buske Kirschbaum et al. 2000). Local factors contribute to the effect of cortisol in different situations and in different tissues. The GR-receptor is subject to autoregulation, co-regulation and occupancy by available circulating glucocorticoids. Under conditions of chronic circulating cortisol levels the number and sensitivity of GR-receptors can be altered (De Kloet, Joels et al. 2005).

Circulating cortisol levels are bound to CBG in blood, differences in local circulating CBG levels can affect the amount of free active cortisol in some tissues. Furthermore the enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD2) catalyzes active cortisol into the inactive cortisone in some tissues. On the contrary, in the amygdala and the hippocampal area of the brain, the type 1 form of 11 β -HSD favors the conversion of cortisone into cortisol, thereby increasing intracellular levels of active glucocorticoids (Rashid and Lewis

2005). Therefore local levels of CBG, 11 β -HSD, and changes in the GR-receptor in different tissues affect the effectivity of circulating cortisol levels. It is possible that local regulators of HPA-axis functioning have become dysregulated in burnout. However, should a dysregulation be manifest in other parts of the HPA-axis, it is unlikely that major outcome variables such as the cortisol awakening response, the diurnal circulating levels, and the feedback mechanism, remain unaffected.

Overall we can conclude that even though we did measure the right parameters for HPA-axis disturbances, the HPA-axis does not seem to be dysregulated in burnout. It can be firmly concluded; there is no diagnostic or predictive role for the HPA-axis in burnout.

IMMUNE FUNCTION

In chapter 5 several indicators of immune function were investigated. The release of pro- and anti-inflammatory cytokines by the innate immune system (monocytes and macrophages) as well as the acquired immune system (e.g. T-cells), provides a more complete picture of immune function than the formerly used Th1/ Th2 response or type 1 and type 2 immunity (Kidd 2003)(Box 2, page 20). The pro-inflammatory cytokines are involved in cellular immunity against intracellular pathogens (e.g. viruses), and the anti-inflammatory pathway is linked to extracellular pathogens related to allergies. We hypothesized in chapter 5 that the increased IL-10 levels are possibly due to a subclinical infection. Rather the increased release of IL-10 by monocytes in the situation of a pathogen burden, e.g. common cold virus, points to an increased risk of becoming sick. The pathogen first encounters the macrophages in the outer lining of the body which are part of the first defense line (lungs, skin, and gut). The increased release of IL-10 by macrophages inhibits T-cell proliferation, and suppresses the release of pro-inflammatory cytokines such as IFN- γ , which increases the likeliness of spreading the invader. Therefore we hypothesize that the increased IL-10 response in burnout is related to acquiring an infection. This hypothesis can be tested by an experimental pathogen challenge, e.g. flu-vaccination or inoculation with a common cold virus in burnout. Vaccination and the response to a challenge may provide insight in the activated lymphocytes and subsequent cytokine release, presumably mediated by IL-10. Interestingly a study by Miller et al showed that while stress was related to a reduced antibody response in an influenza challenge trial, this was not mediated by the observed cortisol levels (Miller, Cohen et al. 2002). Moreover, the personality trait neuroticism, which is related to burnout, was related to a poorer antibody response. High neuroticism was related to a blunted cortisol response, but a mediating role for cortisol in the antibody response was not established (Phillips, Carroll et al. 2005). By no means could we provide a complete review here, but though it is established that cortisol levels are affected in stressful conditions and cortisol is an important mediator of immune function, it is not obvious that cortisol mediates the link between stress and immune dysregulation. In our thesis we did not find a functionally

dysregulated HPA-axis, nor were there changes in the effect of dexamethasone on immune function.

Immune-to-brain communication may form an alternative mechanism. Though there was no change in the release of IFN- γ and TNF- α , we did not measure the release of the pro-inflammatory cytokines IL-6 and IL-1, which are involved in sickness behavior. IL-1 and IL-6 are released in the brain in response to a stressor, and may consequently induce behavioral changes observed in stress related disorders like burnout (Maier and Watkins 1998; Dantzer 2001). A suggested test of pro-inflammatory cytokine release in vitro would be the activation of monocytes by IL-1 β , which increases the release of TNF- α and IL-6. Considering the absence of a dysregulated HPA-axis in burnout, what other mechanism could underlie the observed higher IL-10 response? Elenkov et al. 2002 suggested a role for adrenaline (epinephrine) and noradrenalin (norepinephrine)³, which stimulate APC like monocytes to release IL-10, and in turn inhibit TNF- α release by monocytes and IFN- γ release by T-cells (Elenkov and Chrousos 2002). Because of the effect of adrenaline on heart rate, some studies have focused on heart rate as a possible end-point for an adrenaline mediated dysregulation. Studies which focused on the SAM-axis in relation to work-stress are not conclusive, though Schnorpfeil observed a positive correlation between high job demands and blood pressure, but not with plasma adrenaline or noradrenalin (Schnorpfeil, Noll et al. 2003). Others did not find such correlation (Riese, Van Doornen et al. 2004). Sluiter et al. showed a correlation between reported health complaints and higher adrenaline levels (Sluiter, Frings-Dresen et al. 2001), in a normal healthy working population. Burnout patients have shown a higher resting heart-rate than controls, but no higher blood pressure (De Vente, Olff et al. 2003), or a change in catecholamines (Moch, Panz et al. 2003). In a study on CFS in adolescents higher baseline adrenaline levels were observed, and less sensitive adrenaline receptors in monocytes, resulting in decreased IL-10 release (Kavelaars, Kuis et al. 2000). These studies are by no means a complete review, but it may become clear that despite some findings of higher catecholamine levels, no clear pattern emerged. Therefore a role for catecholamines in the dysregulation in immune function in burnout can neither be confirmed nor rejected.

³ The Sympatho-medullary axis has not been mentioned throughout this thesis. The first response to stress is the fast activation of the adrenal medulla to release predominantly adrenaline and some noradrenaline. These hormones are released in the brain as well, acting as neurotransmitters, through different pathways. Adrenaline is the fight-flight hormone, it increased the heart rate, blood flow and respiration. Blood sugar levels are increased and it has suppressive effects on the immune system as well.

DHEAS

The burnout group showed higher levels of the hormone DHEAS (Chapter 5), but no change in cortisol/DHEAS ratio. Since the cortisol levels are not affected, there may be a role for DHEAS in burnout. The few studies on burnout showed no deviations in serum or plasma DHEAS (Grossi, Perski et al. 2003; Moch, Panz et al. 2003). We measured DHEAS levels in saliva instead, which are correlated with plasma DHEAS levels (Herbert, Goodyer et al. 1996), and salivary DHEAS has been used in studies on depression and chronic stress (Vedhara, McDermott et al. 2002; Assies, Visser et al. 2004). However, despite the reported stability of DHEAS, the correlation between the two sampling days in our study was albeit significant, rather small ($r = .24$). We plead for a study which validates the correlation between salivary DHEAS and circulating plasma levels, and test the stability of salivary DHEAS over several days. DHEAS mediates immune function, with immunopotentiating effects (Kroboth, Salek et al. 1999; Chen and Parker 2004), and DHEAS has been related to changes in cytokine function (Chen and Parker 2004). Therefore it is possible that the higher DHEAS level in burnout is related to the immune dysregulation. Based on our findings we cannot draw firm conclusions, the role of DHEA(S) and its effect on immune function in burnout remains to be elucidated.

CONCLUSIONS AND FUTURE DIRECTIONS

Based on the findings in this thesis we have to conclude that there is no diagnostic or predictive value for cortisol measurements in burnout. Though we observed an increased IL-10 response and higher DHEAS levels in burnout, these variables were not related to the complaints. In the longitudinal study the correlations between the initial exhaustion score, the change in exhaustion and depression were related with the cortisol awakening response. However these effects are marginal, and only became apparent over longitudinal repeated measurements, and the correlations can be ascribed to changes within persons, as well as changes between the burnout persons. Therefore as we already discussed in chapter 4, these findings are of limited relevance and merely point to the fact that while there is large variability between persons, most variance remains to be explained within persons. Therefore these findings are not useful for diagnostic or predictive purpose either. Correlations between psychological and the physiological variables are lacking, inconsistent or hard to interpret throughout other studies as well (Pruessner, Gaab et al. 1997; Bargellini, Barbieri et al. 2000; Rief and Auer 2000; Dickerson, Gruenewald et al. 2004; Hjortskov, Garde et al. 2004; Peeters, Nicolson et al. 2004; Gaab, Rohleder et al. 2005; Janszky, Lekander et al. 2006). Differences in time dynamics, circadian rhythms, and other confounders affect the physiological measurements, which reduces the chance of finding any correlations with the psychological domain. For example the questionnaires about the complaints are filled out separately, sometimes a few weeks apart from the cortisol samples. Sleep quality on the other hand, was reported immediately after awakening but

nevertheless failed to show a correlation with the awakening cortisol level in the cross-sectional and the longitudinal study. Neither did the subjectively reported stress per measurement, nor the general stress during the day show a relation with cortisol. Though fatigue and sleep quality were reported at the day of blood sampling, they failed to show any consistent correlation with the immune variables (chapter 5). Potential confounders were well investigated in relation to cortisol, controlled for by a control group, or introduced as covariates. Circadian rhythms of cortisol were well studied throughout this thesis, and therefore not likely to have affected our findings.

As long as it is not clear what physiological variables are the main contributors to the complaints observed in burnout, it will be hard to find correlations between the two, and even harder to be able to use this knowledge for diagnostic or predictive purposes.

THERE IS NO OBVIOUS DISTURBANCE OF THE HPA-AXIS IN BURNOUT.

Considering the findings in this thesis, what options remain for physiological dysregulation in burnout? There are several possibilities. First of all, let it be clear that the complaints observed in burnout represent disturbances in physiology somehow, but at the present state of knowledge we are not yet capable of finding out what type of dysregulations are manifest, or how they are related to the observed complaints.

One option is that several mediators are involved, which all may show a minor disturbance, but can altogether affect the allostatic load. Results of studies in burnout and CFS on several possible mediators however do not point in that direction (Parker, Wessely et al. 2001; Cleare 2003; Grossi, Perski et al. 2003; Moch, Panz et al. 2003). Other studies added up several variables as a general estimation of the 'allostatic load'. These studies are not conclusive either (Schnorpfeil, Noll et al. 2003; Hellhammer, Schlotz et al. 2004; Langelaan, Bakker et al. 2006). Still this type of research, browsing several variables at a time, is of vital importance. The significant findings in the immune study of chapter five are in line with this type of research. The first results point towards an increased stimulated monocyte IL-10 release and increased DHEAS levels in burnout. Future studies should reveal the relevance of these findings. Multivariate regression analysis or multilevel analysis are useful statistical tools to check several mediators for their role in burnout. The longitudinal type of research that was done in chapter 4, within a group of burnout persons provides more information on subtle (multiple) disturbances while controlling for possible confounders. Another possibility is that while all outcome variables were measured peripherally, the disturbance in fact hides centrally, e.g. in the actions of the neurotransmitters serotonin, dopamine, noradrenalin or acetylcholine. A theoretical framework has been build to relate changes in balance between these transmitters as neuromodulators in psychopathology (Tops 2004, Chapter 5, 6). Cortisol is suggested as a mediator in these pathways. The downstream peripheral measurement of several variables could be to far away from the actual central dysregulation. It is possible that central mechanisms have become

dysregulated in burnout, but that the peripheral cortisol levels are buffered through the actions of numerous mediators of the HPA-axis. The actions of CBG and 11 β -HSD which interfere with local cortisol levels were mentioned before. A more direct approach for central dysregulation was suggested in chapter 3; such as the combined DEX/CRH test, or CRH or ACTH infusion. However the relevance of these tests in burnout, which does not show a disturbance in peripheral cortisol, remains questionable.

The idea that some components of the HPA-axis may be affected whereas others are not, is part of a whole new area of research. Several components of the HPA-axis, e.g. the GR-receptor show small differences in their genetic make-up. These so called 'polymorphisms' show continuous variation within the population. Under similar conditions, polymorphisms can give rise to products which show differences in their functionality (van Rossum, Russcher et al. 2005). As a consequence people can be different in the functionality of these products. Recently different GR-receptor gene polymorphisms were found to be differentially related to sensitivity for the Trier Social Stress Task (Wust, van Rossum et al. 2004). These polymorphisms may represent a vulnerability for changes in the HPA-axis. For example a more resistant receptor shows reduced feedback in response to a stressor, thus the allostatic load may be particularly high in a person with this resistant GR-receptor polymorphism. This could be the basis for a disturbed HPA-axis function in stress-related conditions. Indeed the glucocorticoid resistance characteristic for depression is found to be related to polymorphic changes in the GR receptor (van Rossum, Binder et al. 2006). On the other hand the hypersensitivity observed in PTSD was unrelated to common GR-receptor polymorphisms (Bachmann, Sedgley et al. 2005).

Although it is possible that there are changes in GR-receptor functioning due to polymorphisms in some burnout persons, the group as a whole does not show changes in the DST or the dexamethasone effect on cytokine release which acts via the GR-receptor on lymphocytes. Changes in GR-receptor functionality are unlikely to be the main correlate of burnout, however it serves as an example. It is easy to imagine that other components of the HPA-axis show polymorphisms, which may be related to an altered health outcome (Wust, Federenko et al. 2004). In fact PubMed search on 'glucocorticoid' and 'polymorphisms' shows 391 hits (April 2006), among which polymorphisms of the ACTH receptor promoter, the enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1), which converts inactive cortisone into active cortisol, several neural pathways affecting the HPA-axis like the inhibitory GABA-ergic pathway, serotonin, dopamine, and adrenaline. DHEAS and IL-10, which were found to be altered in burnout, show functional polymorphisms as well. This type of research is likely to be more common in the near future. Already a study on a combination of three single nucleotide polymorphisms predicted chronic fatigue syndrome with 76% accuracy (Goertzel 2006). Techniques as DNA micro array; the screening of multiple sets of genes or even several polymorphisms at the same time, boosts this type of research. Though we did not observe changes in HPA-axis functioning, it is not unreasonable that components of the HPA-axis, or other

stress-involved systems may show differences in functionality, which under conditions of chronic work-stress give rise to the complaints observed in burnout.

When we started this research project it was theoretically crystal clear that the HPA-axis should show disturbances in burnout (van Doornen 2000; van Doornen 2001). The results of the pilot study briefly supported this view. However, the results of the projects A and B were unmistakable about the absence of any obvious deviation in the HPA-axis in burnout. These results are not disappointing, as there is no right or wrong in well performed studies. It should be noted that physiological measurements are not as clear-cut, nor 'objective' in comparison to psychological measurements as is often thought. In disorders like burnout the reported complaints form the major source of inconvenience; they represent actual complaints which should be taken seriously irrelevant of the absence of any physiological findings.

The possibility of a disturbance in immune function and the hormone DHEAS in burnout deserves further attention. While our findings do not point to a role for the HPA-axis in burnout, we plead instead for fundamental research to get a better understanding of the HPA-axis and its possible correlates. New research areas are on their way contributing to the knowledge about the relation between stress, the HPA-axis and stress-related clinical disorders.

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NEDERLANDSE SAMENVATTING

(DUTCH SUMMARY)

DE PSYCHOFYSIOLOGIE VAN BURNOUT

Dit proefschrift is een samenvatting van onderzoek wat tussen 2001 en 2004 is uitgevoerd bij de de capaciteitsgroep Gezondheidspsychologie in Utrecht, in samenwerking met het laboratorium voor Psychoneuroimmunologie van het UMC-Utrecht. In drie studies is gekeken of mensen met een burnout fysiologisch ontregeld zijn geraakt en of een herstel van de klachten samengaat met een herstel van de fysiologie. Het idee hierachter is dat de langdurige werk-stress die voorafgaat aan een burnout heeft geleid tot aanpassingen van het stress-regelsysteem en het immuunsysteem van het lichaam. Verder werd verondersteld dat die fysiologische aanpassingen of ontregelingen samengaan met de klachten die waargenomen worden bij burnout, met name vermoeidheid en depressieve klachten.

WAT IS EEN BURNOUT EIGENLIJK?

Mensen met een burnout zijn vooral extreem moe, emotioneel uitgeput en hebben het gevoel ‘opgebrand’ of leeg te zijn. Deze vermoeidheid gaat niet weg na een nacht goed slapen, of een week vakantie. Ze hebben vaak een cynische, afstandelijke houding ten opzichte van hun werk, en hebben het gevoel dat ze verminderd presteren. Daarnaast zijn er nog een reeks klachten zoals concentratie- en geheugenproblemen, hoofdpijn, spierpijn, maag-darm klachten, verstoorde slaap, en een depressieve stemming. Een burnout wordt voornamelijk veroorzaakt door langdurige overbelasting op het werk en onvoldoende herstel, alhoewel thuisfactoren en persoonlijkheid ook een rol spelen. Burnout lijkt op overspannenheid, maar de aanloop naar overspannen zijn is minder lang en de klachten herstellen sneller. Zo’n 9% van de beroepsbevolking in Nederland kan volgens de Utrechtse Burnout Schaal (UBOS) aangemerkt worden als ‘burnout’. In dit proefschrift hebben we ons gericht op mensen met ernstige burnout klachten; de deelnemers zitten in de ziektewet en ontvangen een behandeling vanwege de klachten. Verondersteld werd dat bij ernstige klachten de fysiologische onregeling sterker aanwezig en dus beter meetbaar is. De deelnemers zijn opnieuw gemeten na een behandelingsfase, welke plaatsvond bij een instelling gespecialiseerd in het behandelen van werk-gerelateerde klachten. Zou een afname van de klachten samengaan met een verandering in de fysiologie?

HOE ZIT HET MET DE FYSIOLOGIE?

Om de mogelijke verstoring bij burnout beter te begrijpen is het nodig eerst wat te weten over stress. Tijdens een acute stressrespons (denk aan een aanstormende leeuw, een presentatie geven voor een volle zaal) vinden er razendsnel aanpassingen plaats in het lichaam om aan de eisen van de omgeving te voldoen. In eerste instantie zorgt het activerende, sympathische zenuwstelsel voor de nodige actie (vechten, vluchten, vrezende). De hartslag en ademhaling worden versneld, de bloeddruk neemt toe en je wordt scherp en alert. Tegelijkertijd wordt het parasymphatische zenuwstelsel (rust, groei en herstel) onderdrukt. Uitrusten, eten, verteren, groeien, immuunreacties en dergelijke vragen veel energie en zijn op dat moment minder belangrijk. Het is niet moeilijk voor te stellen dat bij chronische stress en onvoldoende herstel de balans tussen het energievretende sympathische zenuwstelsel en het herstellende parasymphatische zenuwstelsel verstoord kan raken en dat dat nadelige gevolgen kan hebben voor alle betrokken processen. Het woord wat bij dit proces hoort is ‘allostase’, ofwel het stabiel houden van het lichaam door continue aanpassingen van verschillende regelsystemen. De keerzijde van de medaille is de ‘allostatic load’, vrij vertaald ‘allostatische last’, de druk op de regelsystemen door aanpassing aan extreme omstandigheden. Vergelijk dit met het continue verwarmen van een kamer, wat makkelijk gaat onder normale omstandigheden, maar wat problemen kan geven met een open raam en vrieskou. Het hormoon wat een centrale rol speelt in deze processen en in dit proefschrift, is cortisol.

CORTISOL

Cortisol, een glucocorticoïde, zorgt ervoor dat er voldoende energie beschikbaar is, het reguleert de opslag en aanmaak van glucose, onderdrukt het immuunsysteem en beïnvloedt andere hormonen en regelsystemen. Tijdens een stressreactie wordt de hypothalamus-hypofyse-bijnier – as geactiveerd (in het Engels de ‘Hypothalamus-Pituitary-Adrenal’ – as, of HPA-as). In de hersenen, in het gebied wat de hypothalamus heet, wordt het hormoon CRH (Corticotropine vrijmakend hormoon) afgegeven, wat de hypofyse aanzet tot de aanmaak van ACTH (Adrenocorticotrop hormoon). ACTH in het bloed stimuleert de aanmaak en afgifte van cortisol door de bijnieren. Cortisol heeft onder normale omstandigheden een circadiaan verloop, er wordt minder aangemaakt in de loop van de dag, met het laagste niveau in de eerste helft van de nacht en het niveau stijgt weer gedurende de tweede helft van de nacht. In het eerste half uur na het ontwaken wordt er extra veel cortisol afgegeven, de zgn. ‘Cortisol Awakening Response’ (CAR). De cortisolniveaus tijdens de CAR benaderen de hoeveelheid cortisol die bij stress vrijkomen en het is een veelgebruikte maat in stress-gerelateerd onderzoek. Een bijkomend voordeel van cortisol is dat het gemakkelijk te bepalen is in het speeksel, de deelnemers kunnen dat zelf thuis afnemen. Cortisol is in staat zijn eigen aanmaak te remmen, het heeft een negatieve feedback op het niveau van de hypothalamus en de hypofyse waardoor er

respectievelijk minder CRH en ACTH wordt afgegeven en er uiteindelijk dus minder cortisol vrijkomt. Dexamethason, een synthetisch glucocorticoïd, heeft eenzelfde effect als cortisol en is ook in staat de aanmaak van cortisol te remmen. Door proefpersonen te vragen een lage dosis dex in te nemen kan inzicht verkregen worden in de mate waarin cortisol in staat is zijn eigen aanmaak te remmen en is een maat voor de negatieve feedback functie van de HPA-as.

Het was aan het begin van het project aannemelijk dat het cortisolniveau, gemeten meteen na ontwaken, in de loop van de dag, en na inname van dexamethason, ontregeld zou zijn bij burnout. Enkele studies wezen in die richting en ook onderzoek in syndromen die wat betreft klachtenpatroon sterk lijken op burnout, zoals het chronisch vermoeidheidssyndroom (CFS), vitale uitputting en depressie laten verstoorte cortisol niveaus zien. Hoe de verstoring bij burnout er precies uit zou zien was nog niet duidelijk.

EEN ONDERZOEK IN DRIE DELEN.

In drie verschillende onderzoeken is het cortisol gemeten in een burnout groep. Om te kijken of de het cortisol in de burnout groep ontregeld is, zijn de resultaten vergeleken met de resultaten van een gezonde controlegroep: mensen zonder klachten die gewoon aan het werk zijn (hoofdstuk 2, 3 en 5). De mensen in de burnout groep hebben een behandeling ontvangen, de controle groep niet, daarom zijn de resultaten vóór en na de behandeling met elkaar vergeleken (hoofdstuk 2 en 4).

In eerste instantie is er een pilot-onderzoek gedaan met 22 mensen met burnout en 21 controles. In deze groepen is het cortisol na ontwaken en het cortisol in de loop van de dag gemeten. De burnout groep had een significant verlaagd cortisol niveau na ontwaken in vergelijking met de controlegroep. Het dagniveau was niet verschillend. Na 14 therapie sessies is de burnout groep opnieuw gemeten; het cortisol na ontwaken was significant hoger in vergelijking met de voormeting en de burnout klachten waren significant afgenomen. Er was echter geen verband tussen de afname in klachten en de toename in het cortisol na ontwaken.

Dit pilot-onderzoek was veelbelovend en is dan ook herhaald in een grotere groep. In hoofdstuk 3 staat beschreven dat een nieuwe burnout groep van 74 deelnemers en een controlegroep van 35 mensen, in tegenstelling tot resultaten in de pilot, niet van elkaar verschilden in het cortisol na ontwaken en in de loop van de dag. Ook de mate van cortisol suppressie na dexamethason inname was niet verschillend tussen de groepen. Uit onderzoeken in CFS en depressie weten we dat vermoeidheid vaak samengaat met verlaagde cortisolniveaus en depressie met verhoogde cortisol niveaus. Aangezien vermoeidheid en depressieve klachten beide aanwezig zijn in burnout is het mogelijk dat het gemiddelde 'normale' cortisolniveau verbloemd is door de tegengestelde effecten van vermoeidheid en depressie. Dit hebben we getoetst, maar er bleek geen effect van vermoeidheid of depressieve klachten op cortisol in de burnout groep. Omdat deze resultaten in een grotere groep zijn gemeten zijn deze data meer betrouwbaar dan die uit

het pilotonderzoek. De conclusie van dit onderzoek is dat er geen ontregeling van de HPA-as is bij burnout, zoals gemeten in het cortisol ochtendniveau, dagverloop en negatieve feedback na dexamethason inname.

De burnout groep uit dit onderzoek is opnieuw gemeten na een behandelingsperiode, van ongeveer 8 maanden, en nog eens 6 maanden daarna (de 'follow-up' meting)(hoofdstuk 4). De centrale vraag in hoofdstuk 4 was of een afname van de klachten samengaat met een verandering van het cortisolniveau. De burnout klachten waren significant afgenomen na de behandel fase, maar deze verbetering zette niet verder door tijdens de follow-up meting, de klachten bleven stabiel. Ook waren de klachten tijdens de follow-up meting nog steeds hoger in vergelijking met de normale Nederlandse populatie. Het cortisol na ontwaken en na dexamethason inname was niet veranderd op de drie opeenvolgende meetmomenten. Er was wel een significante, maar kleine, afname in het dagniveau van cortisol op de opeenvolgende meetmomenten. Ondanks het ontbreken van duidelijke verschillen in het cortisolniveau tussen de meetmomenten was het zinvol om te kijken naar een samenhang van klachtenafname en het cortisol. Niet iedere persoon herstelt even goed, er is variatie in de afname van klachten tussen personen in de burnout groep. Op dezelfde manier is er variatie in het cortisolniveau tussen personen en het is bekend dat herhaalde metingen van cortisol meer stabiel zijn binnen personen dan tussen personen onderling. Het is dus mogelijk dat veranderingen binnen personen op de opeenvolgende meetmomenten meer informatief zijn dan de verschillen tussen de personen in de burnout groep. Dat hebben we getoetst in een statistisch model. Er kwam uit dat vermoeidheid bij aanvang van de studie samengaat met een hoger cortisol niveau na ontwaken over de drie meetmomenten. De afname van vermoeidheid hangt samen met een afname van het cortisol na ontwaken, en de afname van depressieve klachten hangt samen met een toename in cortisol na ontwaken. Deze uitkomsten waren ongeveer even sterk toe te schrijven aan de verschillen tussen de personen als de veranderingen binnen personen. De uiteindelijke conclusie van dit onderzoek, en de onderzoeken hiervoor, is dan ook dat cortisol niet bruikbaar is om de diagnose burnout mee vast te stellen en informatie over cortisol heeft ook geen voorspellende waarde voor het verloop van de klachten.

IMMUUNSYSTEEM

Een ander onderdeel van het onderzoek was gericht op de vraag of er een ontregeling in het immuunsysteem is. Eerder was gevonden dat mensen met burnout meer verkoudheid, griep-achtige klachten, en maag-darm klachten rapporteren, wat wijst op een verminderde afweer. In het bloed zijn bepalingen gedaan om de aantallen en soorten immuuncellen te meten. Daarnaast is een afweerreactie nagebootst, de cellen werden geactiveerd om de aanmaak van cytokines op te wekken. Cytokines zijn de boodschapperstoffen van het immuunsysteem en kunnen grofweg ingedeeld worden in pro-inflammatoire cytokines, de ontstekingsbevorderende en de ontstekingsremmende, anti-inflammatoire cytokines. Cytokines worden aangemaakt door alle typen immuuncellen, we hebben ons hier gericht

op twee typen immuuncellen: de macrofagen en de T-cellen. Macrofagen zijn vreetcellen die niet-specifiek binnendringende ziekteverwekkers in het lichaam 'opeten'. Stukjes van een ziekteverwekker, bijv. een bacterie, worden daarna aan de buitenkant van de cel gepresenteerd als zogenaamde 'antigenen'. De macrofaag heet nu een antigen-presenterende cel, gaat op zoek naar T-cellen en geeft T-cel lokkende cytokines af. T-cellen zijn onderdeel van het specifieke immuunsysteem. Eén T-cel bindt specifiek aan één soort antigen. Als de T-cel z'n specifieke antigen tegenkomt onder de juiste omstandigheden gaat de T-cel zich delen. Dat heet proliferatie. Ook de T-cel maakt nu verschillende cytokines aan om de rest van het immuunsysteem te mobiliseren en de ziekteverwekker op te ruimen. Dit is, in een notendop, een immuunreactie.

Bij patiënten met CFS of depressie blijkt de balans tussen de aanmaak van de pro- en anti-inflammatoire cytokines verschoven te zijn. Ook is in sommige studies gevonden dat de reactie van het immuunsysteem op dexamethason veranderd is. Dexamethason en cortisol zijn sterke remmers van het afweersysteem, glucocorticoïden worden dan ook veel gebruikt als ontstekingsremmende medicatie. We hebben bij burnout onderzocht of de pro- en anti-inflammatoire cytokines ontregeld zijn, of de balans verschoven is en of de remmende werking van dexamethason op de aanmaak van de cytokines anders is, in vergelijking met een gezonde controlegroep. De cytokines waar we ons op gericht hebben zijn: interleukine 10 (IL-10), een anti-inflammatoir cytokine wat aangemaakt wordt door zowel gestimuleerde macrofagen als gestimuleerde T-cellen; TNF- α (Tumor Necrosis Factor – alfa), een pro-inflammatoir cytokine, in dit onderzoek aangemaakt door gestimuleerde macrofagen en tot slot IFN- γ (Interferon-gamma), pro-inflammatoir aangemaakt door gestimuleerde T-cellen.

Tot slot is in dit onderzoek gekeken naar het cortisol na ontwaken en na dexamethason innamen en is er een ander hormoon van de HPA-as gemeten: dehydroepiandrosterone-sulfaat (DHEAS). DHEAS heeft een aantal functies die tegengesteld zijn aan cortisol en het beïnvloedt ook het immuunsysteem.

SICKNESS BEHAVIOR

Een ander motief om dit onderzoek te doen is een relatief nieuwe tak van onderzoek die zich richt op ziektegedrag ofwel 'sickness behavior'. Op het moment dat je een griepje hebt ga je ander gedrag vertonen, gericht op rust en herstel. Je krijgt koorts, doet er alles aan om het warm te krijgen (rillen, dikke truien aan), je voelt je moe, hebt pijnlijke spieren, krijgt meer slaap maar slaapt onrustiger, hebt minder zin om erop uit te gaan en mensen te zien, minder zin om te eten, en je voelt je akelig, rot en somber. Het is niet toevallig dat veel van deze klachten lijken op wat mensen met een depressie ervaren en op dezelfde manier kan deze gedachtengang doorgetrokken worden voor burnout. Inmiddels is bekend dat verschillende soorten cytokines verantwoordelijk zijn voor dit gedrag. Als je ratten inspuit met IL-1, dan gaan ze ziektegedrag vertonen. Mensen die een acute infectie hebben met het Epstein-Barr Virus (de veroorzaker van de ziekte van Pfeiffer) hebben meer IL-1 en

IL-6 en de hoeveelheid cytokine hangt samen met de malaiseklachten, vermoeidheid, pijn, stemming en verminderd concentratievermogen. Bij burnout was dit nog niet eerder onderzocht en we waren benieuwd of de gemeten cytokines zouden samenhangen met klachten die lijken op ziektegedrag, zoals vermoeidheid, depressie en slaap.

RESULTATEN IMMUNONDERZOEK

In totaal is er bij 56 burnout mensen speeksel afgenomen voor de HPA-as bepalingen en bij 49 van hen is bloed afgenomen voor de immuunbepalingen. Deze resultaten zijn vergeleken met de resultaten van 38 controle deelnemers en staan beschreven in hoofdstuk 5. Het meest opvallende resultaat was dat in de burnout groep significant meer IL-10 afgegeven werd door macrofagen (monocyten, de vreetcellen). De afgifte van het anti-inflammatoire IL-10 uit T-cellen was niet verschillend. Ook de hoeveelheid aangemaakte pro-inflammatoire cytokines TNF- α en IFN- γ was niet anders. De remmende werking van dexamethason op de afgifte van cytokines was niet verschillend tussen de groepen. Net zoals in de eerdere onderzoeken was het cortisolniveau na ontwaken en na dexamethason inname niet verschillend tussen de groepen. De burnout groep had wel een hoger DHEAS niveau dan de controlegroep.

Dit is het eerste onderzoek naar burnout waarbij zo uitgebreid is gekeken naar cytokines. Er zijn aanwijzingen dat een verhoogd IL-10 samengaat met een toegenomen gevoeligheid voor verkoudheid en infectieziekten. In ons onderzoek was er echter geen direct verband tussen verkoudheid of griep-achtige klachten en het IL-10 niveau. Ook was er geen correlatie tussen de gerapporteerde klachten en het IL-10, wat je op grond van de sickness behavior theorie wel zou verwachten. Een verband tussen de burnout klachten en een ontregeld immuunsysteem is dus alleen nog op groepsniveau (burnout versus controlegroep) gevonden. Toekomstig onderzoek moet uitwijzen of en hoe IL-10 betrokken is bij de gevoeligheid voor infecties en de gerapporteerde klachten in burnout.

WAT KUNNEN WE HIER MEE?

De directe toepasbaarheid van deze resultaten is beperkt. Er is wel een begin gemaakt met onderzoek naar ontregelingen in het immuunsysteem. Het immuunonderzoek zou herhaald moeten worden, waarbij specifiekere gekeken wordt naar het verband tussen het cytokine IL-10, de burnout klachten en de gevoeligheid voor infectieziekten. Een voorbeeld van zo'n onderzoek is om te kijken in een burnout groep naar de reactie van het immuunsysteem op een griep prik. Het immuunsysteem raakt hierdoor geactiveerd, de verwachting is dat de burnout groep minder antistoffen gaat aanmaken tegen griep en wellicht dat het IL-10 daar een rol in speelt.

Wat wel duidelijk is geworden is dat het cortisolniveau geen geschikte maat is om een diagnose burnout te stellen en er kan ook niet mee voorspeld worden wie herstelt van de klachten en wie niet. Er is niet zoiets als een te laag of een te hoog cortisolniveau in

burnout. Dit wil nog niet zeggen dat het HPA-as systeem helemaal niet betrokken is bij burnout. Het verhoogde DHEAS niveau in burnout is een mogelijke aanwijzing dat er toch iets aan de hand is. Ook zijn er lokale factoren die het cortisolniveau ter plaatse direct beïnvloeden. Die factoren zouden kunnen bijdragen aan de mate waarin cortisol effectief is, wat weer gevolgen heeft voor bijvoorbeeld de energiebalans en het immuunsysteem. Het kan ook zijn dat meerdere regelsystemen een beetje ontregeld zijn, maar niet voldoende om afzonderlijk te kunnen meten. Er zijn al onderzoeken die zich richten op de 'allostatic load' score, een optelsom van meerdere regelsystemen. Een andere mogelijkheid is dat de ontregelingen zich voor ons onzichtbaar in de hersenen afspelen, op het niveau van neurotransmitters zoals serotonine, dopamine, noradrenaline en acetylcholine. Dat wordt al wat lastiger te meten bij mensen. Het meeste onderzoek naar deze stoffen vindt dan ook plaats bij ratten en muizen, die je een vorm van werk-stress kan geven door ze steeds meer te laten rennen in een rad voor ze hun voedsel krijgen. Een relatief nieuwe tak van onderzoek richt zich op het meten van kleine genetische verschillen tussen mensen. Het idee daarachter is dat ieder onderdeelje in het lichaam, bijvoorbeeld de receptor waar cortisol aan bindt, de GR-receptor, net iets kan verschillen tussen personen. Daardoor kan het zijn dat die GR-receptor bij de ene persoon net iets beter cortisol bindt dan bij de andere. Zo zijn er al verschillen gevonden in de gevoeligheid voor een stresstaak tussen mensen die kleine genetische verschillen in de GR-receptor hebben. Dit is natuurlijk nog maar één voorbeeld. Er zijn al met al nog voldoende richtingen om op te gaan wat betreft onderzoek naar burnout.

Wat hopelijk duidelijk is geworden is dat het *aannemelijk* is dat er bij burnout fysiologische ontregelingen hebben plaatsgevonden, die verband houden met de klachten. De burnout klachten kunnen dus letterlijk 'tussen de oren' zitten, wat de klachten niet minder waar of erg maakt. Het vaststellen van een burnout aan de hand van fysiologische maten is echter op dit moment nog niet mogelijk, het geheel zit complexer in elkaar dan we bij het begin van dit promotieonderzoek hadden kunnen bedenken.

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CURRICULUM VITAE

Paula Maria Christina Mommersteeg was born on March 17 1976 in the village of Haarsteeg, Noord-Brabant. After finishing high school at the D'Oultremontcollege in Drunen in 1994 she moved to Utrecht to study biology at Utrecht University. During her study she participated in various research projects: the electroreception organ of catfish as a model for cytosaticum-induced hearing-loss (dept. of Comparative Physiology, Faculty of Biology, Utrecht University), partner recognition in *Paramecium* (section of Molecular Cell Biology, Faculty of Science, Tohoku University, Sendai, Japan), and the communication between expanding nerve cells and activated mast cells of the immune system (dept. of Pharmacology and Pathophysiology, Faculty of Pharmacy, Utrecht University). As a student, Paula had numerous jobs on the side. Among others, Paula worked as an assistant teacher in the subjects neuro-ethology, evolutionary biology and statistics. In 1998 she participated in the 'Tohoku University Junior Year Programme', allowing her to do six months of biological research in Sendai, Japan. Her fondness for Japanese (sub)culture and cuisine has not waned since then. She finished her undergraduate degree by writing her undergraduate thesis on 'the Neurobiology of Post-traumatic Stress Disorder' at the department of Health Psychology, Faculty of Social Sciences.

Being intrigued by the complex interplay of stress, stress related health outcomes and the role of physiology, she enthusiastically started her PhD study on 'the Psychophysiology of burnout' in 2001. The project was a cooperation between the department of Health Psychology, supervised by Prof. Lorenz van Doornen, and the Psychoneuroimmunologie lab at the Wilhelmina Children Hospital in Utrecht, under supervision of Prof. Cobi Heijnen and Dr. Annemieke Kavelaars. As a PhD student she coordinated three research projects doing the logistics of questionnaire, salivary and blood sampling, maintain contact with several health care institutions and participants, collaborate in burnout-related projects, and analyse and report the data. The results of these projects are presented in this thesis, have been presented in national and international conferences and have been published as research papers in the relevant journals. At present she works as a post-doc at the Psychoneuroimmunology lab on the 'Prospection In Stress-related Military Research' (PRISMO)-project in collaboration with the Central Military Hospital.

Paula lives happily in Utrecht with Anne Baretta, their son Olaf and Vlerk the cat.

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