



# 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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## KEYWORDS

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pression test;  
Fatigue;  
Depression

**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 2 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.

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## 1. Introduction

The burnout syndrome is characterized by excessive exhaustion, a cynical work attitude and feelings of reduced competence (Maslach et al., 2001). In addition, increased irritability, muscular aches and

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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 min after awakening. The CAR is supposed to represent the capacity of the adrenal cortex to produce cortisol (Schmidt-Reinwald et al., 1999). Changes in the CAR have been associated with measures of chronic work stress (Schulz et al., 1998; Lundberg and Hellström, 2002; Kunz-Ebrecht 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 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 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 et al., 2001; Huibers 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 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 et al., 2003b). 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 et al., 1998; Heim et al., 2000; Parker et al., 2001; Gaab et al., 2002; Roberts et al., 2004; Yehuda 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.

## 2. Methods

### 2.1. 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 et al., 1997; Groenestijn 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.

### 2.2. 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 min after awakening, and at 1200 h (before lunch), 1800 h (before dinner) and at 2230 h. Participants were instructed to take an oral dose of dexamethasone (0.5 mg, PO) on the second evening at 2230 h, after taking the saliva sample. On the consecutive morning three saliva samples were collected at 0, 15 and 30 min 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 min 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 (DELFI), as described elsewhere (Dressendorfer 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.

### 2.3. 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 et al., 1997; Pruessner et al., 1997; Kirschbaum 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 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 et al., 1990). Level of depressive symptoms were assessed with the Dutch version of the CES-D, 20 items (Bouma 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.

## 2.4. 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 min after awakening), or day-curve (1200, 1800 and 2230 h) 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. (2003a). 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.

## 3. Results

### 3.1. 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

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

		Burnout ( <i>n</i> =74)	Control ( <i>n</i> =35)	Test variable
Gender	Male:Female ( <i>n</i> )	53:21	25:10	$\chi^2=0.00$
Age	Years	43.9 (8.7)	44.9 (10.5)	$F=0.266$
BMI	kg/m <sup>2</sup>	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 standard deviations) or percentages. \* $p < 0.05$ ; \*\*\* $p < 0.001$

**Table 2** Test variables in the burnout and control group.

			Burnout (n=74)	Control (n=35)	Test value F	
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***	
		Agoraphobia	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 standard deviations). \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

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.

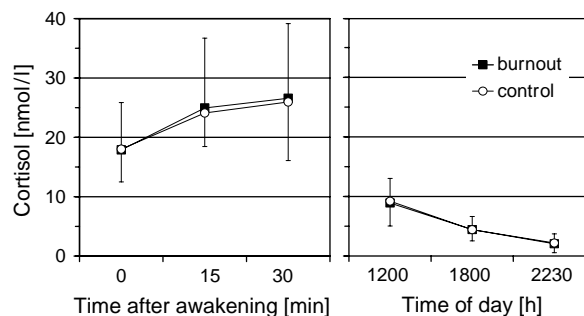
### 3.2. Level of complaints

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).

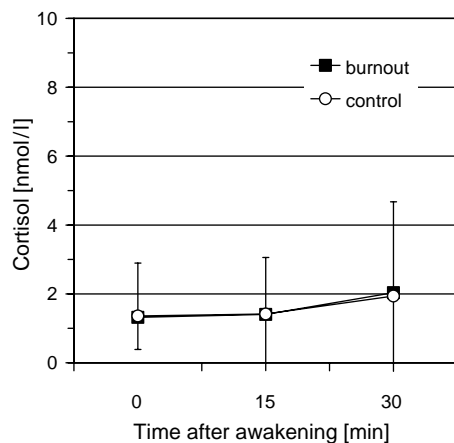
### 3.3. Cortisol awakening response and day-level

In Fig. 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 min after awakening (main effect of time,  $F=36.4$ ,  $df=1.5$ ,  $159$ ,  $p < 0.001$ , partial eta squared  $\eta^2=0.26$ ), and a significant

decline of cortisol during the day (main effect of time,  $F=169.6$ ,  $df=1.4$ ,  $149$ ,  $p < 0.001$ ,  $\eta^2=0.62$ ). There was, however, no difference between the burnout and the control group in cortisol level (group,  $F=0.07$ ,  $df=1$ ,  $105$ ,  $p=.79$ ,  $\eta^2 < 0.01$ ) or rise after awakening (group $\times$ time,  $F=0.12$ ,  $df=1.5$ ,  $159$ ,  $p=.89$ ,  $\eta^2 < 0.01$ ), or in level (group,  $F=0.12$ ,  $df=1$ ,  $104$ ,  $p=.73$ ,  $\eta^2 < 0.01$ ) or decline during the day (group $\times$ time,  $F=.09$ ,  $df=1.4$ ,  $149$ ,  $p=0.86$ ,  $\eta^2 < 0.01$ ). 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,  $t(107)=0.37$ ,  $p=0.72$ .



**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.



**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.

### 3.4. Cortisol awakening response after dexamethasone suppression

Fig. 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 min post-awakening period, (main effect time;  $F=5.9$ ,  $df=1.5$ , 137,  $p=0.003$ ,  $\eta^2=0.06$ ). There was no difference between the burnout ( $n=64$ ) and the control group ( $n=31$ ) in the rise (group $\times$ time;  $F=0.06$ ,  $df=1.5$ , 137,  $p=0.89$ ,  $\eta^2<.01$ ), nor in the mean level after awakening (group;  $F=0.002$ ,  $df=1,93$ ,  $p=0.97$ ,  $\eta^2<0.01$ ). Excluding participants with possible influencing medication and comorbidity of diagnosis did not alter the results.

### 3.5. 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).

### 3.6. 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).

### 3.7. 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.

## 4. 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 (De Vente et al., 2003; Grossi et al., 2004; Mommersteeg et al., in press). 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 min 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 et al., 2003; Moch et al., 2003; Mommersteeg 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 et al., 1999; Pruessner et al., 1999; Grossi et al., 2003), and higher levels during the day (Melamed 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 of 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 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 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 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 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 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 et al., 2003), which implies, however, that a similar 40-60% of drug-free depressed patients do *not* show hypercortisolism (Brown et al., 2004). Moreover, hypercortisolism is not a core characteristic of MDD in outpatients and community samples (Peeters 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 et al., 2003; Broderick 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), (sub-scales 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 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 cannot 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 et al., 2000; Peeters 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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