Alteration of Delay and Trace Eyeblink Conditioning in Fibromyalgia Patients

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Objective: Classical conditioning processes are important for the generation and persistence of symptoms in psychosomatic disorders, such as the fibromyalgia syndrome (FMS). Pharmacologically induced hyper- and hypocortisolism were shown to affect trace but not delay classical eyeblink conditioning. As previous studies revealed a relative hypocortisolism in FMS patients, we hypothesized that FMS patients also show altered eyeblink conditioning. **Methods:** FMS patients (n = 30) and healthy control subjects (n = 20) matched for gender and age were randomly assigned to a delay or trace eyeblink conditioning protocol, where conditioned eyeblink response probability was assessed by electromyogram. Morning cortisol levels, ratings of depression, anxiety as well as psychosomatic complaints, general symptomatology, and psychological distress were assessed. **Results:** As compared with healthy controls, FMS patients showed lower morning cortisol levels, corroborating previously described disturbances in neuroendocrine regulation of the hypothalamus-pituitary-adrenal axis in these patients. Trace eyeblink conditioning was facilitated in FMS patients, whereas delay eyeblink conditioning was reduced, and cortisol measures correlated significantly only with trace eyeblink conditioning. **Conclusion:** We conclude that FMS patients characterized by decreased cortisol levels differ in classical trace eyeblink conditioning from healthy controls, suggesting that endocrine mechanisms affecting hippocampus-mediated forms of associative learning may play a role in the generation of symptoms in these patients. **Key words:** eyeblink conditioning, fibromyalgia, cortisol.

CR = conditioned response; **CS** = conditioned stimulus; **FMS** = fibromyalgia syndrome; **EMG** = electromyogram; **HPA** = hypothalamus-pituitary-adrenal; **SCID** = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; **US** = unconditioned stimulus.

INTRODUCTION

Fibromyalgia syndrome (FMS) is a common clinical syndrome characterized by chronic widespread pain and tenderness (1). Elevated levels of depression, anxiety, and psychosocial stress are frequently reported in FMS patients (2,3). Although the precise pathophysiological mechanisms are still poorly understood, recent studies suggested a neurobiological basis for FMS (altered central nervous system pain processing) (4,5), and the hypothalamic-pituitary-adrenal (HPA) axis has been implicated as essential. Although inconsistent findings are reported, in FMS a chronic hypoactivity of the HPA axis, including low 24-hour urine free (6–8) and basal blood cortisol levels (7,8), could be observed repeatedly. This hypoactivation has been shown to be associated with HPA axis perturbation in terms of a sensitized pituitary with adrenal insufficiency. Several studies (6,7,9,10) showed an exaggeration of adrenocorticotropic hormone during the corticotropin-releasing hormone test, as the insulin tolerance test was accompanied by unchanged cortisol levels. This relatively mild hypocortisolism might develop after prolonged periods of stress that are first characterized by a hyperactivity of the HPA axis, including an excessive release of glucocorticoids (11).

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Basal learning processes, such as classical conditioning, are involved in physiological and neurochemical processing as well as subjective and behavioral expression of pain and, thus, are relevant in the generation of pain symptoms and their persistence (12,13). Classical eyeblink conditioning has been studied intensively in animals (14) and humans (15,16). It can be seen as a translational tool for clinical populations. There are two frequently used kinds of eyeblink conditioning paradigms: delay and trace eyeblink conditioning. The unconditioned stimulus (US), e.g., a weak air puff to the cornea, induces an eyeblink response that serves as unconditioned response. In delay eyeblink conditioning, the conditioned stimulus (CS), e.g., a tone of short duration (e.g., 400 milliseconds) overlaps the US, with both stimuli terminating together. After repeated tone-air puff pairings, the CS is able to elicit an eyeblink without the application of the US. Delay eyeblink conditioning represents an example of learning without the necessity of voluntarily directing attention to stimuli. Here, the cerebellum is the essential neural system (17). In trace eyeblink conditioning, the tone (CS) and air puff (US) are separated by an empty interval (e.g., 600 milliseconds) and an awareness of CS-US contingency is essential (15). Contingency learning permits prediction of the appearance of one stimulus based on the presence of another, and evidence (18,19) suggests that conscious awareness of a contingency is dependent on conditioned associations. On the neural level, trace eyeblink conditioning requires both the cerebellum and the hippocampus (15,20–22). Stress hormones, in particular glucocorticoids, have been shown to modulate classical conditioning (23) and, thus, may affect the generation and persistence of pain symptoms by influencing learning and memory processes (24). Animal studies (25,26) have shown the involvement of stress-sensitive neurons from the hippocampal CA1 and CA3 regions in trace conditioning, and human studies as well demonstrated the critical role of glucocorticoids in eyeblink conditioning. An impairment of eyeblink conditioning during pharmacologically induced mild hypercortisolism and in persons with endogenous hypercortisolism was observed for trace but not delay conditioning processes (23,27), findings supported by the high concentration of glucocorticoid receptors in the hippocam-

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pus. A facilitation of hippocampus-based conditioning could be observed after pharmacologically induced endogenous mild hypocortisolism (28). These results may be of theoretical and clinical significance for pain syndromes, such as fibromyalgia in which a relatively mild hypocortisolism is postulated. However, so far, classical eyeblink conditioning has not been investigated in fibromyalgia patients.

The purpose of the present study was to examine delay and trace eyeblink conditioning in fibromyalgia patients and healthy matched control persons. The existence of a relatively mild hypocortisolism was assessed by morning cortisol profiles. We hypothesized a facilitation of trace eyeblink conditioning in fibromyalgia patients showing a relatively mild hypocortisolism compared with healthy controls, whereas delay eyeblink conditioning was assumed to be unaffected.

METHODS

Participants

The present study, which was approved by the local ethics committee, involved 30 fibromyalgia patients (n = 11 male and 19 female) with a mean age of 40.73 years (range, 30–54 years) and 20 healthy matched controls (n = 9 male and 11 female) with a mean age of 40.95 years (range, 31–55 years). Data were collected from June 2007 to December 2007. Control subjects were recruited from an unselected general population, using flyers and advertisements in the local media. The patient population comprised consecutive FMS patients, recruited from the Hospital for Psychosomatic Medicine Bad Kreuznach, Germany; these patients were diagnosed according to the criteria of the American College of Rheumatology (1). Mean duration of pain was 14.33 years (standard deviation [SD], 8.3), mean number of tender points was 14.6; the patients reported pain in an average of seven regions of their bodies. FMS patients were excluded from participation if they 1) were taking centrally acting pain medication (e.g., morphine derivatives); b) were suffering from mental disorder, neurologic complications, another severe disease, e.g., a tumor, liver, or renal disease; or c) reportedly were experiencing a duration of pain of <6 months or drug abuse. Mental disorders were diagnosed, using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID I/II) (29,30). SCID I and SCID II showed high validity and reliability in American and German studies (29–31). Ratings of depression, anxiety, as well as psychosomatic complaints, global symptomatology, and psychological distress, were acquired using validated standard questionnaires. To assess depressive symptoms, we used the German version of the Center for Epidemiologic Studies Depression Scale (32). This measure is a reliable and valid indicator of depressed mood in both clinical and research populations. Its 20 items are relatively free of content related to pain and functional limitations associated with rheumatologic disorders. The German version of the State-Trait-Anxiety Inventory (33) was used to measure current feelings and a stable disposition characterized by tension and apprehension across time and setting. Both the state and trait versions are reliable and valid and are the most commonly used measures of anxiety in psychological and behavioral medicine research. The short version of the Gießener Beschwerdebogen-24 (34) was used to assess psychosomatic complaints. The 24 unspecific symptoms are grouped in the following four subscales: fatigue; stomach trouble; rheumatic pain; heart trouble. For the assessment of somatization, obsessive-compulsive symptomatology, and interpersonal sensitivity, we used the Symptom Check List-90-R (35) that was designed to characterize global symptomatology and psychological distress.

Control subjects were healthy and carefully matched for gender and age. Exclusion criteria for healthy controls were the same as for FMS patients. Furthermore, none of the control subjects reported the presence of any pain at the time of participation in the study. The study adhered to the guidelines of the Declaration of Helsinki; the local Institutional Review Board approved the study (Landesärztekammer Rheinland-Pfalz); and informed consent was obtained from all subjects before participation.

Salivary Cortisol Sampling

Saliva samples were collected on 2 consecutive days directly before the test day: at awakening; + 15 minutes; + 30 minutes; + 45 minutes; + 60 minutes (awakening cortisol profile). Furthermore, we obtained one saliva sample for each subject immediately before the assessment of delay and trace eyeblink conditioning.

Saliva samples were stored at −20°C and analyzed for cortisol with a time-resolved fluorescence immunoassay (36). Intra- and interassay variabilities were <6% and 12%, respectively. The data of four FMS patients had to be excluded because of technical problems during laboratory data analysis.

Design

Participants entered the research room at 4 PM. Saliva samples were taken, and a bioamplifier electromyogram (EMG) system (Coulbourn Instruments, Allentown, Pennsylvania) was attached for measuring muscle activity of the orbicularis oculi. All participants were randomly assigned to complete a delay or trace eyeblink conditioning protocol and blinded to group assignment. They were asked to fixate their gaze on the wall, to move as little as possible, and to blink naturally. Furthermore, they were informed that an air puff would be delivered to one eye and that they would hear tones.

In both delay and trace eyeblink conditioning protocols, the CS was a 75 dB(A), 400 milliseconds, 1000 Hz pure tone presented binaurally via headphones. The US was a 10 pounds per square inch, 50-millisecond air puff to the left cornea delivered through a tube attached to the headphones.

Both protocols consisted of three periods: 1) an initial air puff familiarization period including six air puffs alone without CS; 2) an acquisition period including three blocks of 20 trials, with each block consisting of 18 CS-US trials and 2 CS alone trials; and 3) an extinction period including 10 trials with CS alone. In trace conditioning, there was a 600-millisecond free interval between CS offset and US onset. The intertrial interval varied between 10 seconds and 14 seconds, with a mean interval of 12 seconds.

Psychophysiological Recordings

We assessed the eyeblink response as peak EMG activity of the left musculus orbicularis oculi. Two electrodes were placed below the left eye with an interelectrode distance of 1.5 cm, and a third (reference) electrode was taped to the forehead. EMG was recorded with a Coulbourne bioamplifier and DasyLab software (IOtech, Cleveland, Ohio) at a sampling rate of 1000 Hz (notch filter, 50 Hz; band-pass filter, 30 to 500 Hz). Data were rectified and integrated with a 10-millisecond time constant. In a visual analysis, we categorized the trials with respect to artifacts (i.e., voluntary or spontaneous eyeblinks at or near the startle stimulus onset, trials with excessive background noise, multiple peaks). For data analysis, we used only data of participants with at least 75% of trials without artifacts.

Data Analysis

In both delay and trace eyeblink conditioning, the unconditioned response was represented as eyeblink response between a stable baseline (50 milliseconds before US onset) and the maximum amplitude in the time interval of 20 milliseconds to 100 milliseconds after US onset. No participant had to be excluded because of not responding to the air puff.

Eyeblinks with amplitudes of at least 15 μV in the time window of 500 milliseconds before CS onset were defined as spontaneous eyeblinks. In both eyeblink conditioning protocols, those trials with spontaneous eyeblinks were rejected.

Eyeblinks with amplitudes of at least 15 μV in the first 100 milliseconds after CS onset were classified as α responses. The α responses are unconditioned (orienting) responses to the tone (37). For both eyeblink conditioning protocols, we observed few α responses during acquisition and extinction period. Their probability did not differ significantly between FMS patients (acquisition: delay: mean, 2.97%, trace: mean, 3.61%; extinction: delay: mean, 2.12%, trace, 2.43%), and healthy control persons (acquisition: delay: mean, 3.48%, trace: mean, 3.22%; extinction: delay: mean, 2.33%, trace: mean, 2.68%). Thus, conditioned responses (CRs) were not influenced by α responses.

In delay eyeblink conditioning, the CR is represented as an eyeblink with an amplitude of at least 15 μV in the time interval of 100 milliseconds to 300 milliseconds after CS onset.

In trace eyeblink conditioning, eyeblinks with amplitudes of at least 15 μV in the time interval of 600 milliseconds to 1000 milliseconds post CS (in a period of 400 milliseconds that precede the US) were categorized as CRs ("adaptive," true CRs) (38). Furthermore, eyeblinks that occurred during the empty interval of 100 milliseconds to 600 milliseconds after the CS were considered as "nonadaptive" responses, because of their poor timing relative to the CS/US, i.e., closure of the eyelid occurs too early, and the eyelid is no longer closed on delivery of the air puff (23,27). The probability of nonadaptive CRs was low and did not differ significantly between FMS patients (mean, 6.23%) and control persons (mean, 5.58%).

All CR probabilities were calculated based on CS-US acquisition trials, only. CS alone trials that were used to implement a partial reinforcement schedule were not included in the calculation of CR probabilities.

Statistical Analysis

Cortisol data were analyzed with a group (patients versus controls) × cortisol awakening profile (1–5) repeated-measures analyses of variance (ANOVA). The magnitudes of unconditioned eyeblink responses during the air puff familiarization period were averaged over the six trials, and the data during acquisition and extinction periods were averaged within blocks. Acquisition data were analyzed with a group (patients versus controls) × block (1–3) repeated ANOVA for both delay and trace eyeblink conditioning. Extinction data were analyzed with a group (patients versus controls) × trial (1–10) one-way ANOVA. To investigate the impact of cortisol, ratings of depression, anxiety, and psychosomatic complaints as well as global symptomatology and psychological distress on CR probability of delay and trace eyeblink conditioning, we used Pearson correlation analyses.

For all statistical analyses, α was 0.05 (two-tailed), and we applied the Greenhouse-Geisser adjustment in the case of violation of the assumption of homogeneity of variances, and adjusted degrees of freedom are reported. In the case of significant main effects or interactions, paired t tests with Bonferroni adjustment were performed. We used Statistical Package of the Social Sciences, Version 14.0.1 for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

Symptom Ratings

In comparison with control persons, FMS patients reported significantly increased total scores of depression ($t(48) = 5.83$, $p < .001$), anxiety ($t(48) = 6.12$, $p < .001$), as well as psychosomatic complaints ($t(48) = 4.89$, $p < .001$) and global symptomatology and psychological distress ($t(48) = 4.67$, $p < .001$) but below the border to clinical characteristic (Table 1).

TABLE 1. Symptom Ratings of Anxiety Symptoms, Depression, Psychosomatic Complaints, and General Symptomatology and Psychological Distress of FMS Patients and Healthy Controls

	Controls (n = 20) M (SD)	FMS Patients (n = 30) M (SD)	Sign. (Between Both Groups) p
ADS	3.6 (2.1)	12 (4.3)	<.001
STAI			
State	13.1 (3.3)	29.4 (5.1)	<.001
Trait	12.3 (4.2)	27.6 (6.7)	<.001
SCL-90			
Total score	0.5 (0.3)	1.2 (0.7)	<.001
Somatization	0.4 (0.2)	1.2 (1)	<.001
Compulsivity	0.1 (0.2)	0.3 (0.5)	.004
Uncertainty in social contact	0.4 (0.3)	1.7 (1.1)	<.001
GBB			
Total score	20.8 (8.4)	37.6 (8.7)	<.001
Fatigue	6.3 (3)	13.1 (7.1)	<.001
Stomach trouble	4.5 (2.4)	6.8 (4.8)	.026
Rheumatic pain	6.1 (2.7)	13.5 (6.9)	<.001
Heart trouble	4 (2.6)	7.5 (6.3)	.022

FMS = fibromyalgia syndrome; SD = standard deviation; ADS = Allgemeine Depressionsskala; STAI = State-Trait-Anxiety-Inventory; SCL = Symptom Check List; GBB = Gießener Beschwerdebogen.

Salivary Cortisol Data

Figure 1 illustrates the awakening cortisol profile of FMS patients and healthy controls obtained 2 days before the test day of eyeblink conditioning assessment. A significant effect of cortisol awakening profile ($F(3,111) = 71.058$; $p < .001$) and group ($F(1,44) = 4.558$; $p = .038$), and a significant cortisol awakening profile × group interaction ($F(3,111) = 25.328$; $p < .001$) were found.

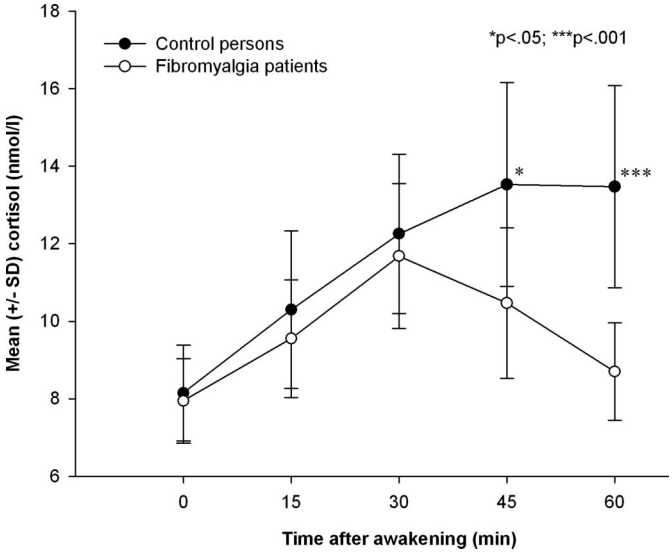

Figure 1. Awakening cortisol profiles (averaged over data of 2 consecutive days) of control and patient groups. *SD* = standard deviation.

Furthermore, we found significantly decreased cortisol values, obtained immediately before the assessment of delay and trace eyeblink conditioning, in FMS patients (mean, 3.12) compared with healthy controls (mean, 4.98) ($t(48) = 2.132$; $p < .05$).

Eyeblink Conditioning

Baseline Eyeblinks

In delay as well as trace eyeblink conditioning, the eyeblink magnitude to the air puff during familiarization did not differ significantly between FMS patients and control persons (delay: mean, 117.7 μV; SD, 20.9; trace: mean, 134.3 μV; SD, 32.8). Probabilities of spontaneous eyeblinks, assessed during the 500-millisecond time window before the CS-US pairs, were not significantly different between the patient and control groups.

Conditioned Responses

Conditioning is normally slower using the trace paradigm, compared with the delay paradigm. To check for this difference under normal conditions, we compared both eyeblink conditioning protocols in the control group. As previously

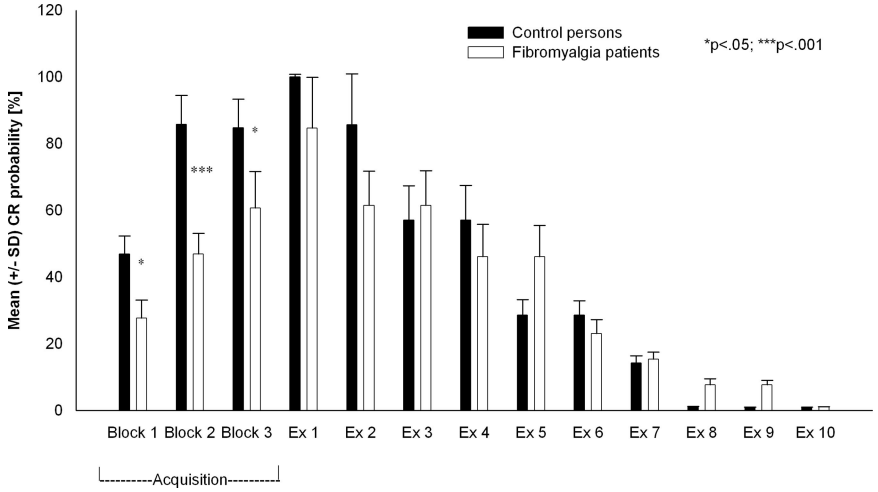

Figure 2. All three acquisition blocks and the extinction (*Ex*) block of delay eyeblink conditioning in control and patient groups. *SD* = standard deviation; *CR* = conditioned response.

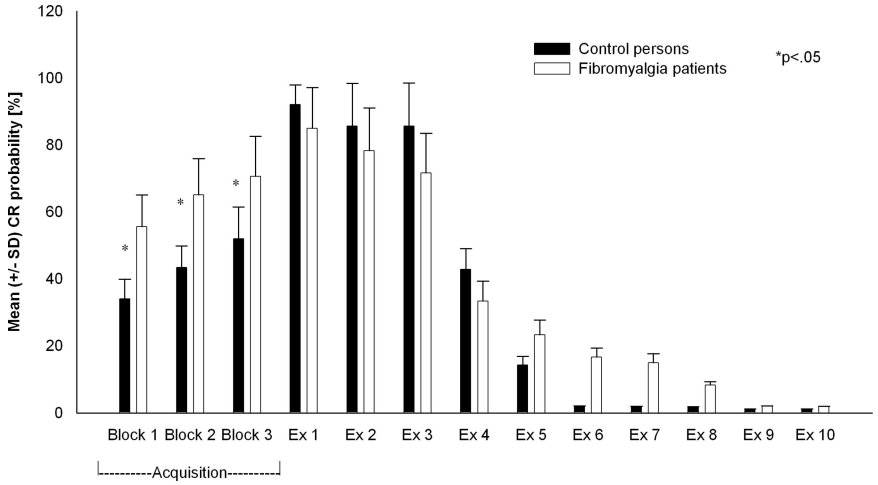

Figure 3. All three acquisition blocks and the extinction (*Ex*) block of trace eyeblink conditioning in control and patient groups. *SD* = standard deviation; *CR* = conditioned response.

demonstrated, delay conditioning was more effective than trace conditioning ($F(1,18) = 33.384$; $p < .001$).

Acquisition

Delay Conditioning

A group × block ANOVA revealed a significant main effect of group ($F(1,21) = 12.002$; $p = .002$). Furthermore, a significant block effect was seen ($F(1,30) = 169.924$; $p < .001$), with CR probability increasing from Block 1 to Block 2 ($p < .001$) to Block 3 ($p = .001$). The interaction between group × block was also significant ($F(1,30) = 12.504$; $p < .001$).

Thus, we found an impaired acquisition probability of delay CRs as well as slower increase in block by block CR probability during acquisition in patients compared with controls (Fig. 2).

Trace Conditioning

We found a significant effect of group for adaptive CRs ($F(1,21) = 6.697$; $p = .017$) as well as a significant block effect ($F(2,38) = 7.351$; $p = .003$), with CR probability increasing from Block 1 to Block 2 ($p = .001$).

Thus, FMS patients showed a higher acquisition probability of trace CRs, with a comparable block by block increase of CR probability to healthy controls (Fig. 3).

Extinction

Delay Conditioning

Although there was no significant effect of group nor a significant difference in the time function between the two groups (no significant group × trial interaction effect), we found a significant effect of trial ($F(4,77) = 12.064$; $p < .001$).

Thus, both patients and controls showed similar delay-conditioned extinction indicated by a trial by trial decrease of CR probability.

Trace Conditioning

Although we found a significant trial effect ($F(5,77) = 18.046$; $p < .001$) as well as a significant group × trial

interaction ($F(5,77) = 2.432$; $p = .048$), there was no significant group effect.

Thus, although both patients and controls showed extinction of trace CRs, patients and controls differed in the time course of extinction indicated by a slower decrease in CR probability during the last extinction trials in patients compared with controls.

Correlation Analyses

We found no significant correlations between the CR probability in delay or trace eyeblink conditioning and the total scores of depression, anxiety, psychosomatic complaints, or global symptomatology and psychological distress. With respect to the subscales, FMS patients showed bilateral relationships between the CR probability in delay eyeblink conditioning and the Gießener Beschwerdebogen-related subscale of rheumatic pain ($r = -.604$; $p = .029$) as well as between the CR probability in trace eyeblink conditioning and the Symptom Check List-90-R-related subscale of uncertainty in social contact ($r = .660$; $p = .014$).

With respect to salivary cortisol levels and eyeblink conditioning, we found no correlation of mean morning cortisol level with CR probability during acquisition in delay eyeblink conditioning but with acquisition-related CR probability in trace eyeblink conditioning ($r = -.642$; $p = .018$). Thus, low levels of morning cortisol were associated with an increase in trace eyeblink conditioning.

DISCUSSION

Our data corroborate previously described disturbances in neuroendocrine regulation of the HPA axis in fibromyalgia patients. The main new finding of the present study is that FMS patients show facilitated trace eyeblink conditioning as well as impaired delay eyeblink conditioning. Although cortisol measures in this patient group did not significantly correlate with delay eyeblink conditioning, they are significantly correlated with trace eyeblink conditioning, with lower cortisol levels related to increased trace eyeblink conditioning. Furthermore, although extinction of delay CRs was not different between the patients and controls, patients showed a slower decrease in CR probability during the last trace-conditioned extinction trials in patients compared with controls.

It is well established that both pharmacologically induced and endogenous mild hypercortisolism impair trace but not delay eyeblink conditioning (23,27). Furthermore, in a recent study (28), a facilitation of trace eyeblink conditioning after a pharmacological suppression of endogenous cortisol production could be shown as delay eyeblink conditioning remained unaffected. However, the present results showed an alteration not only of trace eyeblink conditioning but also of delay eyeblink conditioning in FMS patients characterized by lower cortisol levels compared with healthy control subjects—a finding that failed to confirm our hypothesis as FMS patients and controls were expected to be similar in acquiring delay-conditioned responses.

Previous neuroendocrine studies have found increased adrenocorticotropic hormone but normal cortisol responses after corticotropin-releasing hormone stimulation test (6,7,39,40), suggesting an HPA axis perturbation in terms of a combination of sensitized pituitary with adrenal insufficiency (7,9,10). Although the cerebellum mediates acquisition of delay eyeblink conditioning (17), the cerebellum and hippocampus are involved in the acquisition of trace eyeblink conditioning in both animals (20,21) and humans (15,16). As the present findings of an impairment of delay eyeblink conditioning in FMS patients was not associated with cortisol levels, the facilitation in hippocampus-mediated trace eyeblink conditioning suggests that hippocampal function is supported by circulating or locally relatively decreased cortisol levels. Furthermore, the difference in delay conditioning between FMS patients and healthy controls seems to be not based on the cortisol levels but may be mediated by other factors differing for people with FMS compared with healthy controls.

Because pain is characterized by both sensory and affective aberrations, its chronification can lead to changes in psychological state and affect. Anxiety, depression, and anhedonia as the most prominent affective states in patients with chronic pain can interfere with the patient‘s quality of life (41–43). Also, stressful life-events at the beginning of or during pain states were mostly reported in chronic pain patients (44). Thus, the stress of being in pain for a long time (as in FMS patients) as well as the anxiety- and depression-related affective state might affect cortisol status and conditioning as well, resulting in the current finding of altered delay and trace eyeblink conditioning in FMS patients compared with healthy controls.

Predictability, a process of contingency or associative learning, is fundamental to classical conditioning. Classical conditioning is an adaptive associative process that enables organisms to learn to anticipate events, aversive or otherwise, and classical conditioning processes are assumed to play a role in pain symptom generation and persistence (12,13). Chronic pain is suggested to capture attention (45) and, thus, may be detrimental to other parallel processing. The hypervigilance model of pain perception (46) assumes a heightened sensitivity to experimentally induced pain as well as to nonpainful stimuli (generalized hypervigilance) (47). The state of hypervigilance can be viewed as a state of pain-specific anxiety with higher bodily awareness in which attention is directed toward the sources of a potential or actual threat (48). As awareness is important for trace but not delay eyeblink conditioning, one would suggest an increase in CRs only during trace eyeblink conditioning in FMS patients compared with healthy controls. Thus, the present finding of enhancement of trace eyeblink conditioning but decrease in delay eyeblink conditioning may indicate a facilitation of cognitive awareness-based processing toward an aversive event, whereas more automatically based associations may be slowed down.

The study has several limitations. First, we did not collect blood samples, and thus, we cannot provide plasma data. Earlier studies have shown relative hypocortisolism in basal blood cortisol levels (7,8) and 24-hour urine free cortisol levels (6–8) only. Thus, comparisons with these studies are not possible. Second, although control subjects were recruited

from an unselected general population, the FMS population comprised consecutive patients. Thus, one could argue that this limits the validation of the comparison between patients and controls even more so, as we did not match for differences in the sociocultural level. To make samples comparable, patients and controls were matched for gender and age. In addition, any comorbidity of depression or anxiety, often reported in recent studies, failed in the present FMS sample. This might limit the generalizability to other FMS samples and make comparisons with other studies difficult.

The current results extend findings from eyeblink conditioning research on glucocorticoids conducted under various conditions and may have theoretical and clinical significance not only for FMS patients but also for other symptom groups characterized by a relative mild hypocortisolism that helps to explain the high prevalence of psychosomatic symptoms in patients with these disorders.

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