Neuroendocrine, Cognitive and Structural Imaging Characteristics of Women on Longterm Sickleave with Job Stress–Induced Depression

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Background: *A recent increase in long-term sick leave (LTSL) in Sweden affects mostly women in the public sector. Depression-related diagnoses account for most of the increase, and work-related stress has been implicated.*

Methods: *We examined dexamethasone/corticotropin-releasing hormone (dex/CRH) test responses, magnetic resonance imaging measures of prefrontocortical and hippocampal volumes, and cognitive performance in 29 female subjects fulfilling three core criteria: 1) LTSL>90 days; 2) unipolar depression or maladaptive stress reaction with depressed mood; 3) job-related stress given as a reason for disability. This group was compared with 28 healthy matched controls.*

Results: *The cortisol response to CRH differed markedly between the two groups ($p = .002$), with a dampened response in patients. This difference remained after removing subjects on antidepressant drugs ($p = .006$) or smokers ($p = .003$). Neither hippocampal nor prefrontocortical volumes differed. Performance on hippocampus-dependent declarative memory tests did not differ between groups, but the LTSL group had impaired working memory.*

Conclusions: *Our most salient finding is an attenuated dex-CRH response in patients on LTSL due to job-stress related depression. This is opposite to what has been described in major depression. It remains to be established whether this impairment is the end result of prolonged stress exposure, or a pre-existing susceptibility factor.*

Key Words: Depression, cortisol, CRH, hippocampus, stress, workplace

Sweden has experienced a dramatic increase in long-term sick-leave (LTSL), mainly accounted for by psychiatric diagnoses. The largest increase of LTSL has occurred in the public sector. The underlying causes and potential commonalities that would prompt a study of LTSL as a syndrome in its own right are presently unclear. There are, however, several indications that a study focusing on this growing population is of considerable interest. Thus, the increase in LTSL is largely accounted for by diagnoses of depression, anxiety and maladaptive stress reactions, while the prevalence of psychotic disorders and substance abuse has not increased as a cause for LTSL. The most overrepresented group on LTSL are workers in the health and human services (HHS) sector. Women constitute a majority of the workforce in this sector, and the largest increase in LTSL has been among women, accounting for two thirds of total Swedish LTSL. The Swedish HHS sector has experienced repeated reorganizations and downsizing during the last decade, providing a plausible cause for increased social stress in the work place, and leading to suggestions that this may have contributed to the increase in LTSL. Taken together, these observations suggest that the increase in LTSL may reflect a range of responses to an increased load of social stress. Furthermore, LTSL per se carries with it significant consequences related to altered life style, decreased social interaction, and loss of income.

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Although depressive syndromes and maladaptive stress reactions account for the recently observed increase in LTSL, the underlying statistics are based on insurance databases of clinical diagnoses. This is a potential source of error. However, using validated, structured face-to-face interviews, SCID I and SCID II (First et al 1997a, 1997b) on a sample of 200 private employees on LTSL, we found that about 80% of the participants indeed met diagnostic criteria for major depressive disorder while, for example, personality or substance disorders were rare. Subjectively, 45% of subjects attributed their illness to prolonged job stress, 41% to job stress in combination with factors in their private life and 11% to factors in their private life only (Rylander et al, unpublished data). Participants described a characteristic course, with symptoms gradually evolving over time, initial symptoms of aches and pains, palpitations, fatigue, and irritability. A majority reported pronounced memory and concentration problems. This clinical presentation has also been reported in relation to other chronic stressors (McEwen 2000).

The hypothalamic-pituitary-adrenal (HPA) axis is a key mechanism linking life events and disease. Its activation is an adaptive mechanism in the short term, primarily aimed at coping with acute physical challenges. In contrast, its chronic activation caused by complex psychological demands imposes an "allostatic load." This refers to the wear and tear caused by the demand to maintain regulatory stability at abnormal levels of activation. Depression, decreased hippocampal volume and impaired cognitive function have perhaps attracted the most interest among potential consequences of allostatic load, and may be interrelated through a dysregulation of the HPA axis leading to chronic hypercortisolemia (Holsboer 2000; McEwen 2000).

Early studies of depressive illness described non-suppression of cortisol secretion in the dexamethasone suppression test, DST. It has subsequently become clear that the relation between HPA axis dysfunction and depression is more complex, and hypercortisolism is only seen in approximately half of depressed patients, yielding an only 25% overall sensitivity for the DST (Strohle and Holsboer 2003). Despite this, there is broad agreement that HPA axis dysfunction is of central importance in

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depression (Holsboer 2000; Nemeroff and Owens 2002). To more precisely probe the dynamic status of the HPA axis, an improved challenge test has been developed, in which corticotropin-releasing hormone (CRH) stimulation is given after dexamethasone pre-treatment (the combined Dex-CRH test). This test is thought to have a 80–90% sensitivity for detecting depression (Heuser et al 1994).

The hippocampus is involved in acquisition of declarative memory, and in the regulation of endocrine stress responses. It is rich in glucocorticoid receptors involved in feedback inhibition of the HPA axis, and lesions to this structure lead to elevated resting as well as stress-induced glucocorticoid levels. Glucocorticoids in turn increase hippocampal susceptibility to a wide range of insults. Decreased hippocampal volume has been reported in three conditions which involve stress exposure and/or pathological HPA axis activation, and where also impaired memory function is a common symptom: major depression, post-traumatic stress disorder (PTSD) and Cushing's disease (Bremner et al 1993, 1995, 2000; Sheline et al 1999, 2003; Starkman et al 1992, 2001). Hypercortisolism is present in about 50% of depressed subjects, and is an invariable component of Cushing's disease. In Cushing's disease tumor extirpation has led to normalization of glucocorticoid levels and also to increased hippocampal volumes (Starkman et al 1999). In depression, hippocampal volume reduction has been reported after multiple depressive episodes, but not in first-episode patients (MacQueen et al 2003). Furthermore, a correlation between duration of untreated depressions and hippocampal atrophy was found in female depressed subjects (Sheline et al 1999, 2003). Together, these findings indicate that hippocampal volume loss and by extension potentially also accompanying cognitive impairment may be the result rather than the cause of depression.

Here, we investigated women employed in the HHS sector, recruited on the basis of three core criteria: 1) presence of LTSL with a duration of >90 days; 2) a diagnosis of depression or maladaptive stress syndrome with depressed mood; 3) self-report of job stress as a factor significantly contributing to the disability. This selection was aimed at recruiting a group representative of the factors that account for the recent increase in LTSL, where these three phenomena coincide. To obtain insights into the processes leading to this phenomenon, we evaluated whether this group shows altered HPA-axis function, if their hypothesized chronic stress exposure is reflected in decreased hippocampal volumes, if subjectively reported cognitive impairment would be detected by cognitive tests, and if so whether a relation would exist between hippocampal volume loss and cognitive symptoms. Our primary hypothesis was that the cortisol response would be exaggerated, as previously described in major depression; the secondary hypothesis was that this might be accompanied by structural and cognitive impairments characteristic of a chronic hypercortisolemic state.

Methods and Materials

Subjects and Overall Design

The study was approved by the Karolinska Human Subject Ethics Committee North (Dnr. 01/373). All subjects gave their written informed consent.

Participation Criteria. Participants were subject to the following criteria: Inclusion: female gender; 40–55 years of age; employed in the health care sector or as a teacher, child caretaker, psychologist or social worker in Stockholm; working ≥ 30 h/week for ≥ 3 years in their profession before becoming ill or being included as controls; right handed; learned Swedish in childhood; Exclusion: any ongoing daily medication except estrogen or contraceptives; in the patient group, antidepressants were also allowed, but a subgroup analysis was carried out for antidepressant medication-free subjects; past or present serious medical condition such as neurological, endocrine or psychotic disease; history of head injury with loss of consciousness for a minimum of 10 minutes; hazardous alcohol consumption, as defined by a score of >6 points on the Alcohol Use Disorders Identification Test (Saunders et al 1993); self-reported illicit drug use.

Additional Criteria for the Patient Group. Inclusion: on full-time sick-leave 3–8 months, major depression or adjustment disorder with depressed mood according to DSM IV; factors related to work reported as the main problem on axis IV and present for >6 months.

Additional Criterion for Controls. Exclusion: any past or present psychiatric diagnosis.

Recruitment Process. Details of the patient recruitment procedures are given in Supplement 1. Ultimately, 44 women underwent a diagnostic interview, after which 11 were excluded while two chose not to participate. Following initial inclusion, two of the 31 remaining patients had pathological findings on the MRI brain scan (intrasellar cyst and intrasellar mass, respectively), leaving 29 patients for the data analysis. The characteristics of this sample are given in Tables 1 and 2. The age of this group was 47.3 ± 4.8 (mean ± SD) and mean days on sick leave when contacted were 168.4 ± 33.2, very similar to the 115 subjects that we failed to reach or who declined either contact or participation (age: 46.1 ± 4.1; mean days on sick leave 167.4 ± 33.0).

Controls were recruited through advertising at workplaces in the human services sector in Stockholm county. The ad text and details of recruitment procedure are given in Supplement 1. Seven hundred fifty subjects responded to the ad and were informed and screened by telephone. Ultimately 210 persons were selected as potential controls, to be matched for hormonal

Table 1. Descriptive Characteristics of the Patient and Control Samples

	Patients (n = 29)	Controls (n = 28)	p-Value
Age, years	47.8 ± 4.9	47.6 ± 4.2	.92
Hight, cm	167.4 ± 6.1	167.5 ± 5.3	.95
Weight, kg	71.0 ± 12.2	66.8 ± 9.9	.16
Current nicotine use	10	7	.56
Hormonal phase			
Premenopause	17	15	.79
Perimenopause	2	3	.67
Postmenopause + oestrogen	4	5	.73
Postmenopause − oestrogen	6	5	1.00
Education			
1–9 years	6	3	.47
10–12 years	8	9	.78
>12 years	15	16	.79
Family situation			
Single household	5	4	1.00
Single + children living at home	3	4	.71
Partner + children living at home	13	15	.60
Partner − children living at home	8	5	.53

No differences were found for a number of potentially confounding variables which were analysed. Continuous variables are given as mean ± SD, with corresponding p-values generated using two-tailed t-test. Count variables are given as absolute frequencies, and compared using Fishers Exact Test.

Table 2. Psychiatric Characteristics of the Patient Group

Diagnosis (nr of subjects with each)	
Adjustment disorder with depressed mood	3
Major depression, single episode, partial remission	17
Major depression, single episode, present, moderate	3
Major depression, recurrent, partial remission	6
Intensity of depressive symptoms	
MADRS score (mean ± SD)	16.5 ± 5.6
Age of onset of mood disorder (mean years ± SD)	
For the total group, $n = 29$	44.1 ± 8.4
For the group with recurrent episodes, $n = 6$	32.7 ± 10.6
Comorbidity (nr patients with each comorbid diagnosis)	
Panic syndrome	1
Social phobia	1
Specific phobia	2
Personality disorders	0
Reported axis IV stressors (nr of patients)	
Only work related stressors	14
Work and private related factors	15
Use of antidepressiants (nr of patients)	
SSRI	12
Days on sick leave at investigation day (mean ± SD)	211.3 ± 39.4

status, education, age, etc. to each recruited patient. Finally, 30 right-handed healthy women were recruited. Among these, one subject subsequently had abnormal thyroid-stimulating hormone, while another one reported asthma and daily use of inhalation steroids, leaving 28 subjects for analysis.

During an outpatient visit, all patients underwent a structured psychiatric evaluation (SCID I and II; (First et al 1997a, 1997b). This was in all cases carried out by author IR, a physician with several years of psychiatric experience, who had additionally completed formal coursework on the use of the SCID, and a series of interviews under supervision prior to this study. For resolution of potential diagnostic issues regarding study subjects, an experienced SCID educator was available througout the study. During the outpatient visit, rating of Montgomery-Asberg Depression Rating Scale (MADRS) depression scores were also obtained (Svanborg and Asberg 1994). Assessment of healthy controls was carried out during a corresponding visit. Within 6 weeks of assessment, subjects were admitted to the Karolinska Hospital Clinical Research Centre for the combined Dex-CRH test, an MRI scan of the brain, and a battery of cognitive function tests. Self-report questionnaires were collected for demographic factors. The entire investigation lasted 2 days, and patients slept at home on the intervening night.

Dex-CRH Test and Biochemical Analyses

The test was performed largely as described in Heuser et al (1994). Briefly, subjects received one tablet of 1.5 mg dexamethasone (Dexacortal; Organon, Oss, The Netherlands) with the instruction to take the medication at 11 PM the day before the CRH challenge. On the following day an intravenous catheter was inserted before 2 PM. The subjects rested in a supine position throughout the test. Blood samples were drawn first at 3 PM for the analysis of basal ACTH and cortisol. Within 2 minutes, 100 μg of human CRH (Ferring, Kiel, Germany) were injected. Blood was drawn at 3:30, 3:45, 4:00 and 4:15 PM for analysis of ACTH and cortisol. These time points represent the protocol evaluated in Heuser et al (1994). Analyses were performed by the SWEDAC accredited clinical chemistry laboratory at the Karolinska University Hospital, with details given in Supplement 1. Data for plasma cortisol and ACTH were analyzed independently, using two-factor ANOVA, with subject category as a between-subjects factor, repeated measures over time as a within-subjects factor, and the interaction of these two to assess differential response between groups over time.

Magnetic Resonance Imaging

All examinations were carried out using the same 1.5 Tesla Sigma 5.X scanner (General Electric, Milwaukee, Wisconsin), the standard quadrate head coil and the individuals in head first supine position. The parameters of image acquisition are given in Supplement 1.

Voxel based morphometry (VBM) was used for voxelwise comparison of the local concentration of grey matter between two groups of subjects (Ashburner and Friston 2000). The optimized VBM protocol of Good et al (2001) was used here. Details of the VBM analysis are given in Supplement 1.

Cognitive Evaluation

A battery of tests was run on a Macintosh computer (Apple, Cupertino, California). The entire test procedure lasted 90 minutes, starting either at 2:00 or 3:30 PM. Details of test methodology are given in Supplement 1. Handedness was assessed with the Edinburgh handedness inventory (Oldfield 1971). Verbal intelligence was assessed using the Synonymous test from a Swedish standard intelligence battery, highly correlated with general intelligence as measured by other scales (Dureman and Sälde 1959). Attention was gauged using both a simple, and a complex reaction task. Working memory was examined using a backward digit-span test known to rely on lateral frontocortical activity (Owen 2000). Declarative memory was examined using three tests. 1) A test of associative memory for complex visual cues, based on the procedure in (Ingvar et al 1997); 2) Delayed word recognition; and 3) Picture recognition.

Data from the cognitive tests did not violate criteria of homogenous variances, and were therefore analyzed using one-way ANOVA. The Holm-Bonferroni procedure was used to compensate for multiplicity of testing (Aickin and Gensler 1996).

Results

Patient and Control Characteristics

Characteristics of the two groups are shown in Table 1; psychiatric characteristics of the patient group are shown in Table 2. The groups were closely matched for several variables which could potentially influence the outcomes measured. Importantly, age and hormonal status were virtually identically distributed in the two groups. Two remaining potential confounds were selective serotonin reuptake inhibitor (SSRI) use, and smoking. Subgroup analyses were therefore carried out, as described below, to exclude a confounding influence of these variables.

Dex-CRH Test

Cortisol data from the dex-CRH test are shown in Figure 1A. A highly significant overall change in cortisol over time was present in response to the CRH challenge [$F(4,220) = 67.1$, $p \leq .0001$]. There was also a significant overall difference between the groups [$F(4,220) = 4.2$, $p = .046$]. Most importantly, the response to the CRH challenge over time differed markedly between the two groups, as witnessed by the interaction term [$F(4,220) = 4.5$, $p = .002$]. Despite the reduced power, this differential response remained after removing all 12 subjects treated with antidepressant drugs [$F(4,172) = 3.8$, $p = .006$] or all 17 (10 patients, 7 controls) smoking subjects [$F(4,152) = 2.9$, $p = .02$]. To evaluate

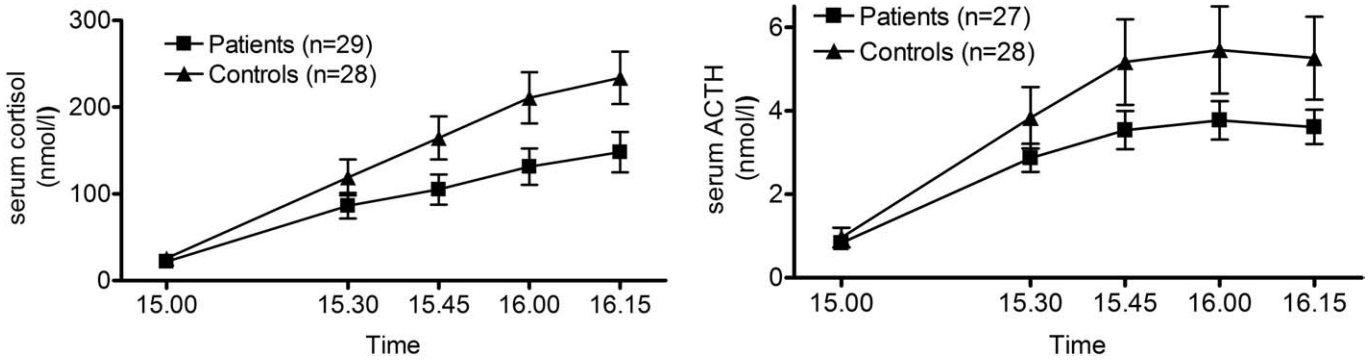

Figure 1. Attenuated cortisol response to an 100 μg i.v. CRH challenge in the patient group compared with controls ($p = .002$). Samples for ACTH analysis from 2 patients were lost by the laboratory, reflected in the lower *n* for this analysis. Results for ACTH were similar to those of cortisol, but variablity was higher, and the difference did not achieve overall statistical significance. Smoking is a known confound in the dex-CRH test; when the 17 smokers (10 patients, 7 controls) in the study were removed, ACTH variability was markedly reduced, and the difference in ACTH response reached significance. For statistics, see Results.

the possible influence of depression severity, a separate analysis was carried out, subdividing patients into those below compared with those above median MADRS. These two subgroups did not differ from each other, and both were lower than controls (data not shown). Finally, to examine if being in first episode versus recurrent depression was of importance for the attenuation of dex-CRH response, those two groups were examined separately. Both groups showed a very similar magnitude of cortisol response attenuation. The analysis had a markedly higher power for the first episode than the recurrent group, due to their respective size ($n = 17$ vs. $n = 6$, respectively). This presumably accounted for the fact that statistical significance for an attenuation was robust in the former [$F(4,196) = 3.2$, $p = .014$, but only at trend level in the latter group [$F(4,128) = 2.1$, $p = .08$].

ACTH data from the dex-CRH test are shown in Figure 1B. ACTH samples for 2 patients were lost by the laboratory, which is reflected in the lower *df* for this analysis. There was a highly significant overall response of ACTH to the CRH challenge [$F(4,212) = 40.1$, $p \leq .0001$]. Similar to cortisol, the average ACTH response curve for the patient group was flatter than for controls, but variability was greater than for CORT values, and the interaction between time and group did not reach significance [$F(4,212) = 1.9$, $p = .11$]. Interestingly, once the 17 (10 patients, 7 controls) smoking subjects were removed, the variability was reduced, and despite the reduced power, the differential ACTH response reached significance [$F(4,144) = 2.4$, $p = .05$].

MRI Analysis of Hippocampal and Prefrontocortical (PFC) Volumes

VBM revealed no difference in a directed search in the temporal lobe, nor was any significant difference found, neither for temporal nor frontal lobe structures, when a global search was subsequently performed. Adding age and performance in declarative memory did not provide a better model fit to the data.

Cognitive Function

Some test data were lost due to computer errors. Actual degrees of freedom for each analysis therefore differ slightly between the analyses, and are given together with the respective results. All results together with their corresponding statistics are shown in Table 3.

The groups did not differ on verbal intelligence. Simple reaction time did not differ between groups, but complex reaction time was significantly longer in patients than controls. The number of missed responses on both tasks, and the number of errors in the complex task did not differ between groups.

A highly significant working memory impairment was found

Table 3. Scores on the Neurocognitive Tests to Assess Verbal Intelligence, Reaction Times, Working Memory, and Long Term Memory

	Patients	Controls	
Verbal intelligence			
Synonym test	23.8 ± 3.1	24.2 ± 2.3	$F(1,53) = .35$, $p = .56$
Reaction time			
Simple reaction task	372.2 ± 104.3	353.5 ± 77.5	$F(1,51) = .55$; $p = .46$
Complex reaction task	411.9 ± 86.6	365.6 ± 60.9	$F(1,52) = 5.2$; $p = .03$
Working memory			
Backward digit span, no corr. seq.	2.5 ± 1.5	4.0 ± 1.8	$F(1,52) = 11.6$; $p = .001$
Backward digit span, no tot. seq.	5.9 ± 1.7	7.6 ± 2.0	$F(1,52) = 11.2$; $p = .002$
Long term memory			
Picture recognition	34.5 ± 4.3	35.9 ± 3.4	$F(1,51) = 1.7$; $p = .19$
Delayed word recognition	17.1 ± 2.5	18.2 ± 1.8	$F(1,52) = 3.5$; $p = .07$
Visual Cues	24.7 ± 8.2	26.3 ± 7.2	$F(1,51) = .6$; $p = .43$

Mean ± SD values are given for the nr of correct responses on each test, as described in Methods, except for the reaction times, which are given in milliseconds. Some test data were lost due to computer failures; actual degrees of freedom are given for each analysis.

in patients versus controls in the backward repeated digit span test, while none of the three long-term memory tests differed.

The analyses above were also carried out for medication-free subjects only versus controls, but results did not differ from those obtained based on the full patient sample.

Discussion

Summary of Findings and Discussion of Their Validity

This study was carried out to explore the pathophysiological mechanism in subjects fulfilling three core criteria: 1) being on LTSL of 90 days duration or longer; 2) having a diagnosis of depression or maladaptive stress syndrome with depressed mood; and 3) presenting a self-report of job stress as a major factor underlying the disability. Subjects with these characteristics account for the recent increase in LTSL in Sweden, and insights into their pathophysiology might therefore aid an understanding of this phenomenon. In this population, we assessed three dimensions implicated in the pathophysiology of depression and related maladaptive stress responses: responsiveness of the HPA axis to a CRH stimulus under dexamethasone feedback inhibition, hippocampal, and PFC volumes, and cognitive function (Holsboer 2000; McEwen 2000). The most salient finding is a marked attenuation of the HPA axis response to CRH challenge in LTSL patients, a pattern opposite to that consistently reported in major depression (Heuser et al 1994; Kunugi et al 2004; Modell et al 1997; Rybakowski and Twardowska 1999). The attenuated HPA axis response is likely of central origin, since the ACTH responses follow a similar pattern. Hippocampal as well as prefrontocortical volumes were unaffected. Declarative memory was unaffected, but working memory and attention were impaired.

The internal validity of our results is likely high. We assessed numerous subject characteristics that could potentially confound the outcome measures. A comparison shows that the groups are very closely matched for all but two variables. Importantly, age and hormonal status, factors demonstrated to influence the dex-CRH test (Kudielka et al 1999), were virtually identically distributed in the two groups. Two variables prompted a closer analysis to exclude their potential confounding influence. First, current smoking, while not significantly different in frequency between groups, showed a trend difference that justified a separate analysis, because smoking is a known confound in the dex-CRH text (Kunzel et al 2003). Second, antidepressant treatment can affect both declarative memory and/or hippocampal volumes (Vermetten et al 2003; Vythilingam et al 2004), and use of antidepressants was obviously restricted to the patient group. We addressed the potential confounding influence of both these variables by subgroup analyses of non-smoking and medication free subjects, respectively, but results were not affected. In fact, the difference in ACTH profiles was strengthened by excluding smoking subjects, making the differential response between groups significant, in a manner consistent with the cortisol findings. Confounding variables are thus unlikely causes of abnormalities found in the patient group, and a blunted HPA axis response of central origin seems to be present in the LTSL group.

Assessing the degree to which the data can be generalized to the population of subjects on LTSL under a depression related diagnosis is more challenging. Ultimately, approximately 10% of the registry based sample was examined. One main set of selection filters along the way, i.e., excluding subjects with medical conditions or ongoing medication, was imposed by the study, had a rationale related to methodological considerations, and is in our opinion unlikely to affect generalizability. Subjects who could not be included due to our failure to reach them, or due to their unwillingness to participate, may on the other hand differ in important characteristics from those who participated in a systematic manner. The likelihood for this type of selection bias is somewhat reduced by the observation that subjects that were ultimately examined did not differ from those who could not be evaluated with regard to the two measures available for all members of the original registry sample, i.e. age and duration of sick leave. However, in absence of other data, we cannot establish that the results are representative of the group of LTSL patients with a depression diagnosis as a whole.

Neuroendocrine Results—Attenuated dex-CRH Response

The finding of attenuated HPA axis response in depressed LTSL subjects was contrary to our expectation. An exaggerated cortisol response in the dex-CRH test has consistently been reported in depression (Heuser et al 1994; Kunugi et al 2004; Modell et al 1997; Rybakowski and Twardowska 1999), increasing in parallel with the number of episodes (Hatzinger et al 2002). The sensitivity of the dex-CRH test to detect depression has been reported at 80%, or as high as 90% if properly adjusted for age (Heuser et al 1994). A failure to find an elevated dex-CRH response in our subjects could possibly have been attributed to the fact that the vast majority of them had first-episode depression. The up-regulated dex-CRH response in acute depression seems to represent a neuroadaption developed during the course of illness, as shown by the finding that healthy high-risk subjects did not have a premorbid HPA activation prior to disease onset (Ising et al 2005), and that patients with a first episode of depression still had a normal response in the dex-CRH test, and an attenuated response when in complete remission (Rybakowski and Twardowska 1999). However, the predominance of first episode depression in our sample cannot account for the observation of the opposite result, i.e., a marked attenuation of the dex-CRH response.

Dexamethasone suppression has commonly been thought to gauge the sensitivity of hippocampal glucocorticoid receptors to mediate feedback inhibition of the HPA axis. It has subsequently been realized that the dex-CRH test largely taps into HPA function downstream of the hippocampus. Importantly, the test might primarily probe stress-induced hypothalamic recruitment of vasopressin co-expression in CRH neurons, which acts to potently augment actions of CRH (Holsboer 2000). Despite this, available central and peripheral indices of the stress axis indicate that in typical, melancholic depression, the dex-CRH response largely reflects upregulated central CRH activity (for review, see Kasckow et al, 2001). Interpreted within this framework, our findings would indeed indicate that a lowered drive of central stress system components is present in our patient sample. This suggests an underlying pathophysiology distinct from what has typically been described in major depression, and instead similar or identical to that previously described for atypical depression, an entity characterized by an attenuated activity of the CRH and norepinephrine systems involved in both endocrine and behavioral stress responses (Gold and Chrousos 2002). Interestingly, LTSL subjects commonly reported chronic musculoskeletal pain. It has previously been described that a hypoactive HPA axis in atypical depression may lead to an insufficiently restrained function of the immune system, in turn leading to chronic, low grade inflammatory states (Gold and Chrousos 2002). The link between such a pro-inflammatory shift and atypical depression may, however, only be relative. More recently, a generally

attenuated ability of cortisol to inhibit proinflammatory cytokines has been described in subjects fulfilling major depression criteria, without stratification for atypical features (Miller et al 2005).

Before concluding that our findings in LTSL subjects reflect a hypoactive state of central stress systems in this population, studies on PTSD need to be considered. For reasons which are not well understood, an upregulated activity of central CRH systems is present in this condition despite attenuated HPA axis activity (reviewed in Kasckow et al 2001). However, important differences exist between the two conditions. The stressors underlying PTSD are acute and life threatening. In contrast, stressors in depression in general, and in our LTSL sample in particular, are of lower magnitude, primarily social, and chronic. Furthermore, although findings of reduced hippocampal size in PTSD similar to those in chronic depression have been reported (Bremner et al 1995), a subsequent twin study indicated that this may represent a pre-existing vulnerability factor rather than the result of the intense, acute stress-exposure characteristic of this condition (Gilbertson et al 2002).

Integrating these considerations, we therefore favor the interpretation that our dex-CRH results are indicative of hypoactive central stress-axis circuitry similar to what has been described for atypical depression (Gold and Chrousos 2002). A final consideration is whether this hypoactivity is part of a primary underlying pathophysiology, or is a secondary result of being on LTSL, as opposed to being actively engaged in work. Although effects secondary to being on LTSL would be of considerable interest to study, we do not think they offer a likely explanation for our findings. This is because our observations of attenuated dex-CRH response are in line with, and expand on, a previous report, which also found evidence for HPA-axis hypoactivity in women scoring high on measures of "burn out." In that study, low baseline as well as dex-inhibited salivary cortisol was obtained, despite subjects being engaged in work to normal extent (Pruessner et al 1999).

Depression severity as measured by the MADRS did not distinguish between dex-CRH responses, with the potential limitation that depression ratings in our patient group were generally low, as the majority of patients were in partial remission. The lack of relation between depression severity and magnitude of dex-CRH blunting may suggest that the latter is related to trait rather than state. Our observations still leave unresolved whether such a hypoactivity reflects an end-stage of chronic, primarily social stress in the work-place, possibly justifying the commonly used concept of a "burn out"; or, perhaps more interestingly, whether a pre-existing inability to mount an adequate stress response might predispose subjects in our population to developing a maladaptive syndrome which superficially resembles major depressive illness, but is in fact a pathophysiologically distinct entity, similar or identical to what has been described for atypical depression (Gold and Chrousos 2002; Kasckow et al 2001).

Structural and Cognitive Measures

We found no differences in hippocampal or PFC volumes between our LTSL population and controls. Hippocampal volume reductions have been observed in major depression, and are proposed to result from actions of elevated cortisol feeding back onto hippocampal cells (Holsboer 2000; McEwen 2000; Sheline et al 1999, 2003). In addition to the hippocampus, prefrontal cortex (PFC) has also been implicated in regulation of stress responses (Diorio et al 1993), in structural and functional consequences of stress in rodents (Brown et al 2005; Cook and Wellman 2004; Radley et al 2005; Wellman 2001), and in depression in humans (Drevets et al 1997). Importantly, recent studies indicate a higher abundance of glucocorticoid receptors in the subhuman primate and human PFC compared with the rodent brain, indicating a potentially higher relative importance of this region in both responses to, and consequences of, stress in humans (Lupien et al 2005).

Support for a role of cortisol as mediator of volume changes have been reported in the extreme form of hypercortisolism, Cushing's disease (Brown et al 2004; Starkman et al 2001), although hypercortisolism as a mediator of hippocampal volume loss and cognitive impairment in depression is not yet unequivocally established (O'Brien et al 2004). Two characteristics of our study population make the lack of structural differences unsurprising in retrospect. First, a vast majority of our population had first episode depression. Hipocampal volume loss has been reported to correlate with duration of untreated depression (Sheline et al 2003), and in agreement with that observation, a recent study in women with first episode depression related to another stressor, a cancer diagnosis, also failed to find hippocampal volume changes (Inagaki et al 2004). Our data would thus be consistent with those studies. Furthermore, assuming cortisol to be the mediator of structural hippocampal and prefrontocortical pathology in depression, our finding that the HPA axis is hypoactive rather than hyperactive in our sample of LTSL depression is not predictive of structural changes.

However, it is well established that both hippocampus-dependent declarative memory and PFC-dependent working memory can be influenced by stress and cortisol even in the absence of structural changes. Of interest for the present study, PFC-mediated working memory has been shown to be more sensitive to changes in glucocorticoid levels than declarative memory. Furthermore, PFC function and working memory specifically are modulated by cortisol in an inverted U-shaped manner, presumably reflecting the relative occupancy ratio of glucocorticoid and mineralocorticoid receptors (Lupien et al 2005). Impaired working memory and attention observed in our LTSL population are therefore consistent with the attenuated HPA axis response which was found in parallel. In fact, the finding of impaired working memory may directly reflect an inability to mount an adequate HPA axis response to support normal performance on this test. Similar to the neuroendocrine stress response, this could reflect consequences of chronic stress, pre-existing vulnerability, or both.

Two interpretations are commonly given for the rapid rise in disability attributed to stress in the workplace: abuse of the benefit system and depression-like pathology. In fact, data are lacking to substantiate either. We report an unexpected attenuation, rather than accentuation, of HPA axis response in depressed subjects on LTSL under a diagnosis of depression, resembling the pattern previously described for atypical depression. A neuroendocrine dysregulation in these subjects would conventionally be interpreted as reflecting consequences of long-term stress exposure. An intriguing alternative possibility is that a pre-existing impaired ability to mount an adequate HPA axis response to social stressors may contribute to an inability to cope. Longitudinal data from this cohort will be forthcoming that will help evaluate this hypothesis.

IR and KW contributed equally to this article.

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