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# Stress Management Skills, Cortisol Awakening Response and Post-Exertional Malaise in Chronic Fatigue Syndrome

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## Abstract

Chronic Fatigue Syndrome (CFS) is characterized in part by debilitating fatigue typically exacerbated by cognitive and/or physical exertion, referred to as post-exertional malaise (PEM). In a variety of populations, the cortisol awakening response (CAR) has stood out as a marker of endocrine dysregulation relevant to the experience of fatigue, and may therefore be particularly relevant in CFS. This is the first study to examine PEM and the CAR in a sample of individuals with CFS. The CAR has also been established as a stress-sensitive measure of HPA axis functioning. It follows that better management of stress could modulate the CAR, and in turn PEM. In this cross-sectional study, we hypothesized that greater perceived stress management skills (PSMS) would relate to lower reports of PEM, via the impact of PSMS on the CAR. A total of 117 adults (72% female) with a CFS diagnosis completed self-report measures of PSMS and PEM symptomatology and a two-day protocol of saliva collection. Cortisol values from awakening and 30 minutes post-awakening were used to compute the CAR. Regression analyses revealed that greater PSMS related to greater CAR and greater CAR related to less PEM severity. Bootstrapped analyses revealed an indirect effect of PSMS on PEM via the CAR, such that greater PSMS related to less PEM, via a greater CAR. Future research should examine these trends longitudinally and whether interventions directed at improving stress management skills are accompanied by improved cortisol regulation and less PEM in individuals with CFS.

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COI All authors declare that they have no conflicts of interest.

Contributors Daniel Hall and Emily Lattie managed the literature searches, statistical analyses, and wrote the first draft of the manuscript. Michael Antoni, Sara Czaja, Nancy Klimas, and Mary Ann Fletcher designed the study and wrote the original protocol. Dolores Perdomo assisted in study recruitment and management, and assisted with the literature searches. All authors contributed to and have approved the final manuscript.

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### Keywords

Cortisol; Chronic Fatigue Syndrome; Stress Management; HPA Axis

Chronic Fatigue Syndrome (CFS) is a poorly understood medical condition, characterized in part by profound chronic fatigue as well as an acute increase in fatigue following exertion, referred to as post-exertional malaise (PEM). Given the paucity of effective treatments for CFS, there is an ongoing search for potential intervention targets based on the limited understanding of the mechanisms that govern symptom expression. One plausible target is neuroendocrine regulation, which can be reflected in patterns of cortisol secretion from the hypothalamic pituitary adrenal (HPA) axis. Patients with CFS are known to show a pattern of hypocorticolism, accompanied by an attenuated cortisol awakening response (CAR; Powell et al., 2013). Results of two recent meta-analyses found that, of measures of cortisol dysregulation, the CAR is most relevant to the experience of fatigue, including greater burnout and exhaustion, and may therefore be particularly relevant in CFS (Chida and Steptoe, 2009; Powell et al., 2013). To date, less attention has been paid to relationships between cortisol dysregulation and PEM. Whether an attenuated CAR relates to greater PEM in the context of CFS remains untested. This study fills that gap in the literature by examining the relationship between the CAR and PEM in patients presenting with CFS.

Importantly, PEM may be distally influenced by a variety of psychosocial factors such as stress and negative mood (Lutgendorf et al., 1995; Morris & Maes, 2013). Conversely, having greater perceived stress management skills (PSMS), may relate to less PEM since PSMS has been related to less fatigue in CFS patients in prior work (Lattie et al., 2012). Taken together, it is plausible that one's perceived ability to manage stress (PSMS) may influence symptoms such as PEM by modulating one's CAR, reflecting HPA-axis re-regulation. The present study thus examined the associations among PSMS, CAR and PEM in persons diagnosed with CFS. We also examined the indirect relationship between PSMS and reports of PEM, via the CAR. It was hypothesized that higher PSMS would relate to lower reports of PEM, via the impact of PSMS on the CAR.

## Methods

### Participants and Procedures

Participants in the present study were recruited for a larger study of stress and coping processes in persons with CFS. Preliminary findings from this study have been published elsewhere (Lattie et al., 2012). Participants were recruited via physician referral, support groups and special events including local CFS conferences, as well as via advertisements on CFS-related websites. In order to be eligible, participants were required to have a physician-determined CFS diagnosis according to the Centers for Disease Control and Prevention (CDC) criteria (Fukuda et al., 1994), to be fluent in English, live within the study area, have an active home telephone line, and be between the ages of 21 and 75 years.

Potential participants could be excluded for cognitive impairment or if they met criteria for schizophrenia, bipolar disorder, or substance abuse, or were actively suicidal. The Short

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Portable Mental Status Questionnaire (Pfeiffer, 1975) was used to determine marked cognitive impairment and participants were excluded if they demonstrated diminished cognitive capabilities, as indicated by having made four or more errors on this measure. Potential psychiatric exclusions were assessed using a brief screening (First et al., 2002) adapted from the Structured Clinical Interview for the DSM-IV (American Psychological Association, 2000). Participants were also excluded for the presence of a medical condition (e.g., AIDS, lupus, rheumatoid arthritis) that would influence biological processes associated with CFS symptomology, or if they endorsed taking medications that could modulate immune and neuroendocrine functioning.

Eligible participants signed an informed consent form and were scheduled for a home visit by a study staff member. During the home visit, the study staff member administered a battery of measures regarding psychosocial status and CFS symptoms and provided the participant with 8 Salivette® tubes. Participants provided saliva samples from two consecutive weekdays within one week of the home visit. For each of the collection days, participants were asked to take a sample upon awakening, 30 minutes after awakening, at 4 pm and at 9 pm. Participants were also asked to self-report the time of sampling on the label of each salivette. Participants were instructed to abstain from eating or drinking before and between the first two samples each day, and to avoid eating a large meal an hour before the afternoon and evening samples. Participants were also asked to avoid alcohol for at least 12 hours prior to sample collection and to avoid vigorous exercise on sample collection days. Following the collection of samples, participants were instructed to freeze the Salivette® tubes in their home freezers in order to keep the salivary cortisol stable until it was retrieved by a member of the study staff. The present study only focused on the awakening and 30 minutes post-awakening saliva samples.

## Measures

**Perceived stress management skills (PSMS)—**The Measure of Current Status (MOCS; Carver, 2006) was used to assess PSMS. Items on the MOCS are based on personal characteristics and behaviors that are associated with efficient stress management abilities, such as “I am able to use mental imagery to reduce any tension I experience” and “I can clearly express my needs to other people who are important to me.” Participants were asked to rate their perceived ability to appropriately respond to challenges and demands of daily life on a 5 point scale which ranged from “1 - I cannot do this at all” to “5 – I can do this extremely well.” The 17 items on the MOCS were summed to compose an overall stress management skill measure, with higher scores indicating greater PSMS (Penedo et al., 2006). In the present sample, the MOCS demonstrated a high degree of internal consistency (Cronbach’s $\alpha = .85$).

**Post-exertional malaise (PEM)—**The PEM item from the CDC CFS Symptom Inventory (Wagner et al., 2005) was used to measure PEM symptoms over the past month. Participants were asked to rate on two separate five point scales the frequency (“1 – A Little of the Time” to “5 – All of the Time”) and intensity (“1 – Very Mild” to “5 – Very Severe”) of “Unusual fatigue following exertion that lasts for at least 24 hours”. The frequency and

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intensity scores were then multiplied to create the PEM severity score. If PEM was not endorsed, a PEM score was entered as 0.

**Perceived Stress—**The Perceived Stress Scale (PSS; Cohen et al., 1983) was used to measure participants' perceived life stress. The PSS consists of 14 items on a four point scale ("0 – Never" to "4 – Very Often") which ask the rater to indicate the frequency with which they have experienced aspects of emotional stress. Items were summed to create a total score, and had high internal consistency (Cronbach's $\alpha = .87$). The PSS was used in the present study to provide validation that greater PSMS was indeed associated with less perceptions of stress over the past 4 weeks.

**Salivary Cortisol—**After being retrieved from participants by a member of the study staff, saliva samples were frozen at −20°C until enough samples were accumulated to be assayed in batches. On the day of the assay, saliva samples were thawed, vortexed and centrifuged at 1500 RPM for 15 minutes. Samples were then assayed using the Salimetrics high sensitivity ELISA kit (State College, PA).

## Statistical Analyses

Statistical analyses were performed using SPSS version 19.0. Awakening and 30 minutes post-awakening cortisol values from Day 1 and Day 2 were averaged. The resulting values were used to calculate participants' cortisol awakening response (CAR). The CAR was operationalized using two area under the curve (AUC) computations, consistent with recommendations from Powell et al. (2013). The CAR derived from the area under the curve with respect to the ground (CARg) during the first 30 minutes after awakening, and from the area under the curve with respect to increase from baseline (CARi) were calculated using the formulas outlined by Pruessner et al. (2003). A commonly used parameter for modeling total cortisol secretion, CARg is less subject to measurement error associated with variability in the awakening measurement than other CAR measures (i.e., CARi), and has been positively related to chronic stress (Chida and Steptoe, 2009). However, CARi can also yield important information about morning output relative to one's baseline (Powell et al., 2013). Both CARg and CARi had non-normal distributions, and were thus transformed using $\ln(x+1)$ prior to analyses of direct and indirect effects.

Participant adherence to the saliva collection timing protocol was also assessed using patients' self-reported collection times. For each day of sampling, the difference between the second sample time (T2) and the waking sample (T1) was calculated. If T2 was taken 15-45 min after T1, the sample was deemed "adherent" based on criteria we have established elsewhere (Hall et al., 2011).

As a validity check on our use of PSMS scores, we calculated Pearson's *r* correlations between participants' PSS and PSMS scores.

For the main analyses, we first we used multiple regression to relate CARg and CARi with PEM severity. Next we regressed CARg and CARi on PSMS scores. Finally, to test whether PSMS scores had an indirect effect on PEM levels via the CARg or CARi, linear regression analyses and an SPSS macro developed by Preacher and Hayes (2008) were used. This

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macro allows for the estimation of the indirect effect using bootstrapping in order to obtain confidence intervals of the indirect effect. Based on commonly observed relations between gender and age on cortisol output (Chida and Steptoe, 2009), gender and age were used as covariates in these analyses.

## Results

Of the 161 individuals approached to participate in the study, 134 were eligible and 17 declined participation in the study, primarily due to time constraints, resulting in a final sample of 117. Major reasons for ineligibility included living outside the study area (n = 9), the absence of a CFS diagnosis (n = 6), and having an exclusionary medical condition (n = 5). The majority of participants in the sample were women (n = 97) and non-Hispanic White (n = 92). The average age was 50.7 years (SD = 11.5). Most participants were married or in a monogamous relationship (52.1%) and had at least a college degree (55.6%). At the time of assessment, patients reported that CFS symptoms had been present for on average 6.8 years (SD=6.2) with a range of 0.5 to 35.6 years. Symptoms were reported to occur with a frequency between “a few times a month” and “several times a month” with moderate severity as the mode. The symptoms reported as being most frequent were PEM, muscle pain, cognitive difficulties, and unrefreshing sleep. Additional demographic information on study participants has been previously published (Lattie et al., 2012).

Participants overall had high adherence (97% on Days 1 and 2) to the saliva sample timing protocol, with T2 samples on average sampled 32.25 minutes (SD = 8.84 minutes) after T1. Descriptive statistics of the main study variables are presented in Table 1. As seen in Table 1, CFS patients tended to experience PEM symptoms more than once per month with at least moderate intensity. Participants’ PSS scores were significantly related to their PSMS scores such that lower perceived stress was associated with greater perceived stress management skills ($r = -0.55$, $p < .01$).

Controlling for gender and age, there was a significant relationship between the CARg and PEM severity ($\beta = -0.25$, $p < .01$), indicating that greater CARg was associated with lower PEM severity (see Table 2). The relationship between PSMS and the CARg was also significant, ($\beta = 0.19$, $p < .05$), and bootstrapped analyses revealed an indirect effect of PSMS on PEM via the CARg (95% C.I. = −.11 to −.01). Because this confidence interval does not contain zero, results indicate that the indirect effect is significantly different from zero (Preacher and Hayes, 2008). The CARi was not significantly associated with PEM severity or PSMS, and no indirect effect of PSMS on PEM via the CARi was evident.

## Discussion

Results of the present study support the hypothesis that (a) greater CARg is associated with less post-exertional malaise (PEM) severity, (b) greater perceived stress management skills (PSMS) relate to greater CARg, and (c) greater PSMS relates to lower PEM levels via greater CARg. This is the first study to document a relationship between the CAR and PEM, and is in line with recent meta-analytic findings that the CAR is most relevant to the experience of fatigue (Powell et al., 2013). Further, this is the first study to document a

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relationship between PSMS and the CAR. These findings add to the complex literature on the CAR as a measure of HPA axis functioning that may be relevant to the experience of PEM in CFS patients. Here, we also introduce the concept that the CAR may partially explain the relationship between perceived stress management skills and PEM.

It should be noted that the CARg, but not CARi was implicated in these associations. This finding is important for several reasons. First, it underscores the importance of measuring both CARg and CARi as recommended by Powell and colleagues (2013). Additionally, this finding suggests that CARg is particularly relevant to PEM and PSMS in CFS. One potential explanation is that CARg, but not CARi, reflects the magnitude of waking cortisol levels. Higher cortisol levels upon awakening have recently been linked with remission of symptoms among former CFS patients (Nijhof et al., 2014), suggesting that higher morning cortisol levels reflect healthier neuroendocrine functioning in this population. As this population is known to exhibit hypocorticolism (Powell et al., 2013; Nijhof et al., 2014), greater morning cortisol output upon awakening, which is directly measured by CARg, may serve as a buffer against CFS symptoms such as PEM. One potential explanation for this link is that hypocorticolism results in poorer utilization of cortisol, which is used for to energy metabolism, potentially related to poorer recovery after heightened physical exertion (Powell et al., 2013) via inhibitions in mitochondrial respiration (Morris & Maes, 2013). Alternatively, hypocorticolism in CFS may result in poorer peripheral blood mononuclear cell responses to inflammatory cytokines over time via glucocorticoid receptor insensitivity, resulting in increased inflammatory states both chronically and in response to physical exertion (for review, see Sorenson & Jason, 2013). Elevated levels of peripheral pro-inflammatory cytokines have been related to PEM through multiple immune-inflammatory pathways (Morris & Maes, 2013).

Our finding that greater PSMS related to a greater CARg suggests that some aspect of PSMS may also influence neuroendocrine functioning. Previously, greater PSMS have been related to less distress in persons with medical conditions such as cancer (Penedo et al., 2006; Faul et al, 2010) as well as in those with CFS (Lattie et al., 2012). Participants' PSMS scores were comparable to the Faul et al. (2010) general cancer sample, which also had a comparable gender and age distribution to that of our sample.

To our knowledge, no study to date has reported CFS patients' PEM scores using the CDC CFS Symptom Inventory. The current sample's mean score suggests that these CFS patients tend to experience PEM symptoms more than once per month with at least moderate intensity. Finally, CARg and CARi values in our sample were comparable (within 1SD) to what has been previously reported for patients with CFS within the first 30 minutes post-awakening (Nater et al., 2008; Nijhof et al., 2014).

Limitations of this study include the cross-sectional nature of the design. Future work should examine the longitudinal impact of changes in PSMS on PEM via the CAR. Nijhof and colleagues (2014) recently demonstrated that increases in CAR predict CFS remission among adolescent patients. While cross-sectional in nature, our findings suggest that adults with CFS may similarly benefit from increases in CAR perhaps due to improvements in PSMS. However, alternative explanations may account for these associations. For instance,

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PEM could potentially influence CAR as a result of physical inactivity; alternatively, perceived stress, and consequently PSMS, could be influenced by CAR disturbance. Relatedly, future studies may benefit from examining additional predictors of CAR in CFS (e.g. childhood trauma, depressed affect, acute stress, menstrual cycle, oral contraception use, day of the week, disability level) not included in this report in future replications of our findings (Nater et al., 2008; Heim et al., 2009; Roberts et al., 2010). Finally, we averaged cortisol levels between two consecutive days of saliva sampling. Future studies implementing longitudinal analyses may benefit from examining between-day variability in morning cortisol levels as it relates to PEM in CFS, or by adding additional morning saliva samples (e.g. every 10-15 minutes post-awakening) to measure the CAR.

These results contribute to a limited literature on psychoneuroendocrinology in CFS and support stress management skills as a potential target for future behavioral intervention trials, as improved PSMS after intervention may be accompanied by normalized endocrine processes and, indirectly, improved symptom severity. Past stress management interventions have demonstrated the ability to increase PSMS (Penedo et al., 2006) in other medical populations, and to increase morning cortisol levels in CFS (Roberts et al., 2009), therefore results of this study support a clinically applicable target for intervention research to reduce PEM among individuals with CFS.

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**Table 1**

Descriptive Statistics of Main Study Variables

| | M | SD | Range | r (*p*) |
|---|---|---|---|---|
| PSMS | 42.09 | 8.83 | 21 - 63 | |
| PEM | | | | |
| Frequency | 3.45 | 1.60 | 0 - 5 | |
| Intensity | 3.42 | 1.35 | 0 - 5 | |
| Total Severity | 13.59 | 7.68 | 0 - 25 | |
| PSS | 31.20 | 9.12 | 10 - 56 | |
| Cortisol T1 | | | | |
| Day 1 (ug/dl) | 0.43 | 0.70 | 0.02 - 4.93 | |
| Day 2 (ug/dl) | 0.40 | 0.57 | <.01 - 4.68 | 0.50 (*<.001)* |
| Avg (ug/dl) | 0.42 | 0.55 | 0.01 - 4.76 | |
| Cortisol T2 | | | | |
| Day 1 (ug/dl) | 0.57 | 0.78 | <.01 - 6.84 | |
| Day 2 (ug/dl) | 0.43 | 0.29 | 0.01 – 1.55 | 0.44 (*<.001)* |
| Avg (ug/dl) | 0.50 | 0.47 | 0.01 - 4.06 | |
| CARg | 13.79 | 14.88 | 0.26 – 132.38 | |
| CARi | 1.21 | 4.19 | −20.49 – 11.32 | |

Note: N=117; PSMS=Perceived Stress Management Skills; PEM=Post-Exertional Malaise Severity; PSS=Perceived Stress Scale; Cortisol values are given as ug/dl; T1=Sampled upon awakening; T2=Sampled 30 minutes post-awakening; CARg=cortisol awakening response calculated using area under the curve with respect to ground using timepoint-averaged cortisol values; CARi= cortisol awakening response calculated using area under the curve with respect to increase using timepoint-averaged cortisol values.

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## Table 2

Tests of Direct and Indirect Effects

| Path | β * | *p* / 95% CI |
|---|---|---|
| PSMS → PEM | −0.06 | .57 |
| CARg Indirect Effect | −0.04 | −0.11 – −0.01 |
| PSMS → CARg | 0.19 | .04 |
| CARg → PEM | −0.25 | .01 |
| CARi Indirect Effect | −0.07 | −0.07 – 0.01 |
| PSMS → CARi | 0.17 | .12 |
| CARi → PEM | −0.10 | .35 |

Note: N=117. Analyses controlled for patient's gender and age. β =Standardized Coefficient;

* Indirect effect is unstandardized; CI=Confidence Interval; PSMS=Perceived Stress Management Skills; CARg= cortisol awakening response calculated using ln(x+1) transformed area under the curve with respect to ground; CARi= cortisol awakening response calculated using ln(x+1) transformed area under the curve with respect to increase; PEM=Post-Exertional Malaise Severity.