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# Linking disease symptoms and subtypes with personalized systems-based phenotypes: A proof of concept study ☆

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ABSTRACT

A dynamic systems model was used to generate parameters describing a phenotype of Hypothalamic–Pituitary–Adrenal (HPA) behavior in a sample of 36 patients with chronic fatigue syndrome (CFS) and/or fibromyalgia (FM) and 36 case-matched healthy controls. Altered neuroendocrine function, particularly in relation to somatic symptoms and poor sleep quality, may contribute to the pathophysiology of these disorders. Blood plasma was assayed for cortisol and ACTH every 10 min for 24 h. The dynamic model was specified with an ordinary differential equation using three parameters: (1) ACTH-adrenal signaling, (2) inhibitory feedback, and (3) non-ACTH influences. The model was "personalized" by estimating an individualized set of parameters from each participant's data. Day and nighttime parameters were assessed separately. Two nocturnal parameters (ACTH-adrenal signaling and inhibitory feedback) significantly differentiated the two patient subgroups ("fatigue-predominant" patients with CFS only versus "pain-predominant" patients with FM and comorbid chronic fatigue) from controls (all $p$'s < .05), whereas daytime parameters and diurnal/nocturnal slopes did not. The same nocturnal parameters were significantly associated with somatic symptoms among patients ($p$'s < .05). There was a significantly different pattern of association between nocturnal non-ACTH influences and sleep quality among patients versus controls ($p$ < .05). Although speculative, the finding that patient somatic symptoms decreased when more cortisol was produced per unit ACTH, is consistent with cortisol's anti-inflammatory and sleep-modulatory effects. Patients' HPA systems may compensate by promoting more rapid or sustained cortisol production. Mapping "behavioral phenotypes" of stress–arousal systems onto symptom clusters may help disentangle the pathophysiology of complex disorders with frequent comorbidity.



## 1. Introduction

In medical research a fundamental shift is underway to redefine disease taxonomies, moving from descriptive categories based on "signs and symptoms" to a new framework that explains disease symptoms within the context of underlying molecular and environmental causes (National Research Council, 2011). At the core of this endeavor is the need for novel bioinformatic approaches that help link symptom clusters with phenotypes (arising from the interplay of genetic and environmental causes). This approach may be particularly important in understanding diseases, such as functional somatic disorders or psychosomatic conditions, in which the biological etiology is poorly understood, and psychosocial factors play a role in precipitating or perpetuating the disease process. The primary aim of this study is to conduct a "proof of concept" investigation of whether a phenotype of stress-arousal system behavior will provide novel insights into disease symptoms and subtypes among patients with fibromyalgia (FM) and/or chronic fatigue disorder (CFS).

Altered Hypothalamic–Pituitary–Adrenal (HPA) system function may be an important contributing mechanism in the onset or maintenance of FM, CFS and psychosomatic conditions (i.e., disorders caused or aggravated by stress and psychological distress). Existing paradigms for quantifying and understanding the role of the HPA has yielded an inconsistent body of literature

☆ Please see Brief Commentary by Gordon Broderick found on page 1045 of this issue.

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(Miller et al., 2007; Tanriverdi et al., 2007), making it difficult to translate these findings into improvements in clinical care. This may reflect the fact that the HPA is a dynamic feedback-regulated system, which is often modeled with statistics poorly equipped to characterize reciprocal regulatory control as it occurs dynamically.

CFS and FM are debilitating and costly disorders characterized by "medically unexplained symptoms" (Aaron et al., 2000). They are associated with "a loss of HPA axis resiliency" (Crofford et al., 2004) and altered HPA dynamics following pharmacological challenge (Tanriverdi et al., 2007; Van Den Eede et al., 2007); however, the nature of the alterations is inconsistent across studies (Tanriverdi et al., 2007). Moreover, the extent to which HPA function differs in CFS versus FM is unclear. On the one hand, CFS and FM are highly comorbid (Aaron et al., 2000), suggesting some common pathophysiological mechanisms. On the other, genetic studies suggest that it may be useful to differentiate pain-predominant syndromes (i.e., FM with or without comorbid fatigue) from fatigue-predominant ones (i.e., CFS without FM)(Geenen and Bijlsma, 2010; Kato et al., 2009). Moreover, as pain can disturb sleep, fatigue could reflect a different etiology in FM (Geenen and Bijlsma, 2010). Negative feedback sensitivity of the HPA is generally heightened in CFS (Jerjes et al., 2007; Van Den Eede et al., 2007) but blunted in FM (Lentjes et al., 1997), which leaves the expected HPA profile associated with comorbidity uncertain. Hence, a model of HPA system behavior that can be fitted to a given individual regardless of comorbidity could potentially provide a platform for personalized treatment.

Somatic symptoms and sleep disturbance are core symptoms of CFS and FM, which are also related to HPA function and the role of cortisol as a stress-responsive and anti-inflammatory hormone. The onset of functional disorders is often preceded by psychological stress or infection (Theorell et al., 1999), and early adversity may also increase risk (Heim et al., 2009). Sleep disturbance is a core symptom of FM. For example, one US study of 500 FM patients reported that 95% of the sample reported poor sleep, which predicted pain (Bigatti et al., 2008). Both stress and poor sleep have reciprocal relations with HPA and pro-inflammatory activity (Adam et al., 2006; Irwin and Cole, 2011; Zeiders et al., 2011). One theory is that FM and CFS are associated with an immunologic disturbance (Moldofsky, 1995; Patarca-Montero et al., 2001). Cytokines can cause neuroinflammation and "sickness behaviors" that closely resemble the kinds of somatic symptoms reported by patients with functional somatic disorders, such as fatigue, concentration difficulties, enhanced pain sensitivity and mood symptoms (Dantzer and Kelley, 2007). Cytokines can also modulate glucocorticoid receptor phosphorylation, potentially leading to longer-lasting changes in the HPA signaling dynamics and function (Pace et al., 2007). Cortisol is a powerful anti-inflammatory hormone; hence, in theory, if its inhibitory feedback signaling via the glucocorticoid receptor were impaired, this could potentially act as a permissive or perpetuating factor that could amplify reciprocal effects among stress, sleep behaviors and inflammatory activity.

Allostasis, a leading theoretical model of physiological regulation, can be defined as *the optimization of system dynamics to facilitate adaptive functional responses to a certain context* (Boyce and Ellis, 2005; Kitano, 2007; Sterling, 2011). A canonical principle of system function is that there are crucial trade-offs between responsiveness and robustness (i.e., maintaining function despite perturbation)(Kitano, 2007), which are shaped in part by the system parameters (Kitano, 2007). An HPA system with a "high steady state gain" – e.g., characterized by heightened cortisol responses to ACTH and/or blunted feedback control – can generate more rapid or sustained cortisol responses. Henceforth, we will refer to this theoretical pattern of allostatic optimization as the "high sensitivity phenotype." In theory, a high sensitivity phenotype would facilitate faster or more sustained cortisol responses to stressors or mitogen stimulation, which could help counter-balance excess neuroinflammatory activity. However, as optimization comes with robustness trade-offs, the highly sensitive phenotype would also be more volatile and vulnerable to intense or unanticipated psychological or immunological stressors (Carlson and Doyle, 2000).

To better evaluate the utility and added insights of the proposed dynamic systems model and high sensitivity phenotype, it is important to have an appropriate comparison model. Frequently used measures are the cortisol awakening response (CAR – the rapid increase in cortisol over 30 min post-awakening) and the diurnal (or nocturnal) slope (i.e., the change from awakening to the evening nadir) (Adam et al., 2006; Sephton et al., 2000). These measures quantify circadian rhythms, which help the body meet changing demands throughout the day for neurocognitive alertness and immune cell trafficking (Sephton et al., 2000); however, the slope method does not quantify faster dynamics occurring over the time-course of minutes to hours.

This study represents a "proof of concept" intended to investigate the feasibility and utility of (1) quantifying a high-sensitivity "system behavioral phenotype" of a key stress–arousal system, the HPA axis, (2) relating this phenotype to disease symptoms, and (3) investigating whether the phenotype reveals disease subtypes within a heterogenous patient sample with chronic fatigue syndrome (CFS) and/or fibromyalgia (FM). Hence, the primary thrust of this work is not based in the specifics of the HPA axis, the mathematical model or the patient population *per se*, but rather in exploring a potentially important and novel method relevant to refining the taxonomy of diseases with complex biological and environmental origins. This is the first study to explore whether a personalized system behavioral phenotype of HPA activity relates to health.

## 2. Methods and materials

### 2.1. Participants

This study represents a secondary analysis of published data from a larger study (Crofford et al., 2004) focused on HPA function as the primary outcome. Forty individuals with FM, CFS, or both disorders and 40 healthy controls, individually matched for gender, menstrual status, and age within four years, were recruited from rheumatology, infectious disease or primary care outpatient clinics at the University of Michigan Medical Center. In addition, control subjects were sedentary as defined by no regular exercise for a minimum of 2 months prior to the study. ACTH data and/or blood draws could not be completed for four participants, leaving complete data available for 36 matched patient–control pairs ($n = 72$). All diagnoses were made using the 1990 American College of Rheumatology and the 1994 Center for Disease Control and Prevention criteria. Patients were interviewed by a single physician and final diagnoses were completed by a team of three physicians who reviewed the physical exam data and medical history. Patients with Major Depressive Disorder (MDD) were excluded. Of the 36 patients with complete ACTH and cortisol data available, 14 individuals met criteria for CFS (by both the 1998 and 1994 definitions), and did not meet criteria for FM. The remaining 22 participants were considered *pain-predominant*, because they all met criteria for FM, and 19 additionally met criteria for the more recent 1994 case-definition of CFS. As this study is focused on the potential use of the phenotype to help redefine disease taxonomies, we elected to examine symptoms across the whole patient sample, and then examine whether the phenotype differed between subgroups based on predominant symptom profiles, which differs from the approach taken in prior published work from this study (Crofford et al., 2004). In that study, the FM group was complicated