Scandinavian Journal of Psychology, 2011, 52, 71–82 DOI: 10.1111/j.1467-9450.2010.00844.x

Health and Disability

Cognitive deficits in relation to personality type and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in women with stress-related exhaustion

AGNETA SANDSTRÖM,[1] JONAS PETERSON,[1] ERIK SANDSTRÖM,[2] MATTIAS LUNDBERG,[3] INGA-LILL RHODIN NYSTROM,[4] LARS NYBERG[5] and TOMMY OLSSON[1]

[1]*Departments of Public Health and Clinical Medicine, Umeå University Hospital, Umeå, Sweden*
[2]*Anesthesia and Intensive care, Östersund, Sweden*
[3]*Department of Psychology, Umeå University, Umeå, Sweden*
[4]*Quranten Stress and Trauma Institute, Umeå, Sweden*
[5]*Radiation Sciences and Integrative Medical Biology, Umeå University Hospital, Umeå, Sweden*

Sandström, A., Peterson, J., Sandström, E., Lundberg, M., Rhodin Nystrom, I.-L., Nyberg, L. & Olsson, T. (2011). Cognitive deficits in relation to personality type and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in women with stress-related exhaustion. *Scandinavian Journal of Psychology 52*, 71–82.

Exhaustion caused by long-term work-related stress may cause cognitive dysfunction. We explored factors that may link chronic stress and cognitive impairment. Personality, psychiatric screening, and behavior were assessed by self-reporting measures in 20 female patients (mean age 39.3 years; range 26–53) with a preliminary diagnosis of stress-related exhaustion and in 16 healthy matched controls. Cognitive performance was investigated with a detailed neuropsychological test battery. Cortisol axis function was assessed by urinary and saliva collections of cortisol, dexamethasone suppression, Synacthen response, and corticotropin-releasing hormone (CRH) tests. Proinflammatory cytokines were measured. Hippocampal volumes were estimated by magnetic resonance imaging. Multivariate and univariate statistical methods were used to explore putative differences between groups and factors linked to cognitive impairment.

Cognitive function clearly differed between groups, with decreased attention and visuospatial memory in the patient group, suggesting frontal cortex/medial temporal cortex-network dysfunction. Increased harm avoidance and persistence was present among patients, with lowered self-directedness linked to lower quality of life, increased anxious and depressive tendencies, and experiences of psychosocial stress. Attention was decreased with concomitantly impaired visuospatial memory. The pituitary (adrenocorticotropic hormone, ACTH) response to CRH was decreased in patients, with an increased cortisol/ACTH response to CRH. However, cortisol production rates, diurnal or dexamethasone-suppressed saliva cortisol levels, and the cortisol response to Synacthen were unaltered. Hippocampal volumes did not differ between groups. These findings suggest that cognitive dysfunction in stress-related exhaustion is linked to distinct personality traits, low quality of life, and a decreased ACTH response to CRH.

Key words: Stress, personality, cognition, HPA-axis, prefrontal cortex, multivariate analysis.

Agneta Sandström, Department of Stroke and Brain Injury, County Council of Jamtland, Box 2102, SE-83102, Sweden. E-mail: agneta.sandstrom@jll.se

INTRODUCTION

Chronic stress refers to a state of ongoing physiological and psychological arousal. This state can affect the immune system, neuroendocrine systems and information-processing in the brain, and may produce physical and psychological damage over time. Notably, we and others have suggested that work-related stress leading to long-term sick leave is closely linked to cognitive dysfunction (Ohman, Nordin, Bergdahl, Slunga Birgander & Stigsdotter Neely, 2007; Rydmark, Wahlberg, Ghatan *et al*., 2006; Sandstrom, Rhodin, Lundberg, Olsson & Nyberg, 2005).

A number of factors may putatively link to cognitive impairment in subjects exposed to chronic stress. This includes personality factors, neuroendocrine abnormalities – especially regarding the hypothalamic-pituitary-adrenal (HPA) axis, immune system activation and hippocampal dysfunction/morphology.

Personality may be a major factor contributing to individual psychological vulnerability (Cloninger, Svrakic & Przybeck, 2006). Notably, the personality trait persistence may contribute to the development of stress-related disorders (Bergdahl, Marell, Bergdahl & Perris, 2005; Elovainio, Kivimaki, Puttonen, Heponiemi, Pulkki & Keltikangas-Jarvinen, 2004).

In addition, the personality dimensions of harm avoidance (HA) and self-directedness (SD) have been associated with depression and anxiety in numerous studies (Farmer & Seeley, 2009; Nery, Hatch, Nicoletti *et al*., 2009). High scores in HA and low scores in SD may thus link to a reduced ability to cope with stress and a genetic vulnerability to develop depression (Farmer, Mahmood, Redman, Harris, Sadler & McGuffin, 2003; Marijnissen, Tuinier, Sijben & Verhoeven, 2002).

A consistent feature of chronic stress is activation of the cortisol, or HPA, axis, which may link to cognitive dysfunction. Increased glucocorticoid (mainly cortisol in humans) levels are thus known to impair memory performance (Wolf, 2009). Interestingly, different patterns of activation of the HPA axis have been found in different neuropsychiatric disorders (Gold & Chrousos, 2002; Nemeroff & Vale, 2005; Sapolsky, Romero & Munck, 2000). Major depression in a substantial proportion of patients has been linked to an increased cortisol production rate, which may be due to increased secretion of corticotropin (CRH) in combination with decreased negative feedback in this hormone axis (Holsboer, 2000). In contrast, studies of patients with post-traumatic stress syndromes and chronic burnout have given divergent results regarding HPA axis activity (de Kloet, Vermetten,

Lentjes *et al*., 2008; Fries, Dettenborn & Kirschbaum, 2009; Sonnenschein, Momersteeg, Houtveen, Sorbi, Schaufeli & van Doornen, 2007; Yehuda, 2001). Of interest, a recent study in patients with job-induced depression showed a marked attenuation of HPA-axis response to CRH-stimulation (Rydmark *et al*., 2006).

The hippocampal formation has been suggested to be a key link between stress hormones and cognitive function. This brain area is an important target for glucocorticoid effects on the brain and conversely, an intact hippocampus may be crucial for a normal feedback function in the HPA axis as well as for memory functions (Seckl & Olsson, 1995). Hippocampal volumes are decreased in patients with long-standing major depression and in postmenopausal women with high perceived stress scores (Gianaros, Jennings, Sheu, Greer, Kuller & Matthews, 2007). This may be most evident in the CA1 region of the hippocampus (Drevets, Price & Furey, 2008).

There is also a suggested link between the immune system, cognitive function and the HPA axis. Increased secretion of proinflammatory cytokines such as interleukin-1β (IL-1β), IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) may thus directly or indirectly (via activation of the HPA axis) contribute to cognitive dysfunction (Dantzer, O'Connor, Freund, Johnson & Kelley, 2008; Elenkov, Iezzoni, Daly, Harris & Chrousos, 2005).

Taken together, although most researchers would probably agree that a multitude of factors interact in stress conditions, few published studies have simultaneously assessed the relative influence of multiple factors on stress conditions. The objective of the present study was therefore to use a multivariate statistical approach to examine whether patients with work-related exhaustion and controls differed on an extensive set of biological, psychological and immunological variables.

METHODS AND MATERIALS

Subjects

Twenty-four consecutive female patients referred to the Quranten Institute of Stress and Trauma with a preliminary diagnosis of work-related exhaustion were included in the study (Table 1). We enrolled only women in this study to ensure a homogenous sample population. Notably, there is a clear overrepresentation of women with work-related exhaustion in Sweden (Swedish National Social Insurance Board, 2003). All subjects had had a sick leave period of at least 3 months due to symptoms related to work-related exhaustion: exhaustion, sleeping problems, and depersonalization (Maslach, Schaufeli & Leiter, 2001). In addition, prior to sick leave, the subjects had had symptoms of exhaustion for long periods of time. They all had identifiable stressors in their work situations, and job-related stress was reported as the main reason for disability. All subjects reported problems with concentration and/or memory, and complained about emotional instability.

Table 1. *Group characteristics*

Demography	Patients n = 20	Control subjects n = 16
Age years; mean (range)	39.3 (26–53)	38.6 (27–50)
Males/females	0/20	0/16
Education years; mean (range)	14 (11–18)	15 (12.5–18)
Major Depression	1	0
Minor Depression	6	0
Dysthymia	2	0
Partial Remission of Depression	2	0
Panic Anxiety	4	0
Anxiety Disorder NUD	6	0
Generalized Anxiety	2	0
Axis I diagnosis	12 (60%)	0

Eighteen healthy control subjects were recruited from the Northern Sweden part of the WHO MONICA (*Moni*toring of trends and determinants in *ca*rdiovascular diseases) (Pedoe, 1988) by matching subjects according to age, body mass index (BMI), and education. All control subjects were thoroughly examined by an endocrinologist (JP), including a physical examination and blood tests to exclude concomitant medical disorders. Patients and controls suffering from associated medical disorders, alcohol abuse, and history of severe head trauma were excluded, as were subjects treated with anxiolytic or psychotropic drugs, excepting selective serotonin reuptake inhibitors. Postmenopausal women and subjects with a BMI greater than 30 (kg/m^2) were excluded from both groups. One patient used oral contraceptives.

Two subjects were excluded because of pathological findings on the MRI brain scan; one patient was diagnosed with Hallerworden Spatz disease and one control had an arachnoidal cyst. One patient was excluded because of alcohol abuse; one control and one patient were excluded because of BMI over 30. Two patients decided not to participate. After these exclusions, 20 patients and 16 healthy controls remained for the study.

Participation was based on informed consent. The study was approved by the ethical committee at Umeå University, Sweden.

Measures

Personality factors and behavioral data

Self-report questionnaires. The Burn-out Tedium Measure (Pines, Aronsson, Kafry, 1981) is a 21-item questionnaire measuring physical, emotional, and mental exhaustion at work. Items are scored on a seven-point scale ranging from never (1) to always (7).

The PSQ (perceived stress questionnaire) is a 30-item self-rating instrument designed to assess perceived stress during the previous month. Items are scored on a four-point scale ranging from almost never (1) to usually (4) (Levenstein, Prantera, Varvo *et al.*, 1993).

The WHO-QOL (World Health Organization – Quality of Life) assesses quality of life during the previous two weeks under four domains: physical health, psychological health, social relationship, and environment. The included 26 items are scored on a five-point scale ranging from not at all (1) to very much (5). Higher scores indicate better quality of life.

The TCI (temperament and character inventory) contains 238 items with true/false answers. TCI assesses four temperament features and three character dimensions. The four temperament features are: *novelty seeking* (NS), impulsive vs. rigid; *harm avoidance* (HA), anxious vs. risk-taking; *reward dependence* (RD), approval seeking vs. aloof; and *persistence* (P), overachieving vs. underachieving. The three character dimensions are: *self-directedness* (SD), executive functions such as tolerance, tendency toward forgiveness and helpfulness; *cooperativeness* (C), legislative functions such as being tolerant and helpful; and *self-transcendence* (ST), judicial functions such as being intuitive, judicious, and aware.

Psychiatric screening. The PRIME-MD was used for psychiatric screening. This system consists of two components: a one-page patient questionnaire (PQ) and a 12-page clinical evaluation guide comprising a structured interview (CEG) containing modules for mood, anxiety, eating disorders, alcohol abuse, social phobia, and obsessive-compulsive disorder. The PRIME-MD system has been constructed to conform to DSM-IV criteria (American Psychiatric Association, 1994; Spitzer, Kroenke, Linzer, deGruy & Hahn, 1994).

The Severity of Psychosocial Stressors Scale (DSM-III-R) was used for coding overall severity of psychosocial stressors that may have

contributed to the development, recurrence, or exacerbation of a mental disorder. Events are coded from none to catastrophic in six levels (American Psychiatric Association, 1994).

Neuropsychological examination. The following neuropsychological tests were used to investigate cognitive function: Wechsler's Adult Intelligence Scale – Revised (WAIS-R) was used to estimate general cognitive abilities (Wechsler, 1955, 1996). The Rey Osterrieth Complex figure test (ROCF) is designed to measure visuospatial constructional ability and visuospatial memory (Meyers, Meyers, 1995).

The Claeson Dahl inventory of learning and memory – Revised (CD), measures efficacy in the ability to immediately recall auditorily presented verbal materials, and the ability to recollect the words attached to the learning situation. (Nyman, 1998; Nyman & Bartfai, 2000). The Intermediate Visual and Auditory Continuous Performance Test (IVA) is a measure of impulsivity, response inhibition, and general consistency of response times, it is used to measure the ability to stay on task, to identify problems related to sustaining attention and effort over time, as well as total variability of the speed of mental processing, and is sensitive to an unusual prevalence of slow reaction times. The IVA also measures the reaction times of all correct responses and is sensitive to problems related to slow mental processing (Riccio, Reynolds, Lowe, 2001; Sandford & Turner, 1995). The IVA consists of two major components: (1) the Full Scale Response Control Quotient (FullScRCQ) based on equal weights of the Auditory Response Control Quotient (AUDRCQ) and the Visual Response Control Quotient (VISRCQ); and (2) the Full Scale Attention Quotient (FullScAQ) based on equal weights of the Auditory Attention Quotient (AUDAQ) and the Visual Attention Quotient (VISAQ). The AUDRCQ and VISRCQ are based on equal weights (1/3 each) of their respective *Prudence, Consistency,* and *Stamina* scales. *Prudence* is a measure of impulsivity and response inhibition, *Consistency* measures the general consistency of response times and is used to measure the ability to stay on task, and *Stamina* is used to identify problems related to sustaining attention and effort over time. The AUDAQ and VISAQ are based on equal weights (1/3 each) of their respective *Vigilance, Focus,* and *Speed* scales. *Vigilance* is a measure of inattention*, Focus* reflects the total variability of the speed of mental processing and is sensitive to an unusual prevalence of slow reaction times, and *Speed* measures the reaction time of all correct responses and is sensitive to problems related to slow mental processing. All tests have been described in detail elsewhere (Sandstrom *et al.*, 2005).

Routine blood tests. Patients and controls were screened with routine blood analyses, (e.g., liver and kidney function tests, electrolyte levels, and thyroid hormone levels), at the Department of Clinical Chemistry, Umeå University Hospital to exclude diseases that may interfere with further testing. No pathological findings were revealed.

HPA axis. HPA-axis tests were performed within ten days after cessation of a menstrual bleeding (i.e., during the follicular phase of the menstrual cycle). On day one, a 24 h urinary collection was done. On day 2, saliva was collected for measurements of cortisol at 7, 11, 16, 19 and 23 hrs. No food, tobacco, or tooth brushing was allowed during the preceding sampling. This was followed by a low-dose dexamethasone (DEX) suppression test in which subjects ingested 0.25 mg DEX (Decadrone® MSD) after the 23.00 saliva sample. On the following morning a saliva sample was collected at 07.00 for estimations of cortisol. On day 4 a short adrenocorticotropic hormone (ACTH) stimulation test was performed at 08.30 in the morning: Following an overnight fast subjects rested for 30 minutes, after which a blood sample was obtained from an antecubital vein, 1 microgram tetracosactid (Synacthen®), was then administered by intravenous (i.v.) injection. Venous blood samples were drawn 30 and 40 minutes after the injection (Rasmuson, Olsson & Hagg, 1996). On day 6 a CRH test was done. During the CRH test, subjects fasted from 10.00. They received an indwelling antecubital venous catheter at 13.00. Two blood samples were obtained with a 15-minute interval prior to the i.v. injection of CRH (1 microgram/kg b.w.). Samples were drawn at 5, 10, 15, 30, 50, 60, 90, and 120 minutes after the injection and immediately put on ice.

Urine samples were extracted by dichlorometane and analyzed for cortisol by Spectria Cortisol RIA (Orion Diagnostica, Finland) at the Department of Clinical Chemistry, Umeå University Hospital with a total coefficient of variance (CV) < 20% at 50 nmol/L.

Serum cortisol, saliva cortisol, and plasma ACTH levels were analyzed at the Department of Clinical Chemistry, Umeå University Hospital. S-cortisol was measured by Immulite 2000 (DPC) in clinical routine. Salivary cortisol was measured in clinical routine by Spectria, Orion Diagnostica, Finland, according to the manufacturer's procedure for salivary cortisol. P-ACTH was measured by Immulite 2000 (DPC), standardized against MRC reference preparation 74/555, in clinical routine. The CVs were <10% for serum cortisol, <12% for saliva cortisol, and <12% for P-ACTH. Serum thyroid stimulating hormone (S-TSH) was analyzed by Roche Elecsys reagents on a Modular E170 analysis in an accredited laboratory with a total CV <10% at 1-10 mIU/L. S-free T3 and T4 were analyzed by Roche Elecsys reagents on a Modular E170 analysis in an accredited laboratory with a total CV <10% at 15-30 pmol/L and 5-20 pmol/L, respectively.

Cytokines. Blood samples were drawn between 08.00 and 10.00 hours. All samples were stored at –70 °C until analyzed in plasma with enzyme-linked immunoassays for IL-1ß, IL-6, IL-1 receptor antagonist, and TNF-α (all from R&D Systems, Abingdon, UK).

Hippocampal volume. The hippocampus was investigated with Tl-weighted magnetic resonance imaging (MRI) in 1 mm coronal slices using a 0.5 T superconducting magnet (Philips, Netherlands), as has been described earlier (Elgh *et al.*, 2006). The following measurements were performed on both the right and left sides of the brain (Kier, Kim, Fulbright & Bronen, 1997): (1) The CA1 region. A horizontal line from the lateral corner of the hippocampal sulcus to the medial corner of the temporal horn was measured. This line describes the thickness of the hippocampus, including the white matter of the superficial medullary lamina of subiculum medially and of the alveus laterally (the grey matter of CA1 lies between these two white matter areas). (2) The CA2/3 regions. A vertical line from the same lateral corner of the hippocampal sulcus was measured, describing the thickness of the CA2/3 regions. (3) Hippocampal area. The total cross-sectional area (in mm^2) of the hippocampus was measured with a grid placed on the hippocampus.

Procedure

Psychological data were collected during two test sessions scheduled two or three days apart. Each session lasted about two hours. In session one, a psychologist interviewed each subject, and the Assessment of DSM-IV Axis I disorders (PRIME MD) was administered. The Perceived Stress Questionnaire (PSQ), WHO Quality of Life questionnaire (WHO-QOL), Pines Burn-out Tedium measure, and TCI were distributed, to be completed at home. Neuropsychological testing was introduced in session one and was completed in session two. Self-report questionnaires were collected in session two. In session three, the patients underwent a full physical examination by an endocrinologist, followed by MRI. Biological data were collected ten days after cessation of a menstrual bleeding.

Statistical analyses

Multivariate analyses were conducted using SIMCA software, version 11.5. SIMCA provides a multivariate statistical method based on projection methods (principal component analysis) that can handle matrices with more variables than subjects (Eriksson, Johansson, Kettaneh-Wold, Trygg, Wikström & Wold, 2006; Henningsson, Sundbom, Armelius & Erdberg, 2001).

Projection to latent structures by means of partial least squares (PLS) can be seen as an extension of the principal component analysis (PCA), where one or many response variables in a *y*-matrix can be predicted from a set of variables in an *x*-matrix. PLS can thereby be used as a generalized multiple regression method that can cope with multiple collinear *x* and *y* variables. With this approach, cases are represented as a swarm

of points in a *K*-dimensional space (*K* = number of variables), and the swarm of points is then projected down onto a lower-dimensional plane or hyper-plane. The coordinates of the points on this hyper-plane provide a compressed representation of the observation, and the direction vectors of the hyper-plane provide a corresponding representation of the variables.

A total of 157 variables were included in the original partial least squares discriminant analysis (PLS-DA) data set (included variables are presented in the appendix). In order to extract the most important variables in the model, a VIP value (variable importance in the projection) was calculated. VIP is an indication of how important the individual variable is to the entire model. A value above 1.0 indicates that the variable is relevant for explaining the model. To reduce the number of variables, a stricter cut-off (i.e., >1.2) was used. This left 34 variables to be explained.

In selected analyses, the non-parametric Mann Whitney test was used to test for differences between cases and controls and χ^2 tests for proinflammatory cytokines. A p-value <0.05 was considered statistically significant. Data are shown as mean ± SD (standard deviation). SPSS v14.0 was used for the univariate statistical analyses.

RESULTS

Participant characteristics

Sociodemographic characteristics and the distribution of DSM-Axis disorders among the subjects are shown in Table 1. There were no significant group differences regarding age or education level. Affective disorder was present in 60% of patients, based on PRIME MD results. The most-reported disorders were minor depression and anxiety disorder. Criteria for more than one DSM-IV diagnosis were fulfilled in seven individuals. One patient fulfilled DSM-IV criteria for major depression. None of the control subjects reported affective disorder based on PRIME MD results.

Multivariate statistical analysis

In order to examine the most important variables in the model, discriminating patients from controls, PLS-DA was conducted. To avoid circularity the variables Burn-out and Perceived Stress were excluded from the model. In this analysis, grouping (patient or control) was used as a dummy *y*-variable.

As shown in Fig. 1A, 19 out of 20 patients were separated from controls along the first principal component. The model was significant with a high explained variance and a good predictive value. Thirty-four variables had substantial influence in the separation of the groups.

SIMCA DA modeling revealed four main clusters of variables explaining differences between patients and controls (Fig. 1B and Table 2). These consisted of one cluster (cluster 1) containing 6 personality variables and 4 behavioral variables; one cluster (cluster 2) of 11 variables describing cognitive measures; one cluster of 8 variables (cluster 3) describing HPA axis variables; and one cluster of 3 variables (cluster 4) measuring biological/immunological variables. These clusters were further compared between groups.

Cluster 1: Personality factors and self report measures. Patients had higher scores than controls in "harm avoidance" and "persistence" with lower scores on "self-directedness" (Fig. 1B and Table 2). Patients also scored significantly lower in WHO-QOL, psychological well-being, and quality of environment. In addition, depressive tendencies and experiences of psychosocial stress were significantly higher in the patient group.

Cluster 2: Cognitive variables. Attention measures were decreased in patients, including response control measures and the attention quotient (Fig. 1B and Table 2). Patients also had impaired visuospatial memory ability according to the Rey Osterrieth Complex figure test, and significant decreases in both immediate and delayed response.

Cluster 3: HPA-axis variables. Data were obtained from 19 patients and 13 controls. In all, 30/1216 (2.5%) samples from 10 subjects (6 patients, 4 controls) were not analyzed due to laboratory handling errors or insufficient amounts of saliva. No significant difference between groups was found regarding urinary cortisol levels (data not shown), diurnal saliva cortisol levels, or DEX suppression of cortisol (i.e., feedback function at the pituitary level; Fig. 3A). Significantly decreased reactivity on the pituitary level was found in patients, with lower ACTH levels 30–90 minutes after CRH injection and a lower ACTH area under the curve response to CRH (Fig. 1B, Fig. 2A, Table 2). The cortisol/ACTH area response to CRH was slightly higher in patients versus controls, with the 30 minute response being a significant predictor for group categorizing (Fig. 1B, 2B, Table 2). Patients also had a tendency toward higher cortisol response to Synacthen®, which was not statistically significant (Fig. 3B).

Cluster 4: Anthropometry, thyroid hormones, interleukin 1-β. The location of the variables T4, IL-1β, and BMI in the statistical analysis indicates that these variables are positively correlated to being a patient but also to each other (Fig. 1B).

Patients had significantly lower circulating levels of TSH versus controls, while free T4 levels were slightly higher in patients (Table 2). A significantly higher proportion of patients had detectable levels of IL-1β (χ^2 [1] = 5.78, p = 0.016).

DISCUSSION

This study verifies specific cognitive impairments linked to work-related stress exhaustion. In a multivariate analysis we find that this is associated with a distinctive pattern of personality, neuroendocrine, and immunological dysfunctions. The clear separation of the two groups indicates that the patient group is a homogenous group according to the included variables.

The problems with attention, visuospatial learning, and memory are consistent with other studies of stress-induced deficits in visuospatial capacity and working memory (Lupien, Evans, Lord *et al*., 2007; Lupien, Fiocco, Wan *et al*., 2005; Morgan, Doran, Steffian, Hazlett & Southwick, 2006; Rydmark *et al*., 2006). The pattern of cognitive deficits, with intact performance on tests with familiar verbal materials along with slowed speed and impaired performance on tests with novel non-verbal stimuli, suggests frontal cortex/medial temporal cortex-network dysfunction. This is well in line with recent data from rodents and humans, suggesting that chronic stress may impair attention control in conjunction with disrupted plasticity in prefrontal cortex networks (Liston, McEwen & Casey, 2009). The fact that patients performed well on verbal memory tests and neuropsychological tests that are dependent on pre-experimentally

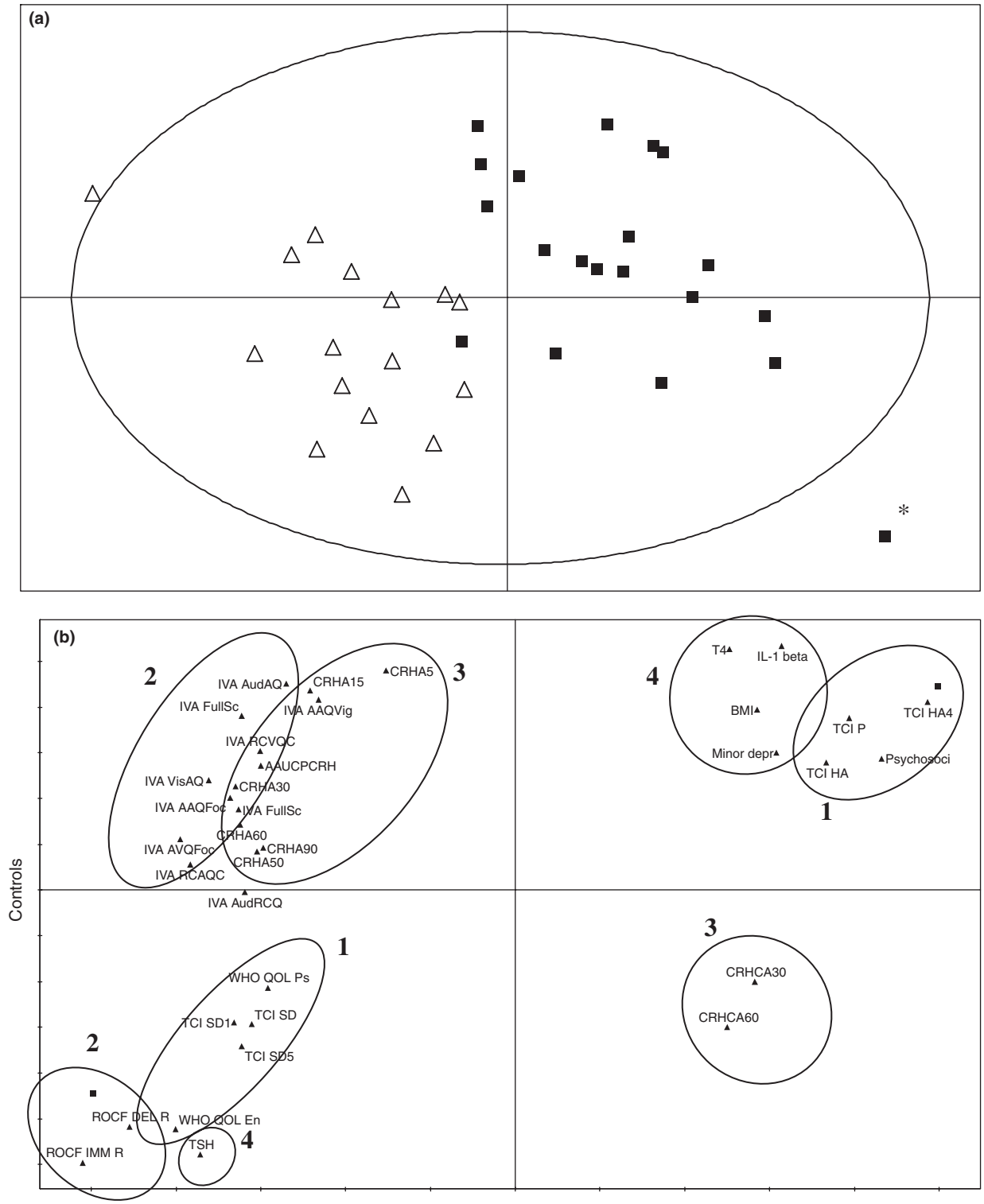

Fig. 1. (a) Results from the discriminant analysis (PLS-DA), detecting variables separating patients from controls. The score plot, containing 34 variables, indicating a clear separation between patients and controls. Minimal overlap indicates a powerful model. One outlier was detected (P*: this patient fulfilled the criteria for major depression). Patients and controls were significantly separated along component 1 (left/right). Explained variance (R^2) = 0.78 with predictive value (goodness of prediction); Q = 0.59. ¢= Patients, Δ=Controls. (b) Variables contributing to the separation of patients and controls. Only variables with a VIP-value >1.2 was included (34 variables). Variables clustered together are strongly associated. Variables located on the right side of Origo were positively correlated to patients and negatively correlated to controls, and vice versa for variables located on the left side of Origo. Cluster 1 = personality factors and behavioural variables, cluster 2 = cognitive variables, cluster 3 = HPA axis variable, cluster 4 = Biological variables. Note: Full variable names are given in table 2.

acquired knowledge, both according to normative data and compared to controls, indicates that this group of patients had a high premorbid functional level.

Our evaluation of personality measures links to earlier data suggesting that harm avoidance and self-directedness are predictors of vulnerability to depressive symptoms and anxiety (Cloninger

Table 2. *Summary of variables explaining model (VIP> 1.2) in Simca PLS-DA in Figure1*

		Patients		Controls		Mann-Whitney
Simca VIP Variables	VIP[2] (cum)	Mean	±SD	Mean	±SD	p-value
CLUSTER 1 PERSONALITY /BEHAVIORAL						
TCI- HA4 (harm-avoidance, asthenia)	2.06	63.1	12	46.3	9.9	<0.001
TCI- P (persistence)	1.71	61.2	14.6	47.3	9.8	0.003
TCI- HA (harm avoidance, total score)	1.49	55.2	10.7	45.2	8.5	0.003
TCI- SD1 (self directedness, responsefulness)	1.36	42.6	15.8	53.8	6.1	0.070
TCI- SD5 (self directedness, congruence)	1.35	44.2	12	53.4	8.7	0.019
TCI- SD (self directedness, total score)	1.27	41.8	15	52.5	9.5	0.026
Psychosocial stressors	1.83	50	9.6	41.5	11.8	0.001
WHO QOL (quality of life) Environment	1.78	60	9.9	70.1	7.4	0.036
WHO QOL Psychological	1.21	41.5	11.8	50	9.6	<0.001
Prime MD Minor Depression	1.32	1.2	1.8	0	0	0.022
CLUSTER 2 COGNITION						
ROCF Imm (Rey Osterrieth complex figure, immediate recall)	2.27	33.3	12.1	54.4	14.1	<0.001
ROCF Del (delayed recall)	2.03	34.4	11.9	52.4	14.7	0.002
IVA- AVQFoc (attention, visual quotient, focus)	1.64	91.4	16	107.9	12.9	0.001
IVA- RCAQC (response control, attention quotient, consistency)	1.57	93.7	17.4	110.6	12.9	0.003
IVA- VisAQ (visual attention quotient)	1.53	87.2	15.2	103.9	12.9	0.003
IVA- FullScAQ (full scale attention quotient)	1.47	84.3	22.3	101	14	0.004
IVA- AAQFoc (auditory attention quotient, focus)	1.44	97.8	14.7	110.1	11.7	0.006
IVA- FullScRCQ (full scale response control quotient)	1.37	97.5	13.9	108.9	11.6	0.011
IVA- AudAQ (auditory attention quotient)	1.34	83.4	23.8	97.9	15.2	0.019
IVA- RCVQC (response control, visual quotient consistency)	1.31	100.4	16.6	111.7	10.3	0.016
IVA- AudRCQ (auditory response control quotient)	1.30	96.6	15.2	108.2	11.1	0.029
CLUSTER 3 HPA-AXIS						
AAUCPCRH (ACTH area under curve after CRH)	1.47	2 262.3	838	3 071.4	1232	0.039
CRHA 30 (p-ACTH release after CRH stimulation, 30 min)	1.53	27.8	12.4	40.1	15.3	0.016
CRHA 60	1.47	21.3	9.3	29.8	10.1	0.031
CRHA 15	1.39	25.2	11.3	37.3	27.4	0.180
CRHA 50	1.34	24.5	10.7	34.1	13.2	0.038
CRHA 90	1.29	13.5	3.5	16.8	4.9	0.046
CRHCA 60 (s-Cortisol/p-ACTH after CRH stimulation, 60 min)	1.28	29.8	13.8	22.1	7.6	0.161
CRHCA 30	1.25	21.3	10.9	14.4	4.8	0.043
CLUSTER 4 BIOLOGICAL						
TSH (S-Thyroid stimulating hormone)	1.83	1.4	.68	2.3	1	0.008
T 4 (free thyroxin)	1.21	14.3	1.52	13.4	1.46	0.064
IL-1 β (interleukin-1 beta)	1.41	.24	.33	.024	.060	0.015
BMI (body mass index)	1.24	23.4	2.99	21.3	2.36	0.041

et al., 2006; Elovainio *et al.*, 2004; Farmer *et al.*, 2003). Harm avoidance may thus be a marker of emotional vulnerability to depression whereas self-directedness reflects executive functions that protect a person from depression (Cloninger *et al.*, 2006). As in the above-mentioned studies, patients had higher scores in harm avoidance and lower scores in self-directedness compared to controls; they also had significantly higher scores in persistence. High persistence scores, although of potential value in modern organizations, may be maladaptive for individuals that fail to change behavior when severe/long-term stress occurs. Persistence is by this view a vulnerability factor for stress-related symptoms, and high-persistence individuals are prone to externalize their individual problems (Bergdahl *et al.*, 2005; Cloninger *et al.*, 2006). A genetic disposition to avoidant and persistent behavior may therefore predispose individuals to sickness and lower general well-being. Importantly, decreased psychological health appears to ''prime'' individuals to be influenced by ''mood bias'' and to report bad life experiences and affirm negative feelings, thereby influencing results in self-directedness and depression measures (Leung, Lee, Wong, Li, Yip & Khong, 2008).

Psychosocial stress separates patients from controls. This shows that work-related stress is not the only factor responsible for the reported illness. Minor depression also contributes to explain the experience of stress and work-related exhaustion in this model, but importantly, major depression was present in only one individual in our patient group.

The hippocampus plays an important role in memory formation, spatial navigation, and emotional processing, all neuropsychological domains known to be affected in stress-related diseases (Lee, Ogle & Sapolsky, 2002; Seckl & Olsson, 1995; Sheline, 2003; Smith, 2005; Warner-Schmidt & Duman, 2006). Data from experimental and human studies on long-term stress, including major depression, suggest that reductions in hippocampal volume may develop as a possible protective reaction to increased excitotoxic signals. This may be confined to subregions of the hippocampal formation, notably the CA1 region (Drevets *et al.*, 2008).

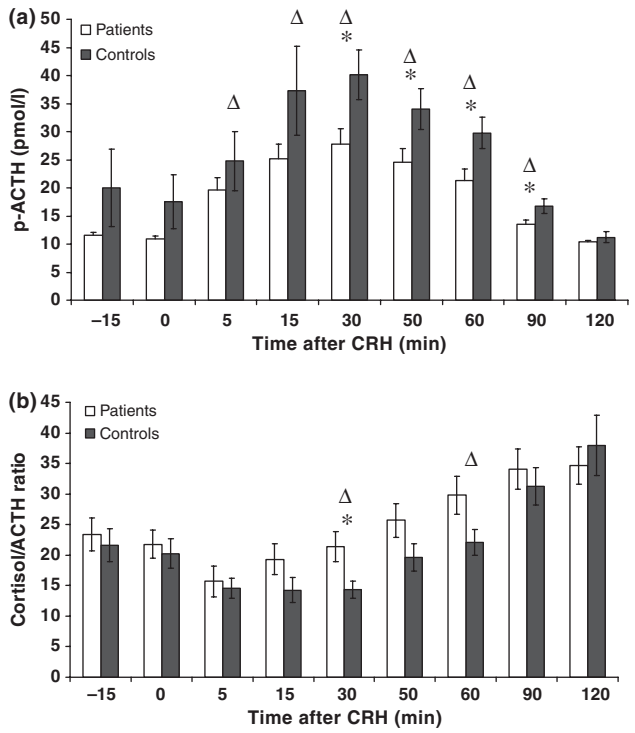

Fig. 2. (a) ACTH and cortisol responses to CRH stimulation (1 μg/kg, i.v), P-ACTH response to CRH. Data are means ± SD. *= $p < 0.05$. Δ = Variables with a Simca VIP-value >1.2. (b) S-cortisol/P-ACTH response to CRH. Data are means ± SD. *= $p < 0.05$. Δ= Variables with a simca VIP-value >1.2.

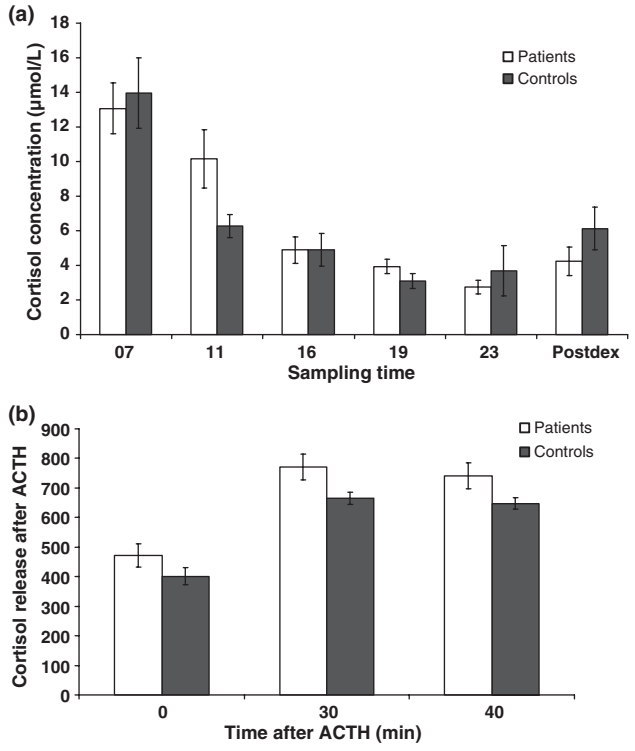

Fig. 3. (a) Diurnal saliva cortisol levels including saliva cortisol after dexamethasone suppression. Data are means ± SD. (b) Serum cortisol response after ACTH (Synacthen®) stimulation. Data are means ± SD.

However, we found no differences in hippocampal volumes between patients and controls, despite separate analyses of the hippocampal subregions. This does not preclude that functional changes in forebrain-limbic circuits may influence symptomatology in these patients. It is therefore of further interest to investigate possible functional alterations in the hippocampus and other brain areas, including the prefrontal cortex.

We found an interesting pattern regarding HPA axis activity. The pituitary (ACTH) response was decreased with a tendency for increased cortisol/ACTH response after CRH. This pattern resembles somewhat what has been repeatedly found in subjects with major depression (Gold & Chrousos, 2002). However, cortisol production rates (based on free urinary cortisol levels), diurnal rhythmicity, feedback sensitivity (estimated by the DEX suppression test), and the cortisol response to ACTH (Synacthen®) were unaltered. Hypercortisolemia, with increased cortisol production rates associated with an increased responsiveness at the adrenal cortex level, is present in about 50% of patients diagnosed with major depressive disorder (Bremner, Vythilingam, Vermetten, Anderson, Newcomer & Charney, 2004; Gillespie & Nemeroff, 2005), and cognitive impairment is a common feature of this disease (Drevets, 2001). In contrast, other neuropsychiatric disorders, including post-traumatic stress, fibromyalgia, and chronic fatigue syndrome, have been suggested to be linked to lowered levels of circulating cortisol and increased feedback sensitivity (Heim, Ehlert & Hellhammer, 2000; Yehuda, 2001); but these findings have not been consistent (de Kloet *et al*., 2008). Findings from burnout patients have shown conflicting results, with increased awakening response (Grossi, Perski, Ekstedt, Johansson, Lindstrom & Holm, 2005), decreased (Pruessner, Hellhammer & Kirschbaum, 1999), or normal (Mommersteeg, Heijnen, Verbraak & van Doornen, 2006). A recent study showed that lower diurnal cortisol variability in burnout patients was related to slower cognitive performance (Osterberg, Karlson & Hansen, 2009). Therefore, this patient group seems to have a distinctive HPA axis pattern, different from that seen in major depression and other neuropsychiatric disorders.

Recently, patients with job stress-induced depression were reported to have impaired working memory in association with an attenuated ACTH and cortisol response to corticotropin-releasing hormone (CRH) (Rydmark *et al.*, 2006). Notably, patients who had major depression or adjustment disorder with depressed mood according to DSM IV were included in this study. It is of interest that the only patient who fulfilled the criteria for major depression in our study was a clear outlier in the multivariate analysis of the data. This suggests that different clusters (of personality measures, cognitive dysfunction, and neuroendocrine responses) may be seen depending on the presence of major depression in the clinical phenotype of these patients. In the study by Rydmark *et al*., DEX suppression was used before the CRH injection (i.e., the DEX-CRH response) (Rydmark *et al.*, 2006). This test may probe stress-induced hypothalamic recruitment of vasopressin co-expression in CRH neurons, acting to augment CRH effects (Keck, Wigger, Welt *et al.*, 2002). It would thus be of interest to study DEX-CRH responsiveness in subgroups of patients with long-term stress/chronic burnout with and without concomitant major depression.

A higher proportion of patients versus controls in our study had detectable circulating levels of IL-1β. Proinflammatory cytokines,

including Il-1ß, IL-6, and TNF-α, may modulate the activity of the HPA axis at several levels (De Kloet, Oitzl & Schobitz, 1994; Muller & Schwarz, 2007). In addition, pro-inflammatory cytokines are suggested to induce major depressive disorders in vulnerable individuals (Dantzer *et al.*, 2008) and depressive illness is accompanied by elevated cytokine production (Anisman & Merali, 2003). Cytokines may also influence cognition (Capuron & Dantzer, 2003), and interferon therapy is known to affect cognition and mood (Valentine & Meyers, 2005).

We cannot, based on this cross-sectional study, conclude anything about causality. However, it is tempting to suggest that a persistent personality phenotype enhances the vulnerability to stress-related disease that leads to alterations in HPA-axis functions, decreased prefrontal lobe function, and decreased excitatory network function, a combination leading to decreased executive attention.

Our study results may be partly hampered by the limited number of subjects. Importantly, ordinary statistical methods are not applicable where there are more variables than subjects, especially with collinear variables. The objective of PLS-DA is to find a model that separates classes of observations and to understand which variables carry the class separating information. Instead of considering one variable at a time, all variables are analyzed simultaneously, reducing the risk of type I and type II errors (Eriksson *et al.*, 2006). Our statistical method is widely accepted for this type of study, but new study groups are still needed to verify our findings in larger cohorts of subjects.

In summary, our data suggest an intimate link between cognitive performance, personality, well-being and neuroendocrine dysfunction in the phenotypic expression of stress-related cognitive dysfunction.

The authors wish to thank Inger Arnesjö for assistance during data collection, Markku Fagerlund for interpretation of MRI data, Christer Albano for valuable comments on multivariate statistics and Mats Lekander for valuable comments on proinflammatory cytokines. Funding for this study was provided by the European Union/Swedish Research Council (Eurostress), County Councils of Jämtland and Västerbotten and the Åke Wibergs Foundation. The funding agencies had no role in study design, in the collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

REFERENCES

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn). Washington, DC: American Psychiatric Press.

Anisman, H. & Merali, Z. (2003). Cytokines, stress and depressive illness: brain-immune interactions. *Annual Review of Medicine*, *35*(1), 2–11.

Bergdahl, J., Marell, L., Bergdahl, M. & Perris, H. (2005). Psychobiological personality dimensions in two environmental-illness patient groups. *Clinical Oral Investigation*, *9*(4), 251–256.

Bremner, J. D., Vythilingam, M., Vermetten, E., Anderson, G., Newcomer, J. W. & Charney, D. S. (2004). Effects of glucocorticoids on declarative memory function in major depression. *Biological Psychiatry*, *55*(8), 811–815.

Capuron, L. & Dantzer, R. (2003). Cytokines and depression: the need for a new paradigm. *Brain Behaviour Immunology*, *17* Suppl 1, S119–124.

Cloninger, C. R., Svrakic, D. M. & Przybeck, T. R. (2006). Can personality assessment predict future depression? A twelve-month follow-up of 631 subjects. *Journal of Affecive Disorder*, *92*(1), 35–44.

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W. & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience*, *9*(1), 46–56.

de Kloet, C., Vermetten, E., Lentjes, E., Geuze, E., van Pelt, J., Manuel, R., et al. (2008). Differences in the response to the combined DEX-CRH test between PTSD patients with and without comorbid depressive disorder. *Psychoneuroendocrinology*, *33*(3), 313–320.

De Kloet, E. R., Oitzl, M. S. & Schobitz, B. (1994). Cytokines and the brain corticosteroid receptor balance: relevance to pathophysiology of neuroendocrine-immune communication. *Psychoneuroendocrinology*, *19*(2), 121–134.

Drevets, W. C. (2001). Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current Opinion of Neurobiology*, *11*(2), 240–249.

Drevets, W. C., Price, J. L. & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Structure and Function*, *213*(1–2), 93–118.

Elenkov, I. J., Iezzoni, D. G., Daly, A., Harris, A. G. & Chrousos, G. P. (2005). Cytokine dysregulation, inflammation and well-being. *Neuroimmunomodulation*, *12*(5), 255–269.

Elgh, E., Lindqvist Astot, A., Fagerlund, M., Eriksson, S., Olsson, T. & Nasman, B. (2006). Cognitive dysfunction, hippocampal atrophy and glucocorticoid feedback in Alzheimer's disease. *Biological Psychiatry*, *59*(2), 155–161.

Elovainio, M., Kivimaki, M., Puttonen, S., Heponiemi, T., Pulkki, L. & Keltikangas-Jarvinen, L. (2004). Temperament and depressive symptoms: a population-based longitudinal study on Cloninger's psychobiological temperament model. *Journal of Affective Disord*, *83*(2–3), 227–232.

Eriksson, L., Johansson, E., Kettaneh-Wold, N., Trygg, J., Wikström, C. & Wold, S. (2006). *Multi and Megavariate data analysis* (2nd edn, Vol. Umetrics AB). Umeå Sweden: Umetrics AB.ISBN-10:91-973730-2-8, ISSBN-13: 978-91-73730-2-9.

Farmer, A., Mahmood, A., Redman, K., Harris, T., Sadler, S. & McGuffin, P. (2003). A sib-pair study of the Temperament and Character Inventory scales in major depression. *Archives of Genetic Psychiatry*, *60*(5), 490–496.

Farmer, R. F. & Seeley, J. R. (2009). Temperament and character predictors of depressed mood over a 4-year interval. *Depression and Anxiety*, *26*(4), 371–381.

Fries, E., Dettenborn, L. & Kirschbaum, C. (2009). The cortisol awakening response (CAR): facts and future directions. *International Journal of Psychophysiology*, *72*(1), 67–73.

Gianaros, P. J., Jennings, J. R., Sheu, L. K., Greer, P. J., Kuller, L. H. & Matthews, K. A. (2007). Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. *Neuroimage*, *35*(2), 795–803.

Gillespie, C. F. & Nemeroff, C. B. (2005). Hypercortisolemia and depression. *Psychosomatic Medicine*, *67* Suppl 1, S26–28.

Gold, P. W. & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Molecular Psychiatry*, *7*(3), 254–275.

Grossi, G., Perski, A., Ekstedt, M., Johansson, T., Lindstrom, M. & Holm, K. (2005). The morning salivary cortisol response in burnout. *Journal of Psychosomatic Research*, *59*(2), 103–111.

Heim, C., Ehlert, U. & Hellhammer, D. H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology*, *25*(1), 1–35.

Henningsson, M., Sundbom, E., Armelius, B. A. & Erdberg, P. (2001). PLS model building: a multivariate approach to personality test data. *Scandinavian Journal of Psychology*, *42*(5), 399–409.

Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*, *23*(5), 477–501.

Keck, M. E., Wigger, A., Welt, T., Muller, M. B., Gesing, A., Reul, J. M., et al. (2002). Vasopressin mediates the response of the combined dexamethasone/CRH test in hyper-anxious rats: implications for path-

ogenesis of affective disorders. *Neuropsychopharmacology*, *26*(1), 94–105.

Kier, E. L., Kim, J. H., Fulbright, R. K. & Bronen, R. A. (1997). Embryology of the human fetal hippocampus: MR imaging, anatomy, and histology. *AJNR American Journal of Neuroradiology*, *18*(3), 525–532.

Lee, A. L., Ogle, W. O. & Sapolsky, R. M. (2002). Stress and depression: possible links to neuron death in the hippocampus. *Bipolar Disord*, *4*(2), 117–128.

Leung, K. K., Lee, T. M., Wong, M. M., Li, L. S., Yip, P. S. & Khong, P. L. (2008). Neural correlates of attention biases of people with major depressive disorder: a voxel-based morphometric study. *Psychological Medicine*, 1–10.

Levenstein, S., Prantera, C., Varvo, V., Scribano, M. L., Berto, E., Luzi, C., et al. (1993). Development of the Perceived Stress Questionnaire: a new tool for psychosomatic research. *Journal of Psychosomatic Research*, *37*(1), 19–32.

Liston, C., McEwen, B. S. & Casey, B. J. (2009). Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *The Proceedings of the National Academy of Sciences U S A*, *106*(3), 912–917.

Lupien, S. J., Evans, A., Lord, C., Miles, J., Pruessner, M., Pike, B., et al. (2007). Hippocampal volume is as variable in young as in older adults: implications for the notion of hippocampal atrophy in humans. *Neuroimage*, *34*(2), 479–485.

Lupien, S. J., Fiocco, A., Wan, N., Maheu, F., Lord, C., Schramek, T., et al. (2005). Stress hormones and human memory function across the lifespan. *Psychoneuroendocrinology*, *30*(3), 225–242.

Marijnissen, G., Tuinier, S., Sijben, A. E. & Verhoeven, W. M. (2002). The temperament and character inventory in major depression. *Journal of Affective Disorder*, *70*(2), 219–223.

Maslach, C., Schaufeli, W. B. & Leiter, M. P. (2001). Job burnout. *Annual Review of Psychology*, *52*, 397–422.

Meyers J. E. & Meyers K. R. (1995). *Rey Complex Figure Test and Recognition Trial*. Odessa: Psychological Assessment Resources, Inc.

Mommersteeg, P. M., Heijnen, C. J., Verbraak, M. J. & van Doornen, L. J. (2006). Clinical burnout is not reflected in the cortisol awakening response, the day-curve or the response to a low-dose dexamethasone suppression test. *Psychoneuroendocrinology*, *31*(2), 216–225.

Morgan, C. A., III, Doran, A., Steffian, G., Hazlett, G. & Southwick, S. M. (2006). Stress-induced deficits in working memory and visuo-constructive abilities in Special Operations soldiers. *Biological Psychiatry*, *60*(7), 722–729.

Muller, N. & Schwarz, M. J. (2007). The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Molecular Psychiatry*, *12*(11), 988–1000.

Nemeroff, C. B. & Vale, W. W. (2005). The neurobiology of depression: inroads to treatment and new drug discovery. *Journal of Clinical Psychiatry*, *66* Suppl 7, 5–13.

Nery, F. G., Hatch, J. P., Nicoletti, M. A., Monkul, E. S., Najt, P., Matsuo, K., et al. (2009). Temperament and character traits in major depressive disorder: influence of mood state and recurrence of episodes. *Depression and Anxiety*, *26*(4), 382–388.

Nyman, H. (1998). Claeson-Dahls test för inlärning och minne- reviderad version. Unpublished manuscript, Stockholm.

Nyman, H. & Bartfai, A. (2000). *Klinisk Neuropsykologi*. Lund: Studentlitteratur.

Ohman, L., Nordin, S., Bergdahl, J., Slunga Birgander, L. & Stigsdotter Neely, A. (2007). Cognitive function in outpatients with perceived chronic stress. *Scandinavian Journal of Work Environment and Health*, *33*(3), 223–232.

Osterberg, K., Karlson, B. & Hansen, A. M. (2009). Cognitive performance in patients with burnout, in relation to diurnal salivary cortisol. *Stress*, *12*(1), 70–81.

Pedoe, H. T. (1988). The World Health Organization MONICA Project (Monitoring Trends and Determinants in Cardiovascular Disease): a major international collaboration. *Journal of Clinical Epidemiology*, *41*, 105–114.

Pines, A., Aronsson, E. & Kafry, D. (1981). *Burnout from tedium to personal growth*. New York: Free Press.

Pruessner, J. C., Hellhammer, D. H. & Kirschbaum, C. (1999). Burnout, perceived stress, and cortisol responses to awakening. *Psychosomatic Medicine*, *61*(2), 197–204.

Rasmuson, S., Olsson, T. & Hagg, E. (1996). A low dose ACTH test to assess the function of the hypothalamic-pituitary-adrenal axis. *Clinical Endocrinology*, *44*(2), 151–156.

Riccio C. A., Reynolds C. R. & Lowe P. A., (2001). *Clinical applications of continuous performance test: Measuring attention and impulsive responding in children and adults*. New York: Wiley.

Rydmark, I., Wahlberg, K., Ghatan, P. H., Modell, S., Nygren, A., Ingvar, M., et al. (2006). Neuroendocrine, cognitive and structural imaging characteristics of women on long-term sick leave with job stress-induced depression. *Biological Psychiatry*, *60*(8), 867–873.

Sandford, J. & Turner, A. (1995). Interpretation manual for the intermediate visual and auditory continuous performance test. Unpublished manuscript, Virginia.

Sandstrom, A., Rhodin, I. N., Lundberg, M., Olsson, T. & Nyberg, L. (2005). Impaired cognitive performance in patients with chronic burnout syndrome. *Biological Psychology*, *69*(3), 271–279.

Sapolsky, R. M., Romero, L. M. & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, *21*(1), 55–89.

Seckl, J. R. & Olsson, T. (1995). Glucocorticoid hypersecretion and the age-impaired hippocampus: cause or effect? *Journal of Endocrinology*, *145*(2), 201–211.

Sheline, Y. I. (2003). Neuroimaging studies of mood disorder effects on the brain. *Biological Psychiatry*, *54*(3), 338–352.

Smith, M. E. (2005). Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. *Hippocampus*, *15*(6), 798–807.

Sonnenschein, M., Mommersteeg, P. M., Houtveen, J. H., Sorbi, M. J., Schaufeli, W. B. & van Doornen, L. J. (2007). Exhaustion and endocrine functioning in clinical burnout: an in-depth study using the experience sampling method. *Biological Psychology*, *75*(2), 176–184.

Spitzer RL, W. J., Kroenke K, Linzer M, deGruy FV, Hahn 3rd, et al. (1994). Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 study. *JAMA*, *272*, 1749–1756.

Swedish National Social Insurance Board. (2003). *Exhaustionsyndromes* (No. ISBN 91-7201-786-4). Stockholm: Swedish National Social Insurance Board.

Valentine, A. D. & Meyers, C. A. (2005). Neurobehavioral effects of interferon therapy. *Current Psychiatry Reports*, *7*(5), 391–395.

Warner-Schmidt, J. L. & Duman, R. S. (2006). Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus*, *16*(3), 239–249.

Wechsler, D. (1955). *Manual for the Wechsler Adult Intelligence Scale*. New York: The Psychological Corporation.

Wechsler, D. (1996). *Wais-R Wechsler Adult Intelligence Scale- Revised* (trans. by A. Bartfai, H. Nyman & B. Stegmann). Stockholm: Psykologiförlaget.

Wessely, S., Nimnuan, C. & Sharpe, M. (1999). Functional somatic syndromes: one or many? *Lancet*, *354*(9182), 936–939.

Wolf, O. T. (2009). Stress and memory in humans: twelve years of progress? *Brain Research*, *1293*, 142–154.

Yehuda, R. (2001). Biology of posttraumatic stress disorder. *Journal of Clinical Psychiatry*, *62* Suppl 17, 41–46.

Received 22 October 2009, accepted 10 May 2010

APPENDIX

Variable acronyms	Full names of variables
All variables included in Simca-DA set	
N/A	Age
N/A	Education
N/A	Length
N/A	Weight
BMI	Body mass index
PSQ score	Perceived Stress Questionnaire
N/A	Burnout score
World Health Organization (WHO)	
WHO-QOL	Quality of life
WHO-QOL Physical	Physical health
WHO-QOL Psychological	Psychological well-being
WHO-QOL Social relations	Social well-being
WHO-QOL Environment	Quality of environment
Temperament and Character Inventory (TCI)	
TCI-NS	TCI Novelty seeking
TCI-NS1	Novelty seeking *Excitable*
TCI-NS2	Novelty seeking *Impulsive*
TCI-NS3	Novelty seeking *Excessive*
TCI-NS4	Novelty seeking *Disorderly*
TCI-HA	Harm avoidance
TCI-HA1	Harm avoidance *Anxiety*
TCI-HA2	Harm avoidance *Fear*
TCI-HA3	Harm avoidance W*ariness*
TCI-HA4	Harm avoidance *Asthenia*
TCI-RD	Reward Dependence
TCI-RD1	Reward Dependence *Sociable*
TCI-RD3	Reward Dependence *Approval seeking*
TCI-RD4	Reward Dependence *Affectionate*
TCI-P	Persistence
TCI-SD	Self-directedness
TCI-SD1	Self-directedness *Responsible*
TCI-SD2	Self-directedness *Purposeful*
TCI-SD3	Self-directedness *Resourceful*
TCI-SD4	Self-directedness *Self-accepting*
TCI-SD5	Self-directedness *Congruent*
TCI-C	Cooperativeness
TCI-C1	Cooperativeness *Tolerant*
TCI-C2	Cooperativeness *Empathetic*
TCI-C3	Cooperativeness *Helpful*
TCI-C4	Cooperativeness C*ompassionate*
TCI-C5	Cooperativeness *Righteous*
TCI-ST	Self-transcendence
TCI-ST1	Self-transcendence *Intuitive*
TCI-ST2	Self-transcendence *Judicious*
TCI-ST3	Self-transcendence *Aware*
Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)	
N/A	Major Depression
N/A	Minor Depression
N/A	Dysthymia
Part rem dep	Partial remission of depression
Anxiety NUD	Anxiety with non-ulcer dyspepsia
Gen anxiety	Generalized anxiety
N/A	Panic anxiety
N/A	Psychosocial stressors
Wechsler Adult Intelligence Scale — Revised (WAIS-R)	
N/A	Digit span
Pict completion	Picture Completion
Pict arrangement	Picture arrangement
N/A	Digit symbol
Rey Osterrieth complex figure test (ROCF)	
OCF, IMM R	Rey Osterrieth complex figure test, immediate recall
ROCF DEL R	Rey Osterrieth complex figure test, delayed recall

APPENDIX (Continued)

Claeson-Dahl test for learning and memory (CD)	
CD ENC	Verbal memory encoding
CD R	Verbal memory delayed recall
Intermediate Visual and Auditory Continuous Performance Test (IVA)	
FullScRCQ IVA	Full-scale response-control quotient
AudRCQ IVA	Auditory response-control quotient
VisRCQ IVA	Visual response-control quotient
FullScAQ IVA	Full-scale auditory quotient
AudAQ IVA	Auditory attention quotient
VisAQ IVA	Visual attention quotient
RCAQPrud IVA	Response-control auditory quotient prudence
RCAQC IVA	Response-control auditory quotient consistency
RCAQS IVA	Response-control auditory quotient stamina
RCVQP IVA	Response-control visual quotient prudence
RCVQC IVA	Response-control visual quotient consistency
RCVQS IVA	Response-control visual quotient stamina
AAQVig IVA	Attention Auditory Quotient vigilance
AAQFoc IVA	Attention Auditory Quotient focus
AVQVig IVA	Attention Visual Quotient Vigilance
AVQFoc IVA	Attention Visual Quotient Focus
AVQSpe IVA	Attention Visual Quotient Speed
Routine blood tests	
SR	Sedimentation rate
LPK	Leukocyte particle concentration
TSH	Thyroid stimulating hormone
T4	Tetrajodtyronin
T3	Trijodtyronine
CORRCA	Corrected calcium
Cytokines	
IL-1 beta	Interleukin 1- beta
TNF-alpha	Tumour necrosis factor alpha
IL-1ra	Interleukin1-receptor antagonist
IL-6	Interleukin 6
HPA-axis	
24UKORT	Cortisol in urine 24 hours
SALIVC_MV	Cortisol in saliva morning value
SALIVC11	Cortisol in saliva at 11.00
SALIVC16	Cortisol in saliva at 16.00
SALIVC19	Cortisol in saliva at 19.00
SALIVC23	Cortisol in saliva at 23.00
POSTDEX	Cortisol in saliva post dexamethasone per os.
SUPPR	Suppression of cortisol in saliva after dexamethasone
SALCAUC	Cortisol in saliva area under curve
CRHC_15	Cortisol in serum Cortisol 15 min before CRH
CRHC0	Cortisol in serum Cortisol at injection time for CRH
CRHC5	Cortisol in serum Cortisol 5 min after CRH injection
CRHC15	Cortisol in serum Cortisol 15 min after CRH injection
CRHC30	Cortisol in serum Cortisol 30 min after CRH injection
CRHC50	Cortisol in serum Cortisol 50 min after CRH injection
CRHC60	Cortisol in serum Cortisol 60 min after CRH injection
CRHC90	Cortisol in serum Cortisol 90 min after CRH injection
CRHC120	Cortisol in serum Cortisol 120 min after CRH injection
CRHCDELT	Cortisol in serum Maximal increase in cortisol after CRH injection
CRHCPROC	Cortisol in serum CRHCDELT divided with baseline cortisol
CRHA_15	Cortisol in serum ACTH release 15 min before CRH injection
CRHA_0	Cortisol in serum ACTH release at time for CRH injection
CRHA_5	Cortisol in serum ACTH release 5 min after CRH injection
CRHA15	Cortisol in serum ACTH release 15 min after CRH injection
CRHA_30	Cortisol in serum ACTH release 30 min after CRH injection
CRHA_50	Cortisol in serum ACTH release 50 min after CRH injection
CRHA_60	Cortisol in serum ACTH release 60 min after CRH injection
CRHA_90	Cortisol in serum ACTH release 90 min after CRH injection

APPENDIX (Continued)

CRHA_120	Cortisol in serum ACTH release 120 min after CRH injection
CRHADELT	Cortisol in serum Maximal increase in ACTH after CRH injection
CRHAPROC	Cortisol in serum CRHCADELT divided with baseline ACTH
CRHCA_15	Cortisol in serum Cortisol divided with ACTH 15 min before ACTH
CRHCA0	Cortisol in serum Cortisol divided with ACTH at ACTH injection
CRHCA5	Cortisol in serum Cortisol divided with ACTH 5 min after ACTH
CRHCA15	Cortisol in serum Cortisol divided with ACTH 15 min after ACTH
CRHCA30	Cortisol in serum Cortisol divided with ACTH 30 min after ACTH
CRHCA50	Cortisol in serum Cortisol divided with ACTH 50 min after ACTH
CRHCA60	Cortisol in serum Cortisol divided with ACTH 60 min after ACTH
CRHCA90	Cortisol in serum Cortisol divided with ACTH 90 min after ACTH
CRHCA120	Cortisol in serum Cortisol divided with ACTH 120 min after ACTH
SYN0	Cortisol in serum Cortisol at Synachten injection
SYN30	Cortisol in serum Cortisol 30 min after Synachten
SYN40	Cortisol in serum Cortisol 40 min after Synachten
Synmax	Cortisol in serum Maximal level of cortisol after Synachten
SYNDELTA	Cortisol in serum Maximal increase of cortisol after Synachten
SYNPROC	Cortisol in serum SYNDELTA divided by baseline cortisol level
CAUCPCRH	Cortisol in serum Cortisol area under curve after CRH
AAUCPCRH	Cortisol in serum ACTH area under curve after CRH
CAUCCORR	Cortisol in serum Cortisol area under curve corrected
AAUCCORR	Cortisol in serum ACTH area under curve corrected
Magnetic Resonance Imaging (MRI) of Hippocampus	
footdx	foot dexter
heightdx	height dexter
subicdx	subic dexter
footsin	foot sinister
heightsin	height sinister
subicsin	subic sinister
areadx	area dexter
areasin	area sinister
index dx	index dexter
index sin	index sinister
absdxmin	side difference