Influence of stress systems and physical activity on different dimensions of fatigue in female fibromyalgia patients

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Abstract

Objective: Fatigue is a defining characteristic and one of the most debilitating features of fibromyalgia syndrome (FMS). The mechanisms underlying different dimensions of fatigue in FMS remain unclear. The aim of the current study was to test whether stress-related biological processes and physical activity modulate fatigue experience.

Methods: Using an ambulatory assessment design, 26 female FMS patients reported general, mental, and physical fatigue levels at six time points per day for 14 consecutive days. Salivary cortisol and alpha-amylase were analyzed as markers of neuroendocrine functioning. Participants wore wrist actigraphs for the assessment of physical activity.

Results: Lower increases in cortisol after awakening predicted higher mean daily general and physical fatigue levels. Additionally, mean daily physical activity positively predicted next-day mean general fatigue. Levels of physical fatigue at a specific time point were positively associated with momentary cortisol levels. The increase in cortisol after awakening did not mediate the physical activity – fatigue relationship. There were no associations between alpha-amylase and fatigue.

Conclusion: Our findings imply that both changes in hypothalamic-pituitary-adrenal axis activity and physical activity contribute to variance in fatigue in the daily lives of patients with FMS. This study helps to paint a clearer picture of the biological and behavioral underpinnings of fatigue in FMS and highlight the necessity of interdisciplinary treatment approaches targeting biological, behavioral and psychological aspects of FMS.

Key words: ambulatory assessment; fatigue; fibromyalgia; HPA axis; physical activity; autonomic nervous system

Introduction

Fibromyalgia syndrome (FMS) is a chronic widespread pain condition with unknown etiology, which is accompanied by fatigue, sleep disturbances, and other somatic complaints (1). Although fatigue is a major and very debilitating complaint in this population, most research focuses on pain (2). We therefore set out to assess biological and behavioral factors that might explain fluctuation of fatigue in FMS, focusing on endocrine and autonomic activity on the one hand and objectively recorded physical activity on the other.

Chronic stress presents a constant challenge to the organism and has been discussed to threaten health and, amongst other things, lead to heightened fatigue levels (3). High levels of chronic stress and related changes in the hypothalamic-pituitary-adrenal (HPA) axis as well as the autonomic nervous system (ANS) (the main regulatory biological stress systems) activity have therefore also been discussed as mechanisms of FMS symptom development and exacerbation (4). The association between stress, HPA functioning, and fatigue is most likely driven by the involvement of the hypothalamus in energy homeostasis (5). This is reflected in HPA axis' regulatory effects on a variety of target cells, for example the immune system (6). In more detail, changes in HPA activity occur when energy balance changes. This contributes to a change in peripheral cytokine levels, which, via cytokines' effects on various brain networks, presumably supports energy conservation (7). In this regard, fatigue may indicate a negative energy balance (8) triggering resting behavior and thereby energy conservation (9, 10). As a system linking peripheral sensations and the central nervous system, the ANS also plays a key role in maintaining energy levels. For instance, studies demonstrated an association between orthostatic intolerance, central regulation and fatigue (11). In line with this observation, the dopaminergic neurotransmitter system, which is involved in reward and goal processing, has been shown to be clearly linked to fatigue (12, 13). The most important peripheral marker of measuring HPA axis activity is cortisol which shows a distinct diurnal

rhythm (14). The increase in cortisol after awakening, also referred to as “cortisol awakening response” (CAR), has been discussed to reflect the regulatory capability of the HPA axis (15, 16) and, as such, to be a very important marker in fatigue and pain research (17). For instance, there is evidence of a reduced daily cortisol output (18, 19) and a reduced increase in cortisol after awakening (20) in patients with FMS. Concerning ANS activity, most studies in patients with FMS indicate a basal hyperactivity (21). A relatively new surrogate marker of ANS activity is the enzyme salivary alpha-amylase (sAA, 22). SAA activity has a diurnal rhythm with a sudden decrease in the morning, the “alpha-amylase awakening response” (AAR), and a steady subsequent increase with highest levels in the late afternoon (23). While there is still no final agreement on the underlying mechanisms and meaning of these morning changes in sAA activity, the AAR has been related to various disease states (22). For instance, there is first evidence of an alteration of the AAR in patients with post-traumatic stress disorder (24). It can therefore be assumed that AAR is an important marker of ANS activation in stress-related disorders. To the best of our knowledge, there have not been any studies investigating the AAR in FMS. It might be suspected that reduced HPA axis (e.g. flattened CAR) and increased ANS activity contribute to fatigue manifestation in FMS. However, there are only two studies assessing intra-individual associations between HPA axis or ANS activity and fatigue in patients with FMS. McLean and colleagues (25) found no association between cortisol and fatigue in patients with FMS. Riva and colleagues (26), assessing the ANS, found a negative association between physical (but not mental) fatigue and 24h epinephrine, as well as heart rate during stress provocation. The inconsistent findings might be due to short assessment periods (one and two days, respectively). An investigation of longer temporal periods is warranted in order to heighten the validity of conclusions. Further, Riva and colleagues did not account for within-day fluctuations of fatigue and used a controlled hospital-hotel setting, which might not be applicable to everyday life. In accordance with the findings of Riva and colleagues, there is research suggesting that measuring fatigue on

multiple dimensions is warranted in patients with FMS (27). However, most studies on FMS did not account for the multidimensional nature of fatigue. To the best of our knowledge, there have not been any studies investigating how the AAR (or sAA levels in general) relates to fatigue in FMS.

Everyday life physical activity is an important behavioral mechanism that might influence fatigue directly or indirectly, via alterations in HPA axis or ANS activity. Of the two studies using everyday life settings in FMS samples, one did not find objectively recorded physical activity levels to be predictive of subsequent momentary fatigue (28), and the other found negative associations of objectively recorded physical activity with subjects' estimates of their general and physical fatigue levels during the last three months (29). These findings seem to contradict laboratory findings and patient reports of symptom exacerbation due to enhanced physical activity (30). In a recent analysis, we found a negative association between physical activity and fatigue only under low chronic stress, and no association between physical activity and subsequent cortisol or sAA levels in a sample of healthy young adults (31). To our knowledge, no study so far has assessed the direct interplay between objectively measured daily physical activity, neuroendocrine activity, and fatigue in patients with FMS in an everyday life setting.

In sum, studies are needed that assess associations between HPA axis as well as ANS activity with fatigue a) in the everyday life of patients with FMS to ensure high ecological validity, b) over a sufficiently long period of time, c) using a design that is suitable for detecting within-individual as well as within-day and between-day changes, and d) measuring fatigue on different dimensions. In a sample of patients with FMS, we expect fatigue levels to be negatively predicted by HPA axis and physical activity but positively predicted by ANS activity. We also expect the physical activity – fatigue association to be mediated by HPA axis and ANS activity.

Method

Participants

The current analyses are based on a data from a sub-sample (excluding 4 persons with missing actigraphy data) of a larger study on psychobiological mechanisms in FMS. Previous findings in the whole sample have been reported in Fischer et al. (32) and Linnemann et al. (33). Data collection took place between March 2013 and August 2014. Participants were recruited via advertisement in local newspapers, information leaflets placed in practices of local general practitioners, rheumatologists, and in rheumatology clinics, and via self-help groups. Because of the influence of sex on biological markers and the higher prevalence of fibromyalgia as well as higher fatigue levels in women in general (34, 35), this study focused on female fibromyalgia patients. Further inclusion criteria were speaking German fluently, being between 18 and 65 years of age, and fulfilling the Fibromyalgia Research Criteria (36, questionnaires used see following sections). To rule out any other explanation of fatigue and due to their influences on neuroendocrine parameters, exclusion criteria were a BMI above 30kg/m², current pregnancy or breast-feeding, irregular menstrual cycle, working night shifts, current major depressive disorder, substance abuse within the last two years, eating disorder within the last five years, lifetime psychotic or bipolar disorder, and any unmedicated medical condition that affects endocrine or autonomic functioning (compare 16, 37). Participants received 80 EUR for taking part in the study. The study protocol was approved by the institutional review board of the Department of Psychology, University of Marburg, and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Study protocol

Eligible participants (as assessed during the telephone interview) were invited to the laboratory for an introductory session. During this session, baseline questionnaires (see following sections) were completed and participants were instructed in the use of a pre-programmed iPod touch®, in saliva sampling, and in how to wear the actigraph. Data collection took place over an assessment period of 14 days, with six time points of data entry each day (at awakening, 30 minutes later, at 11am, 2pm, 6pm, and 9pm) starting on the day after the introductory session. Each time point of assessment took about 4 minutes to complete (including saliva sampling). At each of these time points, participants answered several questions regarding their fatigue, pain, and stress level on the pre-programmed (iDialogPad App, momentary self-report data, G. Mutz, Cologne) iPod touch®, followed by a saliva sample. The saliva samples at awakening and 30 min after awakening were used to calculate the cortisol awakening response (CAR) and the alpha-amylase awakening response (AAR, see “biological measures”). After the 14-day ambulatory assessment period, participants returned the iPods, actigraphs, and saliva samples to the study personnel in a final laboratory session. In this session, they also answered some follow-up questions concerning compliance with and reactivity to the testing procedures.

Questionnaires

In accordance with the Fibromyalgia Research Criteria (36), the self-report measures *Widespread Pain Index* (WPI) as well as *Symptom Severity Score* (SSS) were used. The WPI measures in how many of 19 body areas participants experienced pain during the last three months. The SSS measures severity of fatigue, waking unrefreshed, and subjective cognitive impairment on a scale from 0 (“no problems”) to 3 (“severe problems”). Criteria were satisfied if the WPI was higher or equal to 7 pain sites and the SSS score was higher or equal to 5, or, alternatively, if the WPI was 3-6/19 and the SSS $\geq 9/12$.

The first two questions of the *Patient Health Questionnaire 9* (PHQ-9, 38) were used to exclude patients who currently met one or two of the two main criteria of a current depressive episode according to DSM IV (i.e. who had experienced depressed mood or anhedonia on more than half of the days during the past two weeks). WPI, SSS, and PHQ-9 were assessed during the telephone interview.

Participants completed detailed medical histories¹, gynecological histories, and a list of current medication, which had been mailed to them after initial screening via telephone. These documents were brought to the introductory session and checked for compatibility with eligibility criteria.

Momentary measures of fatigue and pain

To assess changes in fatigue in everyday life, participants rated their general, mental, and physical fatigue levels at each of the 6 time points on each day. Phrasing and scaling were based on items of the Multidimensional Fatigue Inventory (39) that represent the respective subscales general fatigue, mental fatigue, and physical fatigue (34) and re-phrased so as to refer to the present moment. The item “At the moment... I feel fatigued” was used to measure general fatigue. “At the moment...I can concentrate well” was measured as a sign of mental fatigue. “...I feel physically fit” was assessed to measure physical fatigue on a momentary basis. Each item was scaled from 0 (not at all) to 4 (very much) (40). Pain was assessed on a visual analog scale “At the moment, I am in this much pain:” from 0 (no pain) to 100 (worst imaginable pain).

Measures of stress

Chronic stress was assessed during the introductory session using the screening scale (SSCS) of the Trier Inventory for the Assessment of Chronic Stress (41). This scale consists of 12

¹ Of all the physical conditions assessed, thyroid dysfunction and high blood pressure emerged as significant predictors of general fatigue and were therefore included in the following statistical procedures.

items that measure the occurrence of various stress experiences within the last three months on a scale from 0 (“never”) to 4 (“very often”). Momentary stress levels were measured using the item “At the moment, I feel stressed out” from 0 (not at all) to 4 (very).

Control variables

Sleep quality had predictive value for general fatigue levels in one of our previous studies (42). Therefore, participants rated their sleep quality every morning at the first measurement time point using the item “How well did you sleep last night?” (on a visual analog scale from 0 to 100). The item was based on the sleep quality item of the Pittsburgh Sleep Quality Index (PSQI; 43). Further control questions concerned eating, drinking, and smoking behavior (“Did you eat/drink/smoke within the last two hours?”), as well as the intake of medication (“Since the last data entry, have you used additional medication for your pain?”), which were all measured and included in the pre-analyses to test for their influence on the outcomes dichotomously (0 “no”, 1 “yes”). However, as none of these variables had any significant influence on the outcomes, they were not included in the final models. The time of the first data entry each day was used as awakening time. “Time since awakening” (in minutes) was calculated to consider individual diurnal rhythms in our statistical analyses.

Biological measures

Saliva samples were collected using the SaliCap® system (IBL, Hamburg, Germany). Utilizing a visible countdown within the application, participants accumulated saliva in their mouths for two minutes and subsequently salivated into a pre-labeled polypropylene tube via a straw. As final step of each electronic assessment, participants entered the number of the specific plastic tube they used into the iPod. They were instructed to store saliva samples in their freezers or refrigerators and return them to the laboratory at the follow-up appointment, which was scheduled right after the collection period.

Biochemical analyses were conducted at the Biochemical Laboratory of the Department of Clinical Biopsychology, University of Marburg. Samples were kept frozen at -20°C , and on the day of analysis, thawed and centrifuged at $1620 \times g$ for 11 min. Salivary cortisol (sCort, 44) levels were measured using a commercially available enzyme-linked immunoassay (IBL, Hamburg, Germany). As a measure of ANS activity, salivary alpha-amylase (sAA, 22) was extracted from saliva samples using a kinetic colorimetric test and reagents from Roche (Roche Diagnostics, Mannheim, Germany). Inter- and intra-assay variance for both assays was below 10%. Awakening responses were calculated by subtracting the first from the “+30 min” - measurement time point. The CAR refers to a rise in cortisol within 30 to 45 minutes after awakening, while the AAR represents a decline within the same time frame (15, 22). We excluded “awakening” and “+30 min” samples that were collected more than 15 minutes from the instructed time points from analyses.

Actigraphy

For objective measurement of physical activity, participants wore a triaxial wrist actigraph (Somnowatch, Randersacker, Germany) on their non-dominant wrist recording movement counts for every 1-second interval continuously during the 14 days of data collection. Recordings started at 6am on the morning of the first day of measurement and the signal was sampled at 32 Hz with 12 Bit ADC. Participants were instructed to take off the actigraph when bathing, swimming, or taking a shower. As we were interested in everyday-life physical activity in these analyses, night recordings were excluded. The excluded time span was based on the awakening and sleeping times participants reported on their iPods at awakening. Movement counts were aggregated per minute (sum score). Time spans during which the actigraph had obviously not been worn (mean activity count $<10/\text{minute}$) were excluded from analyses. Finally, mean values of the movement sum scores between two measurement time points (awakening until 11am, 11am until 2pm, 2pm until 6pm, 6pm until 9pm, 9pm until

sleeping time – considering the actual time participants completed their iPod reports) as well as daily mean scores (awakening until sleeping time) were calculated.

Statistical procedure

As time points were nested within persons, we used hierarchical linear models for statistical analyses, using the HLM program (45). All χ^2 tests for the fatigue outcomes were statistically significant ($p < .001$); this indicates that there is variance in the outcomes by person, which justifies the use of hierarchical linear modeling. General fatigue, mental fatigue, physical fatigue, movement scores, sCort and sAA values, pain, and stress were considered as level-1 variables. At the person level (level 2), the intercept (β_0) was modeled as a function of BMI, thyroid dysfunction (yes/no), high blood pressure (yes/no), WPI score, and SSCS score. Age did not turn out to be a relevant predictor of any fatigue dimension in our analyses and was thus not included in the analyses. As we collected data at the level of time points within days as well as at a daily level, separate respective analyses were conducted. In these analyses, mean daily values of the different fatigue dimensions were used. As subjective sleep quality was measured once daily, it was included in the analyses at level 1 concerning daily measures and as person mean at level 2 for within-day analyses only. Further, time since awakening was included in within-day analyses at level 1 to account for diurnal patterns of biological parameters, fatigue, and physical activity. The abovementioned control variables were also checked for their influence on the respective outcome. As no association have been observed with outcome variables, they were not included in our final models. As a measure of effect size, we calculated “ $Pseudo-R^2 = (\sigma^2_{reference\ model} - \sigma^2_{final\ model}) / \sigma^2_{reference\ model}$ ”, where the reference model is the final model excluding the predictor in question (46). The compliance rate on level 1 was 96% (i.e. on average, participants responded to the iPod on 54 out of 56 occasions relevant for the analyses). Missing data were automatically listwise excluded per measurement time point per person by the HLM program. There were no

missing data regarding age, BMI, the PHQ-9, WPI, and SSS on level 2, because this information had been gathered by a research assistant during the screening interview and checked for completeness. Concerning the SSCS, missing data has been mean imputed (which concerned 3 values in the current sample).

Results

Thirty-two women completed the 14 days of assessment, of whom three did not wear actigraphs due to incompatibility with their jobs. Two further data sets had to be excluded because of technical difficulties with the App that was used to collect momentary self-report data, and one data set was excluded because of technical difficulties with the actigraph. Thus, the final sample for the current analyses comprised 26 FMS patients with a mean age of 53 (± 7) years. Most patients were living with a partner (i.e. married or in a stable relationship, 88.5%) and 57.8% of the participants worked at least part time, with the remaining participants being retired (23.1%), unemployed (11.5%), or on sick leave (7.7%). On average, 11 (± 4) pain sites, a symptom severity of 8 (± 2), and an illness duration of 10 (± 7) years were reported. Table 1 depicts momentary fatigue, pain, and stress mean values across the 14 days of assessment. The intraclass correlation (*ICC*) of general fatigue was 0.39 (mental fatigue: *ICC*=0.29, physical fatigue: *ICC*=0.15), indicating that 61% of the variance in general fatigue (71% in mental fatigue, 85% in physical fatigue) was explained at the level of time points. The course of fatigue dimensions and physical activity throughout the day (mean across 14 days of assessment) can be seen in Figure 1. As mental fatigue and physical fatigue were assessed in an inverted way (as subjective ability to concentrate and subjective physical fitness), positive unstandardized coefficients (UCs) indicate a negative association with the respective construct.

Pain and fatigue levels co-varied within participants, which was true for every fatigue dimension (general fatigue: *Pseudo-R*²=0.11; mental fatigue: *Pseudo-R*²=0.09, physical

fatigue: $Pseudo-R^2=0.13$, see Table 2). No association was found between momentary sCort value and levels of general fatigue or mental fatigue, but a positive association was found with physical fatigue (see Table 2, $Pseudo-R^2$ for physical fatigue: 0.02). This indicates that cortisol levels were higher when patients felt more physically fatigued. On a daily basis, CAR negatively predicted mean daily general fatigue ($UC=-0.01$, $t\text{-ratio}=-2.18$, $p=.039$, $Pseudo-R^2=0.05$) as well as mean daily physical fatigue ($UC=0.00$, $t\text{-ratio}=2.08$, $p=.048$, $Pseudo-R^2=0.05$), but was not associated with mean daily mental fatigue ($UC=-0.00$, $t\text{-ratio}=-0.10$, $p=.921$). SAA activity was neither associated with any fatigue dimension on a momentary basis (general fatigue: $UC=-0.00$, $t\text{-ratio}=-0.98$, $p=.338$, mental fatigue: $UC=0.00$, $t\text{-ratio}=0.43$, $p=.671$, physical fatigue: $UC=0.00$, $t\text{-ratio}=0.65$, $p=.522$), nor was there any association between AAR and any fatigue dimension on a daily basis (general fatigue: $UC=0.00$, $t\text{-ratio}=1.91$, $p=.067$; mental fatigue: $UC=-0.00$, $t\text{-ratio}=-0.51$, $p=.618$, physical fatigue: $UC=-0.00$, $t\text{-ratio}=-0.06$, $p=.952$).

There was no immediate effect of physical activity on any fatigue dimension (see Table 2) or on pain ($UC=0.01$, $t\text{-ratio}=0.617$, $p=.543$). However, physical fatigue negatively predicted subsequent physical activity ($UC=6.67$, $t\text{-ratio}=5.49$, $p<.001$, $Pseudo-R^2=0.04$). Neither general fatigue ($UC=-0.95$, $t\text{-ratio}=-1.28$, $p=.466$), nor mental fatigue ($UC=1.83$, $t\text{-ratio}=1.38$, $p=.179$), nor pain ($UC=0.06$, $t\text{-ratio}=0.99$, $p=.331$) was associated with subsequent physical activity. Results from analyses considering daily measures show that mean daily physical activity levels were associated with higher mean daily general fatigue levels the next day ($UC=0.00$, $t\text{-ratio}=2.35$, $p=.027$, $Pseudo-R^2=0.05$), and higher physical activity levels were associated with same-day higher stress levels ($UC=5.38$, $t\text{-ratio}=4.62$, $p<.001$, $Pseudo-R^2=0.05$). However, the interaction effect of mean daily stress x mean daily physical activity on next-day mean daily fatigue was not significant ($UC=0.00$, $t\text{-ratio}=1.29$, $p=.199$). Furthermore, neither momentary sCort ($UC=0.00$, $t\text{-ratio}=0.31$, $p=.759$) nor momentary sAA

values ($UC=-0.04$, $t\text{-ratio}=-0.52$, $p=.611$) were associated with physical activity since the last measurement time point. Additionally to table 2, which depicts complete models of momentary fatigue levels, complete models predicting same-day mean associations (including the daily effects of sleep quality) can be accessed in the online supplement.

As an association was found between mean daily physical activity and mean next-day general fatigue as well as between CAR and mean daily general fatigue, it seemed reasonable to expect a mediation of the physical activity – fatigue association by the CAR. However, physical activity did not turn out to be a predictor of next-day CAR ($UC=-0.00$, $t\text{-ratio}=-0.98$, $p=.339$), which is a violation of the 2nd requirement for mediation (47). Therefore, the CAR had to be ruled out as mediator between physical activity and fatigue. The predictive effect of mean physical activity on next-day mean general fatigue and the predictive effect of the CAR on mean general fatigue therefore seem to be independent of each other.

Discussion

We found that higher momentary cortisol values were associated with higher immediate physical fatigue in patients with FMS. Additionally, we found evidence that the CAR is a negative predictor of following general and physical fatigue. There was no immediate association between physical activity and any of the fatigue dimensions or pain measured on a momentary basis (within days). Mean physical activity level throughout the day, however, positively predicted mean daily general fatigue levels the next day. Neither the CAR nor momentary cortisol values were associated with physical activity. Moreover, there was no association between sAA (either momentary values or AAR) and any fatigue dimension or preceding physical activity.

The finding that a reduced CAR was intra-individually associated with higher fatigue symptoms during the remainder of the day complements research showing a reduced CAR in

FMS (20) or in other chronically fatigued populations (17). If we assume that the CAR reflects the regulatory capability of the HPA axis (15, 48), current results implicate that on days when this capability was reduced (i.e., a lower CAR was observed), the participants reported higher fatigue levels. This assumption is also interesting with regard to the discussion about the CAR reflecting a process of anticipating and preparing for the day's demands (16). In concert with the association of immediate cortisol values with physical fatigue, this implies that changes in daily HPA axis activity might indeed play an important role in symptom exacerbation in FMS. In contrast, we did not find an association between CAR and pain levels in a recent analysis of the same sample of patients with FMS (32). This may indicate a specific effect of changes in CAR on fatigue levels as opposed to pain.

The finding of a positive association between fatigue and cortisol on a momentary basis was unexpected and also, at first glance, seems to contradict research showing a relative hypocortisolism in FMS patients when compared to healthy populations. However, importantly, this study used a within-subject analysis approach, meaning that the finding indicates that the more an individual's cortisol value deviates from the person-mean (positive direction), the higher their fatigue level at that specific time point. The finding does *not* imply that FMS patients with higher cortisol levels have higher fatigue levels than those with lower cortisol levels (inter-individual comparison). Future studies will have to have a closer look into the association between cortisol levels and fatigue at a specific time point in populations with higher and lower mean HPA axis activity. For example, it has been suggested that the sensitivity of target cells (immune cells) towards cortisol decreases in the face of chronic stress (6), which would in turn explain possible differential effects of circulating cortisol.

To our knowledge, this is the first investigation of associations between sAA, a rather new marker of autonomic activity, and fatigue symptomatology in patients with FMS. However, our analyses did not show sAA to be a significant predictor of fatigue. Thus, our results imply

that diurnal autonomic activation is not associated with increases or decreases in daily fatigue in FMS, which constitutes a valuable addition to current research on the role of ANS activity in FMS symptomatology. Due to the multitude of possible settings, stress measures, and ANS markers, more research is needed to paint a clearer picture of ANS functioning in association with symptom exacerbation in FMS. Future studies will thus have to include markers of different aspects of the autonomic nervous system to achieve a more comprehensive view.

The null results of HPA or ANS activity being a mediator between physical activity and fatigue levels speak for an independence of the influence of HPA axis activity and physical activity on fatigue on a daily basis. However, this does not automatically imply that there are no long-term effects of physical activity on fatigue that are mediated or moderated by HPA axis or ANS activity. Long-term prospective studies which address these assumptions, combining everyday with laboratory assessments, are lacking.

Our results further suggest that everyday physical activity is not responsible for immediate symptom exacerbation in patients with FMS. On the other hand, our participants seemed to reduce their physical activity when feeling physically fatigued. This finding is in accordance with other studies in chronic pain patients, which showed a decrease in physical activity when higher fatigue was reported (28, 49). Additionally to these studies, our results suggest that the physical fatigue dimension is responsible for the effect on subsequent physical activity, which again underlines the importance of measuring fatigue multidimensionally. The null finding of an association between physical activity and mental fatigue is in line with another recent study (29). The fatigue-enhancing effect of previous-day physical activity must be interpreted in light of the fact that participants reported higher levels of stress on days with increased physical activity. It is therefore conceivable that increased physical activity reflected having a “busy day” as opposed to being physically active as part of leisure activities or exercise. However, as feeling stressed is not a direct measure of “busyness”, this interpretation remains

speculative. Nevertheless, from this perspective, our results do not contradict studies showing that patients with FMS benefit from exercise programs (for an overview see 50) or that physical activity is negatively associated with longer-term fatigue levels (29). Rather, our findings underline the fact that patients with FMS might find it hard to begin and adhere to exercise programs (e.g. 51) in view of physical fatigue experience. Future studies should compare leisure physical activity (or exercise) with everyday life physical activity in the context of work or other obligatory activities in terms of their influence on fatigue in FMS and follow up on the recovery.

Our findings show that different dimensions of fatigue are influenced by different biological and behavioral factors. Specifically, the physical dimension of fatigue was more strongly related to markers of the HPA axis, whereas mental fatigue was associated neither with CAR nor with momentary cortisol. Despite not being a perfect match with our design, Riva and colleagues (26) also found physical, but not mental, fatigue to be associated with urinary epinephrine levels. This implies that patients probably benefit most from interdisciplinary treatment approaches targeting biological and psychological aspects of fatigue. Clearly, more research is needed on this matter.

One major strength of our study is the high ecological validity due to its ambulatory assessment approach. The assessment period of 14 days with five measurements each day produced a sufficiently high number of observations, and enhances statistical power and reliability. Due to these multiple observations, we were able to detect within-individual as well as within-day and between-day associations. Another strength is the objective and continuous assessment of physical activity. Furthermore, analyses were controlled for various potential confounders such as sleep quality or time since awakening. On the other hand, internal validity is always a critical issue in studies using ambulatory assessment designs, because it cannot be completely ruled out that measures are influenced by unassessed

variables. While momentary assessment protocols offer the opportunity to examine prospective associations, they do not allow for a conclusion of general causality. Therefore, our promising finding of changes in HPA axis activity in the morning being associated with fatigue should now be complemented by studies with higher internal validity. Additionally, our sample size of 26 might have led to an underestimation of random effects (52). A sample size of about 20-30 is, however, well within the range of other studies on patients with FMS using similar designs, whereas a study period of 14 days (resulting in a large sample size at level 1) exceeds those of most comparable studies (e.g. 28, 53, 54). Given that we additionally exclusively interpret fixed effects referring to level-1 variables, we are confident about the validity of our findings. Excluding male patients with FMS as well as FMS patients who met the main criteria of a major depressive episode reduced the representativeness of our sample. Specifically the latter might also have reduced the variance in inter-individual cortisol levels (as depression was found to be associated with higher cortisol levels (55)). However, doing so allowed us to study the relationships between fatigue, physical activity, and HPA activity in FMS while at the same time ensuring that none of our results were attributable to the confounding influence of sex or depression.

In sum, we showed that HPA axis activity plays a critical role in fatigue experienced by patients with FMS during their normal daily living. ANS activity did not turn out to be a predictor of any fatigue dimension on a momentary or a daily basis. Furthermore, everyday life physical activity had no immediate effect on fatigue or pain exacerbation. The effects of HPA axis functioning and physical activity were independent of each other (concerning their influence on each other as well as on fatigue). Moreover, the physical fatigue dimension appeared to be more strongly associated with HPA axis functioning, whereas mental fatigue was not. Thus, our recommendation is to include different dimensions of fatigue in future studies, which ideally combine different levels of observation (subjective, behavioral,

biological) in a long-term longitudinal design using both ambulatory and laboratory assessment strategies. Health care professionals should now consider the role of physical fatigue when trying to enhance physical activity in patients with FMS.

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All authors have completed the Unified Competing Interest form and declare that they have no competing interests to report.

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Figure legend

Fig. 1 Daily profiles of physical activity (upper left), general fatigue (upper right), mental fatigue (lower left), and physical fatigue (lower right) averaged across 14 days of measurement (mean $\pm$ standard error of mean), N = 26, general, mental, and physical fatigue were assessed on a scale from 0 (not at all) to 4 (very much).

Table 1

Descriptive analyses of relevant parameters

	<i>M (±SD)</i>
At the moment...	
... I am in this much pain (0-100)	49.59 (±24.79)
... I feel fatigued (0-4)	2.21 (0.98)
... I can concentrate well (0-4)	1.99 (0.74)
... I feel physically fit (0-4)	1.64 (0.80)
... I feel stressed out (0-4)	1.48 (1.04)
“How well did you sleep last night?”	66.02 (23.38)

Note. Mean and standard errors of the items at four measurement time points per day (11am, 2pm, 6pm, 9pm) over 14 days, sleep quality was reported at awakening once daily

Table 2

Hierarchical linear models predicting momentary general, mental, and physical fatigue (N=26) using restricted maximum likelihood.

Outcome	General fatigue			Mental fatigue			Physical fatigue		
fixed effects	<i>UC</i>	<i>SE</i>	<i>t-ratio</i>	<i>UC</i>	<i>SE</i>	<i>t-ratio</i>	<i>UC</i>	<i>SE</i>	<i>t-ratio</i>
intercept	1.98	0.12	16.36***	2.24	0.13	17.43***	2.05	0.13	15.21***
level 2									
• Sleep quality (person mean)	0.00	0.01	0.14	0.01	0.01	1.69	0.00	0.00	0.25
• BMI	0.07	0.02	3.27**	0.03	0.02	1.63	-0.03	0.02	-1.71
• SSCS	0.03	0.01	2.65*	0.01	0.01	0.99	-0.00	0.01	-0.05
• WPI	0.05	0.02	2.59*	-0.02	0.03	-0.64	0.00	0.01	0.26
• Thyroid dysfunction	-0.43	0.13	-3.32**	-0.08	0.15	-0.44	0.03	0.11	0.30
• High blood pressure	0.86	0.12	6.97***	-0.08	0.12	-0.67	0.05	0.25	0.21
level 1									
• time since awakening	0.00	0.00	3.33***	-0.00	0.00	-3.61***	-0.00	0.00	-5.23***
• momentary pain	0.01	0.00	5.65***	-0.01	0.00	-6.86***	-0.02	0.00	-7.78***

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• momentary stress	0.26	0.05	5.30***	-0.12	0.02	-4.70***	-0.01	0.03	-0.29
• momentary cortisol value	-0.00	0.00	-0.03	-0.01	0.00	-1.89	-0.01	0.01	-2.73*
• physical activity 2-3 hours before measurement	0.00	0.00	0.22	-0.00	0.00	-1.39	-0.00	0.00	-0.88
random effects	<i>SD</i>	<i>VC</i>	χ^2	<i>SD</i>	<i>VC</i>	χ^2	<i>SD</i>	<i>VC</i>	χ^2
Intercept	0.39	0.15	423.97***	0.45	0.20	664.42***	0.37	0.14	391.45***
momentary pain	0.01	0.00	75.29***	0.01	0.00	45.91**	0.01	0.00	50.49**
momentary stress	0.22	0.05	130.49***	0.09	0.01	48.46**	0.11	0.01	47.71**
momentary cortisol level	0.02	0.00	45.59**	0.01	0.00	41.94*	0.02	0.00	48.07**
physical activity	0.00	0.00	26.31	0.00	0.00	29.59	0.00	0.00	21.55

Note. *UC*: unstandardized coefficients, *SE*= standard error, *SD* = standard deviation, *VC* = Variance Component, *SSCS* = Screening Scale for Chronic Stress – Subscale of the Trier Inventory for Chronic Stress, *WPI* = Widespread Pain Index, *CAR* = cortisol awakening response; *** $p < .001$, ** $p < .01$, * $p < .05$, for general fatigue, higher values imply a higher level of the construct (a positive association implies an increase in

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general fatigue with an increase in the respective predictor); for mental and physical fatigue, higher values imply a lower level of the construct (a positive association implies an increase in mental or physical fatigue with a decrease in the respective predictor)

Table(s)

Stress systems, physical activity and fatigue in FMS – online supplement daily associations

Stress systems, physical activity and fatigue in FMS – online supplement daily associations

random effects	<i>SD</i>	<i>VC</i>	χ^2	<i>SD</i>	<i>VC</i>	χ^2	<i>SD</i>	<i>VC</i>	χ^2
Intercept	0.37	0.14	359.70***	0.45	0.21	575.75***	0.32	0.10	290.89***
average same-day pain	0.01	0.00	35.38	0.00	0.00	24.36	0.01	0.00	66.85***
sleep quality	0.00	0.00	34.75	0.00	0.00	25.08	0.00	0.00	37.68*
CAR	0.01	0.00	37.05	0.00	0.00	20.78	0.01	0.00	24.67
average same-day physical activity	0.01	0.00	39.03*	0.00	0.00	18.42	0.00	0.00	25.38

Note. *UC*: unstandardized coefficients, *SE*= standard error, *SD* = standard deviation, *VC* = Variance Component, *SSCS* = Screening Scale for Chronic Stress – Subscale of the Trier Inventory for Chronic Stress, *WPI* = Widespread Pain Index, *CAR* = cortisol awakening response; *** $p < .001$, ** $p < .01$, * $p < .05$, for general fatigue, higher values imply a higher level of the construct (a positive association implies an increase in general fatigue with an increase in the respective predictor); for mental and physical fatigue, higher values imply a lower level of the construct (a positive association implies an increase in mental or physical fatigue with a decrease in the respective predictor)

Figure(s)