Stress
The International Journal on the Biology of Stress

ISSN: 1025-3890 (Print) 1607-8888 (Online) Journal homepage: informahealthcare.com/journals/ists20

Cognitive impairment in patients with stress-related exhaustion

I. H. Jonsdottir, A. Nordlund, S. Ellbin, T. Ljung, K. Glise, P. Währborg & A. Wallin

To cite this article: I. H. Jonsdottir, A. Nordlund, S. Ellbin, T. Ljung, K. Glise, P. Währborg & A. Wallin (2013) Cognitive impairment in patients with stress-related exhaustion, Stress, 16:2, 181-190, DOI: 10.3109/10253890.2012.708950

To link to this article: https://doi.org/10.3109/10253890.2012.708950

Published online: 17 Sep 2012.

Stress, March 2013; 16(2): 181–190

ISSN 1025-3890 print/ISSN 1607-8888 online
DOI: 10.3109/10253890.2012.708950

informa
healthcare

Cognitive impairment in patients with stress-related exhaustion

I. H. JONSDOTTIR[1], A. NORDLUND[2], S. ELLBIN[1], T. LJUNG[3], K. GLISE[1,4], P. WÄHRBORG[5], & A. WALLIN[2]

[1]*The Institute of Stress Medicine, Gothenburg, Sweden,* [2]*Department of Psychiatry and Neurochemistry, The Institute of Neuroscience and Physiology, The Sahlgrenska Academy, The University of Gothenburg, Mölndal, Sweden,* [3]*County Council of Jämtland and Mid Sweden University, Östersund, Sweden,* [4]*Department of Public Health and Community Medicine, The Institute of Medicine, The Sahlgrenska Academy, The University of Gothenburg, Gothenburg, Sweden, and* [5]*Area of Work Science, Business Economics, and Environmental Psychology, Department of Landscape Planning, Swedish University of Agricultural Sciences, Alnarp, Sweden*

(*Received 25 January 2012; revised 28 June 2012; accepted 1 July 2012*)

Abstract

Patients who seek medical care for stress-related mental health problems frequently report cognitive impairments as the most pronounced symptom. The purpose of the present study was to compare cognitive function in patients with stress-related exhaustion with that in healthy controls, using a comprehensive battery of cognitive tests. We also explored whether neuropsychological findings were related to severity of illness measured using the Shirom–Melamed burnout questionnaire and hospital anxiety and depression scale. Thirty-three patients (15 males) and 37 healthy controls (11 males), mean age 46 years [standard deviation (SD) 3.9] and 47 years (SD 4.3), respectively, were included in the final analysis. Five cognitive domains were assessed: (1) speed, attention and working memory, (2) learning and episodic memory, (3) executive functions, (4) visuospatial functions and (5) language. The most pronounced difference between patients and controls was seen on executive function, when tested with a multidimensional test, including aspects of speed, control and working memory. The patients also performed poorer on Digit span, measuring attention span and working memory as well as on learning and episodic memory, when measured as delayed recall and the difference between immediate and delayed recall. Delayed recall was the only test that was significantly related to severity of burnout symptoms among the patients. This could reflect poor cognitive sustainability in the patients with the highest burnout scores, as this particular test was the last one performed during the test session. This study clearly shows that cognitive impairment should be considered when evaluating and treating patients who seek medical care for stress-related exhaustion.

Keywords: *Burnout, executive function, exhaustion, memory function, neuropsychological function*

Introduction

Increased long-term sickness absence is becoming a major concern in many countries, and the foremost cause for this increase is generally considered to be related to increased psychosocial stress (Bultmann et al. 2005; Henderson et al. 2005). One known consequence of long-term psychosocial stress is burnout which is defined as a mental condition that has developed as a result of continuous stress exposure, particularly related to psychosocial factors at work (Melamed et al. 2006). The theoretical basis for the term burnout differs, however, depending on the available self-report instruments constructed to assess the condition (Maslach et al. 2001; Shirom and Melamed 2006).

Even though symptoms of burnout originally were described as job related, it is now clear that burnout symptoms can be seen in relation to different types of non-work-related factors, such as caregiver burden and family-to-work conflict (van Daalen et al. 2009; Klaric et al. 2010; Lindstrom et al. 2011). In a recent article, the question of non-work determinants as possible causes of workers' mental health is raised and the authors conclude that these factors are largely

Correspondence: I. H. Jonsdottir, The Institute of Stress Medicine, Carl Skottsbergs gatan 22B, SE-413 19 Gothenburg, Sweden. Tel: + 46-31-3420716. Fax: + 46-31-414273. E-mail: ingibjorg.jonsdottir@vgregion.se

underinvestigated (Beauregard et al. 2011). Questionnaires or clinically defined diagnoses that do not consider whether the exposure is due to work or non-work factors, but rather to symptoms and functional consequences, are thus important to consider in future research in this area.

In 2003, the National Board of Health and Welfare proposed clinical diagnostic criteria for 'Exhaustion disorder' (ED), and the criteria were introduced into clinical practice in Sweden in 2005. One of the objectives was to improve diagnostics in cases of stress-related exhaustion/clinical burnout, and the criteria were assigned the code F43.8A of the International Classification of Diseases and Related Health Problems (ICD-10; World Health Organisation 1992). One major difference when compared with other definitions (e.g. burnout) is the causality; hence, the diagnostic criteria state that identifiable stressor(s) should have been present for at least 6 months. According to this criterion, the stressors could be either work related or non-work related. The symptoms of ED and burnout seem to be closely related, and we have previously shown that the majority of patients fulfilling the diagnostic criteria for ED can also be defined as burnt-out (Jonsdottir et al. 2009; Glise et al. 2012).

One of the symptoms included in the definition of burnout is cognitive weariness, which refers to the feeling of being slow and having reduced mental agility (Melamed et al. 2006). Persistent complaint of impaired memory is also listed as one of the six symptoms in the ED criteria that among four other core symptoms should be present most of the day, nearly every day, during the same 2-week period (Table I). It is well documented, mainly from animal research, that chronic stress affects several brain structures including the hippocampus, amygdala and prefrontal cortex and that these structural changes have also been found to cause impaired memory (McEwen 2000; Lupien et al. 2009).

One of the first studies to directly address the relationship between burnout and cognitive failure was published by van der Linden et al. (2005), showing impaired attention in people with high burnout. The first study including a clinical patient population was published the same year by Sandstrom et al. (2005), demonstrating that female patients with chronic burnout showed significant reduction in non-verbal memory and auditory and visual attention compared with healthy control subjects.

Ohman et al. (2007) demonstrated that chronic stress outpatients showed a pattern of impaired executive performance compared with matched controls, and Rydmark et al. (2006) showed that female patients on sick leave with work-related stress and depression showed impaired working memory and reaction time compared with healthy controls.

Table I. Diagnostic criteria for exhaustion disorder according to the National Board of Health and Welfare.

(A) Physical and mental symptoms of exhaustion with minimum 2 weeks duration. The symptoms have developed in response to one or more identifiable stressors which have been present for at least 6 months.
(B) Markedly reduced mental energy, which is manifested by reduced initiative, lack of endurance or increase of time needed for recovery after mental efforts.
(C) At least four of the following symptoms have been present most of the day, nearly every day, during the same 2-week period:
1. Persistent complaints of impaired memory.
2. Markedly reduced capacity to tolerate demands or to work under time pressure.
3. Emotional instability or irritability.
4. Insomnia or hypersomnia.
5. Persistent complaints of physical weakness or fatigue.
6. Physical symptoms such as muscular pain, chest pain, palpitations, gastrointestinal problems, vertigo or increased sensitivity to sounds.

(D) The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
(E) The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse and a medication) or a general medical condition (e.g. hypothyroidism, diabetes and infectious disease).
(F) If criteria for major depressive disorder, dysthymic disorder or generalised anxiety disorder are met, ED is set as co-morbid condition.

In contrast, Osterberg et al. (2009) reported that patients with burnout, despite considerable subjective problems, did not underperform on any neuropsychological test except for a small impairment on a cognitive speed test. The general tendency across previous studies is, however, that patients with stress-related burnout seem to show problems with cognitive control functions, such as attention, concentration, working memory and flexibility.

The discrepancies seen among previous studies may be partly explained by the heterogeneity of the study populations. Another explanation could be related to methodology as different studies have used a variety of different neuropsychological tests.

As previous studies have shown that several different domains can be affected, we included a test battery covering all the cognitive domains considered to be relevant in studying the consequences of chronic stress exposure. Thus, the purpose of this study was to examine all the cognitive domains that plausibly could be affected in patients with stress-related exhaustion and to compare the performance with those in healthy controls. The choice of tests was made in harmony with the recommendations of the American Academy of Neurology covering all the plausible relevant cognitive domains: speed/attention, memory, visuospatial, language and executive functions (American Academy of Neurology 1996).

We also aimed to explore whether neuropsychological findings are related to the level of burnout, depression, anxiety and self-reported memory within the patient group. Our hypothesis was that the patients would perform poorly on several of the cognitive domains, particularly speed, attention and executive function. Our second hypothesis was that performance for some of the tests could be related to severity of symptoms in the patient group.

Materials and methods

Participants

This study consists of ambulatory patients ($n = 40$) with stress-related exhaustion, all of whom fulfilled the clinical diagnostic criteria for ED (F43.8A, Table I). All patients included in this study were referred to an outpatient stress clinic from primary care units or occupational health care centres. The referral criteria were (1) 'probable ED' with no apparent somatic disorder or abuse that could explain the exhaustion and (2) a maximum duration of sick leave of 6 months.

Consecutive inclusion was applied, i.e. all patients entering the clinic, eligible to participate in this study, were asked to participate, until the intended number of patients was reached. All patients were ambulatory at the time of the study, and none had received inpatient care as a result of their illness. All patients included in the study fulfilled the ED criteria and co-morbid depression and/or anxiety was allowed (see diagnostic procedure for a detailed description), but patients with recurrent depression were not included. Forty-five per cent of the patients were on full-time sick leave, and an additional 40% were on part-time sick leave.

Forty-nine healthy controls were recruited from an ongoing longitudinal cohort study including mainly health care workers and social insurance officers from Region Västra Götaland in western Sweden. Initially, 275 individuals reported interest in participating in the study, and were found eligible after pre-screening through e-mail or telephone contact. Among these, 107 were interested in progressing to the screening procedure. Consecutive inclusion was then carried out of those who fulfilled the inclusion criteria and who were eligible to participate in the study according to exclusion criteria. Four individuals (one woman and three men), originally recruited as healthy controls, were found, during the screening procedure, to fulfil the criteria for exhaustion and were offered help at the clinic.

Exclusion criteria for both groups were obvious problems in understanding the Swedish language, brain damage of any kind, anaemia, current infection, diabetes mellitus, thyroid problems, vitamin B12 deficiency, other somatic diseases judged by a physician to affect the neuropsychological outcome and excessive consumption of alcohol (scores > 10) according to the Alcohol Use Disorders Identification Test. Medication that could influence the results was not allowed (e.g. temporary beta blockers or medication with codeine). Self reports on health status together with blood analyses which measure haemoglobin, erythrocyte sedimentation rate, blood glucose concentration, thyroid hormones and homocysteine were used to ensure that exclusion criteria were not fulfilled. Antidepressants were allowed for the patients, and 38% of the patients (10 females and 5 males) were on antidepressants at the time of the study. Smoking and snuff were allowed, but not during the test day.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Regional Ethical Review Board in Gothenburg. All subjects included in the study gave written informed consent.

Diagnostic procedures

A senior physician at the clinic carried out the diagnostic procedure on the patients and obtained an extended anamnesis with a clinical examination. The one page patient questionnaire Primary Care Evaluation of Mental Disorders (Spitzer et al. 1999), based on the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2000), was completed by each patient, and the results were used as support in the diagnostic procedure for mood disorders. Whenever necessary, this included a structured interview to identify presence of any mood and/or anxiety disorders.

The diagnostic criteria for ED were used as inclusion criteria (Table I). In order to be diagnosed with ED, it is essential that the physician together with the patient is able to identify one or more stressors that have been present for at least 6 months. The criteria do not specify the type or intensity of the stress exposure, but it is implicit that it should be significant enough to provoke the stress symptoms. The physician assessed the complete ED diagnostic criteria with the patient. Criteria A and B (for explanation of respective capital letter, see Table I) are obligatory criteria as well as the presence of at least four out of six symptoms listed under C. Also, the condition should cause significant distress and/or impairment of important areas of functioning (D), and no symptoms should be due to direct physiological effects of a substance or a general medical condition (E). Finally, if the patient meets the criteria for a major depressive disorder, dysthymic disorder or generalised anxiety disorder, these diagnoses are set first and ED is set as a co-morbid condition. All the patients included fulfilled the ED criteria, but the majority also fulfilled the diagnostic criteria for depression and/or anxiety (Table III).

Patients with chronic fatigue syndrome and fibromyalgia are seldom referred to the clinic, but as

there is a substantial overlap of symptoms, special attention to these diagnoses was always given during the diagnosis procedures. If these diagnoses were reached, the patient did not fulfil the criteria for ED and the patient was thus not eligible to enter the study according to the inclusion criteria.

Self-reported memory

All patients entering the clinic were asked, by using a simple four-level questionnaire, to appraise their memory today as compared with before they became ill. The four different response alternatives were as follows: (1) memory function is not affected, (2) an obvious impairment in memory function, which is not noticeable to relatives, (3) both and my relatives I myself notice poorer memory function and (4) memory function is so poor that it is causing severe problems in everyday life. This questionnaire was designed by the research group with the original purpose of exploring whether the patients were experiencing any memory problems. This simple question is a part of a larger screening battery used for clinical purposes and not originally designed to be part of this study.

Neuropsychological testing

The choice of tests was made in harmony with recommendations by the American Academy of Neurology (1996) with the aim of assessing the cognitive domains: *speed, attention and working memory, learning and episodic memory, executive, visuospatial and language functions* (Table II).

Speed, attention and working memory. Speed and attention describe the cognitive functions by which a person concentrates on and processes some features of the environment to the relative exclusion of others. Digit Symbol from Wechsler's Adult Intelligence Scale Revised (WAIS-R; Wechsler 1981) was used to assess speed and attention. The participants were asked to transcribe as many symbols as possible, according to a coding key, during 90 s. Digit span from WAIS-R was used to assess the attention span: for this, the participants were asked to repeat digits forwards and backwards (Wechsler 1981). Both tests are some of the most frequently used for assessing this domain.

Learning and episodic memory. Episodic memory is the memory of events or episodes that one has experienced personally, at a particular time and place. Wechsler's logical memory (WLM) from the Wechsler Memory Scale Revised (WMS-R) was used, comprising both immediate and delayed recall (Wechsler 1987).

Executive functions. Executive functioning is a goal-directed behaviour, optimising performance in order to reach the goal. Parallel serial mental operations (PaSMO) is a measure of mental control and tracking. In the test, the participant was asked to recite the alphabet, stating the number of the letter after each letter, i.e. A-1-B-2-C-3, as described by Lezak (2004). Performance was measured in time (s) with a faster time indicating better performance. The Stroop test, Victoria version, is a short form of the classical Stroop colour word test (Regard 1981). Performance was measured in time (s), with faster time indicating better performance.

Visuospatial function. Visuospatial function refers to thought processes involving visual and spatial awareness, which include comprehending and conceptualising visual representations and spatial relationships when performing a task. The visual object and space perception (VOSP) Silhouettes subtest was used, which is considered to be sensitive to brain injury in general (Rapport et al. 1998).

Language. Language is symbolic representation in which a symbol represents something other than itself, according to set rules. Two tests, such as Boston

Table II. Neuropsychological tests and cognitive domains.

Cognitive domain	Specific functions and neuropsychological tests
Speed, attention and working memory	Digit symbol (WAIS-R)[⋆]
	*Attention span/working mem*ory: Digit span (WAIS-R)[⋆]
Learning and memory	*Verbal episodic mem*ory: logical memory (WMS-R)[†]
Executive functions	*Mental con*trol: PaSMO[‡]
	*Distractibi*lity: Stroop colour word test, Victoria version[¶]
Visuospatial functions	*Percept*ion: Silhouettes (VOSP)[§]
Language	*Nam*ing: Boston naming test[‖]
	*Syntax comprehens*ion: Token test, subtest V[#]

Notes: WAIS-R, The Wechsler Adult Intelligence Scale Revised; WMS-R, Wechsler Memory Scale Revised; PaSMO, parallel serial mental operations; VOSP, the visual object and space perception battery; [⋆] Wechsler (1981); [†] Wechsler (1987); [‡] Lezak (2004); [¶] Regard (1981); [§] Rapport et al. (1998); [‖] Kaplan and Weintraub (1983); [#] Bandera et al. (1985).

naming test and Token Test, were used to measure performance related to language. The Boston naming test was used to assess naming impairment (Kaplan and Weintraub 1983). The Token Test, subtest V, was used to test syntax comprehension (Bandera et al. 1985).

Self-reported mental health

Shirom–Melamed Burnout Questionnaire. Self-reported burnout was evaluated by using the Shirom–Melamed Burnout Questionnaire (SMBQ). The questionnaire includes 22 items, which measure different aspects of burnout syndrome, including physical fatigue, emotional exhaustion, tension, listlessness and cognitive weariness as defined by Melamed et al. (1992). The SMBQ correlates strongly with the Maslach Burnout Inventory, another widely used instrument for the measurement of burnout (Maslach et al. 1996). A mean score above 3.75 on the SMBQ total score is a cut-off to define high burnout based on quartile splits (Grossi et al. 2003), and Stenlund et al. (2007) reported the mean score on the total scale in patients with burnout as 5.7 for females and 5.6 for males.

In this study, burnout was defined as having a mean score above 4.0 on the SMBQ scale. As the majority of the patients scored above 4.0, we used the median score (≥ 5) when analysing whether symptoms of burnout within the patient group were related to neuropsychological outcome. Cronbach's alpha for the SMBQ burnout total score was 0.98.

Hospital anxiety and depression scale. The Hospital anxiety and depression (HAD) scale was used to assess self-reported depression and anxiety in both patients and controls. It was originally developed for non-psychiatric clinics to detect states of depression and anxiety (Zigmond and Snaith 1983), and the scale performs well in assessing cases of anxiety disorders and depression in different patient populations as well as in the general population (Bjelland et al. 2002). Scores of 0–7 are defined as non-cases, and a score ≥ 8 is defined as a possible case of depression or anxiety. Cronbach's alpha for the HAD subscale was 0.89 and that for the anxiety subscale was 0.88.

Test procedure

The study included three visits to an outpatient stress clinic in Gothenburg. In the first visit, the healthy controls were invited to a screening (fasting in the morning); the second visit included the completion of questionnaires and blood sampling for other research purposes and the third visit was spent performing neuropsychological testing. The patients performed screening and completion during the ordinary visits at the clinic, but the neuropsychological testing of the patients was performed on a separate occasion, similar to the control group. All tests were performed at the same clinic and they were administered in a standardised sequence; Boston naming test, logical memory immediate recall, Digit symbol, Digit span, Token test, VOSP Silhouettes, Stroop, PaSMO and logical memory delayed recall. The testing was conducted during one session of 40 min without any break.

Statistical analysis

The original inclusion groups comprised 40 patients (20 females and 20 males) and 49 healthy controls (29 females and 20 males). However, as the mean age differed significantly between patients and controls [mean age for the patients was 46.3 years [standard deviation (SD) 5.5] and that for the controls was 49.3 years (SD 6.6; $p = 0.016$)], we included only participants aged between 40 and 55 years in the analysis when comparing patients and controls regarding neuropsychological function. Thus, the main analysis in this paper includes 33 patients (18 females and 15 males) and 37 controls (26 females and 11 males). These groups did not differ regarding age or educational level, but the percentage of individuals with high level of burnout, depression and anxiety differed significantly between patients and controls (Table III). All 40 patients originally recruited were included when separate analysis was conducted only among the patient group. The baseline characteristics for this total group of patients were similar to the demographics for the subgroup of 33 patients reported in Table III.

Student's *t*-test and Chi-square test were used to analyse basic characteristics between patients and controls. Kolmogorov–Smirnov tests revealed that all test outcomes, except for the Boston naming test, logical memory immediate and delayed recall and digit symbol, were not normally distributed. Thus, the Mann–Whitney *U*-test was used to analyse the neuropsychological test performance between patients and controls for all tests. The four test outcomes that were normally distributed were initially also analysed using Student's *t*-test, and no difference regarding the results was seen between the two analyses. Thus, all comparisons between patients and controls were made by using Mann–Whitney *U*-tests.

The Mann–Whitney *U*-test was also used to compare neuropsychological outcome when the patients were split into two groups according to self-reported symptoms of burnout, depression and anxiety. For all tests, $p < 0.05$ was considered statistically significant. When analysing data using scores from questionnaires, only participants with complete data were included in each analysis. This implies that the number of observations can vary

Table III. Demographics for patients and controls.

	Patients ($n = 33$)	Controls ($n = 37$)	p-value
Sex (male/female)	(15/18)	(11/26)	0.174*
Age (years)	46.3 (SD 3.9)	46.9 (SD 4.3)	0.555†
Educational level (years)	14.6 (SD 2.6)	14.5 (SD 2.6)	0.552†
Percent scoring > 4.0 on burnout measured with SMBQ	70%	3%	<0.0005*
Percent with depression (clinical diagnoses)	73%	N/A	
Percent with anxiety (clinical diagnoses)	76%	N/A	
HAD score			
≤ 7	73%	100%	<0.0005*
≥ 8	27%	0%	
HAD-anxiety score			
≤ 7	39%	91%	<0.0005*
≥ 8	61%	9%	

Note: Values represent mean and SD. N/A, not applicable; SMBQ, Shirom–Melamed Burnout Questionnaire; HAD, Hospital and anxiety depression scale; * Pearson Chi-square test; † Student's t-test.

somewhat from one analysis to another. Data were imputed for seven participants (two controls and five patients) who failed to complete the PaSMO test, as previous clinical experience indicates that this most probably was due to poor executive function. Thus, these individuals were assigned the longest time measured (144 s). All data are presented as means and SDs unless otherwise stated. All analyses were carried out by using SPSS version 15.01.

Results

Neuropsychological test outcome

Speed, attention and working memory. Digit span, both forwards and backwards, differed significantly between patients and controls, with the patients performing worse on both ($p = 0.028$, $p = 0.025$). No significant difference was seen between patients and controls on the Digit symbol test (Table IV).

Learning and memory. Logical memory immediate recall, delayed recall and the difference between immediate and delayed recall were compared between the groups. Patients and controls did not differ in terms of immediate recall, while delayed recall and the difference between immediate and delayed recall differed significantly, with the patients performing worse ($p = 0.012$, $p = 0.001$; Table IV).

Executive functions. The performance on Stroop colour word test did not differ significantly between patients and controls, while a significant difference was seen regarding the performance on PaSMO ($p = 0.001$; Table IV). Recalculating the data without data imputation did not change this, as a significant difference between patients [mean 73.2 s (SD 23.4)] and controls [mean 55.6 s (SD 16.1)] was still seen ($d = 0.42$, $z = -3.360$, $p = 0.001$).

Visuospatial function. There was no significant difference between patients and controls in terms of visuospatial function measured by the VOSP Silhouettes test (Table IV).

Language. The patient group did not differ from controls in terms of performance of the two language tests used in this study: Boston naming test and token test (Table IV).

Table IV. Neuropsychological test outcome in patients ($n = 33$) and controls ($n = 37$).

	Domain	Controls mean (SD)	Patients mean (SD)	z Value	Effect size	P
Digit symbol	SAW	58.9 (12.0)	54.0 (12.9)	−1.696	0.20	0.090
Digit span forwards	SAW	8.1 (2.3)	7.0 (1.7)	−2.071	0.25	**0.038**
Digit span backwards	SAW	6.7 (2.1)	5.7 (1.8)	−2.243	0.27	**0.025**
Logical memory immediate recall I	LM	26.8 (6.4)	24.8 (6.3)	−1.308	0.16	0.191
Logical memory delayed recall II	LM	24.1 (6.5)	19.8 (6.6)	−2.513	0.30	**0.012**
Logical memory differences I–II	LM	2.7 (2.6)	5.0 (3.1)	−3.225	0.38	**0.001**
PaSMO (s)	EF	60.4 (25.6)	81.8 (32.1)	−3.426	0.41	**0.001**
Stroop (s)	EF	21.5 (5.1)	25.0 (8.0)	−1.833	0.22	0.067
VOSP Silhouettes	VSP	21.0 (4.0)	21.0 (3.3)	−0.421	0.05	0.674
BNT	L	54.0 (2.9)	53.2 (3.2)	−1.106	0.13	0.269
Token test	L	20.8 (1.4)	20.0 (2.1)	−1.567	0.19	0.117

Notes: Data were analysed using Mann–Whitney U-tests. Effect size is given as Cohen's d. Significant differences are emboldened. PaSMO, parallel serial mental operations; VOSP, the visual object and space perception battery; BNT, Boston naming test; SAW, speed, attention and working memory; LM, learning and memory; EF, executive function; VSP, visuospatial functions; L, language.

Neuropsychological test performance and self-reported memory

Data on self-reported memory were available for 34 patients, included in this study. Twenty-four per cent ($n = 8$) reported their memory function as being unaffected, 41% ($n = 14$) reported an obvious impairment in memory function but not noticeable to relatives, 32% ($n = 11$) stated that both themselves and their relatives noticed poorer memory function and one male patient reported his memory function as being so poor that it caused severe problems in his daily life. There was no difference between males and females for self-rated memory. Self-reported memory was dichotomised into two groups: group 1 ($n = 22$) included those who answered alternative 1 or 2 on the memory question (indicating either intact memory or less pronounced memory loss) and group 2 ($n = 12$) who chose alternative 3 or 4 on the self-rated memory item (indicating pronounced memory loss clearly affecting daily life). Patients who reported poorer memory function (group 2) did not perform differently on any neuropsychological test included in this study when compared to patients who reported intact memory function or less pronounced impairment (data not shown).

Is neuropsychological test performance related to symptoms of burnout, depression, anxiety and use of antidepressants?

Neuropsychological test results were further investigated within the patient group in relation to the level of mental health measures. Age and education did not differ when the patients were split into two groups, using high and low scores for burnout, depression or anxiety. For the burnout measure, the patients were divided into two groups according to the median split. Patients who scored ≥ 5 on the burnout scale SMBQ ($n = 15$) were compared to those who scored lower than 5 ($n = 25$). These two groups did not differ significantly in age [mean 45.5 years (SD 4.2) and 47.2 years (SD 6.1), $p = 306$] or education [mean 15.4 years (SD 3.2) and 13.7 years (SD 2.1), $p = 0.90$]. No differences were seen between the groups on any neuropsychological test except for performance on logical memory delayed recall, which was poorer in patients with higher perceived level of burnout ($p = 0.03$; Table V).

Patients who scored ≥ 8 on the HAD-anxiety subscale ($n = 25$) performed significantly worse on both delayed recall [mean 17.3 (SD 5.2) compared with 23.2 (SD 6.1), $z = -2.804$, $r = 0.45$, $p = 0.005$] and immediate recall [mean 22.1 (SD 4.9) compared with 27.4 (SD 6.8), $z = -2.568$, $r = 0.41$, $p = 0.010$] when compared with patients with lower anxiety scores ($n = 14$). Performance on other neuropsychological tests did not differ between patients reporting high and low symptoms of anxiety.

Patients who scored ≥ 8 on the HAD subscale for depressive symptoms ($n = 11$) did not differ on any neuropsychological outcome except for performance on VOSP which was worse in patients with higher degree of depressive symptoms compared with patients who scored <8 on the HAD subscale ($n = 29$), [mean 18.9 (SD 3.1) compared with 21.5 (SD 3.1), $z = -2.338$, $r = 0.037$, $p = 0.019$].

As almost 40% of the patients were on antidepressants, we were interested in seeing whether patients on antidepressants ($n = 15$) differed regarding performance on the neuropsychological tests compared with patients not on antidepressants ($n = 25$). No significant difference was seen regarding any test performance. The only test showing p-value < 0.10 was for performance on Digit span backwards. The mean value for the patients on antidepressant was 5.0 (SD 1.24) compared with the mean value 6.2 (SD 2.2) for patients not on antidepressants. Other p-values ranged between 0.136 and 0.906.

Table V. Neuropsychological test outcome in patients with higher ($n = 15$) and lower ($n = 25$) burnout (BO) scores, determined by median split on SMBQ (higher burnout defined as ≥ 5).

	Domain	Patients lower BO mean (SD)	Patients higher BO mean (SD)	z Value	Effect size	p
Digit symbol	SAW	56.2 (12.5)	50.2 (11.4)	−1.552	0.25	0.121
Digit span forwards	SAW	6.7 (1.2)	7.5 (2.2)	−0.516	0.08	0.606
Digit span backwards	SAW	5.6 (1.5)	5.9 (2.6)	−0.227	0.03	0.820
Logical memory immediate recall I	LM	25.2 (6.0)	21.9 (5.9)	−1.614	0.26	0.106
Logical memory delayed recall II	LM	21.0 (5.9)	16.7 (5.9)	−2.173	0.35	**0.030**
Logical memory differences I–II	LM	4.3 (3.2)	5.1 (2.9)	−0.721	0.12	0.471
PaSMO (s)	EF	81.1 (35.1)	82.5 (32.6)	−0.666	0.10	0.505
Stroop (s)	EF	23.2 (7.5)	26.5 (7.4)	−1.737	0.27	0.082
VOSP Silhouettes	VSP	21.4 (2.8)	19.7 (3.8)	0.215	0.03	0.215
BNT	L	53.2 (3.9)	52.9 (2.5)	−0.562	0.09	0.574
Token test	L	20.0 (2.1)	19.9 (2.1)	0.491	0.07	0.491

Notes: Data were analysed using Mann–Whitney *U*-tests. Effect size is given as Cohen's d. Significant differences are emboldened. PaSMO, parallel serial mental operations; VOSP, the visual object and space perception battery; BNT, Boston naming test; SAW, speed, attention and working memory; LM, learning and memory; EF, executive function; VSP, visuospatial functions; L, language.

Discussion

Patients with stress-related exhaustion performed significantly worse on several neuropsychological tests as compared with healthy controls. The most pronounced difference between patients and controls was seen on the executive test PaSMO, with speed and working memory components. For the somewhat simpler executive test (Stroop), data did not reach statistical significance when patients and controls were compared. The performance on digit span, measuring attention span and working memory was poorer for the patient group, as was memory assessed with WLM delayed recall.

Previous research indicates that several brain structures are affected by chronic stress, resulting in probable functional consequences for the patients with stress-related mental health problems. Our results indicate consistent impairments within the domains speed/attention, episodic memory and executive function. We thus partly confirm previous studies on similar groups of patients (Ohman et al. 2007; Osterberg et al. 2009), and we found a well-defined pattern of impairments in several functions. Our data are in line with previous data from Sandstrom et al. (2005), showing that memory performance, as well as attention, is impaired in female patients with burnout.

Most of the cognitive functions that were reduced in our patient group are associated with the same brain structures that have previously been reported to be affected by stress-related disorders, i.e. hippocampal and frontal structures (Sandstrom et al. 2005; Osterberg et al. 2012). However, the patients did not perform worse on the Boston naming test and VOSP Silhouettes. According to previous research, there are some indications that stress may contribute to the onset of Alzheimer's disease (AD), at least according to animal models (Tran et al. 2010). Impairment in episodic memory may be an early sign of AD (Celsis 2000), but recent research from our group indicates that pure memory impairment is a rather benign condition and that incipient AD is characterised by impairment in several other cognitive domains, typically visuospatial and language (Nordlund et al. 2010a,b). The absence of visuospatial and language problems among the patients in this study thus does not support the development of AD, although this needs to be further explored in future studies.

One interesting observation is that the only test that was related to severity of burnout symptoms among the patients was performance on logical memory delayed recall. This was also the last test conducted during the 40-min long test session. One conceivable explanation for this result is that patients with the highest burnout level are more exhausted at the end of the test and that cognitive exhaustion as a result of performing the tests could explain this relationship rather than that the symptoms of burnout are truly and exclusively related to delayed recall. Thus, the sustainability of the patients to perform cognitive tasks for a longer period of time could be poorer among patients with higher burden of burnout symptoms. This raises a methodological consideration when testing patients with exhaustion, and caution should thus be taken in the interpretation of impaired results, depending on how the test session was designed and how long and demanding the session is. Thus, some kind of counter-balancing cognitive tasks should be included when patients are tested with extensive batteries. This is important in order to ensure that the observed cognitive impairment is not entirely due to fatigue from performing the test session.

We confirm the results of Osterberg et al. (2009) showing that there is no significant relationship between the patients' subjective memory complaints and performance on memory tests. We have, however, in this study used a simple self-rated question solely asking the patients to rate their memory function. According to the test outcome, the patients have somewhat more pronounced problems related to, for example, executive function and attention. Thus, when asked explicitly about memory function, the patients may not relate the question to other impairments such as attention. Furthermore, this question was designed by the research group to be used in the clinic to rate whether the patients perceive that they have memory problems. This is thus not a validated instrument for self-rated memory, and further studies are needed, using validated and reliable instruments, to explore whether neuropsychological test outcome is related to self-perceived cognitive functions.

Among the two tests measuring executive function, only the multidimensional test PaSMO, which reflects more complexity, discriminated patients from controls. A borderline significance was seen for the Stroop test. Providing more complexity to the test situation may thus better reveal the cognitive impairment in this patient group, as shown by Ohman et al. (2007) when a divided attention (i.e. executive) condition revealed the most explicit memory deficit in a chronic stress group when compared to controls. Osterberg et al. (2009) also raised the question of whether the complexity of the testing was too low to detect the cognitive impairment experienced by the patients included in their study.

There are several limitations to this study. Firstly, there is quite some overlap between depression, anxiety and burnout—a problem that is difficult to escape as symptoms of depression and anxiety are typically reported in patients with stress-related exhaustion. We did not include patients with recurring depression and separate analyses, dividing the patients based on symptoms of depression, showed no relationship between symptoms of depression and

cognitive function except for performance on VOSP Silhouettes.

We also performed analyses to compare patients with and without co-morbid depression according to clinical assessment, and no differences in neuropsychological test outcome were seen between the groups. Similar results were obtained by Sandstrom et al. (2005), showing no difference in neuropsychological function in female patients with burnout with and without co-morbid depression.

Some patients were on antidepressants, but an additional analysis did not show any significant differences between patients with and without treatment for any test performance. Due to small group sizes, this study cannot thoroughly explore whether medication with antidepressant is of importance for neuropsychological performance, but according to our additional analyses, this does not seem to be the case.

Overall, the relatively small number of patients limits the power of the sub-analyses performed and increases the risk of chance findings. We found a strong internal consistency for the instruments used to measure symptom severity of mental health, but whether symptom severity and use of antidepressants are indeed related to test performance should be explored in a larger group of patients.

We are also faced with a limitation regarding the test procedure. Most tests were performed in the early afternoon, but due to difficulties in organising the testing according to the working schedule of mainly the controls, some tests were performed before lunchtime. No tests were performed in the early morning or late in the afternoon/evening. Lastly, it is impossible to predict the long-term outcome of the patients based on cross-sectional data. More longitudinal studies are needed in order to be able to give the patient a reasonably reliable prognosis.

We conclude that patients with stress-related exhaustion showed cognitive impairment compared with healthy controls with the most pronounced effect seen for executive function and to some extent for attention. Overall, memory function also seems to be impaired but was significantly related to symptoms of anxiety. Thus, the overall memory impairment in these patients might rather be attributed to the anxiety component than to the actual exhaustion. This needs to be further explored in future studies. The difference between immediate and delayed recall was, however, not related to anxiety, indicating that loss of information over time might be a pure consequence of exhaustion.

The performance on neuropsychological tests does not seem to be strongly related to mental symptoms among patients with stress-related exhaustion, and the finding that severity of burnout symptoms is related to delayed recall could be explained by the cognitive exhaustion of conducting the overall test session, as delayed recall was the last test performed during the session.

Cognitive impairment is one of the most pronounced symptoms clinically reported by this group of patients, and our results indicate a consistent impairment within the domains speed/attention, episodic memory and executive functions. These impairments need to be considered when evaluating and treating patients with stress-related mental health problems.

A broader implication of our results is that many people in working life today are suffering from burnout-like symptoms, including exhaustion. Further studies are warranted to explore whether the cognitive impairment seen in patients on sick leave due to stress-related exhaustion is also seen among people still working, but at risk of developing exhaustion.

Acknowledgements

We would like to thank Karin Nygren and Marie-Louise Norberg for their valuable help with the screening procedure and monitoring of this study. We also thank Maria Larsson and Karin Skallström for valuable help during the test procedure.

Declaration of interest: This study was supported by a grant from the Swedish government. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

American Academy of Neurology 1996. Assessment: Neuropsychological testing of adults. Considerations for neurologists. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 47(2): 592–599.

American Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders. 4th ed., Washington, DC: American Psychiatric Association.

Bandera R, Capitani E, Della Sala S, Spinnler H. 1985. Discrimination between senile dementia Alzheimer type patients and -education matched normal controls by means of a 6-test set. Ital J Neurol Sci 6(3):339–344.

Beauregard N, Marchand A, Blanc ME. 2011. What do we know about the non-work determinants of workers' mental health? A systematic review of longitudinal studies. BMC Public Health 11:439.

Bjelland I, Dahl AA, Haug TT, Neckelmann D. 2002. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 52(2):69–77.

Bultmann U, Huibers MJ, van Amelsvoort LP, Kant I, Kasl SV, Swaen GM. 2005. Psychological distress, fatigue and long-term sickness absence: Prospective results from the Maastricht Cohort Study. J Occup Environ Med 47(9):941–947.

Celsis P. 2000. Age-related cognitive decline, mild cognitive impairment or preclinical Alzheimer's disease? Ann Med 32(1):6–14.

Glise K, Ahlborg G, Jr, Jonsdottir IH. 2012. Course of mental symptoms in patients with stress-related exhaustion: Does sex or age make a difference? BMC Psychiatry 12(1):18.

Grossi G, Perski A, Evengard B, Blomkvist V, Orth-Gomer K. 2003. Physiological correlates of burnout among women. J Psychosom Res 55(4):309–316.

Henderson M, Glozier N, Holland Elliott K. 2005. Long term sickness absence. BMJ 330(7495):802–803.

Jonsdottir IH, Hagg DA, Glise K, Ekman R. 2009. Monocyte chemotactic protein-1 (MCP-1) and growth factors called into question as markers of prolonged psychosocial stress. PLoS One 4(11):e7659.

Kaplan E, Weintraub S. 1983. Boston naming test. 2nd ed., Philadelphia, PA: Lea & Febiger.

Klaric M, Franciskovic T, Pernar M, Nembic Moro I, Milicevic R, Cerni Obrdalj E, Salcin Satriano A. 2010. Caregiver burden and burnout in partners of war veterans with post-traumatic stress disorder. Coll Antropol. 34(Suppl 1):15–21.

Lezak M. 2004. Neuropsychological assessment. New York: Oxford University Press.

Lindstrom C, Aman J, Norberg AL. 2011. Parental burnout in relation to sociodemographic, psychosocial and personality factors as well as disease duration and glycaemic control in children with Type 1 diabetes mellitus. Acta Paediatr 100(7): 1011–1017.

Lupien SJ, McEwen BS, Gunnar MR, Heim C. 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 10(6):434–445.

Maslach C, Jackson SE, Leiter MP. 1996. Maslach burnout inventory. 3rd ed., Palo Alto, CA: Consulting Psychologists Press.

Maslach C, Schaufeli WB, Leiter MP. 2001. Job burnout. Annu Rev Psychol 52:397–422.

McEwen BS. 2000. Protective and damaging effects of stress mediators: Central role of the brain. Prog Brain Res 122:25–34.

Melamed S, Kushnir T, Shirom A. 1992. Burnout and risk factors for cardiovascular diseases. Behav Med 18(2):53–60.

Melamed S, Shirom A, Toker S, Berliner S, Shapira I. 2006. Burnout and risk of cardiovascular disease: Evidence, possible causal paths, and promising research directions. Psychol Bull 132(3):327–353.

Nordlund A, Rolstad S, Gothlin M, Edman A, Hansen S, Wallin A. 2010a. Cognitive profiles of incipient dementia in the Goteborg MCI study. Dement Geriatr Cogn Disord 30(5):403–410.

Nordlund A, Rolstad S, Klang O, Edman A, Hansen S, Wallin A. 2010b. Two-year outcome of MCI subtypes and aetiologies in the Goteborg MCI study. J Neurol Neurosurg Psychiatry 81(5): 541–546.

Ohman L, Nordin S, Bergdahl J, Slunga Birgander L, Stigsdotter Neely A. 2007. Cognitive function in outpatients with perceived chronic stress. Scand J Work Environ Health 33(3):223–232.

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

Osterberg K, Karlson B, Malmberg B, Hansen AM. 2012. A follow-up of cognitive performance and diurnal salivary cortisol changes in former burnout patients. Stress, Epub 24 January. DOI: 10.3109/10253890.2011.648972.

Rapport LJ, Millis SR, Bonello PJ. 1998. Validation of the Warrington theory of visual processing and the Visual Object and Space Perception Battery. J Clin Exp Neuropsychol 20(2): 211–220.

Regard M. 1981. Cognitive rigidity and flexibility: A neuropsychological study. Victoria: University of Victoria.

Rydmark I, Wahlberg K, Ghatan PH, Modell S, Nygren A, Ingvar M, Asberg M, Heilig M. 2006. Neuroendocrine, cognitive and structural imaging characteristics of women on longterm sickleave with job stress-induced depression. Biol Psychiatry 60(8):867–873.

Sandstrom A, Rhodin IN, Lundberg M, Olsson T, Nyberg L. 2005. Impaired cognitive performance in patients with chronic burnout syndrome. Biol Psychol 69(3):271–279.

Shirom A, Melamed S. 2006. A comparison of the contruct validity of two Burnout measures in two groups of professionals. Int J Stress Manag 13(2):176–200.

Spitzer RL, Kroenke K, Williams JB. 1999. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 282(18):1737–1744.

Stenlund T, Ahlgren C, Lindahl B, Burell G, Knutsson A, Stegmayr B, Birgander LS. 2007. Patients with burnout in relation to gender and a general population. Scand J Public Health 35(5):516–523.

Tran TT, Srivareerat M, Alkadhi KA. 2010. Chronic psychosocial stress triggers cognitive impairment in a novel at-risk model of Alzheimer's disease. Neurobiol Dis 37(3):756–763.

van Daalen G, Willemsen TM, Sanders K, van Veldhoven MJ. 2009. Emotional exhaustion and mental health problems among employees doing 'people work': The impact of job demands, job resources and family-to-work conflict. Int Arch Occup Environ Health 82(3):291–303.

van der Linden D, Keijsers GP, Eling P, Van Schaijk R. 2005. Work stress and attentional difficulties: An initial study on burnout and cognitive failures. Work Stress 19:23–36.

Wechsler D. 1981. WAIS-R manual. New York: The Psychological Corporation.

Wechsler D. 1987. Wechler memory scale-revised manual. San Antonio, TX: The Psychological Corporation.

World Health Organisation. 1992. ICD-10 classifications of mental and behavioural disorder: Clinical descriptions and diagnostic guidelines. Geneva: World Health Organisation.

Zigmond AS, Snaith RP. 1983. The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370.