

## Salivary Cortisol Release and Hypothalamic Pituitary Adrenal Axis Feedback Sensitivity in Fibromyalgia Is Associated With Depression But Not With Pain

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**Abstract:** Results on hypothalamic-pituitary-adrenal (HPA) axis function in fibromyalgia are heterogeneous and studies that integrate psychological and biological mechanisms in the search for pathways to fibromyalgia are rare. The goal of the study was to evaluate cortisol release and HPA axis feedback regulation in fibromyalgia and its association with psychopathology and pain. Beneath assessment of pain thresholds and self-report of pain, salivary free cortisol release over the day before and after intake of 0.5 mg of dexamethasone was measured in 21 female patients with fibromyalgia and 26 control women. Depression was assessed by questionnaires and clinical interview. We found reduced feedback sensitivity and slightly enhanced cortisol release in patients with fibromyalgia compared with healthy control subjects. Post hoc analyses showed that these effects are exclusively found in those patients, who also had major depressive disorder. Patients with fibromyalgia had lower pain pressure threshold, whereas heat pain thresholds were comparable with control subjects. Pain pressure and heat pain thresholds were not associated with cortisol release. On the other hand measurements of affective pain experience and depression were positively correlated with salivary cortisol over the day. Our results support the hypotheses that HPA axis related alterations are associated with affective disturbances, for example, depression, in patients with fibromyalgia.

**Perspective:** The presented data suggest depression to be an important factor in HPA axis-related dysfunction in fibromyalgia. This might be one explanation for equivocal findings in the literature.

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**Key words:** Fibromyalgia syndrome, HPA axis, salivary cortisol, pain, depression.

Fibromyalgia is a common disorder, with a prevalence of 3.4% in the female population.<sup>46</sup> The syndrome is characterized by widespread and chronic musculoskeletal pain, increased sensitivity to palpation, fatigue, sleep disturbance, and morning stiffness.<sup>46</sup> Patients also frequently report elevated levels of depression, anxiety, and psychosocial stress.<sup>44,45</sup> The etiology of fibromyalgia

remains unknown and findings regarding potential pathophysiological mechanisms are inconsistent. However, increasing evidence suggests an increased sensitivity to pain mediated by central nervous system, with deficiencies in the endogenous pain inhibitory control subjects.<sup>9,11,14,23,36,38</sup> However, increasing evidence suggests an increased sensitivity to pain mediated by central nervous system, with deficiencies in the endogenous pain inhibition. Adding to that, increased pain sensitivity has been found not only for one physical stressor, namely pressure, but also for electrical current, heat, and cold.<sup>9,24,34</sup> However, also diverging results have been reported.<sup>7</sup>

Because stress has been suggested to be one etiological factor in fibromyalgia, dysfunctions in hypothalamic-pituitary-adrenal (HPA) axis have been investigated intensively. Both hyperactivity and hypoactivity of the

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HPA axis have been reported. Increased basal cortisol levels have been observed,<sup>5</sup> whereas other studies reported decreased 24-hour urinary free cortisol and low morning cortisol release in fibromyalgia.<sup>6,16,18</sup> Normal 24-hour cortisol and diurnal patterns of ACTH and cortisol secretion have been reported as well.<sup>1,25,26,28</sup> Findings regarding alterations in diurnal variation, for example, flattened diurnal cycle, of cortisol secretion are also inconsistent.<sup>5,6,20,27,37</sup> Of note, reduced cortisol release in fibromyalgia is associated with depressive symptoms<sup>17,18</sup> and experiences of childhood trauma.<sup>37</sup>

Several studies have evaluated alterations in feedback regulation of the HPA axis using the standard (1 mg) dexamethasone (DEX) suppression test (DST), which is typically used to identify non-suppression of cortisol in the context of HPA axis hyperactivity and impaired feedback sensitivity, for example, in major depression.<sup>4</sup> Increased rates of non-suppressors among patients with fibromyalgia were reported in 2 studies,<sup>10,27</sup> but non-suppression was associated with depression. Several other studies reported lower rates of non-suppressors among patients with fibromyalgia compared with rates of non-suppressors among control subjects,<sup>15,16,31</sup> raising the possibility of increased negative feedback sensitivity in fibromyalgia. The standard DST almost completely suppresses cortisol secretion in healthy individuals. To identify increases in negative feedback sensitivity, the dose of DEX must be lowered to 0.5 mg. To our knowledge, only one study used the low dose DST in fibromyalgia, reporting enhanced cortisol suppression, whereas the suppression of ACTH was unaltered.<sup>42</sup>

In line with studies suggesting reduced adrenal output in fibromyalgia, reduced cortisol secretion has been observed in response to ACTH<sub>1-24</sub> stimulation,<sup>3,19</sup> although negative results have been reported as well.<sup>16</sup> In another study we found that fibromyalgia patients showed lower total cortisol release to a social stressor and also to exogenous ACTH, but normal free cortisol and ACTH levels compared with control subjects.<sup>40</sup> Interestingly, lower total cortisol but normal free cortisol concentrations in fibromyalgia has been reported before.<sup>25</sup>

The role of HPA axis functioning in FMS for the etiology of the disorder is still unclear. Further insights might be gained by studying the association of the putative HPA axis pathophysiology with fibromyalgia pain (spontaneous pain, pain sensitivity), the core symptom of fibromyalgia, and with psychopathological changes, namely depression. The aims of the present study were the assessment of HPA axis functions and their associations with FMS pain and depression. Investigating a sample of inpatients with fibromyalgia, we hypothesize a high amount of depressive symptoms in this sample, and, thus rather elevated cortisol levels and reduced feedback sensitivity than lowered cortisol release and enhanced feedback.

## Materials and Methods

### Participants

Patients with fibromyalgia were inpatients and were recruited at the "Medizinisch-Psychosomatische Klinik

Bad Bramstedt." The clinic is oriented towards behavioral medicine and combines medical, psychotherapeutic and socially therapeutic measures. The female control subjects were recruited by means of local advertising. Patients were diagnosed by their physician according to criteria of the American College of Rheumatology.<sup>46</sup> All patients with fibromyalgia were diagnosed with widespread chronic musculoskeletal pain and increased sensitivity to palpation with no medical causes identified. Exclusion criteria were current eating disorders, alcohol or drug dependence, current or lifetime psychosis, and bipolar disorder. Women with additional medical illnesses that could explain pain symptoms were excluded. Included control subjects never had sought psychiatric or psychotherapeutic treatment and did not suffer from any current or lifetime DSM-IV Axis I disorder or medical illness. The protocol was approved by the ethics committee of the medical faculty of the University of Marburg, Germany; all subjects gave written informed consent.

Twenty-three women with fibromyalgia (FMS) and 26 healthy control subjects (HC) participated in the study. Two of the patients have to be excluded, one due to missing cortisol data and one because she forgot to take the DEX. Sociodemographic data are presented in Table 1. Although there was no significant difference between the groups with respect to age, FMS patients had a significantly higher body mass index. The 2 study groups differ also with respect to education. The patients were at the hospital for a 14.9-day average (SD, 16.7). As expected patients with fibromyalgia had higher scores on the complaint scale as well as on the pain experience scale and depression scale (see Table 1). Twelve patients and none of the control subjects took any medication. The other 9 patients took medications for several different complaints: hypothyroidism (n = 3), gastrointestinal symptoms (n = 3), hypertension (n = 4), and depression (n = 1).

### Procedure

All patients with fibromyalgia underwent a part of a clinical interview (SCID-I) assessing major depression disorder using the section "affective disorders" only.<sup>43</sup> Depressive mood state was also measured using the Depression Scale (D-S)<sup>49</sup> and the Beck Depression Inventory (BDI).<sup>2</sup> The BDI consists of 21 items with a total score range from 0 to 63. A score above 17 is interpreted as reflecting clinical relevant depression. All participants performed the D-S but only the patients also completed the BDI. Further the psychosomatic complaints were assessed by the Complaint Scale, the "Beschwerde Liste" (BL).<sup>48</sup> The BL consists of 24 items which were scored on a 4-point Likert scale. Several predominantly somatic complaints are assessed, for example, breathlessness, weakness, breast pain, neck pain, nausea, irritability, perspiration, sleeplessness, fatigue, and dizziness. To assess the clinical (endogenous) pain, we used the Pain Experience Scale (PES, German: Schmerzempfindungsskala, SES,<sup>12</sup>), which is a scale derived from the McGill Pain Questionnaire. The questionnaire follows a multidimensional approach, assessing 2 components of pain, namely sensory (10 items)

**Table 1. Questionnaire Data and Pain Thresholds: Basic Statistics (Mean/SD) and Results of t Tests**

	FMS (N = 21)	HC (N = 26)	T TEST
Age	49.1 (8.7)	46.5 (6.1)	$t_{45} = 1.239$ , NS
Educational level (8 <sup>th</sup> grade/ high school/ college)	8/8/4	3/11/12	$\chi^2 = 6.07$ , $P = .05$
Body mass index	27.1 (4.9)	23.4 (2.5)	$t_{44} = 3.302$ , $P = .002$
Duration of illness/FMS diagnosis	21.4 mo	—	
Complaint Scale	38.9 (11.8)*	9.8 (6.1)	$t_{41} =$ -10.345, $P < .001$
Depression Scale	20.1 (9.0)	4.3 (2.74)	$t_{45} = -8.321$ $P < .001$
Beck Depression Inventory	14.2 (7.4)	—	
SCID diagnosis major depressive episode	11	—	
Pain Experience Scale			
Affective	31.2 (9.8)	19.5 (5.9)	$t_{45} = -5.248$ , $P < .001$
Sensory	20.7 (4.1)	14.4 (4.9)	$t_{45} = -4.344$ , $P < .001$
Heat Pain			
Threshold (C°)			
Control Point	42.40 (1.6)	42.26 (1.7)	$t_{45} = -0.266$ , NS
Tender Point	41.98 (1.6)	42.48 (2.0)	$t_{45} = 0.927$ , NS
Pain Pressure			
Threshold (kg/cm <sup>2</sup> )			
Control Point	2.4 (1.4)	3.8 (1.6)	$t_{45} = 3.332$ , $P = .002$
Tender Point	2.1 (1.0)	3.2 (0.9)	$t_{45} = 3.513$ , $P = .001$

Abbreviations: FMS, Fibromyalgia syndrome; HC, healthy control subjects.

\*Only 17 FMS patients.

and affective (14 items) pain experiences. Items were scored on a 4-point Likert scale ranging with a total range between 24 and 96.

Saliva was collected at 9 time points: wake up, +15 minutes, +30 minutes, +45 minutes, and +60 minutes, at 8 AM, 11 AM, 3 PM, and 8 PM. After the first day, the participant took 0.5 mg of DEX at 11 PM. The following day, saliva collection was repeated according to the identical protocol.

Saliva was collected using salivette collection devices (Sarstedt, Rommelsdorf, Germany) and stored at room temperature until completion of the session. Salivettes were stored at -20°C until biochemical analysis. The free cortisol concentrations in saliva were determined using a time-resolved immunoassay with fluorometric detection. Inter- and intra-assay coefficients of variance were below 10% for all analyses.

Heat and pressure pain were tested at 1 tender point (upper edge of the trapezius) and 1 control point (center of the volar forearm) at the left and right side of the body. Mean values were calculated for statistical analyses.

Heat pain thresholds were tested using the "PAIN and THERMAL sensitivity tester" (PATH-Tester MPI 100, PHYWE SYSTEME GmbH, Göttingen). The temperature of the thermode (9 cm<sup>2</sup>) started with 37°C and increased by 0.7°C/s until the participant indicated that the heat sensation was slightly painful. There were eight consecutive trials with a 10-second interval between each trial. The mean value of the 5 last heat pain threshold estimates was computed for further analysis.

Pressure pain was tested using a hand-held dolorimeter (Pain Diagnostics and Thermography Inc, New York). The surface of the pressure probe was 1 cm<sup>2</sup>. Pressure was enhanced continuously from zero by a rate of 1 kg/s until the participant indicated that the pressure was slightly painful. After the first measurement, 2 more measurements were conducted, about 1 cm proximal and distal, respectively.

## Statistics

Statistical analyses were performed using SPSS Version 15.0. Sociodemographic data, data from questionnaires measuring depression, pain, and somatic complaints as well as pain sensitivity data were analyzed using the Students *t* test for continuous data,  $\chi^2$  test, and ANOVA, respectively. Further, Persons correlation analysis was used. Cortisol release was analyzed via ANOVA with repeated measurements. To compute a measure of the extent cortisol suppression, percentage of suppression was calculated:

$$\text{mean}(t1 - t9) \frac{100}{\text{cortisol/day1}} * (\text{cortisol/day1} - \text{cortisol/day2})$$

As a measurement for total cortisol release the area under the curve (AUC) was calculated using the following formula<sup>30</sup>:

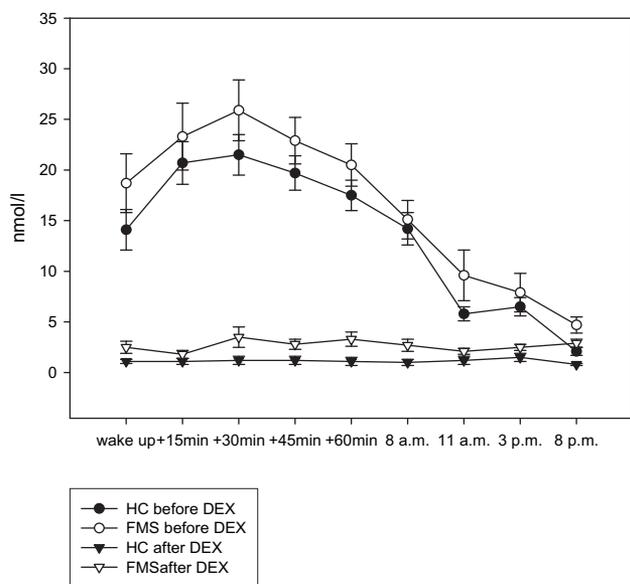
$$AUC = \frac{C_n - C_1}{2} + \sum_{i=1}^{n-1} C_i$$

Furthermore the cortisol slope was calculated as proposed by Sephton et al.<sup>32</sup> The cortisol slope provides a measure of the diurnal change pattern of the cortisol profile.

## Results

### Cortisol Day Curve and DST

A 2×2×9 ANOVA (main factor group: control subjects vs FMS, main factor condition: pre and post DEX, main factor time: 9 measurement points of cortisol assessment) with repeated measurement of the factors condition and time was performed to compare



**Figure 1.** Cortisol release (mean/SEM) before and after dexamethasone (DEX) intake in patients with fibromyalgia (FMS) (n = 21) and healthy control subjects (HC) (n = 26).

patients with fibromyalgia and control subjects (see Fig 1). The following effects could be revealed: a significant effect of the factor time ( $F_{8,360} = 50.493, P < .001$ ), a significant effect of the factor condition ( $F_{1,360} = 194.683, P < .001$ ), and the time by condition interaction effect ( $F_{8,360} = 54.193, P < .001$ ). There was only a trend toward a group effect ( $F_{1,45} = 3.057, P = .087$ ). These results reflect the natural course of cortisol release over the day and its suppression after DEX administration. As also shown in Fig 1, there are only slight differences between patients and the control group with patients having higher cortisol release. Accordingly, the area under the curve (AUC) before DEX intake did not differ significantly between patients and control subjects ( $t_{45} = -1.376, P = .176$ ). There was no significant effect of the variable BMI, which has been shown to be a critical mediator of cortisol release, when introducing it as covariate into the analyses. There was also no difference between FMS patients with and without intake

of medication. Furthermore, FMS patients had a flatter cortisol slope ( $-.69$ ) compared with the control group ( $-.81$ ), but the difference did not reach statistical significance ( $P = .37$ ).

When comparing mean percentage of cortisol suppression a significant difference between patients and control subjects could be revealed (t test:  $t_{45} = 3.386, P = .001$ ). The control group showed an average cortisol suppression of 94.1% (5.1), patients with fibromyalgia had a lower percentage of cortisol suppression, namely 83.8% (14.2).

Although there were no significant correlations between percentage of cortisol suppression and questionnaire data and sensitivity to pain, respectively, significant positive associations were found between the AUC before DEX and the complaint scale, the depression scale and affective pain experiences (Table 2).

### The Impact of Major Depression Disorder on Cortisol Release

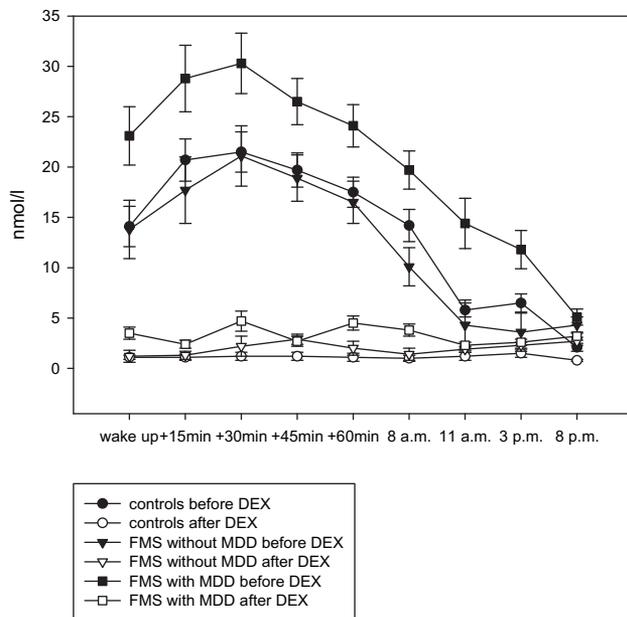
For explorative purposes, we divided the patients group in those with a diagnosis of major depression disorder (MDD) (n = 11) and those without (n = 10). The diagnosis was established with the SCID interview. Subgroups did not differ concerning age, body mass index, educational level, duration of illness, and psychosomatic complaints. Patients with comorbid MDD had a higher depression score (BDI 17.5 (5.8) vs 10.6 (8.1),  $t_{19} = -2.243, P = .037$ ).

Cortisol release before and after DEX was analyzed via  $3 \times 2 \times 9$  ANOVA with repeated measurement with the main factor group (control subjects, fibromyalgia patients with MDD, fibromyalgia patients without MDD), main factor condition (cortisol release before DEX, cortisol release after DEX) and time (9 measurement points of cortisol assessment over the day; see Fig 2). The following significant effects could be revealed: main effect of the factor group ( $F_{2,44} = 5.043, P = .011$ ), main effect of condition ( $F_{1,44} = 188.165, P < .001$ ), main effect of time ( $F_{8,352} = 43.655, P < .001$ ), condition by group interaction effect ( $F_{2,44} = 3.578, P = .036$ ), and a condition by time interaction effect ( $F_{8,352} = 46.140, P < .001$ ). The results reflect the natural time course of cortisol and its

**Table 2. Correlations Between Pain Thresholds, HPA Axis, and Questionnaire Data**

	PES: AFFECTIVE	PES: SENSORY	PSYCHOSOMATIC COMPLAINT SCALE	DEPRESSION SCALE	CORTISOL: AUC	MEAN % SUPPRESSION
HPT control point	$r < .01$	$r = -.01$	$r = -.13$	$r = -.13$	$r = .01$	$r = -.24$
HPT tender point	$r = -.08$	$r = .01$	$r = -.11$	$r = -.15$	$r = -.07$	$r = -.12$
PPT control point	$r = -.26\ddagger$	$r = -.21$	$r = -.42^*$	$r = -.40^*$	$r = .05$	$r = -.01$
PPT tender point	$r = -.36^*$	$r = -.31\ddagger$	$r = -.45^*$	$r = -.46^*$	$r = -.03$	$r = .10$
Psychosomatic Complaint Scale	$r = .72^*$	$r = .67^*$	—	$r = .86^*$	$r = .41^*$	$r = -.23$
Depression Scale	$r = .61^*$	$r = .46^*$	$R = .86^*$	—	$r = .25\ddagger$	$r = -.14$
PES: Affective	—	$r = .90^*$	$R = .72^*$	$r = .61^*$	$r = .36^*$	$r = -.22$
PES: Sensory	$r = .90^*$	—	$R = .67^*$	$r = .46^*$	$r = .16$	$r = .13$

Abbreviations: PES, Pain Experience Scale; HPT, heat pain threshold; PPT, pain pressure threshold; AUC, area under the curve. \* $P < .01$ ,  $\ddagger P < .05$ ,  $\ddagger P < .1$ .



**Figure 2.** Cortisol release (mean/SEM) before and after dexamethasone (DEX) intake in fibromyalgia patients (FMS) with comorbid major depression disorder (MDD) ( $n = 11$ ) and without MDD ( $n = 10$ ) BDI scores and healthy control subjects (HC) ( $n = 26$ ).

suppression after DEX. Post hoc tests revealed no differences between control subjects and fibromyalgia patients without MDD. On the other hand fibromyalgia patients with MDD had significantly higher cortisol release compared with patients without MDD ( $P = .040$ ) and control subjects ( $P = .013$ ) (see also Fig 2). Parameter estimation revealed that the MDD group had higher cortisol levels at the following measurement points ( $P < .05$ ): before DEX: wake-up, +30, +45, +60, 11 AM, 3 PM, 8 PM, after DEX: wake-up, +15, -30, -60, 8 AM, 8 PM. Furthermore differences at trend level ( $P < .1$ ) could be revealed at 8 AM before DEX, 8 PM before DEX, and +45 after DEX. The cortisol slope did not differ between patients with and without depression. Again, there was no significant effect of body mass index or intake of medications on endocrine data.

### Pain Measures and Depression

Table 1 shows that the patients with fibromyalgia had significantly higher levels of depression and psychosomatic complaints than the healthy control women. Similarly and not surprising, the sensory and affective pain levels were markedly higher. For note, also the healthy control women did not present pain-free because they were instructed to rate all forms of pain in the recent past. Although the heat pain thresholds were comparable between patients and control subjects, the patients group showed significantly lower pressure pain thresholds.

We performed correlation analyses between experimental pain measures and questionnaire data (pain scales, complaint scale, depression scale). No significant associations could be revealed between heat pain

thresholds and questionnaire data (see Table 2). There were significant negative correlations between pressure pain thresholds at the tender point on the one hand and the depression scale, the complaint scale as well as the scales for the affective and sensory pain experiences on the other hand (see Table 2). Further, we found significant negative correlations between pressure pain thresholds at the control point and the depression scale, the complaint scale and the scale for the affective pain experience but not between pressure pain threshold and the sensory pain experience.

These findings suggest that high levels of depression and psychosomatic complaints are associated with an increased sensitivity to pressure pain. Similarly, a state with affective and psychosomatic problems appears related with high levels of clinical pain as significant positive correlations indicate in Table 2.

### Discussion

Based on the assumption that dysfunctional HPA axis regulation is of pathophysiological relevance in stress-related pain syndromes such as fibromyalgia syndrome, the present study aimed to evaluate HPA axis response and its association with psychopathology and pain. First of all, there was only a slightly higher cortisol release and reduced feedback sensitivity after DEX in patients with fibromyalgia compared with healthy control subjects, which did not reach statistical significance. As shown in Table 2, there were significant positive correlations between cortisol release (AUC) and depression, somatic complaints and effective pain experiences. Accordingly, we further compared fibromyalgia patients with and without major depression disorder and found patients with MDD to have a more pronounced cortisol release. Second, FMS patients had a lower pain pressure threshold compared with healthy control subjects—as to be expected—whereas sensitivity to heat pain was unaltered. The experimental pain measures were not correlated with HPA axis measurement.

The main goal of the study was to evaluate cortisol release and HPA axis feedback regulation in fibromyalgia. Overall, our results in part support the hypothesis of a slightly enhanced cortisol release over the day together with reduced feedback sensitivity. To our knowledge, only one study measured also salivary free cortisol over the day and reported also elevated cortisol levels.<sup>5</sup> Almost all other studies that evaluated free cortisol assessed 24-hour urinary cortisol, but results remain inconsistent.<sup>1,6,16,18,25,26</sup> Furthermore, in the study presented here the diurnal course of cortisol seemed to be unaltered in patients with fibromyalgia, which has been reported in an earlier study.<sup>28</sup> On the other hand, the feedback sensitivity was reduced even when using only 0.5 mg of DEX. This does not confirm a recent study of our group<sup>42</sup> but is in line with others reporting a higher rate of cortisol non-suppressors after 1 mg DEX for patients with fibromyalgia.<sup>10,27</sup> In that context it has been suggested that comorbid depressive symptom may play a role in HPA axis dysregulation in fibromyalgia.<sup>10</sup> Of note for depressive disorders

enhanced basal cortisol release as well as reduced feedback sensitivity has been reported (see Reference 29 for review).<sup>29</sup> In fact, when comparing fibromyalgia patients with and without MDD only those with a diagnosis of comorbid MDD showed HPA axis dysregulation. Patients without MDD had free cortisol release comparable to healthy control subjects which is in line with a recent study.<sup>40</sup> Despite the fact that these subgroups were very small, our data emphasize the relevance of comorbid depressive symptoms on HPA axis regulation in fibromyalgia. This might be one explanation for the heterogeneous results in these patients in earlier studies. The relevance of comorbidity has been shown for other disorders before.<sup>8,39,41</sup> Furthermore, cortisol release was not only associated with depression, as shown by a close to significant correlation with the depression score, but also with psychosomatic complaints and the affective component of clinical pain. On the other hand, the sensory component of clinical pain as well as the experimental pain measures (pressure pain threshold, heat pain threshold) were not associated with cortisol release. This further strengthens the assumption that HPA axis alterations are related to affective changes.

Although the present study is in line with others reporting a decreased pain pressure threshold both at tender points and so called control points, we could not confirm findings of a reduced heat pain threshold (see Reference 7 for review).<sup>7</sup> In most of the studies, also in our earlier one,<sup>24</sup> the heat pain thresholds appeared decreased in fibromyalgia patients although rarely to the level of decrease in the pressure pain thresholds. However, in a very recent study of Staud et al.<sup>35</sup>—as in the present study—no change in heat pain thresholds was observed. Staud et al. concluded that the heat pain thresholds are not very indicative of the central sensitization, which they consider to be the core of pathophysiology in fibromyalgia. According to these considerations, weak effects as regards heat pain thresholds, which do not consistently pass the level of significance, are likely. However, measuring pressure pain is almost comparable to documenting tenderness, which is a major diagnostic criterion for fibromyalgia. Therefore, the effect sizes of comparisons between FMS patients and healthy individuals in this parameter have to be huge by logic. In contrast, the effect sizes for comparisons, for which other physical stressors have been used, probably are much smaller and the significance of findings depends on various additional factors. In consequence, only the activation of mechanosensitive nociceptors in the skin and in deeper tissue by noxious pressure let FMS patients appear outstandingly pain sensitive but not the activation of other nociceptive pathways.

There are a number of major limitations of the current study. First, the sample size was very small. Thus, despite of significant results which are conform to our hypotheses and makes type II error unlikely, the results have to be confirmed by a larger sample. This is espe-

cially important for the subgroup analyses. We did not assess confounding gynecological data as menstrual cycle phase, menopause status, and intake of oral contraceptives, which are known to influence HPA axis function.<sup>22</sup> Some of the patients took medications, but due to the small sample of each medication group it was not possible to analyze possible effects on this variable. Furthermore, it has been emphasized to collect salivary diurnal cortisol over several days.<sup>21</sup> In this study we examined the cortisol day profile only at 1 day, which is also a limitation. The sample of fibromyalgia patients might be biased toward higher levels of psychopathology because fibromyalgia without any co-morbid psychological disorders are not that likely admitted to a hospital of the given type. For a clearer interpretation of our data, it would have been useful to investigate also a group of patients suffering solely from major depression disorder. Thus, future studies should clarify whether HPA axis alterations are primary due to the affective symptomatology, for example, major depression disorder. It further must be mentioned, that depression is not the only form of psychopathology that might be of interest in fibromyalgia. Accordingly, a further limitation is that only the affective section of the SCID was done in the present study and, thus, there were no information on other comorbid disorders. Further studies should also take anxiety disorders into account, for example, PTSD, which is frequent in FMS.<sup>33</sup> Of note, PTSD is also known to influence HPA axis regulation but is predominantly characterized by reduced cortisol release and enhanced feedback sensitivity.<sup>47</sup> Interestingly a similar pattern of endocrine disturbances has been also found in FMS.<sup>40,42</sup> Thus, other comorbid disorders than depressive disorder may also contribute to varying results in the literature. In the line of inconsistent findings in endocrine fibromyalgia research another interesting future perspective lies in the investigation of different subtypes of depression, namely melancholic and atypical depression, which are characterized by in part opposite HPA axis related alteration.<sup>13</sup>

In summary, our data support the hypotheses that HPA axis related peculiarities are associated with affective disturbances, for example, depression, in FMS patients. Further studies should evaluate well defined and larger subgroups of fibromyalgia patients to confirm these preliminary data. Identifying subgroups of patients with fibromyalgia with distinct psycho-endocrine patterns might have important impact on treatment strategies focussing on the specific combination of symptoms and underlying pathophysiology.

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