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Stress exacerbates pain in the everyday lives of women with fibromyalgia syndrome—The role of cortisol and alpha-amylase

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ABSTRACT

Objective: Although fibromyalgia syndrome (FMS) is a chronic condition, its cardinal symptom pain is known to fluctuate over the day. Stress has often been claimed to exacerbate pain; however, there is barely any evidence on whether or not this is true on a day-to-day basis (and, alternatively, on whether pain leads to increased stress levels). Using an ecologically valid measurement design, we tested whether and how stress and pain are intertwined in participants with FMS. We additionally examined the role of the two major stress-responsive systems, the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, as potential mediators of this relationship.
Methods: An ambulatory assessment study was conducted over the course of 14 days. On each day, 32 females with FMS provided six diary entries on momentary stress and pain levels. Saliva samples were collected at the same time points to determine cortisol and alpha-amylase as indicators of stress-responsive systems.
Results: Higher stress at a given measurement time point was associated with higher reported pain levels at the subsequent time point (UC = 1.47, $p < 0.001$), but not vice versa (UC < 0.01, $p = 0.179$). The stress-pain relationship was neither mediated by momentary cortisol nor by alpha-amylase; however, momentary cortisol was independently associated with momentary pain (UC = 0.27, $p = 0.009$).
Conclusion: Stress seems to be a powerful exacerbating factor for pain as experienced by patients with FMS in their everyday lives. Cortisol may be involved in the diurnal fluctuation of pain levels in patients with FMS. Future studies should identify relevant daily stressors in persons with FMS and scrutinize the mechanisms underlying the cortisol-pain relationship.

1. Introduction

Fibromyalgia syndrome (FMS) refers to widespread pain of more than three months duration that cannot be sufficiently explained by any medical condition. According to the American College of Rheumatology (ACR) 2010 diagnostic criteria, a number of ancillary symptoms, such as fatigue, waking unrefreshed, and cognitive symptoms often occur in patients (Wolfe et al., 2010). Prevalence rates range from 2.1% to 5.3% in the general population, with a female preponderance regarding symptom severity (Vincent et al., 2013; Wolfe et al., 2013). The course of FMS is mostly chronic, with a minority of patients reporting symptom improvements over time (Noller and Sprott, 2003; Walitt et al., 2011).

Given the typically chronic course of FMS, it is imperative to identify the mechanisms underlying its perpetuation. Although generally stable, symptoms of FMS are known to show diurnal variation (Harris et al., 2005). In a subgroup of patients with high pain sensitivity, on average, a decline in pain levels was observed from 11 a.m. until the end of each day (Bellamy et al., 2004). However, symptom fluctuations are mostly perceived as unpredictable by the individual patient, leaving him/her in emotional distress and incapable of engaging in his/her daily routine (Dennis et al., 2013). Moreover, the planning of daily activities is severely hampered by the fact that the triggers for symptom flares often remain obscure (Arnold et al., 2008). The question thus arises of what fac-

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tors underlie the experience of symptom exacerbation in patients with FMS.

In the past, a case has been made that stress may be an important perpetuating factor in FMS (Nater et al., 2011). As far as empirical evidence is concerned, a plethora of cross-sectional studies have used questionnaires measuring chronic stress or daily hassles in patients with FMS. In these studies, the magnitude of self-reported stress was linked to pain severity and/or functional impairment (Alok et al., 2011; Dailey et al., 1990; Murray et al., 2007; Smith et al., 2010). These findings suggest that stress can indeed exacerbate symptoms in patients with FMS. However, the validity of these findings may be questioned, since a peak-and-end bias in the retrospective reporting of symptoms has been discussed in the pain literature (Schneider et al., 2011), meaning that reports are influenced by the most intense and recent pain experience. Moreover, the generalizability of single-occasion measurements in a survey or in the laboratory to real-life processes is limited.

In order to answer the question of whether stress exacerbates symptoms of FMS, it is necessary to measure pain close in time to the actual experience in a repeated, ecologically valid manner. Ambulatory assessment approaches offer the possibility to address all of these issues simultaneously (Trull and Ebner-Priemer, 2013). With regard to FMS, only one study has approached this question using such a design (Hazlett and Haynes, 1992), and found no association between stress and pain experience. However, as this study used aggregated stress and pain scores, it might be argued that a potential relationship was overlooked due to information loss as a consequence of data aggregation. Thus, the question of how stress possibly translates into the experience of more intense pain over the day in patients with FMS remains unanswered.

The two major stress-responsive systems, i.e. the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), might be involved in this process. Dysregulations in both systems have been hypothesized to contribute to core symptoms of FMS. At the central level, blunted corticotropin-releasing hormone and locus coeruleus/norepinephrine-sympathetic systems are known to interact, and to enhance pain via descending analgesic pathways (Clauw and Chrousos, 1997). Evidence has accumulated that patients with FMS are characterized by a hypocortisolemic state (Fries et al., 2005). In terms of the SNS, findings generally point to elevated sympathetic activity and attenuated reactivity in patients with FMS (Martinez-Lavin, 2004). Importantly, both cortisol and catecholamines regulate central and peripheral processes involved in pain sensation, including inflammation (Irwin, 2011).

However, although widely assumed in theory, there is barely any empirical evidence that both systems operate as exacerbating factors of pain in FMS, at least not on a momentary basis. In fact, only one ambulatory assessment study has examined the relationship between concurrent cortisol activity and pain intensity (McLean et al., 2005), and reported a positive association within the first hour of awakening, but not later during the day. However, although this study provided valuable insights, the measurement period was rather short (two days).

Taken together, a detailed characterization of the proposed role of stress as an exacerbating factor of pain in real life is missing in FMS research. Moreover, while there is ample evidence of a general dysregulation of the HPA axis and SNS in FMS, almost nothing is known about the role of these systems in the daily fluctuations of pain levels.

Therefore, the first aim of the presented study was to examine the relationship between stress and pain in the everyday lives of persons with FMS. More specifically, we assumed that increases in stress would predict increases in pain. However, since high pain levels may themselves act as a stressor in persons with FMS, we additionally tested whether increases in pain preceded increases in stress levels. Secondly, we were interested in examining the role of biological stress markers as mediators of these prospective associations. Based on the aforementioned evidence, we expected that (1a) momentary stress would predict momentary pain, (1b) stress reported at the previous measurement time point would predict momentary pain, and vice versa, (1c), previous-day mean stress levels would predict subsequent mean daily pain levels, and vice versa, and (2) momentary and daily activity of the HPA axis and SNS would mediate these assumed associations.

Although a female preponderance regarding FMS is not substantiated by more recent epidemiological studies, the severity of symptoms seems to be more pronounced in women, which is why we decided to only include women in our study. By excluding men, we also eliminated several potentially confounding factors that need to be considered in a mixed sample, such as sex differences in the stress-cortisol relationship and in pain perception (Hashmi and Davis, 2014; Kudielka et al., 2009). As it is not feasible to assess central parts of the HPA axis and SNS in an ambulatory assessment study, we measured salivary cortisol and alpha-amylase (sAA; Ditzen et al., 2014) as easily accessible end products of these systems. The latter is an enzyme that is involved in the digestion of starch and can be used as a surrogate marker of the autonomic nervous system (Nater and Rohleder, 2009).

2. Material and methods

2.1. Participants

Potential participants were recruited via advertisements in newspapers, through flyers posted in the practices of general physicians and rheumatologists, and via self-help groups[1]. Persons were included if they were female, fluent in German, and between 18 and 65 years of age. In addition, all participants needed to fulfill the Fibromyalgia Research Criteria (Wolfe et al., 2011), a modified version of the ACR 2010 diagnostic criteria (Wolfe et al., 2010; see below). Exclusion criteria were body mass index (BMI) above 30 kg/m^2; pregnancy, breast feeding, or irregular menstrual cycle, current episode of major depression, any major psychiatric disorder (substance abuse within the past two years, lifetime psychotic or bipolar disorder, eating disorder within the past five years), and any unmedicated medical condition known to affect endocrine or autonomic functioning. We chose to exclude participants suffering from major depressive disorder, as the opposing pattern of HPA axis abnormalities (hypercortisolism in major depression vs. hypocortisolism in FMS) may confound a potential relationship between cortisol and pain levels (Riva et al., 2010; Stetler and Miller, 2011). The total sample consisted of 32 women. Each received 80 Euro for participation. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Department of Psychology, University of Marburg, Germany). All participants provided written informed consent.

2.2. Study protocol

An ambulatory assessment design was used. Participants were pre-screened for eligibility via telephone and informed about the study aims and procedures. Eligibility was confirmed during an initial study appointment, during which several questionnaires were administered. Participants were then instructed on how to handle an electronic diary device (iPod touch®) to answer several questions at six prompts throughout the day (upon awakening, +30 min, 11 am, 2 pm, 6 pm, 9 pm). Similarly, they were trained in the collection of saliva samples, which had to be collected immediately

[1] The same data set has been used in a report investigating the effects of music listening on stress and pain: (Linnemann et al., 2015).