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Original Article

The association of somatic arousal with the symptoms of upper airway resistance syndrome

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ABSTRACT

Objectives: We tested the hypothesis that the symptoms of upper airway resistance syndrome (UARS) are manifestations of chronic stress. To accomplish this, we utilized the score on a self-report questionnaire for somatic arousal (a component of stress) to compare somatic arousal between UARS patients and healthy controls and, among all participants, to correlate the level of somatic arousal with the severity of UARS symptoms.

Methods: We administered the Mood and Anxiety Symptom Questionnaire anxious arousal subscale (MASQaas; a 17-item questionnaire with increasing levels of arousal scored 17–85) to 12 UARS patients and 12 healthy controls and compared scores between groups. For all participants, we correlated the MASQaas scores with scores for the Epworth Sleepiness Scale (ESS), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, Pittsburgh Sleep Quality Index (PSQI), SF-36 Health Survey, and Perceived Deficits Questionnaire (PDQ; assessing cognitive function).

Results: Compared to healthy controls, UARS patients demonstrated increased somatic arousal (MASQaas scores of 18 ± 2 and 28 ± 7, respectively; $p < 0.0001$). For all participants, the MASQaas scores correlated significantly with scores of the ESS ($r = 0.64$; $p = 0.0008$), the FACIT-Fatigue scale ($r = -0.89$; $p < 0.0001$), the PSQI ($r = 0.70$; $p = 0.0002$), SF-36 Physical component ($r = -0.78$; $p < 0.0001$), SF-36 Mental component ($r = -0.74$; $p < 0.0001$), and the PDQ ($r = 0.89$; $p < 0.0001$).

Conclusions: Our findings suggest that UARS patients have increased levels of the stress component, somatic arousal, proportionate to the severity of their symptoms.

1. Introduction

The pathophysiology of upper airway resistance syndrome (UARS) is incompletely understood. In the popular paradigm of UARS, recurrent arousals related to respiratory effort (respiratory effort-related arousals (RERAs)) lead to sleep fragmentation and daytime sleepiness [1]. However, the evidence supporting this paradigm is scant. Moreover, the popular paradigm does not explain why, when compared to obstructive sleep apnea patients, UARS patients have increased alpha frequency in their sleep electroencephalogram [2,3], instability of sleep stages with intruding pre-arousal phenomena [4], and a greater prevalence of central sensitization syndromes [3] (CSSs; like fibromyalgia [5], irritable bowel syndrome (IBS) [6], and war-related illness [7]). It is clearly appropriate to question the adequacy of the traditional paradigm, and to consider an alternative paradigm of UARS that offers a more integrated explanation of the unique features of the disorder.

In our recently published study comparing inspiratory airflow dynamics during sleep between 12 UARS patients and 12 rigorously screened healthy controls, we proposed an alternative paradigm of UARS [8]. In the study, we found little difference between UARS patients and healthy controls in objective sleep architecture or fragmentation, despite clear differences in subjective assessments of sleep quality and daytime sleepiness/fatigue [8]. Bringing together previous findings regarding alpha frequency intrusion into sleep and sleep stage instability among UARS [2–4] and IBS [6,9] patients, we suggested that rather than being considered a disorder of increased *sleep fragmentation*, UARS should be considered a disorder of *chronic stress* [10]. By "chronic stress", we mean "a condition in which the hypothalamic–pituitary–adrenal axis

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and the sympathetic nervous system (SNS) are chronically activated." In our paradigm, the chief stressor of the UARS patient is mild pharyngeal collapse during sleep.

Consistent with our paradigm, UARS patients manifest a wide variety of symptoms that have been associated with chronic stress, such as fatigue, insomnia, headaches, irritable bowels and bladders, body pain, anxiety, and depression [11–15]. Interestingly, many of these symptoms, common among patients with UARS and mild obstructive sleep apnea hypopnea [3], are ameliorated by prevention of pharyngeal collapse during sleep with nasal continuous positive airway pressure [5,16–19], mandibular advancement [20], and rapid palatal expansion [21]. Our alternative paradigm of UARS can account for these varied symptoms of the disorder and their improvement in response to treatments that prevent pharyngeal collapse. However, it has not been demonstrated to date that UARS patients are, in fact, characterized by increased levels of stress compared to healthy controls or that increasing symptom severity among UARS patients is associated with an increasing level of stress.

Increased SNS tone is a marker for stress. "Physical manifestations of increased SNS tone" (also termed *somatic arousal*) are associated with anxiety disorders such as post-traumatic stress disorder and panic disorder where individuals experience "tremors," "sweating," "dry mouth," and "being easily startled" even when not aware of feeling anxious [22]. Among athletes and performing musicians, performance anxiety, with its associated increase in SNS tone, can lead to hand tremors and sweating that interfere with skilled performance but can be diminished by blocking adrenergic receptors [23,24]. Increased SNS tone is also associated with a well-known physiologic stress, hypoglycemia. Healthy research participants made hypoglycemic with exogenous insulin demonstrate increased SNS tone assessed by heart rate variability [25] and manifestations of somatic arousal [26]. Among individuals diagnosed with chronic fatigue syndrome [27], fibromyalgia [28], IBS [29], Gulf War illness [30], and chronic insomnia [31], disorders associated with chronic stress [11–15], investigators have analyzed heart rate variability to demonstrate increased SNS tone. Thus, disorders conceptualized as having a common basis of stress are characterized by increased SNS tone and somatic arousal.

Somatic arousal can be quantified by a self-report questionnaire. In a recent study [32], self-reports demonstrated an increased level of somatic arousal among 12 females with IBS compared to 12 healthy controls. Among all 24 participants, as the level of somatic arousal increased, sleep quality decreased and the severity of sleepiness and fatigue both increased [32]. In this study, we attempt to demonstrate that UARS patients are similarly characterized by increased stress/somatic arousal compared to healthy controls and that increasing symptoms of UARS are associated with increasing levels of somatic arousal. To accomplish this, we measured the level of somatic arousal among 12 UARS patients and 12 healthy controls using a self-report questionnaire, compared levels between the two groups, and, over all participants, correlated the level of somatic arousal with self-report assessments of sleep quality, sleepiness, and fatigue, physical and mental health, self-report and objective assessments of cognitive function, and polysomnographic parameters.

2. Methods

2.1. Recruitment

This study was performed as a secondary analysis of data from published work comparing inspiratory airflow dynamics during sleep between UARS patients and healthy controls [8]. The protocol was approved by the Institutional Review Board of Stony Brook University (SBU). We recruited 12 UARS patients and 12 healthy controls for this study. UARS was diagnosed in patients at the SBU Sleep Disorders Center who (i) complained of sleepiness or fatigue (without symptoms of narcolepsy), (ii) had an apnea–hypopnea index (AHI) of <10 events/h, (iii) presented with inspiratory airflow limitation (IFL) during non-rapid eye movement (NREM) sleep evident by nasal/oral pressure measurement, and (iv) had fewer than two REM onsets during a four-nap multiple sleep latency test performed the day following their polysomnogram (PSG) (the clinical criteria for narcolepsy of the SBU Sleep Disorders Center).

All control participants were recruited by advertisement and prescreened by telephone using a standardized interview to determine eligibility. Healthy controls were ineligible based upon having any medical condition; receiving disability insurance; taking medications other than birth control, vitamins, and nonprescription analgesics; and having any one of a long list of symptoms that are characteristic of patients with CSSs (these symptoms/syndromes are listed in Table 1).

UARS patients and controls were matched for age, gender, and body mass index (BMI). Their age was limited to 45 years and their BMI to 32 kg/m^2 for reasons explained in the parent study [8]. Exclusion criteria for UARS patients included the use of antidepressants, opioids, stimulants, steroids, and cigarettes, and alcohol abuse, which may alter inspiratory airflow dynamics during sleep or somatic arousal. Further, patients with a history of diabetes, patients taking antihypertensives and lipid-lowering medications, and patients with coronary artery disease (CAD), stroke, seizures, and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) were excluded. The reason for their exclusion was the effect the disorders might have on measured stress or the effect the medications might have on polysomnography (lipid-lowering medication) or self-report somatic arousal (adrenergic blocking agents).

2.2. Symptom assessment

All participants underwent an assessment of sleep-related symptoms with the following self-report questionnaires:

1. Epworth Sleepiness Scale (ESS) [33]: This is an eight-item questionnaire assessing daytime sleepiness. Its total score increases with increasing sleepiness from 0 to 24.
2. Functional Assessment of Chronic Illness Therapy-Fatigue, version 4 (FACIT-Fatigue) [34]: This is a 13-item questionnaire assessing fatigue with the total score ranging from 52 (least fatigue) to 0 (greatest fatigue).
3. Pittsburgh Sleep Quality Index (PSQI) [35]: This is a 19-item questionnaire assessing the severity of sleep disturbance that yields a total score with increasing disturbance of 0–21. It has seven subscales for the various components of sleep disturbance scored 0–3.
4. SF-36 version 2 Health Survey (SF-36) [36]: This is a 36-item health survey yielding a profile of physical and mental health and well-being. Higher scores indicate better health with the mean for the general population normalized to 50.
5. Perceived Deficits Questionnaire (PDQ) [37]: This is a 20-item, self-report measure of cognitive dysfunction in multiple sclerosis that assesses attention, retrospective memory, prospective memory, and planning and organization. Increasing perceived cognitive impairment is scored 0–80.
6. Symbol Digits Modality Test (SDMT) [38]: This is a task assessing cognitive impairment. Cognitive function is scored from 0 to 110 with better cognitive function reflected in higher scores.

Table 1
Exclusion criteria for healthy controls.

1.	Any *medical condition*
2.	Receiving *disability insurance*
3.	Taking medications other than birth control, vitamins and non-prescription analgesics
4.	Post-menopausal (12 months without a period) or pregnant status
5.	Heartburn
6.	Any current pain *on a regular basis*
7.	Fatigue during the past month >2/10 (0 = no fatigue; 10 = extreme fatigue)
8.	Any history of the following syndromes
a.	Muscle or joint pain lasting several months *not due to an injury or arthritis*
b.	Chronic fatigue
c.	Pre-menstrual symptoms
d.	Temporomandibular joint disorder
e.	Chemical sensitivity
f	Sick building syndrome
g.	Side effects of silicone breast implants
h.	Chronic whiplash
i.	Undiagnosed chest pain
j.	Chronic pelvic pain
k.	Chronic headache
l.	Chronic low back pain
m.	Chronic insomnia
n.	Hyperventilation or dizziness

2.3. Somatic arousal assessment

Mood and Anxiety Symptom Questionnaire (MASQ) anxious arousal subscale [39] (Appendix 1) is a 17-item, self-report measure of somatic arousal (with the heading "Body Sensation Questionnaire") in which the respondent rates how much each item was experienced over the preceding week on an increasing scale from 1 (never) to 5 (extremely). Increasing total scores reflect increasing somatic arousal (as conceptualized earlier in this article) on a range of 17–85.

2.4. Polysomnography

In the primary study of inspiratory airflow dynamics during sleep, all participants underwent polysomnography using standard clinical methods. The PSGs provide data on sleep architecture and fragmentation that we correlate here with severity of the participants' symptoms.

During the PSG, sleep position was unrestricted. The PSG began between 10:00 and 11:00 pm and ended at 6:00 am (each participant spent between 7 and 8 h in bed). Sleep was monitored using surface electroencephalogram (EEG) activity of the central and occipital regions, submental surface electromyographic activity, and left and right electrooculographic activity. Leg movement was detected using surface electromyographic activity of the right and left tibialis anterior muscle. Airflow at the nose and mouth was monitored semiquantitatively with a nasal pressure catheter [40]. Thoracoabdominal movement was monitored with piezoelectric belts. Oxyhemoglobin saturation (SaO_2) was monitored at the finger using a pulse oximeter. A continuous electrocardiograph (EKG) monitored heart rate and rhythm. All of the data were digitized and stored on a computer for analysis by a single physician, board certified in sleep medicine who was masked to participant group identity.

2.5. Polysomnographic data analysis

The PSG was staged using the Rechtschaffen and Kales criteria [41] to determine wakefulness and the various sleep stages with NREM stages 3 and 4 being combined as *slow wave sleep*. Arousals were scored using the 3-s frequency shift criterion [42]. Our research group has consistently applied these sleep staging criteria to our research to facilitate comparisons between our studies in this field as sleep staging criteria continually change [6,7]. Sleep fragmentation was characterized by an arousal index (spontaneous arousals + apnea/hypopnea arousals + RERAs). The total of sleep stage shifts was not assessed for this study, which did not provide for multiple nights of adjustment to the sleep laboratory [43].

Respiratory events were assessed using methods described previously [6]. An apneic event was defined as a decrease in inspiratory airflow to <20% of waking levels lasting at least 10 s. A hypopneic event was defined as a decrease in inspiratory airflow to <50% of waking levels for at least 10 s, ending with an arousal (there was no classification of hypopnea based upon oxyhemoglobin desaturation in the absence of an arousal). The total of each participant's apneic and hypopneic events was divided by total sleep time to derive an AHI.

Arousals associated with IFL and inspiratory airflow >50% of waking levels were quantified as RERAs. For an arousal to qualify as an RERA, it had to be immediately preceded by a flow-limited breath. Our method for identifying flow-limited breaths in the absence of an inspiratory effort (airway pressure) measurement is detailed in our article describing the primary study [8]. For each patient, the total of RERAs during the study was divided by the total sleep time to provide an RERA index.

2.6. Statistics

All computations were done in the SAS System for Windows, Version 9.3. All *p*-values were based on unpaired *t*-tests except as follows. Correlations were compared with the standard *t*-test used in SAS [44].

3. Results

The UARS participants and healthy controls were matched for gender, each group including nine females and three males. The groups were also matched for age (35 ± 5 and 35 ± 6 years, respectively) and BMI (27 ± 4 and 27 ± 4 kg/m^2, respectively).

In their initial phone screens, the 12 UARS participants were characterized by the symptoms associated with CSS. Two complained of chronic joint and muscle pain, three complained of chronic low back pain, one had chronic pelvic pain, four had premenstrual syndrome, one had temporomandibular joint syndrome, one had IBS, seven complained of chronic fatigue, three complained of chronic insomnia, and three complained of chronic hyperventilation or dizziness. None of the healthy controls had any of these symptoms/syndromes as they were reasons for exclusion from participation (Table 1). Among all participants, a total of 15 (12 controls and three with UARS) had no symptoms of CSS, three had one syndrome, three had two syndromes, two had three syndromes, and one had five syndromes.

As presented in our study of inspiratory airflow dynamics during sleep [8], the two groups demonstrated no differences in indices of sleep architecture and sleep fragmentation. Table 2 demonstrates that only the AHI differed between groups, and this small difference did not produce a difference in sleep fragmentation as indicated by the arousal index. Nevertheless, Table 3 demonstrates that the UARS participants reported poorer sleep quality than did the healthy controls (global PSQI). They also reported more daytime sleepiness (ESS) and more fatigue (FACIT-Fatigue). Similarly, the UARS participants had lower scores for physical and mental health on the SF-36 and perceived themselves as having poorer cognitive function (PDQ), although the objective test of

cognitive function (SDMT) suggested less cognitive impairment in the UARS group, despite the difference not being significant.

The UARS participants had a higher level of self-reported somatic arousal than the healthy controls. UARS participants had a MASQ anxious arousal subscale of 28 ± 7 compared to 18 ± 2 for the healthy controls ($p < 0.0001$). The distribution of MASQ anxious arousal subscale scores for the two groups is illustrated in Fig. 1.

The relationships of the MASQ anxious arousal subscale to the PSQI, ESS, FACIT-Fatigue, SF-36 Physical and Mental components, and PDQ are illustrated in Fig. 2. There was a significant correlation between increased somatic arousal and diminished sleep quality, and increased sleepiness and increased fatigue. Similarly, the level of somatic arousal was negatively correlated with SF-36 Physical and Mental components indicating worsening perceived health with increasing somatic arousal. The level of somatic arousal was positively correlated with the PDQ indicating worsening perceived cognition with increasing somatic arousal. The SDMT was not significantly correlated with the MASQ anxious arousal subscale ($r = 0.20$; $p = 0.35$).

With one exception, the polysomnographic parameters demonstrated few correlations with the level of somatic arousal, sleep quality, sleepiness, fatigue, perceived physical and mental health, or perceived cognitive function. The one exception was "sleep latency" which was significantly correlated with the SF-36 Mental component, the FACIT-Fatigue, and the MASQ anxious arousal subscale (Table 4).

Among all participants, the MASQ anxious arousal subscale score was positively correlated with the number of CSSs ($r = 0.67$; $p = 0.0003$; Fig. 3).

4. Discussion

This study represents a preliminary exploration of the role of stress in the pathophysiology of UARS. Using the MASQ anxious arousal subscale, a self-report instrument quantifying somatic arousal, the physical manifestations of increased SNS tone, we compared the level of stress between 12 UARS patients and 12 healthy controls correlating the level of stress with the severity of symptoms among all participants. We observed that UARS patients can be distinguished from healthy controls by an elevated level of somatic arousal. Further, we found that among all the participants increased somatic arousal was correlated with poorer sleep quality, increased sleepiness, increased fatigue, decreased perceived physical and mental health, and decreased perceived cognitive function (but not objective cognitive function). By contrast, the PSG parameters quantifying the amount and continuity of sleep did not distinguish between UARS patients and healthy controls in a way that could explain the differences between these groups in sleep quality, health, and cognitive function. Finally, we observed over all the participants that the number of CSS syndrome symptoms experienced (symptoms associated with chronic stress) was positively correlated with the level of somatic arousal. This study provides the first *direct* evidence that stress is associated with the symptoms of UARS.

Our study is not the first to identify a parameter whose level separates UARS patients from healthy controls and correlates with the severity of sleepiness and fatigue. Guilleminault et al. [4] conducted such a study using polysomnography to contrast the extent of cyclic alternating pattern (CAP) between 30 UARS patients and 30 controls. They observed considerably more CAP (CAP rate, time, and cycles) among UARS patients than among controls. CAP rate was also significantly correlated with both the level of sleepiness determined by the ESS ($r = 0.38$; $p < 0.01$) and the level of fatigue determined by the Fatigue Severity Scale ($r = 0.51$, $p < 0.0001$). From their findings, they reasoned that UARS patients are distinguished from healthy individuals by sleep stage instability, the parameter quantified by CAP analysis, caused by the mild pharyngeal collapse of UARS and contributing to their sleepiness and fatigue.

Our finding in this study that the level of somatic arousal determined by the questionnaire distinguishes UARS patients from healthy controls and, among all participants, correlates with the levels of sleep quality, sleepiness, and fatigue complements the findings of Guilleminault et al. [4]. We believe that SNS tone underlies both somatic arousal during wakefulness and CAP during sleep. Investigators have found a positive correlation between the level of CAP in stage 2 sleep and the low frequency to high frequency ratio of heart rate variability, an indicator of SNS tone [45]. Thus, by finding increased CAP among UARS patients, Guilleminault et al. [4] have identified increased SNS tone, a marker for increased stress, among these patients during NREM sleep, which complements our finding of somatic arousal among these patients during wakefulness.

Increased SNS tone, posited as the common pathway by which both somatic arousal during wakefulness and CAP during sleep can be associated with UARS, can also account for the significant or nearly significant correlation of polysomnographic sleep latency

Table 2
Sleep data of the UARS participants and healthy controls.

Parameter	UARS participants	Healthy controls	*p*-Value
Time in bed (min)	418.0 (64.5)	421.6 (18.1)	0.86
Total sleep time (min)	357.2 (62.6)	353.6 (44.8)	0.87
Sleep efficiency (%)	88.7 (8.5)	88.7 (5.8)	1.00
Sleep latency (min)	21.3 (22.4)	14.3 (10.9)	0.34
REM latency (min)	79.3 (32.7)	87.5 (30.9)	0.53
Stage 1 (%)	9.9 (3.9)	12.1 (7.3)	0.36
Stage 2 (%)	47.9 (9.5)	50.1 (9.7)	0.60
Slow wave sleep (%)	22.6 (11.2)	20.4 (11.4)	0.63
REM (%)	19.1 (7.0)	17.4 (4.4)	0.49
Apnea hypopnea index	1.6 (1.9)	0.4 (0.3)	**0.035**
RERA index	5.9 (3.6)	6.5 (3.4)	0.67
Arousal index	12.7 (5.8)	10.1 (4.3)	0.22
Heart rate/sleep (mean)	68.9 (10.9)	67.2 (7.4)	0.65

Table 3
Questionnaire assessment of the UARS participants and healthy controls.

Questionnaire[a]	UARS participants	Healthy controls	*p*-Value
	Mean (SD)		
Pittsburgh sleep quality index			
Global	9.1 (4.0)	0.6 (0.5)	<0.0001
Sleep duration	0.8 (1.1)	0.0 (0.0)	0.0464
Sleep disturbance	1.7 (0.7)	0.5 (0.5)	<0.0001
Sleep latency	1.2 (1.2)	0.0 (0.0)	0.0058
Daytime Dysfunction	1.8 (0.9)	0.1 (0.4)	<0.0001
Sleep efficiency	0.7(1.2)	0.1 (0.4)	0.058
Overall sleep quality	2.3 (0.6)	0.0 (0.0)	<0.0001
Need for medication	0.5 (1.1)	0.0 (0.0)	0.12
Epworth sleepiness scale	10 (4)	2 (1)	<0.0001
FACIT-Fatigue[b]	25 (7)	45 (2)	<0.0001
SF-36			
Physical component	49 (8)	59 (2)	0.0005
Mental component	42 (13)	57 (4)	0.0015
Perceived deficits questionnaire			
Global	31 (15)	5 (5)	<0.0001
Retrospective memory	8 (4)	1 (1)	<0.0001
Prospective memory	6 (4)	1 (1)	<0.0001
Planning	8 (5)	1 (2)	0.0002
Attention	9 (4)	2 (2)	<0.0001
Symbol digits modality test	63 (9)	55 (16)	0.1285

[a] Questionnaire scales are found in the Methods.
[b] FACIT-Fatigue scores interpreted as low = more fatigue and, high = less fatigue.

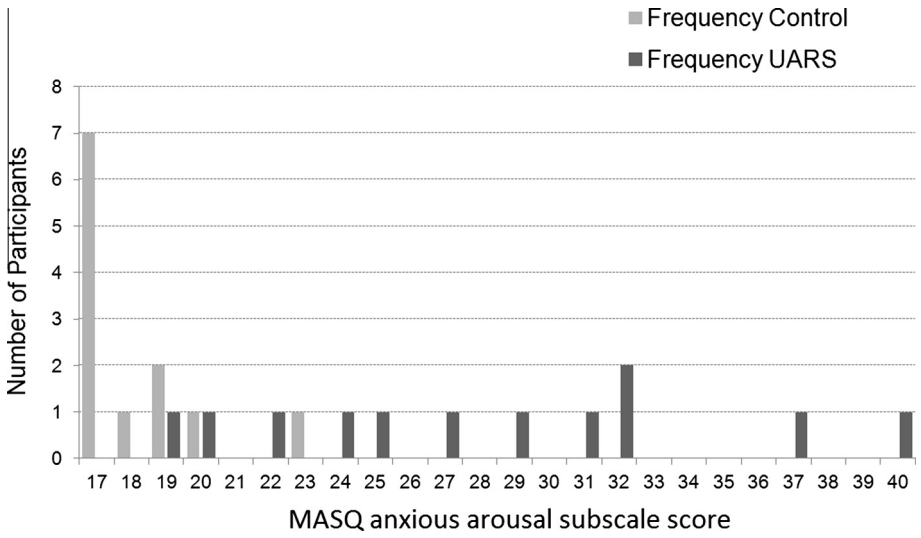

Fig. 1. This figure illustrates the frequency of the MASQ anxious arousal subscale (MASQaas) scores for our 12 UARS patients (dark columns) and 12 healthy controls (light columns). The *Y* axis indicates the number of participants with values of MASQaas indicated on the *X* axis. All but one UARS patient had MASQaas values $\geqslant$20 while all but one healthy control had values $\leqslant$20.

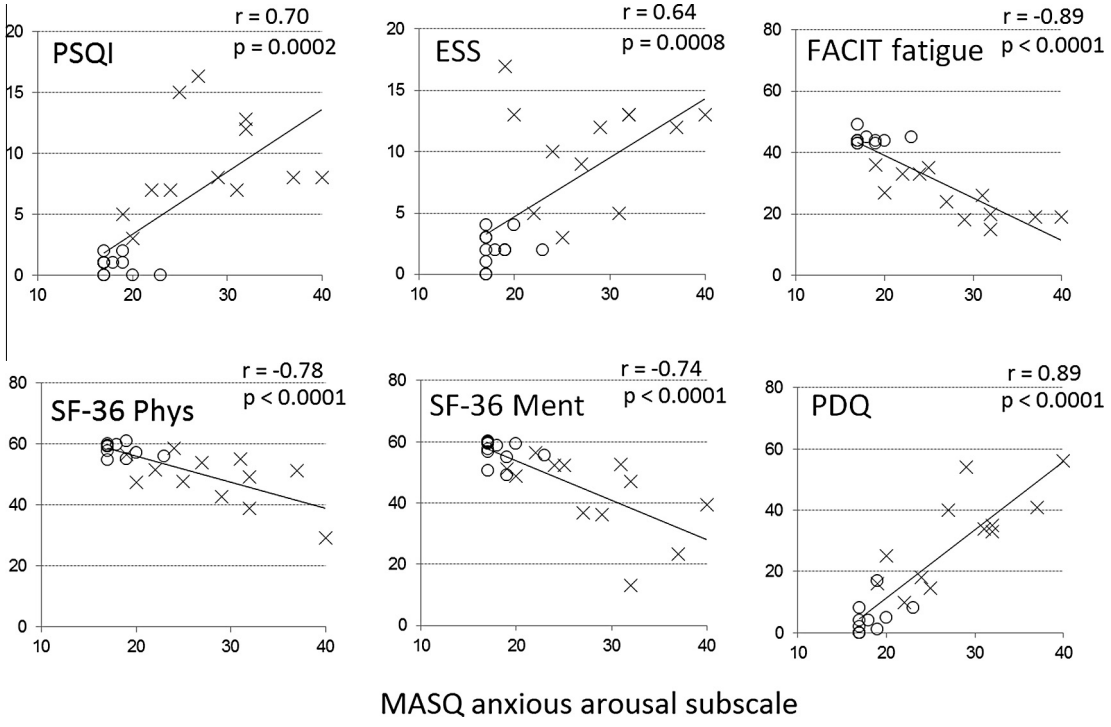

Fig. 2. This figure illustrates the relationship between the MASQ anxious arousal subscale (MASQaas) score and each of six self-report symptom questionnaire scores. These include: the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), the SF-36 version 2 Health Survey Physical component (SF-36 Phys) and Mental component (SF-36 Ment), and the Perceived Deficits Questionnaire of cognitive function (PDQ). UARS patients are designated by Xs while healthy controls are indicated by Os. For all participants, the MASQaas score was highly correlated with each of the questionnaire scores.

with measures of mental health, fatigue, and somatic arousal amongst the study patients (Table 4). The popular paradigm of primary insomnia postulates a state of *physiologic hyperarousal* associated with increased SNS tone that prolongs the sleep latency of the chronic insomnia patient [46,47]. Just as in UARS, the physiologic hyperarousal (increased somatic arousal) of the primary insomnia patient is associated with increased CAP during sleep compared to non-insomniacs [48]. In fact, sleep-onset insomnia is a very common complaint among UARS patients [3]. If, as in primary insomnia, increasing polysomnographic sleep latency in UARS patients reflects increasing physiologic hyperarousal, then increasing sleep latency should predict increasing signs of chronic stress observed in the SF-36 Mental component and the FACIT-Fatigue and the increased somatic arousal observed in the MASQ anxious arousal subscale (Table 4).

In connection with our demonstration of an association between an indicator of stress, somatic arousal, and the symptoms of UARS, two limitations must be acknowledged. Clearly, while we have found an association between UARS and somatic arousal, we have not proven the cause and effect. Specifically, while

Table 4
Correlations of PSG parameters with subjective sleep quality, sleepiness, fatigue, and somatic arousal.

		ESS	FACIT Fatigue	PSQI	MASQaas	SF-36 Physical	SF-36 Mental	PDQ
Time in bed	*r*	−0.04	0.04	0.11	0.16	−0.14	−0.11	0.01
	p	0.85	0.86	0.60	0.45	0.50	0.60	0.97
Total sleep time	*r*	0.07	−0.08	0.04	0.08	0.20	0.04	0.08
	p	0.74	0.72	0.87	0.70	0.34	0.86	0.69
Sleep efficiency	*r*	0.15	−0.03	−0.16	−0.13	−0.09	0.13	0.09
	p	0.48	0.90	0.46	0.54	0.69	0.54	0.67
Sleep latency	*r*	0.26	**−0.42**	**0.35**	**0.40**	−0.16	**−0.70**	−0.04
	p	0.23	**0.043**	**0.097**	**0.051**	0.46	**0.0001**	0.87
REM latency	*r*	0.11	0.06	−0.06	−0.07	0.03	0.10	0.00
	p	0.60	0.79	0.79	0.73	0.90	0.66	0.99
Stage 1 (%)	*r*	−0.33	0.16	−0.09	−0.12	0.11	0.21	−0.21
	p	0.12	0.45	0.68	0.56	0.60	0.32	0.31
Stage 2 (%)	*r*	−0.27	0.11	0.14	0.03	0.19	0.06	−0.14
	p	0.21	0.62	0.52	0.87	0.39	0.79	0.52
Slow wave sleep (%)	*r*	**0.41**	−0.15	−0.08	0.03	−0.13	0.34	0.18
	p	**0.048**	0.47	0.71	0.87	0.52	0.10	0.39
Stage REM (%)	*r*	−0.01	−0.01	0.00	−0.03	−0.17	0.34	0.05
	p	0.97	0.95	1.00	0.88	0.41	0.11	0.83
Apnea hypopnea index	*r*	**0.48**	−0.18	0.15	−0.00	−0.11	−0.01	0.03
	p	**0.018**	0.40	0.47	0.98	0.62	0.95	0.89
RERA index	*r*	0.07	−0.01	−0.23	−0.11	−0.00	0.05	−0.06
	p	0.73	0.97	0.28	0.62	0.98	0.80	0.77
Arousal index	*r*	−0.04	−0.20	0.21	0.32	−0.19	0.06	0.25
	p	0.86	0.36	0.33	0.12	0.38	0.79	0.24
Heart rate/sleep (mean)	*r*	**0.36**	−0.11	−0.09	−0.05	−0.03	−0.02	0.08
	p	**0.09**	0.60	0.67	0.83	0.87	0.92	0.73

r = Pearson correlation coefficients.
p = *p*-Values which are rounded to two significant digits, where possible.
See the Methods for abbreviations of the self-assessment questionnaires. Correlations associated with *p*-values <0.10 are indicated in bold.

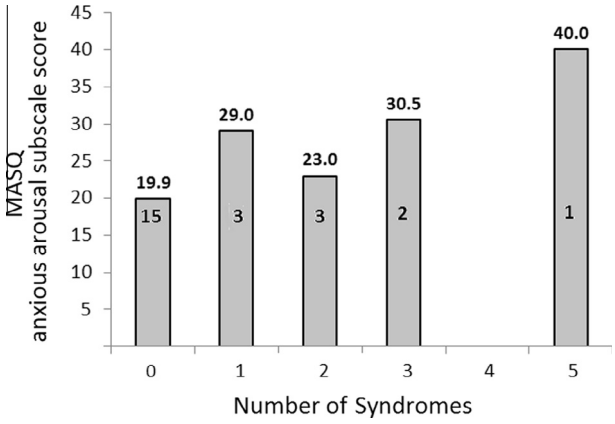

Fig. 3. This figure illustrates the relationship between the MASQ anxious arousal subscale (MASQaas) score and the number of central sensitization syndromes experienced by participants (the syndromes are listed *a–n* in Table 1). The number in each column represents the number of participants having that number of symptoms and contributing their scores to the mean MASQaas represented. By selection criteria, all 12 healthy controls had no syndromes and are contained within the "0" column. The MASQaas was highly correlated with the number of syndromes experienced ($r = 0.67$; $p = 0.0003$).

increasing stress is associated with decreasing sleep quality and increasing manifestations of sleepiness/fatigue and other symptoms, we have not demonstrated that increasing stress "causes" the poor sleep quality and its sequelae. Perhaps, the poor sleep quality and its sequelae are the causes of increased stress among UARS patients. Indeed, the same argument can be made for the relationship of physiologic hyperarousal with primary insomnia discussed above. Perhaps, the state of insomnia leads to the stress manifested as physiologic hyperarousal in primary insomnia patients. If one could block the "stress" mechanism of UARS patients without affecting pharyngeal collapse, and vice versa, one could further elucidate the roles that these two phenomena play in causing the symptoms of UARS. However, there is currently no way to block only the "stress" mechanism of UARS.

This study is also limited by our modest sample size. We were able to find markedly significant correlations between levels of somatic arousal and symptoms of UARS only by analyzing a population of both UARS patients and rigorously screened healthy controls. The resulting broad ranges of somatic arousal and symptom severity enhanced statistical power to demonstrate significant correlations between somatic arousal and symptom severity. We were thus clearly able to show that the difference in stress levels between UARS patients and healthy controls was associated with differences in severity of symptoms between them. However, with only 12 UARS patients, we were less able to draw conclusions about the extent to which differences in the level of somatic arousal between UARS patients correlate with differences in the severity of their symptoms. (Even so, when one relates somatic arousal to symptom severity for the 12 UARS patients alone, there appears to be a good correlation for FACIT-Fatigue (actual $r = -0.77$; $p = 0.003$), SF-36 Physical (actual $r = -0.59$; $p = 0.04$), SF-36 Mental (actual $r = -0.58$; $p = 0.05$), and the PDQ (actual $r = 0.78$; $p = 0.003$), while the correlations for the ESS (actual $r = 0.10$; $p = 0.76$) and PSQI (actual $r = 0.27$; $p = 0.40$) do not achieve statistical significance (Fig. 2 shows the data points).) Moreover, although we did study the correlation of somatic arousal with the frequency and severity of a variety of symptoms reflecting chronic stress, some consequences of chronic stress were not considered. Chronic stress is also associated with metabolic derangements such as hypertension and glucose intolerance [49]. Does the level of somatic arousal also correlate with the metabolic derangements that may be observed in UARS patients? These questions may be answered by utilizing the MASQ anxious arousal subscale in large numbers of UARS patients in a clinical sleep disorder setting, correlating levels of somatic arousal with both the symptoms and metabolic consequences of chronic stress.

Another limitation of our small sample size relates to our finding no significant correlations between parameters reflecting sleep

quality and our participants' symptoms (Table 4). One can argue that our small sample size lacked the power to identify such relationships. A counterpoint, however, is that we did find significant correlations between sleep latency and somatic arousal, and fatigue and mental health, correlations that are intuitively reasonable as explained above.

In conclusion, our study used a self-report questionnaire to measure somatic arousal in order to examine the hypothesis that UARS represents a syndrome of chronic stress. Our findings support the hypothesis and invite further work to more clearly establish the pathophysiology of UARS.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.01.014.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.sleep.2014.01.014.

References

[1] Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. Chest 1993;104(3):781–7.
[2] Guilleminault C, Do Kim Y, Chowdhuri S, Horita M, Ohayon M, Kushida C. Sleep and daytime sleepiness in upper airway resistance syndrome compared to obstructive sleep apnoea syndrome. Eur Respir J 2001;17(5):838–47.
[3] Gold AR, Dipalo F, Gold MS, O'Hearn D. The symptoms and signs of upper airway resistance syndrome: a link to the functional somatic syndromes. Chest 2003;123(1):87–95.
[4] Guilleminault C, Lopes MC, Hagen CC, da Rosa A. The cyclic alternating pattern demonstrates increased sleep instability and correlates with fatigue and sleepiness in adults with upper airway resistance syndrome. Sleep 2007;30(5):641–7.
[5] Gold AR, Dipalo F, Gold MS, Broderick J. Inspiratory airflow dynamics during sleep in female fibromyalgia patients. Sleep 2004;27(3):459–66.
[6] Gold AR, Broderick JE, Amin MM, Gold MS. Inspiratory airflow dynamics during sleep in irritable bowel syndrome: a pilot study. Sleep Breath 2009;13(4):397–407.
[7] Amin MM, Belisova Z, Hossain S, Gold MS, Broderick JE, Gold AR. Inspiratory airflow dynamics during sleep in veterans with Gulf War illness: a controlled study. Sleep Breath 2011;15(3):333–9.
[8] Gold AR, Broderick JE, Gold MS, Amin MM. A comparison of inspiratory airflow dynamics during sleep between upper airway resistance syndrome patients and healthy controls. Sleep Breath 2013;17(4):1169–78.
[9] Rotem AY, Sperber AD, Krugliak P, Freidman B, Tal A, Tarasiuk A. Polysomnographic and actigraphic evidence of sleep fragmentation in patients with irritable bowel syndrome. Sleep 2003;26(6):747–52.
[10] Gold AR. Functional somatic syndromes, anxiety disorders and the upper airway: a matter of paradigms. Sleep Med Rev 2011;15(6):389–401.
[11] Bigal ME, Lipton RB. What predicts the change from episodic to chronic migraine? Curr Opin Neurol 2009;22(3):269–76.
[12] Finestone HM, Alfeeli A, Fisher WA. Stress-induced physiologic changes as a basis for the biopsychosocial model of chronic musculoskeletal pain: a new theory? Clin J Pain 2008;24(9):767–75.
[13] Warnock JK, Clayton AH. Chronic episodic disorders in women. Psychiatr Clin North Am 2003;26(3):725–40.
[14] Selye H. The stress of life. Revised ed. New York: McGraw Hill Book Co.; 1976.
[15] Gulewitsch MD, Enck P, Schwille-Kiuntke J, Weimer K, Schlarb AA. Mental strain and chronic stress among university students with symptoms of irritable bowel syndrome. Gastroenterol Res Pract 2013;2013. http://dx.doi.org/10.1155/2013/206574. Article ID 206574, Epub.
[16] Amin MM, Gold MS, Broderick JE, Gold AR. The effect of nasal continuous positive airway pressure on the symptoms of Gulf War illness. Sleep Breath 2011;15(3):579–87.
[17] Krakow B, Lowry C, Germain A, Gaddy L, Hollifield M, Koss M, et al. A retrospective study on improvements in nightmares and post-traumatic stress disorder following treatment for co-morbid sleep-disordered breathing. J Psychosom Res 2000;49(5):291–8.
[18] Nobre ME, Filho PF, Dominici M. Cluster headache associated with sleep apnoea. Cephalalgia 2003;23(4):276–9.
[19] Takaesu Y, Inoue Y, Komada Y, Kagimura T, Iimori M. Effects of nasal continuous positive airway pressure on panic disorder comorbid with obstructive sleep apnea syndrome. Sleep Med 2011;13(2):156–60.
[20] Ranieri AL, Tufik S, de Siqueira JT. Refractory cluster headache in a patient with bruxism and obstructive sleep apnea: a case report. Sleep Breath 2009;13(4):429–33.
[21] Miller P, Iyer M, Gold AR. Treatment resistant adolescent depression with upper airway resistance syndrome treated with rapid palatal expansion: a case report. J Med Case Rep 2012;6(1):415.
[22] National Institute of Mental Health. Anxiety Disorders. In: US Department of Health and Human Services NIoH, editor. Bethesda, MD; 2009.
[23] Kruse P, Ladefoged J, Nielsen U, Paulev PE, Sorensen JP. Beta-Blockade used in precision sports: effect on pistol shooting performance. J Appl Physiol 1986;61(2):417–20.
[24] Brugues AO. Music performance anxiety—part 1. A review of its epidemiology. Med Probl Perform Art 2011;26(2):102–5.
[25] Vlcek M, Radikova Z, Penesova A, Kvetnansky R, Imrich R. Heart rate variability and catecholamines during hypoglycemia and orthostasis. Auton Neurosci 2008;143(1–2):53–7.
[26] Cryer P, Davis S. Chapter 345. Hypoglycemia. In: Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J, editors. Harrison's principles of internal medicine. New York: McGraw-Hill; 2012. <http://www.accessmedicine.com/content.aspx?aID=9141631>. Accessed 10.10.13.
[27] Boneva RS, Decker MJ, Maloney EM, Lin JM, Jones JF, Helgason HG, et al. Higher heart rate and reduced heart rate variability persist during sleep in chronic fatigue syndrome: a population-based study. Auton Neurosci 2007;137(1–2):94–101.
[28] Chervin RD, Teodorescu M, Kushwaha R, Deline AM, Brucksch CB, Ribbens-Grimm C, et al. Objective measures of disordered sleep in fibromyalgia. J Rheumatol 2009;36(9):2009–16.
[29] Pellissier S, Dantzer C, Canini F, Mathieu N, Bonaz B. Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. Psychoneuroendocrinology 2010;35(5):653–62.
[30] Haley RW, Vongpatanasin W, Wolfe GI, Bryan WW, Armitage R, Hoffmann RF, et al. Blunted circadian variation in autonomic regulation of sinus node function in veterans with Gulf War syndrome. Am J Med 2004;117(7):469–78.
[31] Bonnet MH, Arand DL. Heart rate variability in insomniacs and matched normal sleepers. Psychosom Med 1998;60(5):610–5.
[32] Broderick JE, Gold MS, Amin MM, Gold AR. Self-report somatic arousal correlates with sleep complaints among females with irritable bowel syndrome: a pilot study. J Sleep Disor: Treat Care 2012;1:2.
[33] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540–5.
[34] Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol 2005;32(5):811–9.
[35] Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213.
[36] Ware Jr JE, Kosinski M, Dewey J. How to score version 2 of the SF-36 health survey. Lincoln, RI: QualityMetric Incorporated; 2000.
[37] Sullivan MJL, Edgley K, Dehoux E. A survey of multiple sclerosis. Part 1: perceived cognitive problems and compensatory strategy use. Can. J Rehabil 1990;4:99–105.
[38] Ritvo PG, Fischer JS, Miller DM, Andrews H, Paty DWL. Multiple sclerosis quality of life inventory: a user's manual. National Multiple Sclerosis Society; 1997.
[39] Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J Abnorm Psychol 1995;104(1):3–14.
[40] Hosselet JJ, Norman RG, Ayappa I, Rapoport DM. Detection of flow limitation with a nasal cannula/pressure transducer system. Am J Respir Crit Care Med 1998;157(5 (Pt 1)):1461–7.
[41] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda: US Dept of Health, Education and Welfare; 1968.
[42] EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15(2):173–84.
[43] Agnew Jr HW, Webb WB, Williams RL. The first night effect: an EEG study of sleep. Psychophysiology 1966;2(3):263–6.
[44] Base SAS® 9.3 Procedures Guide: Statistical Procedures. Cary, NC: SAS Institute Inc; 2011. p. 26–28.

[45] Ferini-Strambi L, Bianchi A, Zucconi M, Oldani A, Castronovo V, Smirne S. The impact of cyclic alternating pattern on heart rate variability during sleep in healthy young adults. Clin Neurophysiol 2000;111(1):99–101.
[46] Bonnet MH, Arand DL. Hyperarousal and insomnia: state of the science. Sleep Med Rev 2010;14(1):9–15.
[47] Roth T, Roehrs T, Pies R. Insomnia: pathophysiology and implications for treatment. Sleep Med Rev 2007;11(1):71–9.
[48] Terzano MG, Parrino L. Evaluation of EEG cyclic alternating pattern during sleep in insomniacs and controls under placebo and acute treatment with zolpidem. Sleep 1992;15(1):64–70.
[49] Kyrou I, Chrousos GP, Tsigos C. Stress, visceral obesity, and metabolic complications. Ann N Y Acad Sci 2006;1083:77–110.