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

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6 Investigating the effects of cognitive behavioural treatment on the sympathetic, parasympathetic, and neuroendocrine function: A randomised controlled trial among patients with work-related stress*

Abstract

Background: Prolonged work-related stress is characterised by physiological changes. Physiological parameters are rarely included in studies about the effects of Cognitive Behavioural Treatment (CBT) for work-related stress. We investigated the effects of CBT for work-related stress on the sympathetic, parasympathetic, and neuroendocrine function. *Method*: A randomised controlled trial was conducted, which was part of a larger study on the effectiveness of CBT-based Stress Management Training (SMT). Sixty patients with work-related stress complaints on sickness leave were measured at baseline (T0) and four months later (T1). Patients were assigned to a) individual SMT; b) group SMT; or c) Care As Usual (CAU). SMT comprised twelve sessions conducted by a psychologist. At T0 and T1, patients were exposed to an acute psychosocial stressor consisting of mental arithmetic and public speech. Levels of physiological variables during rest and reactivity and recovery after the stressor were investigated. Physiological variables consisted of blood pressure, heart rate, cardiac output, total peripheral resistance, heart rate variability, salivary alpha-amylase and cortisol. *Results*: Across conditions, baseline systolic blood pressure and systolic and diastolic blood pressure reactivity reduced after the treatment phase. No group differences were found between the SMT conditions and the CAU condition. *Conclusion*: No support was found for beneficial effects of SMT over CAU on sympathetic, parasympathetic, or neuroendocrine functions, which may be due to large inter-individual differences in stress-related conditions and/or outcome measures.

A state of work-related stress can be manifested in several interrelated health domains, such as a) psychosomatic complaints (Bauer et al., 2006), b) psychological distress including anxiety and depressive symptoms, as well as burnout complaints including exhaustion (Bauer et al., 2006; Lindblom, Linton, Fedeli, & Bryngelsson, 2006; Schaufeli & Buunk, 2003), and c) physiological alterations such as elevated heart rate and changed cortisol levels (Grossi et al., 2005; Mommersteeg, Keijsers, Heijnen, Verbraak & van Doornen, 2006a; de Vente, Olff, van Amsterdam, Kamphuis & Emmelkamp, 2003). While a number of studies have documented outcomes of treatment for work-related stress in terms of self-reported complaints, only few studies have focused on the effects of treatment 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 was to investigate the effects of Stress Management Training (SMT), a widely used treatment for work-related stress, on the cardiovascular and neuroendocrine functions in patients with work-related stress.

SMTs are based on cognitive behavioural techniques and typically consist of relaxation training, cognitive restructuring, time-management skills training, and social skills training (Carson & Kuipers, 1998; Jones & Johnston, 2000; Ivancevich, Matteson, Freedman & Philips, 1990). Life style improvement has also been recommended as a treatment component for work-related stress (Maslach, 1982). Effects of these treatment components on physiological functions can be expected through their focus on psychophysiological processes associated with exposure to stressors.

According to several interactional stress models (e.g., Folkman & Lazarus, 1988; Lazarus & Folkman, 1987; Olff, Langeland & Gerssons, 2005), a situation elicits negative emotions and physiological reactions when it is evaluated by the individual as posing a significant threat exceeding coping resources. Consecutively, negative emotions give rise to coping efforts (Folkman & Lazarus, 1988). Adequate coping ends the threat of the stressor, and consequently, negative affect and physiological activation cease (Olff et al., 2005). Persistent exposure to stressors that is not resolved may result in psychosomatic and distress complaints, physiological changes, and functional impairments (Folkman & Lazarus, 1988; Lazarus & Folkman, 1987; Olff et al., 2005). SMT may affect physiological functions either directly, by influencing physiological processes themselves, or indirectly, through affecting psychological processes. Direct beneficial effects of SMT are for example arousal reduction through relaxation techniques (Linden & Moseley, 2006; Miller & Cohen, 2001) or reduction of unhealthy habits, including smoking, excessive alcohol use, inactivity, or dysfunctional sleeping patterns. It is known that an unhealthy life style negatively affects the cardiovascular and neuroendocrine functions (e.g., Chobanian et al., 2003; Ukkola et al., 2001). Indirect effects are prompted by techniques influencing appraisal and coping, such as cognitive restructuring, time-management skills, and social skills (Miller & Cohen, 2001). These effects are indirect since appraisal and coping affect physiological activity through influencing affect. Both positive and negative affect are related to the cardiovascular and neuroendocrine functions (e.g., Brummett, Boyle, Kuhn, Siegler & Williams, 2009; Kario, Schwartz, Davidson & Pickering, 2001; Nabi, Kivimaki, De Vogli, Marmot & Singh-Manoux, 2008; Peeters, Nicholson & Berkhof, 2003; Steptoe, Wardle & Marmot, 2005).

Stress-reducing cognitive behavioural treatments (CBTs) have been demonstrated to affect the

cardiovascular and neuroendocrine functions in healthy individuals (Gaab et al., 2003; Lucini, Riva, Pizzilini & Pagani, 2007; McCraty, Barrios-Choplin, Rozman, Atkinson & Watkins, 1998; McCraty, Atkinson & Tomasino, 2003) and physically ill patients (Antoni et al., 2005; Cruess et al., 2000; van Dixhoorn & White, 2005), and to affect the neuroendocrine function in patients with generalised anxiety disorder (Tafet, Feder, Abulafia & Roffman, 2005) or post-traumatic stress disorder (Olff, de Vries, Güzelcan, Assies & Gersons, 2007). With respect to work-related stress, a meta-analysis has demonstrated that relaxation techniques and multimodal treatments (i.e., treatment consisting cognitive-behavioural techniques, including relaxation techniques) resulted in advantageous physiological changes in relatively healthy samples (van der Klink, Blonk, Schene & van Dijk, 2001).

To our knowledge, the current study is the first that investigates the effects of SMT on the cardiovascular function in a patient sample with work-related stress. Previously, only two other treatment studies have been conducted in patients with work-related stress using neuroendocrine outcome variables (Mommersteeg et al., 2006a; Mommersteeg, Heijnen, Verbraak & van Doornen, 2006b). To assess whether SMT induces cardiovascular and neuroendocrine changes we conducted a randomised controlled trial in which individual SMT and group-SMT were compared with care as usual (CAU). SMT in a group format is common as a preventive intervention for work-related stress but it is less common as an intervention for clinical samples (Schaufeli & Buunk, 2003). As a preventive intervention, SMT in a group format enhances well-being (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 other group members (Yalom, 1985). More social support is associated with more favourable cardiovascular profiles (Roy, Steptoe & Kirschbaum, 1998; Uchino, 2006) and lower cortisol levels (e.g., Kirschbaum, Klauer, Filipp & Hellhammer, 1995; Turner-Cobb, Sephton, Koopman, Blake-Mortimer & Spiegel, 2000; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto & Sandman, 1996). Our first hypothesis was that SMT, whether provided in an individual or group format, would result in larger change in cardiovascular and neuroendocrine variables than CAU.

The present study was a part of a larger project, in which the effectiveness of individual and group-SMT was evaluated. We found no superior efficacy of SMT above CAU based on self-reported work-related stress complaints, except for indications of superior efficacy of individual SMT in the subgroup with lower depression complaints (de Vente, Kamphuis, Emmelkamp & Blonk, 2008). Despite the limited evidence for effectiveness of SMT on work-related stress complaints, the investigation of treatment effects on physiological outcomes merits attention for the following reasons. First, work-related stress complaints and physiological stress indicators do not have one-to-one associations. To illustrate, hypertension is not accompanied with a particular subjective complaint, and in fact remains commonly unnoticed by patients (e.g., Mendez-Luck, Yu, Meng, Jhawar & Wallace, 2004). Moreover, only fifty percent of patients with a major depressive disorder demonstrate elevated cortisol levels (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) indeed support a disturbing effect of retrospective bias in the association between complaints and physiological variables.

In addition to the assessment of overall treatment effects on cardiovascular and neuroendocrine parameters, we investigated whether these 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 from the self-report study (de Vente et al., 2008), our second hypothesis was that SMT is more effective in less severe patients, i.e., subgroups with a shorter duration of complaints, or lower depression or anxiety complaints.

Indices of main stress-regulating subsystems, i.e., the sympathetic nervous system including the Sympathetic-Adrenal-Medullary (SAM) axis, the parasympathetic nervous system, and the Hypothalamic Pituitary-Adrenal (HPA) axis, were measured. Parameters of the sympathetic and parasympathetic system included were heart rate (HR), blood pressure (BP), cardiac output (CO), total peripheral resistance (TPR), and salivary alpha-amylase (AA). Measuring blood pressure alone may be of limited value, because it is the result of differences in both cardiac output and vascular resistance (Berntson, Quigley & Lozano, 2007). Hence, to reveal changes in haemodynamic function that remain unnoticed when studying BP alone, CO and TPR were measured as well. Cardiac vagal activity was measured using heart rate variability and cortisol was taken as a measure of HPA axis activity. Since physiological disturbances associated with work-related stress may become evident as changes of basal values and/or as changed patterns of reactivity to and recovery from stressful situations, both resting values and reactivity to and recovery after an acute psychosocial stressor were examined. Work-related stress complaints and physiological characteristics 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, four months later (T1), 60 patients were measured again.

Eligibility was based on a screening interview by telephone assessing the presence of work-related stress complaints, which was administered by a clinical psychologist. The subsequent intake procedure consisted of a semi-structured diagnostic interview conducted by a clinical psychologist and completion of the Beck Depression Inventory (BDI; Beck & Steer, 1987). During the semi-structured interview the complaint history was assessed and the Composite International Diagnostic Interview (CIDI; World Health Organisation [WHO], 1997) was administered. Inclusion criteria were: 1) endorsement 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/or 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; Beck & Steer, 1987); 3) a traumatic event in the past six months; and 4) a medical condition that might likely account for fatigue (e.g. diabetes); 5) excessive alcohol and/or drug use; and 6) pregnancy. Patients received refund of their travel expenses and a printed report of their blood pressure and heart rate.

General procedure

The ethics committee of the Department of Psychology, University of Amsterdam, 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 baseline (T0) and four months later (T1). The present physiological study was a part of a comprehensive research project, which evaluated effectiveness of individual and group-SMT. Measurements consisted of completing a questionnaire booklet, collecting morning saliva, and attending a psychosocial stress session in the laboratory of the University of Amsterdam. This study reports about the cardiovascular and neuroendocrine outcomes during the psychosocial stress session.

Materials and Measures

Interventions

The interventions consisted of 12-sessions of SMT based on cognitive-behavioural techniques. Individual and group-SMT were described in detail per session 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. A more 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 imposed 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 visits to an occupational physician (OP), general practitioner (GP) and/or a maximum of five treatment sessions by a psychologist or social worker. Seven patients went to see only the OP and/or GP and eight patients received treatment (mean number of sessions = 4.5) of a psychologist or social worker. The mean number of consultations of the OP was 2.9 and of the GP was 1.7.

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.

Psychosocial stressor

The psychosocial stressor consisted of a speech preparation task, a mental arithmetic task, and a speech task in front of a camera and in presence of the experimenter (see Figure 1 for the complete procedure). Psychosocial stressor procedures have demonstrated to enhance perceived stress and reactions in cardiovascular and neuroendocrine measures (e.g., Childs & de Wit, 2009; Izawa et al., 2008; Kirschbaum, Pirke & Hellhammer, 1993; Nicholson & van Diest, 2000; Olff, Mulder, The, de Leij, & Emmelkamp, 1999; de Vente et al., 2003). Detailed information about the procedures is provided elsewhere (de Vente et al., 2003; Chapter 3). To control for time of the day effects, psychosocial stress sessions took place between 13.30 and 16.30 hrs.
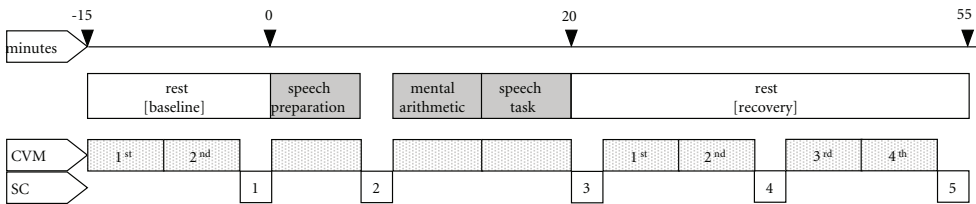
Figure 1: *Time diagram of the psychosocial stress session.*

Note: CVM: cardiovascular measurements; SC: saliva collection

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 work-related emotional exhaustion, depersonalisation/a cynical attitude towards work, 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); Cronbach's alpha in the current sample was 0.91.

Smoking, hours of sleep, height, and weight were assessed by questionnaire. Women were also asked to report on menstrual phase, the use of oral contraceptives, and pre-/postmenopausal status.

Cardiovascular assessment

Heart rate (HR) and blood pressure (BP) were measured performing continuous measurement of finger BP using a Finapres (Ohmeda Finapres type 2300^E, Blood Pressure Monitor) and the software Vsrrp98 (Molenkamp, 1998, University of Amsterdam, The Netherlands). Systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, cardiac output (CO) and total peripheral resistance (TPR) were calculated using the software Beatscope (version 1.1; Finapres Medical Systems, 2002, The Netherlands). Cardiac vagal tone was determined by calculating beat-to-beat heart rate variability, using the root mean square of successive differences (RMSSD) of inter-beat intervals (IBI's): $\sqrt{(1/n \ \Sigma(IBI_i - IBI_{i-1})^2)}$, (Penttilä et al., 2001; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). IBI's were defined as the number of milliseconds between peaks of subsequent systoles in the plethysmographic signal, analysed with Vsrrp98 (version 5.4b). The plethysmographic signal was inspected visually and artefacts and ectopic beats were removed. The obtained measure was called Estimated Heart Rate Variability (EHRV). Mean values of cardiovascular measures were calculated per five minutes. Resting values were defined as mean values during the second baseline phase of the psychosocial stress session (-10 to -5 min. in relation to the start of the psychosocial stressor; see Figure 1). Resting values and mean values during the psychosocial stress session were considered as indicators of basal functioning. Mean values during the psychosocial stress session were only used as such in absence of interaction effects of treatment x phase. For reactivity and recov-

ery, mean values during the stress-inducing tasks and first to third recovery phase, respectively, were related to baseline.

Saliva sampling protocol

Alpha-amylase and cortisol were determined in saliva. Saliva was collected five times during the psychosocial stress session (see Figure 1). For alpha-amylase and cortisol, means of the first (-5 min.) and second (+5 min.) saliva samples were used as resting values. Resting values and mean values during the psychosocial stress session (again, only in absence of significant treatment x stressor-phase interaction effects) were considered indicative of basal functioning. Means of resting samples and the following three samples were analysed to assess acute reactivity and recovery. For alpha-amylase, the third (+20 min., i.e., immediately after cessation of the stressor) saliva sample indicated reactivity, and the fourth (+ 35 min.), and fifth (+50 min.) saliva samples recovery. For cortisol, the third (+20 min.) and fourth (+35 min.) saliva samples indicated reactivity, and the fifth (+ 50 min.) sample recovery.

Saliva collection was performed according to Navazesh (1993). In this method, 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 out 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 samples were stored upon ice until the end of the psychosocial stress session. Immediately after the session, i.e., within 90 min after collection, 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.

Assay of neuroendocrine measures

Alpha-amylase activity was assayed photometrically (Roche, Almere, The Netherlands) after 500-fold dilution of the sample using 5 ethylidene-G_7PNP as substrate. The lower detection limit was 3 U/L. Samples were assayed in duplo and the intra-assay variability was 0.4-2%. The amount of free cortisol was determined using enzyme-immuno assay (EIA). Kits were purchased from Diagnostic System Laboratories (DSL, Veghel, The Netherlands). Sensitivity of cortisol assay was 1 ng/ml. Samples were assayed in duplo. Intra-assay variability was 2-10%.

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 to compare groups on resting values (covariate: resting value at T0) and analyses of variance (ANOVA) for repeated measures to compare groups on reactivity and recovery. With the ANOVA for repeated measures a 'treatment' x 'measurement' x 'stressor-phase'-design was tested. Significant interactions of interest (i.e., treatment x measurement and treatment x measurement

x stressor-phase) were further analysed using post-hoc analyses (Bonferroni-corrected, as implemented in the ANOVA for repeated measures procedure) or simple contrasts (as implemented in the ANOVA for repeated measures procedure). When the assumption of sphericity was violated, results adjusted according to Greenhouse-Geisser's method were presented. As age, gender, smoking, and BMI are known to be related to cardiovascular and neuroendocrine 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 ≥ 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-carried-forward method, was analysed.

For cardiovascular and neuroendocrine measures, outliers (i.e., values ± >3 SDs of the mean) were removed; outliers were < 7%. Some cardiovascular data were missing due to equipment problems (< 2%) and some neuroendocrine data were incomplete due to insufficient saliva (alpha-amylase 3%; cortisol 3%). Because of positively skewed data EHRV and alpha-amylase were analysed using square-rooted values. 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 ($t(79)$ = -2.31, p = .023). For gender, education, severity of any of the stress complaints, or any of the physiological measures (resting and reactivity/recovery), 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 eleven in the CAU condition did not provide physiological data at T1, $\chi^2(N = 60$, df = 2) = 6.73, p = .035.

Sample characteristics per treatment condition are presented in Table 1. Treatment conditions differed on education ($F(2,57)$ = 6.83, p = .002), BMI ($F(2,57)$ = 4.64, p = .014), and proportion of smokers (N = 60, $\chi^2(2)$ = 6.43, p = .041). The SMT-I condition had significantly lower education than the SMT-G and CAU conditions (p = .003, p = .023, respectively), a higher BMI (p = .011) than the SMT-G condition, and more smokers than the CAU condition (p = .015). Education appeared to be a confounder in the analyses of differential treatment on some cardiovascular and neuroendocrine measures. Hence, education was added as a covariate to all analyses. No group differences were found at T0 for cardiovascular and neuroendocrine measures (p-values >.10) and no group differences were found for medication use, sleeping duration, menstrual phase-distribution, and pre-post menopausal state distribution at either T0 or T1 (p-values > .10). Medication use, sleeping duration, menstrual phase distribution, and pre-post menopausal state distribution did not differ between T0 and T1 either (p-values >.10).

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

	SMT-I (n = 24)	SMT-G (n = 21)	CAU (n = 15)
Gender (male / female)	10 / 14 (42 / 58)	10 / 11 (48 / 52)	6 / 9 (40 / 60)
Age (years)	41.96 (9.69)	40.90 (10.21)	46.27 (7.22)
Education (1 [Primary school] – 6 [University]) [b]	2.88 (1.08)	4.24 (1.51)	4.07 (1.44)
Employment (hrs/wk)	37.00 (4.09)	35.67 (5.24)	36.33 (5.45)
Duration of complaints T0 (< 6 / > 6 mnths)	15 / 9 (63 / 9)	8 / 13 (38 / 62)	5 / 10 (33 / 67)
Absenteeism T0 (duration: wks)	10.13 (7.68)	7.86 (7.34)	10.47 (10.08)
Absenteeism T1 (% of working hours)	46.18 (40.61)	39.89 (40.22)	27.80 (36.26)
BMI (kg/m²) [a]	26.33 (4.41)	23.14 (2.44)	25.14 (3.20)
Smokers (yes / no) [a]	8 /16 (33 / 67)	4 /17 (19 / 81)	0 / 15 (0 / 100)

[a] $p < .05$; [b] $p < .01$.

### Change of work-related stress complaints

An extensive report on change of self-reported stress complaints has been provided elsewhere (de Vente et al., 2008). To summarise: all complaints, except Professional competence (Cohen's d: -0.07, $p > .10$), reduced significantly between T0 and T1 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.

Change of physiological measures across conditions

Overall, no change in resting values occurred between T0 and T1, except for SBP. Resting SBP at T1 was lower than at T0 (127 vs. 133 mmHg, respectively), which suggests a certain extent of recovery between T0 and T1. No change of reactivity and recovery was observed between measurements, except for SBP- and DBP-reactivity. Stronger reactivity at T0 of SBP (11.6 vs. 7.4 mmHg; simple contrast: baseline-preparation: $p = .027$) and DBP (4.4 vs. 2.0 mmHg; simple contrast baseline-preparation $p = .013$) was found as compared to T1.

Hypothesis 1: Differential treatment effects on physiological outcomes

Figures 2a-h show descriptive information of SBP, DBP, HR, CO, TPR, EHRV, alpha-amylase, and cortisol during the psychosocial stress session for T0 and T1. In Table 2, statistical outcomes of differences between treatment conditions in change between T0 and T1 of physiological variables regarding resting values, mean values during the psychosocial stress session, and reactivity/recovery are presented.
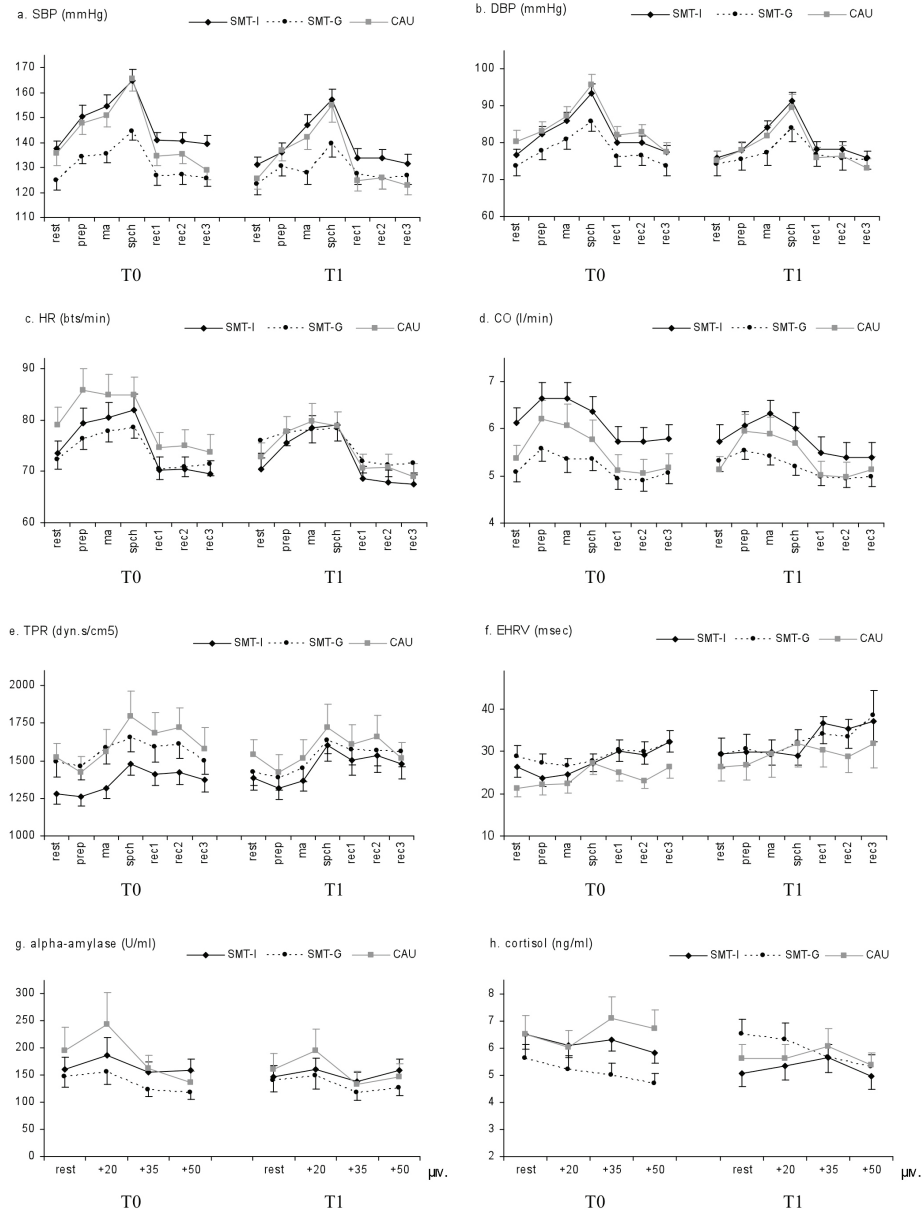
Figures 2a-h: *Means and SEs per treatment condition of cardiovascular and neuroendocrine parameters during the psychosocial stress session at T0 and T1.*

Note: SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CO: cardiac output; TPR: total peripheral resistance; EHRV: estimated heart rate variability; REST: baseline rest phase; PREP: speech preparation; MA: mental arithmetic; SPCH: speech-task; REC: recovery phase; +20 min.: 20 minutes after the onset of the stressor; +35 min.: 35 minutes after the onset of the stressor; +50.: 50 minutes after the onset of the stressor; T0: pre-test; T1: post-test. Multiply the value of salivary cortisol in ng/ml by 2.76 to obtain the level in nmol/L.

Table 2: *Test-results comparing change between T0 and T1 of values during rest (ANCOVA), mean activity, and reactivity/recovery patterns (ANOVA for repeated measures) between treatment conditions.*

| | Resting | | | Overall session mean [a] | | | Reactivity & Recovery | | |
| | T | | | T x M | | | T x M x phase | | |
	df's	F	p	df's	F	p	df's	F	p
SBP	2,51	0.28	.755	2,52	2.10	.132	7.3,189.2	0.76	.626
DBP	2,51	0.68	.511	2,52	1.39	.257	6.9,179.9	0.89	.511
HR	2,51	5.80	**.005**	2,52	2.80	**.070**	8.3,216.7	1.62	.116
CO	2,51	2.20	.121	2,51	1.05	.589	7.3,187.0	0.99	.440
TPR	2,49	0.62	.544	2,50	0.04	.961	6.3,157.4	0.90	.504
EHRV	2,50	1.89	.164	2,51	1.93	.156	8.5,215.8	0.61	.781
AA	2,45	0.94	.399	2,46	0.75	.478	5.8,133.2	1.17	.325
CORT	2,48	3.69	**.054**	2,49	2.30	.111	4.6,113.8	0.63	.666

Note: T: main effect of treatment condition; T x M: Treatment x Measurement interaction; T x M x phase: Treatment x Measurement x phase interaction; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CO: cardiac output; TPR: total peripheral resistance; EHRV: estimated heart rate variability; AA: alpha-amylase; CORT: cortisol; [a] Interpreting differences in mean values during the entire psychosocial stress session as indications of differences in basal functioning is only feasible in absence of a treatment x measurement x phase interaction.

Resting HR and mean HR during the psychosocial stress session decreased between T0 and T1 in the SMT-I (resting HR: 73-70 beats/min., mean HR 75-72 beats/min.) and the CAU (resting HR: 79-73 beats/min, mean HR: 80-74 beats/min.) condition, while resting HR increased (72-76 beats/min.) and mean HR during the psychosocial stress session remained stable (74-75 beats/min.) in the SMT-G condition. Regarding change of resting values, the HR-reduction in the SMT-I condition differed from the HR-increase in the SMT-G condition (p = .008). Concerning change of mean HR during the psychosocial stress session, the reduction in the SMT-I condition was different from the unchanged mean HR in the SMT-G condition (p = .029).

The cortisol level during rest increased between T0 and T1 in the SMT-G condition (5.6-6.6 ng/ml), while it decreased in the SMT-I (resting cortisol: 6.5-5.1 ng/ml) and CAU (resting cortisol: 6.5-5.6 ng/ml) conditions. The increase in cortisol during rest in the SMT-G condition tended to be different from the decrease observed in the SMT-I condition (p = .054).

Per- protocol analysis and imputation of potentially selective dropout
The first hypothesis was also tested by per-protocol analyses. In this manner, contrasts between conditions are enhanced and certainty is obtained that participants received sufficient active SMT

elements. Results were highly similar to the results presented in Table 2, i.e., no new significant results emerged. To assess the potential effects of selective dropout, analyses were repeated after imputation of missing data at T1 with data obtained at T0. Again, outcomes were highly similar to the results presented in Table 2.

Hypothesis 2: Testing differential treatment effects in subgroups – moderator analyses
No different treatment effects on physiological outcomes were observed between subgroups based on complaint duration or on the levels of anxiety or depressive complaints.

Discussion

The aim of this study was to examine the effects of CBT-based SMT on cardiovascular and neuroendocrine measures. No support was obtained for our first hypothesis, which stated that SMT, whether provided in individual or group-format, would have more profound effects on selected cardiovascular and neuroendocrine variables as compared to CAU. However, differences between the SMT-I and SMT-G conditions were observed regarding changes in HR and cortisol. More specifically, the decreases of resting HR and mean HR during the psychosocial stress session in the SMT-I condition differed from the increase of resting HR and the stable mean HR during the psychosocial stress session in the SMT-G condition. The reduction of basal HR in the SMT-I condition suggests a beneficial effect of the treatment, as a lower heart rate indicates lower (hyper)arousal. In addition, the decrease of resting cortisol in the SMT-I condition tended to differ from the increase of resting cortisol in the SMT-G condition. The cortisol reduction in the SMT-I condition suggests a reduction of HPA axis activity and the cortisol increase in the SMT-G condition an elevation of HPA axis activity. The outcomes were robust, as additional analyses where 1) only the participants receiving SMT according to protocol were included, or 2) analyses were based on an imputed dataset adjusted for potential selective drop-out, led to essentially the same results. No support was obtained for our second hypothesis, which stated that treatment effects would be stronger in the subgroups with less severe work-related stress.

Concerning the overall sample, our results are to some extent consistent with the outcomes of our previous work about differential treatment effects on self-reported complaints and work-resumption (de Vente et al., 2008). Similar to significant complaints reductions, a reduction in resting SBP, and reductions of SBP- and DBP-reactivity suggest a beneficial health effect. However, it cannot be excluded that these cardiovascular effects reflect familiarity with the psychosocial stressor.

Regarding the subgroup analyses, our results are inconsistent with our previous work on self-reported complaints and work-resumption. The explanation for finding indications for superior effectiveness of individual SMT on complaints but not on cardiovascular and neuroendocrine outcomes in groups with lower depressive complaints may be related to absence/presence of impairment and opportunity or necessity to change. Levels of self-reported complaints in the subgroup with less depressive complaints were all in the clinical range, leaving opportunity and urgency for

improvement. The levels of physiological measures in the group with less depressive complaints, in contrast, appeared to be about normal. As most clear examples, at pre-test, resting SBP was 125 mmHg and resting DBP was 73 mmHg in the subgroup with lower depressive complaints reflecting close to normal values. In the subgroup with the higher depressive complaints, in contrast, resting SBP was 138 mmHg and resting DBP was 79, indexing borderline hypertensive values (Chobanian et al., 2003). When assuming that the SMT was adequate for treating work-related stress in groups with a lower level of depressive complaints, absence of cardiovascular and neuroendocrine changes may be the reason why effectiveness could not be demonstrated for these outcomes.

A number of methodological aspects of the study may explain the absence of differential treatment effects. First, was the right sample recruited? In other words, had the selected participants been exposed to stressful conditions that had resulted in dysregulation of sympathetic and parasympathetic nervous system and of the HPA axis? Without such dysregulation, cardiovascular and neuroendocrine change is less likely to occur because there is no necessity to improve homeostatic and allostatic balances. The patients in the current sample reported exposure to work-related stressors and clearly demonstrated changes in sympathetic/parasympathetic activity and in cortisol levels as previously reported (Chapter 3; de Vente et al., 2003). Hence dysregulation of the sympathetic and parasympathetic nervous system and the HPA axis appeared present in the current sample.

Second, was the intervention adequate and of good quality? SMT in the present study consisted of standard cognitive behavioural elements and was similar in content and duration as CBT in other studies that reported physiological change (e.g., Antoni et al., 2005; Cruess et al., 2000; McCraty et al., 1998, 2003). Furthermore, therapists were experienced and well trained, treatment integrity was high, and treatment was completed by 82 percent of the participants. In addition, evidence for effectiveness of individual SMT in the subgroup with less depressive complaints on self-reported stress complaints has been obtained (de Vente et al., 2008). Therefore, to assume flawed CBT in this study seems implausible. Alternatively, it could be argued that the CAU was of too good quality, which could have resulted in reduced contrast between conditions. However, as short interventions comparable to our CAU were not successful in achieving improvement of complaints (Bakker et al., 2007; Blonk, Brenninkmeijer, Lagerveld & Houtman, 2006; Huibers et al., 2004; van der Klink, Blonk, Schene & van Dijk, 2003), reduced contrast between conditions does not seem to be a valid explanation for our lack of finding superior effectiveness of SMT. It cannot be excluded, though, that the SMT was insufficient in duration or intensity for this specific clinical sample to cause considerable change, as has been also suggested in our study regarding work-related stress complaints (de Vente et al., 2008).

Third, did we select the appropriate physiological parameters of the physiological processes that are affected by exposure to the stressful conditions? All CBT elements are considered to either directly or indirectly affect stress-related physiological functions reflected in sympathetic, parasympathetic, and HPA axis activity. And although not all cardiovascular and neuroendocrine variables measured were deviant at T0, all measures included have previously been shown to be associated with acute and/or chronic stress (e.g., Rohleder et al., 2004; Schorpfnail et al., 2003; Netterstrøm &

Hansen, 2000; Cacioppo et al., 2000; Vrijkotte, van Doornen & de Geus, 2000; Gump & Matthews, 1999). The selected cardiovascular and neuroendocrine parameters thus appear adequate to study in this context.

Fourth, was the timing of measurements adequately matched with the occurrence of physiological change? The timing of measurements i.e., the interval of four months between T0 and T1 may have been suboptimal, because it may have been too short to demonstrate change in a clinical sample. In particular the beneficial effect of a different way of coping with stressors on physiological parameters may occur with some delay. Others observed a change in cortisol in a group of patients with work-related stress who had received CBT with a six-month interval between measurements (Mommersteeg et al., 2006a). Hence, the time frame in our study may indeed have been somewhat too short.

In addition to the relatively short interval between measurements, another aspect of timing may also have affected the results. At the start of the study the sample demonstrated heterogeneity in progression of the stress process. Consequently, variation in timing of measurement relative to the extent of progression of the stress process may have resulted in increased inter-individual differences. In addition, variation in duration of complaints, sickness leave duration, and working hours at post-test may also have attributed to variation in physiological outcomes. Despite the fact that no significant moderation of treatment effectiveness by complaint duration, sickness leave duration (data not shown), and degree of work-resumption (data not shown) was found, the influences of these variables cannot be entirely discarded yet, as subgroup analyses were based on small subsamples and the variables may have exerted joint or counteractive effects. Thus timing of measurements with respect to progression of the stress process, sickness leave duration, and working hours at post-test may also have been suboptimal.

Finally, did certain non-treatment related conditions, e.g., continuation of occupational stressors, thwart physiological change? Various researchers have stressed the importance of measuring presence of the stressor(s) (Miller & Cohen, 2001; Gump & Matthews, 1999), a variable that is highly controlled for in animal research as well (e.g., Herman, Adams & Prewitt, 1995; McCarthy, Horwatt & Konarska, 1988). Unfortunately, in the present study no quantitative data were available about presence of occupational stressors at T1. Our clinical impression was that a considerable part of the sample remained under continued exposure to a stressor while absent from work. For example, patients reported to be under severe pressure because of reorganisation of the company or legal procedures with respect to (the threat of) job loss. Continued presence of an occupational stressor may indeed have impeded physiological change.

Some limitations of this study should be taken into account when interpreting the results. First, more patients allocated to CAU withdrew from the study than patients allocated to either SMT-condition. The main reason for these participants to end participation was strong disappointment about not obtaining SMT. Some indications for selective dropouts in the CAU-condition were found, i.e., drop-outs had lower SBP-reactivity and -recovery, higher resting and mean EHRV during the psychosocial stress session, and a higher cortisol level at the start of the psychosocial stres-

sor at To than CAU-condition completers (data not shown). Formulating potential consequences of these dropouts for the post-test measurement would be speculative since the differences do not result in clear indications about whether more or less stressed participants dropped out. More specifically, the higher level of EHRV and lower SBP-reactivity and -recovery suggested a lower level of arousal and arousability, while higher resting cortisol indicated a higher stress level.

Second, because of practical limitations, for women the administration of the psychosocial stressor was not planned in the luteal phase. Measuring cortisol in the luteal phase is recommended, because cortisol levels are then more similar to those of males (Kirschbaum, Kudielka, Gaab Schommer & Hellhammer, 1999). Hormonal variation associated with variation in menstrual phase has expectedly enhanced variation in cortisol levels in our study, which probably hindered detection of group differences. Since no evidence was found in this study for effect modification of gender, outcomes were presented collectively for both genders. Joint presentation of results explains, in addition to the enhanced variation in cortisol, also the relatively low cortisol resting levels and reactivity, as women in general demonstrate lower resting levels and reactivity to psychosocial stressors (Kirschbaum et al., 1999; Stroud, Salovey & Epel, 2002). Since we found gender differences for both cortisol and alpha-amylase in a previous study (Chapter 3), we have replicated the analyses for cortisol and alpha-amylase for males only (data not shown), without finding consistent treatment effects, though.

The present study results in two clinically relevant considerations. First, despite the factors that could have diminished or concealed the effects of the SMT on physiological outcomes to some extent, the outcomes of this study do not support the widespread use of SMT as an effective treatment for work-related stress. Conversely, it is also too early to conclude that SMT is not effective in changing these physiological parameters. To start with, additional research is indicated in which the potentially confounding variables such as duration of complaints, duration of sickness leave, and continuing presence of a stressor are standardised to a larger extent. A second clinically relevant consideration is that the SMT for individuals with a higher level of depressive complaints may be improved by putting more effort in directly affecting physiological outcomes. A stronger focus on physiological outcomes seems warranted as blood pressure was considerably elevated in the subgroup with higher depressive complaints, indicating serious health risks.

Future research may be focussed at evaluating interventions that more directly affect physiological outcomes by for example emphasising relaxation techniques and by slowing down the pace of work-resumption. Alternatively, a promising intervention is meditation. In a recent meta-analyses on the effects of stress-reducing interventions on hypertension (Rainforth et al., 2008), transcendental meditation appeared to be the most powerful treatment for blood pressure reduction.

In conclusion, in this study no evidence was obtained that SMT had stronger (beneficial) effects than CAU on parameters of the sympathetic and parasympathetic nervous system or the HPA axis in a clinical sample with work-related stress. Future studies could focus on more extensive treatment and on improved standardisation regarding factors such as timing of measurements and stress-related conditions to reduce inter-individual differences in outcome measures.

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