Title: The Relationship Between Alexithymia and Salivary Cortisol Levels in Somatoform Disorders

Running Head: Alexithymia, Cortisol and Somatoform Disorders

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Abstract

The purpose of this study was to investigate the cortisol levels as function of hypothalamic-pituitary-adrenal axis (HPA) in relation to alexithymia in patients with Somatoform disorders (SFD). 32 patients with somatoform disorder sampled diurnal salivary cortisol, had a psychiatric investigation and filled in questionnaires (TAS-scale; SOMS-scale; HAM-D). Mean TAS-score in the sample was elevated (55.6 ± 9.6), relative to the German Normative sample. 32% of patients were classified as alexithymic based on their TAS scores. Depression scores were moderate (HAM-D 13.2, BDI 16.5). Patients’ alexithymia scores (TAS scale “Difficulty identifying feelings”) were significantly positively correlated with their Somatization-scale scores (SCL-90-R); r=0.3438 p<0.05) and their scores on the GSI on SCL-90-R; r=0.781 p<0.01). Regression analysis with cortisol variables as dependent variables was performed. Cortisol levels (measured by AUC-G, AUC-I and MCS) were best predicted in a multiple linear regression model by lower depressive scores (HAM-D), more symptoms of psychopathology (SCL-90-R)> Cortisol levels were positively correlated to the patients’ scores on the “Somatization severity scale” of SOMS-scale, but negatively correlated to the patients’ scores on the Somatization scale (SCL-90-R). No significant correlations were found between the patients’ Alexithymia-scores (TAS) and cortisol levels. The control-group demonstrated significantly higher levels of cortisol than did the patients with SFD; both tests; p<0.001 for AUC (G) and AUC (I). However, the two groups did not differ in terms of their mean morning cortisol levels (p >0.05)

Author-Supplied Keywords:

Somatoform Disorders – Cortisol – Alexithymia
**Abbreviation:** TAS = Toronto-Alexithymia-Scale; HAM-D = Hamilton-Depression scale; SCL-90-R = Symptom Checklist-90 Revised; GSI = global severity index; SOMS = Screening for Somatoform Symptoms; Somatoform Disorders = SFD; AUC-G = Area under the curve-ground; AUC-I = Area under the curve-increase; MCS = Morning cortisol.
1. Introduction

Somatoform disorders (SFD) are characterized by bodily symptoms that cannot be explained by organic pathology or known physiological mechanisms. Previous studies (e.g. Bach & Bach, 1995; Bankier et al. 2001; Pedrosa Gil et al., 2006) have reported that patients with SFD exhibit elevated levels of alexithymia. Alexithymia is a concept that was developed by Sifneos (1973) and means literally “absence of words for emotion”. Alexithymia is characterised by an inability to describe and identify feelings, by an absence of fantasies, and a tendency to utilise an externally focused analytical cognitive style. The concept of alexithymia has been examined in a variety of different medical and psychiatric disorders (Sifneos, 2000; Naatanen et al, 1999; Pedrosa Gil et al, 2006; Wise et al., 2000). Empirical findings support the conceptualisation of alexithymia (i.e. “absence of words for emotion”) and the clinical impression of an association between somatization and alexithymia (Bankier et al., 2001, Bach et al., 1995, De Gucht et al., 2003).

The stress-alexithymia-hypothesis (Martin et al., 1986) proposes that the inability of alexithymic individuals to identify and express emotion prevents them from coping effectively with stressful events and results in prolonged and elevated autonomic activity. The ensuing chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis is associated with elevated levels of circulating adrenal hormones, most notably cortisol, which in turn lead to stress-related medical and behavioural problems. It has been suggested (e.g. Papciaks et al., 1985; Stone & Nielson, 2001) that when individuals with alexithymia encounter a negative stimulus or event they experience a decoupling of subjective and physiological arousal and that this decoupling increases the risk of developing stress related illness. In line with these suggestions, empirical studies have provided evidence of elevated sympathetic activation, indexed by tonic heart rate (Wehmer et al., 1995) and electrodermal activity (Friedlander et al., 1997), in participants with elevated levels of alexithymia. However, these measures only provide an index of general arousal. In order to directly investigate changes
in the activity of HPA axis it is appropriate to measure the levels of the adrenal hormones, most notably cortisol, that are circulating in the blood. Importantly, previous studies have reported that salivary cortisol concentrations can also be used as an accurate index of activity of the HPA axis (e.g. Melamed et al., 1999, Vedhara et al., 2003). Furthermore, salivary cortisol has been shown to be a reliable marker of stress that is comparable to plasma cortisol (Weibel, 2003). An advantage of using saliva samples as opposed to blood samples is that they can be collected in a non-stressful manner (Kirschbaum and Hellhammer, 1994).

Rief et al. (1998) examined HPA-axis activity in patients with SFD and found higher morning cortisol levels in patients compared to normal controls. However in a second study (Rief et al., 2000), which also included a dexamethasone suppression test (DST), this finding was not be replicated. In another study (Heim et al., 1998) results indicated that female patients with functional chronic pelvic pain exhibited hypofunctional HPA axis, indexed by elevated cortisol. However, it should be noted that these patients did not exhibit any depressive symptoms. This is important as elevated cortisol levels have been consistently reported in patients with depression (e.g. Bhagwagar et al, 2005; O’Brien et Al, 2004). Ehler et al. (2005) examined HPA axis activity in patients with functional gastrointestinal disorders (FGD) and reported two different types of alteration in cortisol levels. Patients with the highest pain ratings were found to exhibit low cortisol levels; whereas patients exhibiting the highest depression scores were shown to have the highest cortisol levels. These findings suggest different psychobiological subgroups for FGD patients; this may also be true of SFD patients. One variable that might account for the contradictory and conflicting findings concerning the relationship between SFD and HPA activity is alexithymia. It is plausible that differences in alexithymia might be related to changes in cortisol levels.
The primary purpose of the present study was to investigate associations between alexithymia, somatization and salivary cortisol as stress-parameter. Based on the above mentioned research strategy, our hypotheses are: (1) There will be a significant positive correlation between the participants’ alexithymia scores and the somatization degree, indexed by scores on the SCL-90-R scale “somatization” and the “Somatization severity scale” on SOMS-scale; (2) There will be a significant positive correlation between HPA activation and alexithymia, such that higher cortisol levels will be related to elevated alexithymia scores in patients with SFD, in agreement to “stress-alexithymia hypothesis”.

2. Methods

2.1. Participants

Thirty-two patients (23 female, 9 men) meeting ICD-10 criteria for SFD and twenty-five healthy controls (19 female, 6 men) took part in the present study. The characteristics of the participants in the two groups are presented in Table 1. For age (p=0.11) and sex (p=0.771) there are no statistically significant differences between patient group with SFD and healthy subjects. 34 patients with SFD provided salivary cortisol samples. Two patients were excluded from analysis because of unusually high cortisol levels (> 1.5 interquartile lengths below / above the 25. / 75. percentile) on more than two sampling points. Two other patients who did not fill in the SCL-90-R were included in analysis.

The patients with SFD, who were recruited from the Psychosomatic Ambulance of the Department at the University of Munich, were outpatients who had been referred from private practice, or from the Department of Internal Medicine, for diagnostic interview and counselling in psychiatric and psychosomatic field. Inclusion criteria for the patient group of the present study were the presence of SFD diagnosed according to ICD-10 (n=15 with the
diagnosis F 45.0; n=14 with F45.1 and n=3 F 45.3). The diagnosis was established through a clinical interview conducted by a trained psychiatrist (P.G.F.), who performed extensive physical and psychological assessment of the patients (after somatic disorders had been excluded during extensive inpatient or outpatient investigation at the medical clinic or in general practice); including checking for the signs and symptoms of somatoform disorders as outlined in the diagnostic criteria cited in the ICD-10 (Hiller et al., 1996). A further aid to the diagnosis of SFD was that the participants’ fulfil the criteria on the SOMS questionnaire (Rief et al., 1997). Exclusion criteria were presence of major medical disorders (e.g. autoimmune-, neoplasms, cardiac-, pulmonary-, or endocrine diseases), psychosis, substance abuse disorders, major affective disorders, co-medication with benzodiazepine or other psychotropic medication, as well as steroid-hormone intake respectively contraceptive medication during the past four weeks. The patients and health subjects were thus in principle drug free in order to minimize pharmacological influence if possible. It should be noted that there was a very high level of psychiatric comorbidity in the patient sample, as thirty-two patients exhibited significant symptoms of other psychiatric disorders: 84% (n = 27) of the patients were affected by psychiatric comorbidity, in first line dysthymia F34.1 (n = 11) and depressive reaction F43.2 (n = 16). Further additional diagnoses were recurrent depressive disorder F 33.0 (n = 3) and eating-disorder (bulimia and others, n = 3). The participants (n=25) in the control group were recruited mainly from the community and from the student population of medical and nursing schools. In comparison to patients with SFD a detailed psychological measurement was not assessed. In general they were in good general health and the presence of a serious medical disease (like autoimmune-, neoplasms, cardiac-, pulmonary-, or endocrine diseases) or a psychiatric disorder were not known.
2.2 Study protocol, procedure
If patients fulfilled inclusion criteria they were asked to participate in the study. During their study visit, patients filled in some of the questionnaires. Patients were instructed to collect saliva samples during the next two days. The study protocol was approved by the Ethical Committee of the University Munich in accordance with the declaration of Helsinki. Written informed consent was obtained from each patient before study inclusion.

2.3. Questionnaires and measures
The SOMS (Rief et al., 1997) is a self-rating questionnaire checking for 53 physical symptoms. The questionnaire includes all 33 physical complaints of the DSM-IV somatization disorder symptom list, the symptoms of ICD-10 somatization disorder, and the ICD-10 somatoform autonomic dysfunction symptom list. This questionnaire requires the participants to report if they had experienced any or all of 53 physical symptoms during the past 2 years. They were instructed only to answer "yes" if the symptoms had a significant influence on their subjective well being and if doctors did not find a sufficient explanation for the complaints. Thus, persons with physical illness were not excluded but were instructed only to report physically unexplained symptoms. Item 54 to item 68 of the SOMS cover all inclusion and exclusion criteria (first complaints before age 30 years, symptom duration, acceptance of doctor's explanation that the complaints do not have a physical origin, doctor visits due to the symptoms, etc.). Adding the number of positively answered symptoms allows computation of the "somatization index" (range from 0 to 33 points), used also in our study. The number of somatization symptoms correlated $r = 0.75$ between self-ratings and interview, confirming the high validity of the SOMS.

The 90-item version of the Symptom Checklist-90 Revised (Derogatis, 1994) reveals different aspects of psychopathology, it assesses patients' current symptoms within a
specified and optimal point-in-time (i.e., the past 7 days). The SCL-90-R includes three global index scales and nine symptom scales that were based on factor analysis and that include diagnostic-specific and non-specific symptoms. Patients are instructed to rate mental health symptoms that have "bothered" them within the past 7 days on a 5-point scale (0–4) ranging from “Not at All” (i.e., a “0” rating) to “Extremely” (i.e., a “4” rating). The symptom scales include the Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism scales. The SCL-90-R index scales include the Positive Symptom Total, Positive Symptom Distress Index, and Global Severity Index. SCL-90-R index and symptom scale scores are represented as T-scores, with a mean of 50 and a standard deviation of 10. Higher T-scores reflect greater number and/or severity of patient self-reported symptoms. We defined a “clinically significant” or “elevated” scale score to be a T-score of 63 or higher, based on recommendations (Derogatis, 1994).

The German version of the 26-item Toronto Alexithymia Scale (TAS-26; Kupfer et al., 2000, 2001) was used in the present study to assess the presence and severity of alexithymia in the participants. This measure includes 26 items that generate scores on three dimensions: “difficulty identifying feelings”; “difficulty describing feelings” and “externally orientated thinking”. This three-factor structure has been replicated in clinical and non-clinical groups. The German version of the TAS-26 was validated with a representative population sample (n=2084) and shows reasonable internal consistency ranging between \( r=.67 \) and \( r=.84 \). The overall TAS-26 scores range from 18 to 90. The cut-off point, which differentiates between alexithymic and non-alexithymic individuals, is \( > 54 \).

The Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) was included in the present study to provide an observer-rated measure of depression severity. This assessment was conducted by a fully trained psychiatrist (P.G.F). The 21-item Beck-Depression-Inventory (BDI; Beck et al., 1961) was utilised in the present study to provide an index of self-rated depression severity.
2.4. Saliva cortisol sampling and biochemical analysis

Saliva samples were collected using a small cotton swab with no additives (Salivette®, Sarstedt, Numbrecht, Germany). Participants were instructed to chew on the swab for 3 minutes, put the swab into the Salivette, note the time of sampling, keep the samples at ambient temperature and return them to the lab within 1 week. Samples were collected from each subject on two days (at both days at 8 a.m. and at 12 p.m., 4 p.m., 8 p.m.) in order to get a circadian profile of cortisol secretion. All saliva samples were stored in the laboratory at -20°C until analysis. Cortisol concentrations were determined employing a highly sensitive chemiluminescence immunoassay (Cortisol Saliva LIA, IBL, Hamburg, Germany). Endpoint detection was done using a chemiluminescence reader (Victor, Perkin Elmer, Rodgau, Germany). The assay shows a relevant cross reaction with the following steroids: Prednisolone (57%), 11-deoxycortisol (12%), corticosterone (2.5%), cortisone (2%) and prednisolone (1%). Patients on steroid treatment were excluded from the study. The lower detection limit of this assay is less than 0.16 ng/ml. To reduce error variance caused by interassay imprecision, all samples from one subject were assayed in the same run. In our study, within-assay CV was 7.2% and 5.4% at 0.8 and 5.0 ng/ml, respectively. Between-assay CV at the same concentrations was 9.45 and 6.6%, respectively.

2.5. Cortisol data analysis

The area under the curve (AUC), which integrates data from the single measurements, was calculated according to two formulas proposed by Pruessner et al. (2003). Eight equidistant measured values from day 1 and day 2 were used. The formulas are derived from the trapezoid formula and contain different forms of information. AUCg (ground) contains more information on cortisol levels, whereas AUCi refers to the increase or decrease over time and therefore provides information on the sensitivity of the system. AUCs were calculated by the following formulae (2) and (3),
\[ AUC_G = \frac{\sum_{i=1}^{n-1}(m_{(i+1)} + m_i)}{2} \]  
(2), and

\[ AUC_I = \left( \frac{\sum_{i=1}^{n-1}(m_{(i+1)} + m_i)}{2} \right) - (n-1) \times m_i \]  
(3)

with \( m \) as the individual measurement (1 to 8 in this case) and \( n \) as the total number of measurements (8). As an usual measure of variability, the coefficient of variation was computed by:

\[ CV = \frac{sd}{m} \times 100\% \]  
(4),

with \( m = \text{mean}\ (m_1, m_2, ..., m_8) \), and \( sd = \text{standard deviation}\ (m_1, m_2, ..., m_8) \).

The morning cortisol level (=MCS) is the average of eight o'clock cortisol level on the two measured days.

### 2.6. Data reduction and statistical analysis

All data were analysed using SPSS for Windows© 11.5. The data were examined for normal distribution using the Shapiro-Wilk Test. According to the scale niveau, \( \chi^2 \)- or T-test was used. Correlations between two parameters were analysed using Pearson coefficient.

To assess whether there are differences between the controls and the participants of the study on the variable cortisol, the t-test for independent samples was performed. Multiple linear regression analyses using a backwards stepwise algorithm was calculated with cortisol measures as dependent variables, age, psychopathology parameters and alexithymia as independent variables. The significance level was set to alpha < .05 for each statistical test.
For the univariate statistic evaluations like the correlations in pairs, only 30 persons enter analysis for the SCL 90. Since for the SCL 90 in two cases no data are present, altogether only 30 persons enter this analysis. With the further parameters all 32 cases entered evaluation. With the use of multivariate procedures only the cases are received, for regarding all parameters information full in the model, all data are thus present into a model (Listwise).

3. Results

3.1. Participant characteristics and psychopathology

Specifically, 23 of the SFD patients were female (mean age= 45.0 years, SD=8.1) and 9 were male (mean age=42.2 years, SD=8.6) compared to the controls where 19 of the sample were female (mean age= 36.3 years, SD=12.7) and 6 were male (mean age= 41.6 Years, SD=16.1). Analysis of the participant characteristics revealed that the two groups did not differ significantly in terms of their age (mean age SFD patients = 44.2 years, Standard deviation=8.2; mean age HC = 37.4 years, SD=13.3); p>0.05 p=0.11. Furthermore, the two groups did not differ significantly in terms of the ratio of males and females making up each group, p>0.05. Inspection of the participants’ educational background (presented in Table 1) revealed that 60% of the SFD patients had completed high school equivalent or higher education (with about 28% of the males and 72% of the females achieving this level of education). The mean SOMS score of 21.4 ± 8.3 indicates moderate to severe level of somatization (Rief et al. 1997). 14 (43.8%) patients had low depression observer ratings (HAM-D< 13), 18 (56.3%) patients showed elevated Hamilton scores (data are not shown in table).(HAM-D= or >14) Subjective general psychiatric symptomatology as indicated by the SCL GSI-score (Global severity index) was significantly elevated (mean T = 64.2 ± 13.6), Phobic anxiety in the SFD patients was also moderately elevated (mean = 58.9, SD=11.5).
3.2. Assessment of Alexithymia

Inspection of the data in Table 1 revealed that the patients showed an elevated TAS total score (Mean = 55.6, SD= 9.6), with 32% of the patients reaching raw values higher than 54 (raw value) as cut off value, respectively T-score 61, which are considered to represent clinically significant alexithymia (Taylor et al., 1997). Patients demonstrated significantly elevated scores on the “Difficulty identifying feelings” sub-score (mean= 60.6, SD= 8.8), statistical test result?; whereas patients scores on the “Difficulty describing feelings” and “Difficulty externally orientated thinking” sub-scales lie nearly within the range of normal values (Mean= 54.6, SD=11.3 and Mean= 45.38, SD= 9.0 respectively .

3.3. Alexithymia and Psychopathology

Patients with higher alexithymia scores reported more frequent symptoms in the SCL-90-R., for more details see Table 2. TAS factor 1 scores (“Difficulty identifying feelings”) were positively correlated with SCL-Somatization-scale (r(n=30?) = .343, p=0.05), but also with other scales (2-9, including the GSI). TAS factor 2 (“Difficulty describing feelings”), was positively correlated with GSI-scale (r = .39, p-value? n=?). TAS factor 3 scores (“Externally-orientated thinking”), were negatively correlated with GSI scores (r(n=30) = -.0.37, p-value?). Obviously TAS factor 1 (“Difficulty identifying feelings”) is most sensitive to psychopathology in comparison to SCL-90R-scales. The “Somatization-severity-score” shows no significant correlations to the TAS scores.

3.4. Analyses of Cortisol

Mean morning cortisol level of the patients with SFD, averaged for day 1 and day 2, was 5.2 ± 3.2 ng/ml, salivary cortisol showed the well-known diurnal decline from morning to afternoon, more details see Table 3. AUC ground [=AUC (G)], as a measure for cortisol level over time was 7.7 ± 3.4 ng/ml; with an AUC increase [AUC (I)] value of − 8.3 ± 7.7 ng/ml. The variation coefficient is 90.0 % ± 25.0 with a decrease of values during the day. Mean
morning cortisol level of the healthy controls, averaged for day 1 and day 2, was 6.7 ± 3.9 ng/ml, salivary cortisol showed for AUC (G) MW = 21,4 and SD = 10,3; and for AUC (I) MW = -29,7 and SD = 24,8., see Table 3. The control-group demonstrated significantly higher cortisol values for AUC (G) and AUC (I) than did patients with SFD (t-test; p<0.001). The mean morning cortisol levels showed no significant difference (t-test; t-value=?, df=?, p >0.05)

3.5. Relationship between Cortisol, Alexithymia and Somatization

The question arises, if cortisol levels depended on the psychopathology, e.g. depression and other psychiatric symptoms (measured on SCL-90-R-scale), in addition, on the alexithymia scores. In attempt to predict the multiple linear regression analyses were conducted with AUC G, AUC I und MCS measures of Cortisol as dependent variables and with age, psychopathology parameters (among others GSI of SCL-90-R) and alexithymia as the predictor variables (measured in TAS-scales), more details see Table 4.

Backwards stepwise regression of data from 30 patients who had complete data indicated that variance of cortisol ground level AUC G was best explained by HAM-Depression-score with negative correlation to AUC-G (-0.44), the global severity index (GSI) of SCL-90-R correlated positively with AUC-G (0.72), the Somatization scale (SCL-90-R) correlated negatively with AUC-G (-0.47), and the Somatization severity scale correlated positively with 0.72 to AUC-G.

This model reached sufficiently high variance prediction (Adjusted R² = .34 (F (30) = 6.2; p = .002). Mean morning cortisol (MCS) could not be sufficiently explained by our variables in a linear regression model. For AUC I likewise, no significant model could be formulated; all variables (except the constant) were excluded. Included and excluded variables and their regression coefficients are shown in Table 3. .
4. Discussion

In the present study we examined the levels of salivary cortisol in a sample of untreated patients with SFD and a group of healthy controls. We also examined the presence of alexithymia in these individuals and tried to establish if there was a relationship between the degree of participant alexithymia and their levels of cortisol. As expected there was a high prevalence of alexithymia features in patients with SFD and a significant positive correlation between alexithymia and somatization as well as more symptoms of psychopathology, measured in SCL-90-R.

Second, contrary to expectations, we found lower cortisol levels in patients with SFD in comparison to healthy subjects. This suggests that SFD is associated with hypofunction of the HPA axis. Against our predictions, no significant correlation was observed between alexithymia scores and cortisol levels. However, observer ratings of depression severity (HAM-D scores) were negatively correlated with cortisol levels. Symptom scores of psychopathology (SCL-90-R) and scores on the “Somatization severity scale” of SOMS-scale were positively correlated with cortisol levels. Conversely, cortisol levels were negatively correlated with the patients’ scores on the Somatization scale (SCL-90-R).

In line with our first hypothesis, we found a high prevalence of alexithymia in our patients with SFD, 32% reaching clinically significant alexithymia, clearly higher values in comparison to non-clinical populations, Kokkonen et al. 2001 (9.4% in male and 5.2% alexithymia-values in female subjects), and Posse et al. (2002) found an prevalence of 7.9% in a non-clinical female population. The correlation of alexithymia with somatization in our sample is in agreement with prior studies (De Gucht et al., 2003; Lipsanen et al., 2004, Waller et al., 2004). Our findings are not consistent with a recent study (Karvonen et al., 2005) that demonstrated a lower prevalence of alexithymia with only 6.0% among patients with somatization and 4.8% among subjects without somatization symptoms.
Our data affirmed the hypothesis of Bagby and Taylor (1997) that impaired emotion-processing capacities that underly alexithymia can lead to a misinterpretation of the somatic sensations that accompany emotional arousal, leading to hypochondria and somatization.

Contrary to second hypothesis, our patients with SFD exhibited reduced cortisol levels in comparison to healthy subjects, suggesting the SFD are associated with a hypofunction of HPA axis. Additionally, also contrary to our predictions, there were no correlations between alexithymia-values and cortisol levels. This does not correspond with the decoupling-hypothesis of Stone and Nielson (2001). In addition, the present findings are inconsistent with other studies (Wehmer et al., 1995) that have reported that alexithymia tends to be associated with tonic physiological hyperarousal. Only a few studies have investigated the cortisol response in patients with alexithymia and they have tended to report especially low basal cortisol levels (Conrad et al., 2002, Henry et al., 1997). This tendency is confirmed by our results.

In the last decade some authors (Chrousos and Gold, 1992; Alfvén et al., 1994) discussed a hypocortisolism as biological marker of stress-related disorders like chronic fatigue syndrome or other idiopathic syndromes. A possible explanation is that –like in patients with Addison´s disease with symptoms of fatigue and malaise- a subtle adrenal insufficiency is associated with involvement of HPA-axis disturbances e.g. in idiopathic syndromes (Ehlert et al., 2001). Heim et al. (2000) summarize in a review that hypocortisolism does not merely represent a specific correlate of PTSD, since similar findings have been reported for healthy individuals living under conditions of chronic stress as well as for patients with several bodily disorders, like chronic fatigue syndrome, fibromyalgia, other SFD. Their hypothesis is that a persistent lack of cortisol availability in traumatized or chronically stressed individuals may promote an increased vulnerability for the development of stress-related bodily disorders.

In the current investigation, depression scores, although moderate, were correlated weakly with somatization. Comorbidity between symptoms of somatization and depression is
well known (Taylor et al., 2004). Rief et al. (1998) confirm a close association between depression and SFD by finding high comorbidity rates between them and SFD have been labelled as “masked depression” (Kielholz, 1973). Basic and clinical research suggests that the pathogenesis of affective disorders, especially depression, is causally related to alterations and activation of the hypothalamic-pituitary-adrenal-axis (HPA): The overactivity of the HPA-system is reflected by enhanced peripheral levels of cortisol and corticotrophin (Holsboer, 2000). But in our investigation at least higher Hamilton depression score correlated with lower cortisol levels, but interestingly not the BDI as self-evaluation scale of depression, so that we should be careful with the interpretation of our data. These conflicting data in our sample could be possibly explained by counteracting effects of psychopathology (especially depression) and somatization, e.g. in it reflects that the somatization in comparison to depressive comorbidity outweighs on the activity HPA axis. However one must consider that no major depressive disorder was present. It is still a matter of controversial debate if depression and alexithymia are distinct or overlapping constructs (Hintikka et al., 2001).

In the present study we reported that alexithymia was strongly correlated with psychopathology. These results are consistent with other other studies (Grabbe et al., 2004) and support the hypothesis that the “difficulties identifying feelings” feature of alexithymia is highly predictive of a broad range of "state" levels of psychopathology, particularly somatization. And in contrast, “difficulties expressing feelings” and “externally orientated thinking” were almost not predictive for any of the SCL-90-R scores. In a recent study, Lin et al. (2005) reported a negative correlation between TAS factor 3 and changes in the cortisol response. Our findings are not consistent with this study.

At least is to explain the contradictory behaviour of measures of Somatization: The Somatization scale (SCL-90-R) correlated negatively with cortisol levels, in contrary the Somatization severity scale (SOMS scale) correlated positively. Of importance it is that the
Global severity index (GSI) of SCL-90-R correlated too with higher cortisol levels, similar to the Somatization severity scale, which also at the other data is comprehensible. In line of the stress-alexithymia-hypothesis (Stone and Nielson, 2001) more psychopathology symptoms were to be also expected. A similar contradictory result related to the psychology measurements so far also in this form one did not report.

Despite the current findings there are a number of issues to be considered. First of all, in our healthy control group only cortisol was measured, we have no measures of psychopathology. On the other hand our sample of patients and healthy subjects are free of major psychiatric disorders and drug free. Secondly, there are some difficulty comparing findings across the studies because different instruments were used. The data generated in the current investigation was mostly normally distributed and therefore correlation analysis within the patients sample generates valuable information. Physiological fluctuations as well as the circadian rhythm of cortisol secretion must be taken into account, and differences in sampling time points or frequency might explain contradictory results in different studies. To get a representative picture of cortisol secretion profiles of 4 samples a day have been collected in our study. As the cortisol secretion is known to be influenced by factors which can hardly be controlled, these profiles were collected twice for each individual. As expected, cortisol levels were highest in the morning samples followed by a decline throughout the day. Further studies would be valuable to investigate the association between alexithymia and cortisol response as endocrine parameter. To conclude, the results from the current investigation suggest that pre-existing hypocortisolism might possible is associated with SFD.
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Table 1: Demographic and clinical characteristics of patients with SFD and healthy controls (Standard deviations are presented in parentheses)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with SFD</th>
<th>Healthy Controls (HC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=32</td>
<td>N=25</td>
</tr>
<tr>
<td>Age</td>
<td>44.2 (8.2)</td>
<td>37.4 (13.3)</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>23 / 9</td>
<td>19 / 6</td>
</tr>
<tr>
<td>Higher education (%)</td>
<td>60%</td>
<td>n.d.</td>
</tr>
<tr>
<td>Somatization severity Index (SOMS)</td>
<td>21.4 (8.3)</td>
<td>n.d.</td>
</tr>
<tr>
<td>Global severity index (SCL-90-R)</td>
<td>64.2 (13.6)</td>
<td>n.d.</td>
</tr>
<tr>
<td>Phobic anxiety (SCL-90-R)</td>
<td>58.9 (11.5)</td>
<td>n.d.</td>
</tr>
<tr>
<td>HAM-D</td>
<td>13.2 (3.9)</td>
<td>n.d.</td>
</tr>
<tr>
<td>BDI</td>
<td>16.5 (9.2)</td>
<td>n.d.</td>
</tr>
<tr>
<td>TAS-26 Total Score</td>
<td>55.6 (9.6)</td>
<td>n.d.</td>
</tr>
<tr>
<td>TAS factor 1: Difficulty identifying feelings</td>
<td>60.6 (8.8)</td>
<td>n.d.</td>
</tr>
<tr>
<td>TAS factor 2: Difficulty expressing feelings</td>
<td>54.6 (11.3)</td>
<td>n.d.</td>
</tr>
<tr>
<td>TAS factor 3: Difficulty externally orientated thinking</td>
<td>45.38 (9.0)</td>
<td>n.d.</td>
</tr>
</tbody>
</table>
Table 2: Correlation between SCL-90-R-scale and Alexithymiascores (TAS)

<table>
<thead>
<tr>
<th></th>
<th>TAS factor 1: Difficulty Identifying feelings</th>
<th>TAS factor 2: Difficulty describing feelings</th>
<th>TAS factor 3: Externally orientated thinking</th>
<th>TAS-26 Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatization Severity Index (SOMS)</td>
<td>0.035</td>
<td>-0.094</td>
<td>-0.115</td>
<td>-0.102</td>
</tr>
<tr>
<td>SCL-90-R-scale</td>
<td>0.847</td>
<td>0.602</td>
<td>0.522</td>
<td>0.571</td>
</tr>
<tr>
<td>(1) Somatization</td>
<td>0.343 *</td>
<td>0.054</td>
<td>-0.317</td>
<td>0.136</td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>0.769</td>
<td>0.077</td>
<td>0.456</td>
</tr>
<tr>
<td>(2) Obsessive-Compulsive</td>
<td>0.542 *</td>
<td>0.396 *</td>
<td>-0.191</td>
<td>0.464 *</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>0.025</td>
<td>0.296</td>
<td>0.007</td>
</tr>
<tr>
<td>(3) Interpersonal Sensitivity</td>
<td>0.748 *</td>
<td>0.388 *</td>
<td>-0.321</td>
<td>0.525 *</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>0.028</td>
<td>0.073</td>
<td>0.002</td>
</tr>
<tr>
<td>(4) Depression</td>
<td>0.723 *</td>
<td>0.474</td>
<td>-0.260</td>
<td>0.554 *</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>0.006</td>
<td>0.150</td>
<td>0.001</td>
</tr>
<tr>
<td>(5) Anxiety</td>
<td>0.685 *</td>
<td>0.381 *</td>
<td>-0.295</td>
<td>0.448 *</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>0.031</td>
<td>0.101</td>
<td>0.010</td>
</tr>
<tr>
<td>(6) Aggression</td>
<td>0.647 *</td>
<td>0.334</td>
<td>-0.268</td>
<td>0.431 *</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>0.062</td>
<td>0.138</td>
<td>0.014</td>
</tr>
<tr>
<td>(7) Phobic Anxiety</td>
<td>0.403 *</td>
<td>0.295</td>
<td>-0.320</td>
<td>0.264</td>
</tr>
<tr>
<td></td>
<td>0.022</td>
<td>0.101</td>
<td>0.075</td>
<td>0.145</td>
</tr>
<tr>
<td>(8) Paranoid Ideation</td>
<td>0.509 *</td>
<td>0.228</td>
<td>-0.368 *</td>
<td>0.317</td>
</tr>
<tr>
<td></td>
<td>0.003</td>
<td>0.209</td>
<td>0.038</td>
<td>0.077</td>
</tr>
<tr>
<td>(9) Psychoticism</td>
<td>0.721</td>
<td>0.272</td>
<td>-0.305</td>
<td>0.417 *</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>0.132</td>
<td>0.090</td>
<td>0.018</td>
</tr>
<tr>
<td>General Severity Index (GSI)</td>
<td>0.781 *</td>
<td>0.397 *</td>
<td>-0.372 *</td>
<td>0.517 *</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>0.024</td>
<td>0.036</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*: The Spearman Rank correlation is significant on the level of 0.05 (two-tail-probability)
Table 3: Mean serum levels (ng/ml) of cortisol for the patients with SFD and healthy controls (Standard deviations are presented in parentheses)

<table>
<thead>
<tr>
<th>Cortisol level (ng/ml)</th>
<th>Patients with SFD (n=32)</th>
<th>Healthy Controls (n=25)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean morning cortisol</td>
<td>5.2 (3.2)</td>
<td>6.7 (3.9)</td>
<td>p = 0.16</td>
</tr>
<tr>
<td>AUC (G)</td>
<td>7.7 (3.4)</td>
<td>21.4 (10.3)</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>AUC (I)</td>
<td>-8.3 (7.7)</td>
<td>-29.7 (24.8)</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

*Significance determined using t-test with adjusted alpha for multiple comparisons
Table 4. Relationship of alexithymia-scores, somatization, depression and GSI (Global severity index) to cortisol variables

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>AUC-G $R^2 = .465$ (p&lt;0.01)</th>
<th>AUC-I $R^2 = .05$ (p=0.22)</th>
<th>MCS (Mean morning cortisol) $R^2 = .08$ (p=0.12)</th>
<th>Dependent variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta^a$</td>
<td>$t$ (p)</td>
<td>$\beta$</td>
<td>$t$ (p)</td>
</tr>
<tr>
<td>Constant</td>
<td>2.16 (0.04)</td>
<td>-0.85 (0.4)</td>
<td>1.61 (0.12)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.13 (0.9)</td>
<td>-0.17</td>
<td>-0.56 (0.58)</td>
</tr>
<tr>
<td>HAM-D</td>
<td>-0.44 +</td>
<td>-2.65 (0.01)</td>
<td>-0.39</td>
<td>-1.17 (0.26)</td>
</tr>
<tr>
<td>BDI</td>
<td>0.04</td>
<td>0.13 (0.9)</td>
<td>0.35</td>
<td>0.96 (0.35)</td>
</tr>
<tr>
<td>Somatization severity scale° (SOMS)</td>
<td>0.54 +</td>
<td>2.91 (0.01)</td>
<td>-0.01</td>
<td>-0.02 (0.99)</td>
</tr>
<tr>
<td>GSI°° (SCL-90-R)</td>
<td>0.72 +</td>
<td>4.18 (0.01)</td>
<td>-0.13</td>
<td>-0.28 (0.78)</td>
</tr>
<tr>
<td>Somatization (SCL-90-R)</td>
<td>-0.47 +</td>
<td>-2.2 (0.04)</td>
<td>0.06</td>
<td>0.18 (0.86)</td>
</tr>
<tr>
<td>TAS, “Total score”</td>
<td>1.03</td>
<td>1.9 (0.07)</td>
<td>-0.65</td>
<td>-0.89 (0.39)</td>
</tr>
<tr>
<td>TAS, “Difficulty identifying feelings”</td>
<td>-0.7</td>
<td>-1.82 (0.08)</td>
<td>0.56</td>
<td>1.07 (0.3)</td>
</tr>
<tr>
<td>TAS, “Difficulty describing feelings”</td>
<td>-0.45</td>
<td>-1.46 (0.16)</td>
<td>0.08</td>
<td>0.2 (0.84)</td>
</tr>
<tr>
<td>TAS, “Externally orientated thinking”</td>
<td>0.56</td>
<td>-1.9 (0.07)</td>
<td>0.58</td>
<td>1.47 (0.16)</td>
</tr>
</tbody>
</table>

a Standardized regression coefficients ($\beta$) are presented which indicate the relative magnitude of prediction for each independent variable. Coefficients printed in bold and marked with + were included in regression function. The other variables were excluded (SPSS backwards method).

b df = 8 / 30

° Number of symptoms; °° General Symptomatic Index SCL-90-R