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A longitudinal study on cortisol and complaint reduction in burnout

Paula M.C. Mommersteeg[a], Cobi J. Heijnen[b], Marc J.P.M. Verbraak[c], Lorenz J.P. van Doornen[a],*

[a]*Department of Health Psychology, Utrecht University, P.O. Box 80.140, 3508 TC Utrecht, The Netherlands*
[b]*Laboratory for Psychoneuroimmunology, Division of Perinatology and Gynaecology, University Medical Center, Office: KC 03.063.0, P.O. Box 85090, 3508 AB Utrecht, The Netherlands*
[c]*HSK-group, St Annastraat 174, 6524 GT Nijmegen, The Netherlands*

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.

* Corresponding author. Tel.: +31 30 253 4690; fax: +31 30 2534718.
E-mail addresses: p.m.c.mommersteeg@fss.uu.nl (P.M.C. Mommersteeg); l.vandoornen@fss.uu.nl (L.J.P. van Doornen).

1. 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 et al., 2001). Its symptoms are depressed mood, increased irritability, inability to relax, disrupted sleep, somatic complaints as aching muscles, headaches, gastrointestinal 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 6-month period towards the normal range in 30-50% of a working population after physical and cognitive intervention (van Rhenen 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 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 et al., 2001; Parker et al., 2001; Parker 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 et al., 1999; Pruessner et al., 1999; Grossi 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 cortisol levels after awakening, and higher and unchanged levels during the day were reported (De Vente et al., 2003; Moch et al., 2003; Grossi et al., 2005; Mommersteeg et al., 2006b).

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 et al., 2006a). In the present study, the same group of burnout participants were measured again after having received treatment and once more at follow-up, about 6 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 et al., 2006b). 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 et al., 1997; Huizenga et al., 1998; Wust et al., 2000b). Perhaps the inter-individual variability obscures any changes in cortisol functioning within persons, that could be observed when measured in a longitudinal settting. 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 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.

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 (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 et al., 2006a). 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.

2.2. 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 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.

2.3. Cortisol measurement protocol

The participants received instructions, filled out questionnaires and collected saliva at home, which were returned by post after completion (Clements & Parker, 1998). Participants were instructed not to brush their teeth, eat or drink coffee or alcohol 30 min 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 min 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 et al., 2000).

During the first 2 days saliva was collected 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 morning of day 3 the dexamethasone-suppressed cortisol levels were determined at 0, 15 and 30 min 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%.

2.4. 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 & 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 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 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 et al., 1995). Finally, the Dutch version of the symptom checklist (SCL-90) was used to assess (psycho)somatic complaints (Arrindel & 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.

2.5. 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 experienced work-related health problems in the past. Every time a saliva sample was taken, time, activity level, perceived stress (Smyth et al., 1998), and food, smoking and drink intake was kept in a paper diary (Canals 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 et al., 1997; Kirschbaum et al., 1999).

2.6. 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 χ^2 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.

2.6.1. 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 et al., 2002), using cortisol as the dependent variable (Hruschka 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 2 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 variance 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.

2.6.2. 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 min after awakening, on two consecutive days. The second model, the DAY-model, contains the daily cortisol samples, taken at 1200 h (noon), 1800 and 2230 h, on 2 consecutive days. In the third model, the suppressed cortisol levels after dexamethasone intake are sampled at 0, 15 and 30 min 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.

2.6.3. 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 min period before taking a sample were all coded '1' if taken and '0' if not taken. Third, activity level in the 30 min 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 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.

3. Results

3.1. Longitudinal group characteristics

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

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

		Baseline $n=74$	Post-treatment $n=62$	Follow-up $n=53$
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%)***

*$p<0.05$, **$p<0.01$, ***$p<0.001$. Means (SD) or number (%)
[a] Wilcoxon signed rank test of baseline—post-treatment and post-treatment—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).

3.2. 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.

3.3. Basic cortisol analysis

Fig. 1 shows the mean cortisol values at baseline, post-treatment and at follow-up, for the cortisol awakening response (CAR), and the day-curve. Fig. 2 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 2230 h 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.

3.3.1. 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

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<0.05, **p<0.01, ***p<0.001. Mean (SD).
[a] Data 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.
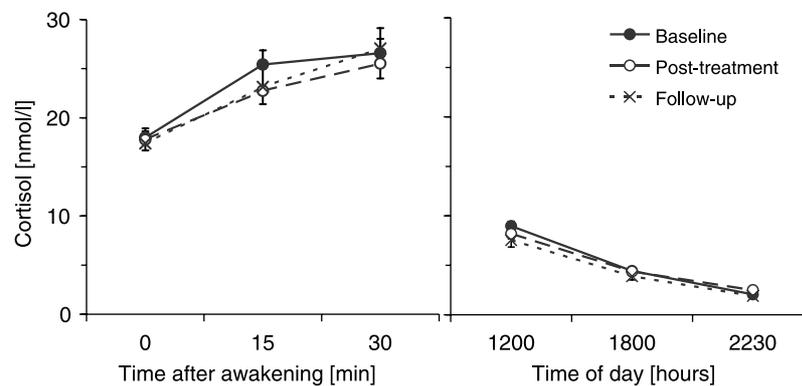
Figure 1 Cortisol after awakening (CAR) (left) and cortisol day-curve (DAY) (right) at baseline, post-treatment and at follow-up. Mean data of 2 days and SEM are shown.

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.

3.3.2. 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
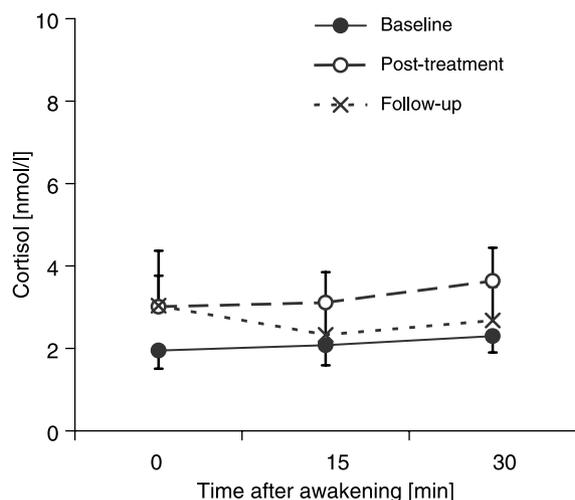

Figure 2 Cortisol awakening response after dexamethasone intake (DST) at baseline, post-treatment and at follow-up. Mean data and SEM are shown.

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 Fig. 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

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 (s.e.)	β[b]		Estimate (s.e.)	Estimate (s.e.)
Basic model[a]					
Intercept	3.402 (0.235)***			4.348 (0.085)***	−0.123 (0.053)*
Slope	0.406 (0.035)***			−0.132 (0.004)***	−0.014 (0.017)
Main effects					
Time-point	0.022 (0.083)			−0.071 (0.034)*	−0.030 (0.042)
Exhaustion baseline	0.241 (0.116)*	0.169			
⊿ Exhaustion[c]	−0.340 (0.108)**	−0.350			
Depression baseline	−0.015 (0.013)	–			
⊿ Depression[c]	0.037 (.014)**	0.283			

*p<0.05, **p<0.01, ***p<0.001. 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 (⊿)=variable at baseline−mean (variable post-treatement and variable follow-up).

confounding variables gender (men=0, women=1)(estimate=−0.302, s.e.=0.084, p<0.001, β=0.205), smoking (estimate=−0.243, s.e.=0.081, p=0.003, β=0.169), antidepressant use (estimate=−0.556, s.e.=0.115, p <0.001, β=0.242) and anti-hypertensive medication (estimate=−0.587, s.e.=0.200, p=0.003, β=0.169). 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.

3.3.3. 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 Fig. 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.

3.3.4. DST-model

The outcome variable cortisol after awakening after dexamethasone intake, or cortisol DST, showed significant variance at sample-level (ICC=0.27), time-point−level (ICC=0.49) and at person-level (ICC=0.24). 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). Fig. 2 shows the DST curves at baseline, post-treatment and at follow-up. The following confounders had a significant effect: gender (estimate=−0.171, s.e.=0.050, p<0.001, β=0.257), and smoking (estimate=−0.108, s.e.=0.046,

$p=0.02$, $\beta=0.167$). 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.

4. 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.

4.1. 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 & Ettema, 1981; Bouma et al., 1995; Bultmann et al., 2000; Schaufeli 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.

4.2. 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 et al., 2006b). 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 et al., 1997; Huizenga et al., 1998; Wust et al., 2000b). 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 et al., 2000a; Kupper 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.

4.3. 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 et al., 2006b). 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 et al., 2006a). 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.

4.4. 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 et al., 1999; Kudielka & Kirschbaum, 2003; Kunz-Ebrecht 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 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 min period before taking a sample. There were no differences between the different sampling days for sleep-quality, hours spent in bed, daily physical complains 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.

5. 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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