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Sick and tired: psychological and physiological aspects of work-related stress

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7 Group Stress-Management Training enhances morning cortisol in patients with work-related stress complaints: neuroendocrine and immunological outcomes from a randomised controlled trial*

Abstract

Background: The effects of Stress-Management Training (SMT) on the neuroendocrine and immune functions in work-related stress is largely unknown. *Method:* In a randomised controlled trial the effects of SMT, either in individual- (SMT-I) or group- (SMT-G) format, was compared to care as usual (CAU). Sixty-one patients with work-related stress were measured at baseline and four months later. SMT comprised twelve sessions conducted by a psychologist. Neuroendocrine measures were basal cortisol and dehydroepiandrosterone-sulphate (DHEAS) levels during the morning, and the cortisol and DHEAS awakening responses (CAR, DAR, respectively). Immune measures were immunoglobulin G (IgG) against Epstein-Barr virus (EBV) and C-reactive protein (CRP). Neuroendocrine and immune measures were determined in saliva. *Results:* The mean basal cortisol level increased in the SMT-G condition, while it decreased in the CAU condition. This group difference remained statistically significant after adjustment for potential non-compliance and potential selective dropout. *Conclusion:* SMT delivered in a group format changes HPA axis activity in patients with work-related stress. It is speculated that social support is a key component in the group treatment which results in changes at the neuroendocrine level.

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Work-related stress is highly prevalent and frequently results in sickness absence or even work-disability (e.g., European Communities, 2004; Houtman, Smulders & Hesselink, 2004; Spreeuwers, Pal & van der Laan, 2005). Work-related stress can be reflected in various domains, such as: a) psychosomatic complaints (Bauer et al., 2006); b) distress complaints such as anxiety, depressive, and burnout complaints (Bauer et al., 2006; Lindblom, Linton, Fedeli & Bryngelsson, 2006; Schaufeli & Buunk, 2003); and c) physiological changes in the stress-systems, i.e., the sympathetic system, the hypothalamus-pituitary adrenal (HPA) axis, and the immune system (Grossi, Perski, Ekstedt, Johansson, Lindström & Holm, 2005; Mommersteeg, Heijnen, Kavelaars & van Doornen, 2006a; Mommersteeg, Keijsers, Heijnen, Verbraak & van Doornen, 2006b; Toker, Shirom, Shapira, Berliner & Melamed, 2005; Sonnenschein et al., 2007; Vedhara et al., 2002; de Vente, Olf, van Amsterdam, Kamphuis & Emmelkamp, 2003).

Stress Management Training (SMT) is widely used to treat stress. While a number of studies have documented the self-reported outcomes in terms of complaints, only few studies have focused on the effects of SMT on physiological functions related to work-related stress, and even fewer have reported on those effects in clinical samples. The goal of the present study is to investigate the effects of SMT on the neuroendocrine and immune functions in patients with work-related stress.

SMT is based on cognitive-behavioural principles, and commonly consists of the following elements: relaxation training, cognitive restructuring, and time-management and social skills training (Carson & Kuipers, 1998; Jones & Johnston, 2000; Ivancevich, Matteson, Freedman & Philips, 1990). In addition, life style improvement has been recommended as a treatment component for work-related stress (Maslach, 1982). Effects of these SMT treatment components on physiological functions can be expected through their focus on psychophysiological processes affected by exposure to stressful conditions.

A model describing psychological and psychophysiological processes has been developed by Lazarus and Folkman (1987; Folkman & Lazarus, 1988), and a similar model focusing in particular on neuroendocrine characteristics has been developed by Olf (e.g., Olf, Langeland & Gerssons, 2005). According to these interactional stress models, a situation elicits negative emotions and physiological reactions when it is evaluated by the individual as posing a significant threat and exceeding coping resources. In turn, negative emotions in their turn give rise to coping efforts (Folkman & Lazarus, 1988). Adequate coping ends the threat of the stressor and consequently, negative affect and physiological activation decrease (Olf et al., 2005). Persistent exposure to stressors that are not resolved may result in psychosomatic and distress complaints, physiological changes, and functional impairments (Folkman & Lazarus, 1988; Lazarus & Folkman, 1987; Olf et al., 2005).

SMT treatment components may affect physiological functions directly and indirectly. Direct effects are for example exerted via relaxation (Miller & Cohen, 2001) and lifestyle improvement, for instance the reduction of smoking, alcohol use, inactivity, or dysfunctional sleeping habits. It is known that these aspects of life style affect neuroendocrine and immune activity (e.g., Kiecolt-Glaser & Glaser, 1988). Indirect effects of treatment components on physiological functions can be achieved by techniques influencing appraisal and coping, such as cognitive restructuring, improv-

ing time-management skills, and enhancing social skills (Miller & Cohen 2001). These effects are indirect since appraisal and coping affect physiological activity through influencing affect. Both negative and positive affect are related to neuroendocrine and immune functions (e.g., Brummett, Boyle, Kuhn, Siegler & Williams, 2009; Kiecolt-Glaser, McGuire, Robles & Glaser, 2002; Peeters, Nicholson & Berkhof, 2003; Steptoe, Wardle & Marmot, 2005).

Cognitive-behavioural interventions have been shown to affect the neuroendocrine and immune functions in healthy individuals (Gaab et al., 2003; Kiecolt-Glaser et al., 1985; McCraty, Barrios-Choplin, Rozman, Atkinson & Watkins, 1998) and physically ill patients (Antoni et al., 2005; Cruess et al., 2000; Miller & Cohen, 2001), and to affect the neuroendocrine function in patients with generalised anxiety disorder (Tafet, Feder, Abulafia & Roffman, 2005) or post-traumatic stress disorder (Olf, de Vries, Güzelcan, Assies & Gersons, 2007). A meta-analysis has demonstrated that relaxation techniques and multimodal treatments consisting of cognitive-behavioural elements and relaxation also resulted in physiological changes in relatively healthy individuals with work-related stress (van der Klink, Blonk, Schene & van Dijk, 2001). To our knowledge, only two studies on the effect of cognitive behavioural treatment (CBT) on neuroendocrine outcome variables have been conducted among patients with work-related stress (Mommersteeg et al., 2006b; Mommersteeg, Heijnen, Verbraak & van Doornen, 2006c). In one of these studies, a low morning cortisol level normalised after six months, when complaints had also diminished (Mommersteeg et al., 2006b). However, this non-controlled study did not allow to fully establish that the observed physiological and health changes resulted from the treatment.

To evaluate the effect of SMT on physiological measures, we conducted a randomised controlled trial, in which individual SMT, group-SMT, and care as usual (CAU) were compared. SMT in a group format is a regular preventive intervention for work-related stress, but it is less common for clinical samples (Schaufeli & Buunk, 2003). It has been demonstrated that SMT in a group format indeed enhances well-being in relatively healthy individuals (e.g., van Dierendonck, Schaufeli & Buunk, 1998; de Jong & Emmelkamp, 2000; van der Klink et al., 2001; Rowe, 2000). Incremental effectiveness of group SMT on physiological outcomes can for instance be expected through the effect of social support by group members (Yalom, 1985). More social support is associated with a lower basal cortisol levels (e.g., Turner-Cobb, Sephton, Koopman, Blake-Mortimer & Spiegel, 2000; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto & Sandman, 1996) and with enhanced immune activity (e.g., Gallagher, Phillips, Ferraro, Drayson & Carrol, 2008; Lutgendorf et al., 2005; Miller, Chen & Cole, 2009). Our first hypothesis states that SMT, provided either in an individual format or in a group format, more profoundly affects the neuroendocrine and immune functions than CAU.

The present physiological study was a part of a larger study, in which effectiveness of individual and group-SMT was evaluated. Previously, no superior efficacy of SMT above CAU was found based on self-reported work-related stress complaints, except for indications of superior efficacy of individual SMT in the subgroup with lower depressive complaints (de Vente, Kamphuis, Emmelkamp & Blonk, 2008). Despite the limited effectiveness of SMT on self-reported work-related stress complaints, it is of interest to investigate treatment effects on physiological outcomes for the

following reasons. First, reported complaints and physiological symptoms are only modestly associated. To illustrate, hypertension is not accompanied with particular subjective complaints, and in fact remains commonly unnoticed by patients (e.g., Mendez-Luck, Yu, Meng, Jhavar & Wallace, 2004), and in only half of the patients with a major depressive disorder elevated basal cortisol levels are observed (Checkley, 1996). Second, self-reported complaints are vulnerable to memory bias (Houtveen & Oei, 2007) and motivated misrepresentation related to reintegration or treatment preferences. Findings of the study of Sonnenschein et al. (2007) are in support of a disturbing effect of retrospective bias in the association between complaints and physiological measures.

Furthermore, we investigated whether treatment effects were moderated by the severity of the stress state. Severity indicators were the duration of complaints (chronic versus non-chronic), and the severity of anxiety and depressive complaints. Consistent with the hypotheses of our self-report study (de Vente et al., 2008), our second hypothesis states that SMT is more effective in changing neuroendocrine and immune parameters in less severe patients, i.e., in patients with a shorter duration of complaints or those with lower depressive or anxiety complaints.

Cortisol and dehydroepiandrosterone-sulphate (DHEAS) were selected as neuroendocrine parameters of HPA axis activity. Parameters selected to investigate immune activity were immunoglobulin G (IgG) against Epstein-Barr Virus (EBV) and C-Reactive Protein (CRP). Work-related stress complaints and neuroendocrine and immune parameters were measured before and after a treatment phase of four months.

Method

Participants

Eighty-one patients with work-related stress, recruited through occupational health services ($n = 61$), general practitioners ($n = 7$), and by self-referral in reaction to advertisements ($n = 13$), were included in the study. At follow-up (T₁), 61 patients were measured again. Eligibility was based on a screening interview by telephone assessing the presence of work-related stress complaints. The interview was administered by a clinical psychologist. The subsequent intake procedure consisted of a semi-structured diagnostic interview administered by a clinical psychologist and completion of the Beck Depression Inventory (BDI; Beck & Steer, 1987). During the semi-structured interview, the complaint history was examined and of a short version of the Composite International Diagnostic Interview (CIDI; World Health Organisation [WHO], 1997) was administered. With use of the CIDI presence of diagnoses described in the tenth edition of the International Classification of Diseases (ICD-10) can be assessed. Inclusion criteria were: 1) fulfilment of the symptoms of neurasthenia, i.e., continuous mental and/or physical fatigue and increased fatigability, and at least two other stress complaints out of the following: dizziness, dyspepsia, muscular aches or pains, tension headaches, inability to relax, irritability, and sleep disturbance; 2) a primary role of (a) work-related stressor(s) in the development of complaints as judged by the patient, the referring clinician, and the clinical psychologist; and 3) presence of impaired daily functioning as indicated by (partial)

sickness absence which had lasted at least two weeks but less than six months. Exclusion criteria were: 1) a primary diagnosis of major depression, social phobia, panic disorder, somatoform disorder, other than undifferentiated, posttraumatic stress disorder, obsessive-compulsive disorder, hypomania, or psychotic disorders, assessed with the short version of the CIDI (WHO, 1997); 2) severe depressive complaints (i.e., conservatively defined as ≥ 25 on the BDI); 3) a traumatic event in the past six months; and 4) a medical condition that could explain fatigue (e.g. diabetes); 5) excessive alcohol and/or drug use; and 6) pregnancy. Patients received refund of their travel expenses.

General procedure

The ethics committee of the Department of Psychology approved the research protocol and all patients gave written informed consent. Participants were randomly assigned to one of the three treatment conditions. Randomisation was performed by a person independent of the study using a computer-generated list of random numbers in blocks of 24. Data were collected at before the treatments phase started (T_0) and four months later (T_1). The present physiological study was a part of a comprehensive project, in which the effectiveness of individual and group-SMT was evaluated. Measurements consisted of completing a questionnaire booklet, collecting morning saliva, and attending a psychosocial stress session in the laboratory of the University of Amsterdam. The outcomes regarding acute stress-reactivity are reported elsewhere. This study gives an account of basal neuroendocrine and immune activity.

Materials and Measures

Interventions

Interventions consisted of 12 sessions SMT based on cognitive-behavioural principles. Individual and group-SMT were comprehensively described in two treatment manuals (Kamphuis, de Vente & Emmelkamp, 2001; de Vente, Kamphuis & Emmelkamp, 2001). The SMT-protocols for individuals and groups consisted of five modules addressing: 1) psycho-education, self-assessment of stressors and complaints, life style improvement, and relaxation techniques (progressive relaxation); 2) cognitive restructuring; 3) time management and goal setting; 4) assertiveness; and 5) evaluation and relapse prevention. An extensive description of the SMT can be found elsewhere (de Vente et al., 2008). It should be noted that the SMTs were given in addition to regular consultations of an occupational physician (OP), that are an essential part of patient collaboration with their rehabilitation, as prescribed by the Dutch legal system. The mean number of OP consultations in the individual SMT (SMT-I) condition was 2.9, and in the group-SMT (SMT-G) was 3.3.

CAU consisted of the regular consultations of an OP, consultations of a general practitioner (GP), and/or a maximum of five treatment sessions by a psychologist or social worker. Fifteen patients went to see only the OP and/or GP and 11 patients received treatment (mean number of sessions = 4.6) of a psychologist or social worker. The mean number of consultations of the OP was 2.9 and of the GP was 1.6.

To determine treatment integrity of the SMTs, therapists registered specific pre-coded interventions each session and wrote down comments on the treatment proceedings. Registrations were performed on standardised treatment registration forms, on which core treatment elements per session were listed. Treatment integrity was high. Delivery of the SMT protocol was registered for 81% percent of the core treatment elements included in the protocol. Of these registered elements, 96% was delivered according to protocol. CAU was measured by self-report using weekly diaries.

Psychological measures and background variables

Burnout complaints were measured with the Maslach Burnout Inventory-General Survey (MBI-GS; Schaufeli & van Dierendonck, 2000), which consists of three subscales: Emotional Exhaustion (5 items), Depersonalisation (4 items), and Professional competence (6 items). Items are scored on 7-point Likert scales (0 = never to 6 = always/daily) and mean subscale scores are calculated. Higher scores reflect higher levels of emotional exhaustion, depersonalisation, and professional competence. Psychometric properties are adequate to good (Schaufeli & van Dierendonck, 2000). Cronbach's alphas in the present sample were .82 for Emotional exhaustion, .81 for Depersonalisation, and .76 for Professional competence.

Distress complaints were measured with the Depression Anxiety and Stress Scales (DASS; de Beurs, van Dyck, Marquenie, Lange & Blonk, 2001) and with the subscale General fatigue of the Checklist Individual Strength (CIS; Beurskens et al., 2000). The DASS comprise three subscales of 14 items each, referring to depressive, anxiety, and stress complaints. Severity of complaints during the past week is rated on 4-point Likert scales that range from 0 (not at all/never applicable) to 3 (very much/most of the time applicable). Higher scores represent higher levels of complaints. Psychometric properties are adequate to good (Nieuwenhuijsen, de Boer, Verbeek, Blonk & van Dijk, 2003; de Beurs et al., 2001). Cronbach's alphas in the present sample were .93 for Depression, .86 for Anxiety, and .93 for Stress. The subscale General fatigue of the CIS consists of eight items. Items are scored on a 7-point Likert scale (1 = false to 7 = true). Lower scores indicate lower levels of fatigue. Internal consistency of this subscale is high (e.g., van der Ploeg, Kleber & van der Velden, 2000). In the current sample Cronbach's alpha was 0.91.

Smoking, hours of sleep, Body Mass Index (BMI), and hour of awakening were assessed by questionnaire. Time of awakening was dichotomised in before and after 9am. It has been demonstrated that morning cortisol levels are significantly lower for persons waking up after 9am compared to waking up before 9am, while cortisol levels of persons waking up in the hours before 9am did not differ from each other (Evans, Clow, Hucklebridge & Lai, 2005). Women were also asked to report on menstrual phase, the use of oral contraceptives, and pre-/postmenopausal status.

Saliva sampling protocol

Saliva was collected during the first hour after awakening, i.e., at awakening, and at 30 and 60 minutes thereafter, and at midday using cotton swabs (non-coated Salivettes™, Sarstedt, Nümbrecht, Germany). Participants were instructed to place it under the tongue or between cheek and teeth

for about three minutes. If the swab was not saturated, it was permitted to slowly move it around in the mouth without chewing on it. The method of saliva collection was explained in a detailed instruction form, on which participants reported the time of awakening and collection of the four samples. Participants were instructed not to have breakfast or to brush their teeth within 15 minutes before a sample was collected and to store all samples in the refrigerator until next day's visit to the laboratory. Morning saliva was collected on a weekday avoiding disturbing influences due to different sleeping habits in weekends.

Saliva was also collected five times during a psychosocial stress session in the laboratory, which was scheduled in the afternoon. Saliva was collected as described by Navazesh (1993). Accordingly, the participant refrains from swallowing for a period of four minutes, allowing the saliva to accumulate in the floor of the mouth. The saliva is spitted into a cup every 60 s. The collection starts with the instruction to void the mouth of saliva by swallowing. Fifteen minutes before the first saliva collection, the participant rinses the mouth with water.

Saliva was homogenised by vigorous shaking using a vortex mixer and clarified by centrifugation (10.000 x g. for 4 min). The clear supernatant was divided in 0.5 ml samples and stored in aliquots at -20°C until analysis.

Neuroendocrine and immune measures

Sensitivity or capacity of the adrenal cortex can be studied with use of the cortisol awakening response (Schmidt-Reinwald et al., 1999). First, all four cortisol morning values were used to study the pattern of cortisol levels after awakening. Second, the cortisol awakening response (CAR) was calculated using the cortisol values during the first hour after awakening. The CAR was defined as the highest cortisol-level in the hour after awakening (i.e., at 30 or 60 minutes after awakening) minus the cortisol level at awakening.

DHEAS demonstrated pronounced morning dynamics, which were characterised by a strong reduction after awakening. All four DHEAS morning samples were used to analyse the pattern of DHEAS levels after awakening. In addition, the DHEAS awakening response (DAR) was calculated by subtracting the lowest DHEAS-level in the hour after awakening (i.e., at 30 or 60 minutes after awakening) from the level at the moment of awakening. This measure was also used as an indicator of adrenal cortex sensitivity or capacity.

The cortisol and DHEAS levels at midday (12.00am) were used as indices of basal HPA axis activity. The cortisol/DHEAS ratio was computed for all morning samples, including the midday sample, as an indicator of hormonal (im)balance (Goodyer, Park, Netherton & Herbert, 2001).

Immune parameters were determined in pre-stressor saliva samples collected during the psychosocial stress session. Anti EBV IgG was used as an index of cellular immunity (Cacioppo et al., 2002) and CRP as an index of the innate inflammatory immune reaction (Black, 2002).

Assays

The salivary concentration of free cortisol and DHEAS were determined using enzyme-immuno assay (EIA). CRP (ultrasensitive kit) and anti-EBV IgG (EBV VCA-IgG type) were examined by enzyme linked immunosorbent assay (ELISA). The kits for cortisol, EBV, and CRP were purchased from Diagnostic System Laboratories (DSL, Veghel, The Netherlands). DHEAS was determined by DSL in Germany. IgG and CRP was examined after 2-fold dilution of the saliva sample. Sensitivity of the cortisol, DHEAS, and CRP assays were 1 ng/ml, 0.08 ng/ml, and 1.6 ng/ml, respectively. All samples were assayed in duplo. Intra-assay variability of cortisol, DHEAS, anti-EBV IgG, and CRP, was 2-10%, 4-6%, 2.4-3.5%, and 1.7-3.6%, respectively.

Statistical analyses

Dropout distribution, baseline differences, and change of complaints were assessed using Chi-square tests, independent and dependent t-tests. The main analyses consisted of analyses of covariance for resting values (covariate: resting value at T₀) and analyses of variance (ANOVA) for repeated measures for reactivity and recovery. With the ANOVA for repeated measures a 'treatment' x 'measurement' x 'time'-design was tested. Significant interactions of interest (i.e., treatment x measurement and treatment x measurement x time) were further analysed using post-hoc analyses (Bonferroni-corrected, as implemented in the GLM procedure) or simple contrasts (as implemented in the GLM procedure). When the sphericity-assumption was violated, results adjusted according to Greenhouse-Geisser's method were presented. As age, gender, smoking, and BMI are known to be related to neuroendocrine and immune measures, all analyses were adjusted for these variables.

The main analyses were performed according to the intention-to-treat principle, using all available data. In order to test the robustness of the findings, two alternative analyses were run. First, a dataset consisting of patients who had received the SMT according to protocol (defined as \geq eight sessions) and patients who had received CAU was analysed. Second, a dataset in which the data missing at T₁ were imputed, using the last-value-carries-forward method, was analysed.

Some physiological data were missing due to insufficient saliva (cortisol: 5%, DHEAS: 10%, anti-EBV IgG: 8%, CRP: 7%). Outliers (i.e., values $\pm >3$ SDs of the mean for cortisol, for all other variables: $\pm >4$ SDs of the mean) were removed for each measure separately (<5%). Because of positively skewed data, DHEAS, cortisol/DHEAS, anti-EBV IgG, and CRP values were transformed (\log_e for DHEAS and cortisol/DHEAS, and square-root for anti-EBV IgG and CRP). Two-sided test were performed, applying a significance level of .10 for interactions and .05 for main effects. All analyses were performed using the Statistical Package for Social Sciences (SPSS, version 15.0 for PC).

Results

Dropout analyses and baseline comparisons between conditions

Dropouts were five years younger than non-dropouts ($t(79) = -2.11, p = .038$). For gender, education, severity of any of the stress complaints, or any of the neuroendocrine or immune measures, dropouts did not differ significantly from non-dropouts (all p -values $> .10$). Three patients in the SMT-I condition, seven in the SMT-G condition, and ten in the CAU condition did not provide physiological data at T₁, ($\chi^2(N = 61, 2) = 5.33, p = .070$).

Sample characteristics per treatment condition are presented in Tables 1 and 2. Treatment conditions differed on education ($F(2,58) = 6.32, p = .003$) and BMI ($F(2,58) = 4.72, p = .013$). The SMT-I condition had significantly lower education ($p = .004$) and higher BMI ($p = .010$) than the SMT-G condition. Education did not appear to be a confounder in the analyses of differential treatment on neuroendocrine and immune measures. Hence, the presented results are not adjusted for education.

No group differences were found for neuroendocrine and immune measures (p -values $> .10$) at T₀ and no between-group differences were found for medication use, sleeping duration, time of awakening, and menstrual phase-distribution at either T₀ or T₁ (p -values $> .10$). An exception to this equivalence pattern was noted for time of awakening at T₁ ($\chi^2(N = 61, df = 2) = 8.15, p = .017$). In the SMT-I condition and CAU condition, all participants woke up before 9am, while four patients (19%) in the SMT-G condition woke up after 9am. Analyses were performed with and without these four patients. Across treatment conditions, medication use, menstrual phase, sleeping duration, and time of awakening did not differ between T₀ and T₁ (p -values $> .10$).

Table 1: Sample characteristics [M (SD) / n (%)].

	SMT-I ($n = 24$)	SMT-G ($n = 21$)	CAU ($n = 16$)
Gender (male / female)	10 / 14 (42 / 58)	10 / 11 (48 / 52)	6 / 10 (38 / 62)
Age (years)	41.96 (9.69)	40.90 (10.21)	45.44 (7.72)
Education (1 [Primary school] – 6 [University]) ^b	2.88 (1.08)	4.24 (1.51)	3.94 (1.48)
Body Mass Index (kg / mtrs ²) ^a	26.33 (4.41)	23.14 (2.44)	25.12 (3.09)
Smokers (yes / no)	8 / 16 (33 / 67)	4 / 17 (19 / 81)	1 / 15 (6 / 94)
Employment (hrs/wk)	37.00 (4.09)	35.67 (5.24)	36.50 (5.30)
Duration of complaints (< 6 / > 6 months)	15 / 9 (63 / 9)	8 / 13 (38 / 62)	5 / 11 (31 / 69)
Absenteeism T ₀ (duration: wks)	10.13 (7.68)	7.86 (7.34)	10.00 (9.91)

^a $p < .05$; ^b $p < .01$.

Change of work-related stress complaints, neuroendocrine measures, and immune measures

An extensive report on change of self-reported work-related stress complaints has been presented elsewhere (de Vente et al., 2008). To summarise: all complaints, except Professional competence (Cohen's d : -0.07, $p > .10$), reduced significantly between pre- and post-test across treatment conditions, (Cohen d 's: 0.31 – 1.10, p -values $< .05$). No differential treatment effects were found. However, subgroup analyses revealed superior effectiveness of SMT above SMT-G and CAU in the subgroup with lower depressive complaints. Across treatment conditions, no changes between measurements of neuroendocrine and immune measures were observed (p -values $> .10$).

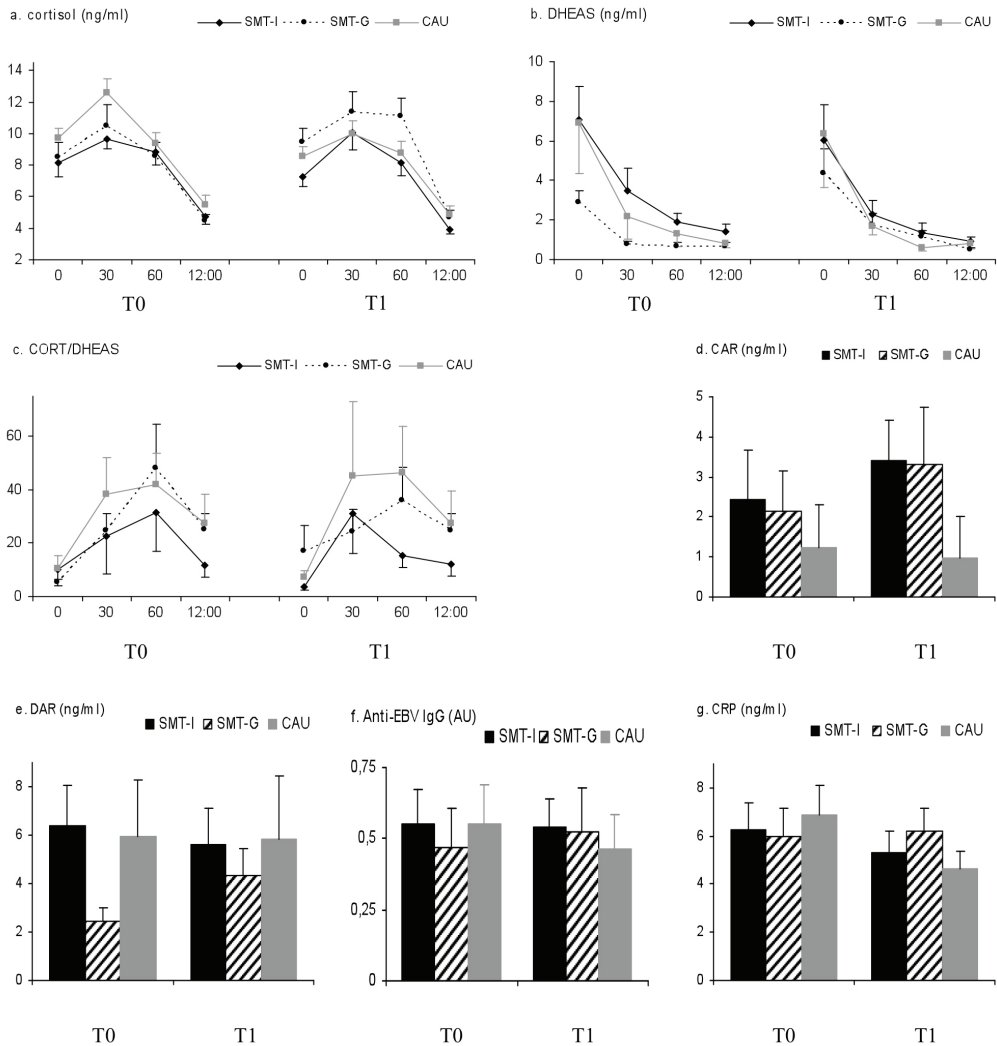
Hypothesis 1: Differences between treatment conditions

Figure 1a-e shows descriptive information about cortisol and DHEAS during the first hour after awakening and at 12.00am, the CAR, the DAR, EBV, and CRP at T₀ and T₁ per treatment condition. In Table 2, statistical results regarding differences between treatment conditions in change of neuroendocrine and immune variables between T₀ and T₁ are presented. For HPA axis activity during the morning, the following test-results are listed: the measurement x treatment interaction, reflecting differences in mean morning levels of neuroendocrine measures between treatment conditions between T₀ and T₁, and the measurement x treatment x time interaction, reflecting differences in the neuroendocrine morning *dynamics* between treatment conditions between T₀

Table 2: Test-results comparing change between T₀ and T₁ of morning activity and basal values between treatment conditions.^a

	mean morning level			morning activity			basal level		
	T * M (ANOVA)			T * M * time for repeated measures)			T * M (ANCOVA)		
	df's	F	p	df's	F	p	df's	F	p
CORT	2,49	3.70	.032	5.4,131.7	1.43	.215	2,49	1.22	.304
DHEAS	2,42	2.29	.115	5.9,122.9	0.65	.687	2,44	0.01	.993
CORT/DHEAS	2,41	0.51	.604	5.5,112.5	1.33	.256	2,43	0.35	.710
CAR	-	-	-	-	-	-	2,48	1.28	.228
DAR	-	-	-	-	-	-	2,42	0.45	.644
anti-EBV IgG	-	-	-	-	-	-	2,50	0.33	.720
CRP	-	-	-	-	-	-	2,49	2.47	.095

Note: T x M: Treatment x Measurement interaction; T x M x time: Treatment x Measurement x time interaction; CORT: cortisol; DHEAS: dehydroepiandrosterone-sulphate; CAR: cortisol awakening response; DAR: DHEAS awakening response; Anti-EBV IgG: Immunoglobulin G against Epstein-Barr virus; CRP: C-reactive protein; ^a All analyses were adjusted for gender, age, smoking, and Body Mass Index.



Figures 1a-g: Means and SEs per treatment condition of HPA axis activity during the morning (i.e., 0, 30, 60 minutes after awakening, and at midday), the CAR, the DAR, and immune measures at T₀ and T₁.

Note: T₀: measurement before the treatment phase; T₁: measurement after the treatment phase, i.e., four months after T₀; SMT-I: individual stress-management training; SMT-G: group stress-management training; CAU: care as usual; DHEAS: dehydroepiandrosterone-sulphate; CORT/DHEAS: cortisol/DHEAS; CAR: cortisol awakening response; DAR: DHEAS awakening response; Anti-EBV IgG: Immunoglobulin G against Epstein-Barr virus; CRP: C-reactive protein. Multiply the value of salivary cortisol in ng/ml by 2.76 to obtain the level in nmol/L.

and T1. All four cortisol and DHEAS samples (0 min. – Midday) were analysed. For basal cortisol and DHEAS levels, the mean levels of the fourth morning sample (Midday) were compared between treatment conditions. For basal immune measures, mean levels of a single pre-stressor sample were compared.

Further inspection of the significant measurement-treatment interaction effect for the mean morning cortisol revealed that it considerably decreased between T0 and T1 in the CAU condition (9.29-8.02 ng/ml) and slightly decreased in the SMT-I condition (7.82-7.35 ng/ml), while it increased considerably in the SMT-G condition (7.98-9.13 ng/ml). The mean cortisol difference between the SMT-G and CAU conditions was statistically significant ($p = .013$).

Exclusion of the four individual who woke up after 9.00 am at T1 did not affect the outcomes of neuroendocrine parameters; the treatment x measurement interaction for cortisol remained statistically significant ($F(2,47) = 5.33, p = .008$).

Analyses of neuroendocrine measures were repeated with exclusion of patients who failed to show a positive rise in cortisol between the first and second/third measurement after awakening at T0, T1, or both (49% of the sample), because it has been suggested that such failure is an indication for non-compliance to the saliva sampling-protocol (Broderick, Arnold, Kudielka & Kirschbaum, 2004; Kudielka, Broderick & Kirschbaum, 2003). However, following the exclusion, the outcomes remained grossly the same, i.e., the treatment x measurement interaction for mean morning cortisol remained statistically significant ($F(2,33) = 5.27, p = .010$) and no new significant results emerged.

The outcome with respect to morning cortisol remained similar when the analyses were adjusted for regression to the mean by adding mean morning cortisol at T0 as a covariate ($F(2,47) = 2.91, p = .056$), or when adding duration of sickness leave ($F(2,46) = 3.10, p = .054$) or complaints duration ($F(2,47) = 3.43, p = .041$) as covariates.

Post-hoc analyses of the statistically significant treatment x measurement interaction for CRP revealed no statistically significant group differences (p -values $>.10$). In summary, group SMT results in an increase of mean morning cortisol while a reduction of mean morning cortisol level was observed following CAU. The effect remained present when data were adjusted for potential non-compliance to the saliva sampling protocol, regression to the mean, duration of sickness leave, or complaints duration.

Per- protocol analysis and imputing potentially selective dropout

The first hypothesis was again tested by per-protocol analyses. In this manner, contrasts between conditions are enhanced and certainty is obtained that participants received sufficient active SMT elements. Outcomes were highly similar to the results presented in Table 3, i.e., the treatment x measurement interaction for mean morning cortisol remained statistically significant ($F(2,46) = 3.32, p = .045$), the treatment x measurement interaction for CRP was no longer statistically significant, and no new significant results emerged.

To examine the potential effects of selective dropout, analyses were repeated after imputation

of missing data at T₁ with data obtained at T₀. Outcomes were again highly similar to the results presented in Table 2; the treatment x measurement interaction of mean morning cortisol remained statistically significant ($F(2,62) = 3.09, p = .053$), the treatment x measurement interaction for CRP was no longer statistically significant, and no new significant results emerged

Hypothesis 2: Testing treatment effectiveness in subgroups – moderator analyses

The second hypothesis stated that SMT may be more effective in less severe patients, i.e., patients with a shorter duration of complaints or those with lower depressive or anxiety complaints. The subgroups for duration of complaints were categorised as chronic (i.e., > 6 months) and non-chronic (i.e., < 6 months). Subgroups with higher or lower levels of depressive complaints and anxiety complaints were based on the median split of the DASS-subscale scores at baseline. No indications were found for moderation of effects of SMT by duration of complaints, depressive complaints, or anxiety complaints. Hence, the second hypothesis was not confirmed.

Discussion

This study examined the differential treatment effects of individual SMT, group SMT, and CAU on measures of neuroendocrine and immunological parameters. Our first hypothesis, which stated that SMT would result in larger changes of neuroendocrine and immune measures than CAU, was partially supported. It was found that group SMT resulted in a statistically significant increase of mean morning cortisol in comparison to CAU. This effect remained significant when excluding potentially invalidly collected saliva samples or when running the analyses on an imputed dataset in which the dropped out patients failed to show any change at all. No support was obtained for our second hypothesis, which stated that treatment effects would be stronger in subgroups with less severe work-related stress.

The increase of morning cortisol in the group that received group SMT is consistent with our previous work on cortisol reactivity to a psychosocial stressor (Chapter 6), with findings in another patient sample with work-related stress (Mommersteeg et al., 2006b), and observations in patients with chronic fatigue syndrome (Roberts, Papadopoulous, Wessely, Chalder & Cleare, 2009). Our results are also in line with the studies among healthy and physically ill groups in the way that cortisol was influenced by cognitive behavioural interventions applied in a group format (Antoni et al., 2005; Cruess et al., 2000; Gaab et al., 2003). Cortisol in these groups, however, decreased, instead of increased. It seems that the direction of cortisol change depends on the initial health status, or factors related to the type of illness.

The treatment component that differs between individual and group SMT and therefore may be responsible for the increase in morning levels of cortisol in the SMT-G condition is social support. Social support is considered to be a particularly powerful therapeutic factor in group format treatments (Yalom, 1985). An effect of social support on neuroendocrine activity in our study is plausible as associations between social support and neuroendocrine activity have been demonstrated

in other contexts (e.g., DeVries, Craft, Glasper, Neigh & Alexander, 2007; Evans & Steptoe, 2001; Kirschbaum, Klauer, Filipp & Hellhammer, 1995; Turner-Cobb et al., 2000; Wadhwa et al., 1996).

The increase of mean morning cortisol in the SMT-G condition suggests that the sensitivity or capacity of the adrenal cortex has increased in the SMT-G condition (Fries, Hesse, Hellhammer & Hellhammer, 2005). Reduced sensitivity or capacity of the adrenal cortex is considered to be a result of excessive activation of the HPA axis, for example by exposure to chronic stressors (Fries et al., 2005). Our study suggests that this reduced sensitivity or capacity of the adrenal cortex can also be reversed again.

The physiological results of the present study are not consistent with the results of differential treatment effects regarding self-reported complaints (de Vente et al., 2008). More specifically, the present study is in favour of superior treatment effect of group-SMT, while the study on self-reported complaints and work-resumption supported superior effectiveness of individual SMT in the subgroup with lower depressive complaints. Discrepancy between physiological measures and self-reported complaints may be partially explained by various sources of bias in self-reported complaints as mentioned in the introduction. Alternatively, variation in physiological measures due to sources of variation such as duration of complaints and extent of work-resumption at the second measurement may have hindered detection of group differences in smaller groups (e.g., subgroups with higher and lower levels of anxiety and depression). One may also suggest that change of complaints and change of physiological measures occur on different time scales. However, in other studies (e.g., Antoni et al., 2005; Mommersteeg et al., 2006b), change of complaints and change of the HPA axis both occurred within a period of six months, suggesting simultaneous change. Moreover, Dahlgren et al. (2005) showed that cortisol diurnal profiles differed between high stress and low stress work-weeks. Similarly, it has been demonstrated that complaints measured on day-to-day basis were considerably associated with physiological HPA axis measures (Dahlgren, Kecklund, Theorell & Åkerstedt, 2009; Sonnenschein et al., 2007). Hence, physiological measures appear to be sensitive to day-to-day change and a time lag between change of physiological measures and self-reported complaints seems unlikely.

Establishment of effectiveness of group SMT in patients with work-related stress on morning cortisol by future studies may have implications for tertiary prevention of work-related stress, which commonly consists of individual treatment (van der Klink et al., 2001). To increase social support in individual SMT, individual treatment sessions may be combined with group sessions. One step further may be to investigate whether individual SMT needs to be replaced by group SMT altogether.

In conclusion, the current study demonstrates that group SMT increases HPA axis responsiveness in patients with work-related stress. Further research should establish whether social support is the active element or crucial factor that causes a treatment effect of group SMT. If this indeed will be found, individually delivered SMT may be improved by emphasising the effective mobilisation of social support, perhaps by combining individual sessions with group sessions.

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