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THEORETICAL REVIEW

# Functional somatic syndromes, anxiety disorders and the upper airway: A matter of paradigms

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SUMMARY

The relationship between the functional somatic syndromes, anxiety disorders and the upper airway (particularly, sleep disordered breathing) remains ambiguous. This ambiguity, despite a growing body of research supporting a relationship, may result from the absence of a paradigm to explain how upper airway dysfunction can promote disorders commonly associated with one's mental health. This review models the functional somatic syndromes and anxiety disorders as consequences of chronically increased hypothalamic–pituitary–adrenal axis activity. It then examines the literature supporting a relationship between these disorders and upper airway dysfunction during wakefulness and sleep. Finally, building upon an existing paradigm of neural sensitization, sleep disordered breathing is linked to functional somatic syndromes and anxiety disorders through chronic activation of the hypothalamic–pituitary–adrenal axis.


## Introduction

Ask many specialists in Sleep Medicine to list the clinical consequences of sleep disordered breathing (SDB) and one can expect the list to include hypersomnolence, systemic hypertension, insulin resistance, hyperlipidemia and atherosclerosis. It is less likely that the list will include migraine headaches, sleep onset insomnia, body pain, irritable bowel syndrome (IBS) and post-traumatic stress disorder. This is so despite a growing body of literature that associates these *disorders of uncertain etiology* with SDB. Sleep Medicine physicians' overlooking the role of SDB in functional somatic syndromes (FSS) and anxiety disorders limits our ability to help patients and limits the growth of our understanding of the relationship.

The phenomenon described above may result from our limited understanding of the sequelae of SDB. Apnea/hypopnea causing recurrent oxyhemoglobin desaturation and sleep fragmentation, does not readily explain the symptoms of FSS and anxiety disorders. One can demonstrate associations in cross-sectional studies and treatment effects in sham-controlled longitudinal studies, but if one cannot provide a rationale, a paradigm, connecting SDB to pain, diarrhea or anxiety, one will have a difficult time convincing anyone about the truth of the relationship.

This review attempts to provide a paradigm explaining the role of the upper airway and SDB in the FSS and anxiety disorders. In this review, I will selectively draw upon the literature of the FSS, anxiety disorders, upper airway and SDB to support the development of the paradigm. This paradigm can be used by investigators to explain existing data and to formulate hypotheses and experiments bringing us closer to an authentic understanding of the role of the upper airway and SDB in the FSS and anxiety disorders.

## The terms and the thesis

For the reader who has not given much thought to the subject of this review, I will begin with a few definitions. The term, *functional somatic syndromes*[1–3] was introduced a little more than a decade ago to describe a group of previously discrete syndromes that were increasingly recognized to overlap in their distribution among people affected. A list of many of the FSS is provided in Table 1. The syndromes affect females more commonly than males (with the exception of war-related illness) and the symptoms associated with

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**Abbreviations**

| | |
|---|---|
| ACTH | adrenocorticotrophic hormone |
| CPAP | continuous positive airway pressure |
| EEG | electroencephalogram |
| FSS | functional somatic syndromes |
| GWI | Gulf War illness |
| HPA | hypothalamic pituitary adrenal |
| IBS | irritable bowel syndrome |
| MCS | multiple chemical sensitivity |
| OSA | obstructive sleep apnea |
| PTSD | post-traumatic stress disorder |
| SDB | sleep disordered breathing |
| TIA | transient ischemic attack |
| UARS | upper airway resistance syndrome |
| WTC | World Trade Center |

all of these syndromes, fatigue, pain, problems with concentration and memory, gastrointestinal hyper/hypomotility, and insomnia are out of proportion to identifiable pathology. To an investigator or a clinician working in Sleep Medicine, my including restless legs syndrome among the FSS may seem inappropriate. Restless legs syndrome, however, is currently thought to share a common pathophysiology with the other listed syndromes.[3] It is also a common complaint among FSS patients[3–5] and so participates in the overlap described above.

The term, *anxiety disorders* (Table 1), refers to a group of disorders characterized by excessive, irrational fear and dread and the physical signs and symptoms of *anxious arousal*.[6] *Anxious arousal* relates to the physical signs and symptoms associated with the feeling of anxiety that include: muscle tension, difficulty swallowing, trembling, twitching, irritability, sweating, nausea, lightheadedness, having to urinate frequently (irritable bladder), feeling out of breath, and hot flashes.

I am using the term, *sleep disordered breathing*, to include every form of *pharyngeal collapse during sleep* including obstructive sleep apnea/hypopnea, upper airway resistance syndrome (UARS) and primary snoring (without symptoms). By UARS, I mean subjective hypersomnolence or fatigue associated with inspiratory airflow limitation during sleep that does not meet the clinical threshold for obstructive sleep apnea/hypopnea (the threshold varies between laboratories). The UARS patient's hypersomnolence/fatigue decreases with effective pharyngeal splinting during sleep using nasal continuous positive airway pressure (CPAP) or an oral mandibular advancement appliance.

The thesis for this review (which underlies the paradigm being developed) is that among patients with FSS and anxiety disorders, SDB serves as a chronic physical stress (or *allostatic challenge*[c])[7] activating the hypothalamic–pituitary–adrenal (HPA) axis and causing the symptoms of FSS and anxiety disorders as manifestations of chronic allostatic challenge. To progressively develop this thesis, I will:

**Table 1**
The functional somatic syndromes and anxiety disorders.

| |
|---|
| *Functional somatic syndromes* |
| Chronic fatigue syndrome |
| Fibromyalgia |
| Migraine/tension headache syndrome |
| Irritable bowel syndrome |
| Temporomandibular joint syndrome |
| War-related illness (Gulf War illness) |
| Multiple chemical sensitivity/sick house syndrome |
| Restless legs syndrome |
| Mitral valve prolapse syndrome |
| Joint hypermobility syndrome |
| *Anxiety disorders* |
| Panic disorder |
| Generalized anxiety disorder |
| Social phobia |
| Posttraumatic stress disorder |
| Obsessive-compulsive disorder |

1) Provide an overview of the relationship between the HPA axis and the symptoms and signs of chronic allostatic challenge as presented by the field's pioneering investigator, Dr. Hans Selye
2) Review the literature supporting the paradigm of FSS and anxiety disorders as manifestations of chronic allostatic challenge
3) Review the literature supporting a role for the upper airway and SDB in the FSS and anxiety disorders
4) Develop, through a review of relevant literature, a model to explain SDB functioning as a chronic allostatic challenge in individuals with FSS and anxiety disorders.

Following the development of the paradigm, I will examine its utility for explaining the existing data on the relationship between FSS, anxiety disorders and SDB. I will also present alternative hypotheses that have been proposed to explain the same relationship.

## Hans Selye and the physiology of chronic *stress*

The study of the physiology of allostasis was begun in the first decades of the twentieth century by the endocrinologist Dr. Hans Selye. By subjecting rats to repetitive physical challenges (he referred to them as *stressors*) Selye produced the *general adaptation syndrome*, a triad of adrenal cortical hyperplasia, thymic atrophy and gastric erosions.[8] Beginning with his description of the general adaptation syndrome (caused by adrenocorticotrophic hormone release from the pituitary), Selye pioneered research into the HPA axis and its effects which he detailed in his annotated bibliography on the literature of stress, *Stress in Health and Disease*,[9] and summarized in his popular book, *The Stress of Life*.[10] Because of their completeness, Selye's writings provide a convenient overview of how activation of the HPA axis can give rise to illness in humans.

Although a detailed description of Selye's model for activation of the HPA axis by an allostatic challenge, involving hormones and the autonomic nervous system,[11] is beyond the scope of this review, several generalizations made by Selye are relevant. First, although a wide variety of allostatic challenges exist, the response they elicit through activation of the HPA axis is non-specific. As a result, one may recognize activation of the HPA axis, but be unable to readily determine the activating allostatic challenge. Second, the response to an allostatic challenge is produced not only by increasing or decreasing the level of mediators. Alterations can also occur in the sensitivity of end organs to those mediators (known as *conditioning*[12]). This complicates studying the activity of the HPA axis by measuring hormone levels. If HPA axis activation increases the sensitivity of end organs to hormones, one may not see an increase in the hormone level despite the increased effect. Third, Selye

[c] The term *allostasis* is meant to contrast with W.B. Cannon's *homeostasis*. While *homeostasis* refers to maintaining stability through achieving constancy of the internal environment, allostasis refers to maintaining stability through change that enables the organism to deal with increased demands. Selye referred to agents that caused an allostatic response in the organism (activation of the HPA axis) as *stressors*. The term *stress*, however, is popularly used to describe only emotional/psychological stress. I use the term *allostatic challenge* to remind the reader that such challenges can also be physical (such as exercise, hypo/hyperthermia, starvation, anemia, and others).

observed that disease in man originates not only from the specific effects of external agents on the body, but also from the response by the body to those agents that function as allostatic challenges. Therefore, Selye believed that activation of the body's non-specific defense system by a variety of agents was one source of illness in humans.

In *The Stress of Life*[10] and in *Stress in Health and Disease*,[9] Selye enumerated the adverse metabolic and functional consequences of *chronic* allostatic challenge. Many of the adverse metabolic consequences that he listed in 1976 (his last revision of the books) have since been associated with SDB (Fig. 1), including (references are to the sleep literature): hypertension[13] and pre-eclampsia,[14] which Selye associated with mineralocorticoids; hyperglycemia,[15] associated with glucocorticoids; myocardial infarction,[16] associated with chronically elevated adrenal corticoids and adrenaline; augmentation of inflammation,[17] associated with mineralocorticoids; erectile dysfunction,[18] polycystic ovaries[19] and growth hormone deficiency,[20] which Selye associated with the body's down-regulating reproduction and growth during a period of allostatic challenge. Table 2 lists Selye's 31 *warning signs of chronic stress* which are the symptoms/behaviors shared in common by patients with FSS and anxiety disorders. The association between the symptoms identified by Selye and chronic allostatic challenge remains the paradigm for many investigators today.[21–23] Thus, in his conception of the consequences of chronic allostatic challenge, Selye united a group of metabolic disorders (Fig. 1) recognized today to be associated with SDB with the symptoms/behaviors of the FSS and anxiety disorders (Table 2).

## FSS, anxiety disorders and chronic allostatic challenge

If Selye was correct in ascribing the symptoms of FSS and anxiety disorders to chronic allostasis, then one might expect evidence of chronic exposure to allostatic challenges among individuals with these disorders. Furthermore, according to Selye's ideas about how allostatic challenges alter the metabolic milieu leading to the general adaptation syndrome, one might expect evidence of HPA axis activation, increased sympathetic nervous system tone, and decreased gonadotrophic and growth hormones among individuals with FSS and anxiety disorders. Finally, because chronic allostatic challenge gives rise to both functional and metabolic disorders, one might expect evidence of the metabolic consequences of chronic allostatic challenge among patients with FSS and anxiety disorders. Indeed, the recent medical literature provides some of this evidence.

Several investigations demonstrate allostatic challenges among FSS patients more commonly than among healthy controls. Chronic fatigue syndrome, fibromyalgia and IBS have all been associated with a history of emotional/physical abuse, surgery, physical trauma and infection.[24–29] While these investigations suggest an association between allostatic challenges known to activate the HPA axis and the FSS, it is not clear that the preceding allostatic challenges were present *chronically*.

HPA axis activity among FSS patients and patients with post-traumatic stress disorder has also been studied extensively. These studies have demonstrated increased HPA axis activity among patients with IBS,[30] decreased HPA axis activity among chronic fatigue syndrome patients[31,32] and conflicting results among fibromyalgia[31,33] and post-traumatic stress disorder (PTSD) patients.[34] The varied findings regarding HPA axis activity between syndromes and the conflicting findings between investigators within syndromes may result both from differing research methods between studies and from difficulty evaluating HPA axis activity when both hormone levels and receptor sensitivities (*conditioning*) must be accounted for. At this time, investigators are still early in the process of unraveling the workings of this complex system.

**Table 2**
Selyes's 31 warning signs of chronic stress.

1. Bodily pain
   A. *Pain in the neck or lower back*
2. Headache
   A. *Migraine headache*
3. Irritable bowel/bladder syndrome
   A. *Diarrhea, indigestion, queasiness in the stomach and sometimes even vomiting*
   B. *The frequent need to urinate*
4. Sleepiness/fatigue
   A. *Predilection to become fatigued and loss of the Joie De Vivre*
5. Cognitive dysfunction
   A. Inability to concentrate, flight of thoughts and general disorientation
6. Depression, irritability
   A. *General Irritability, Hyperexcitation or Depression*
   B. *Impulsive behavior, emotional instability*
   C. *The overpowering urge to cry, or run and hide*
   D. *Premenstrual tension or missed menstrual cycles*
7. Signs and symptoms of anxiety/anxious arousal
   A. *Pounding of the heart*
   B. *Dryness of the throat and mouth*
   C. *Floating anxiety*
   D. *Emotional tension and alertness*
   E. *Trembling, nervous ticks*
   F. *Tendency to be easily startled*
   G. *High pitched nervous laughter*
   H. *Hypermotility* (an increased tendency to move about without any reason)
   I. *Sweating*
   J. *Nightmares*
8. Sleep disorders
   A. *Insomnia*
   B. *Bruxism*
9. Drug dependence
   A. *Increased smoking*
   B. *Increased use of legally prescribed drugs*
   C. *Alcohol abuse and drug addiction*
10. Not classified
   A. *Feelings of unreality, weakness or dizziness*
   B. *Stuttering and other speech difficulties*
   C. *Loss of or excessive appetite*
   D. *Neurotic behavior*
   E. *Psychoses*
   F. *Accident proneness*

The numbered headings are the author's classifications. Words in italics are those of Selye (from Chapter 9 of *The Stress of Life*).[10]

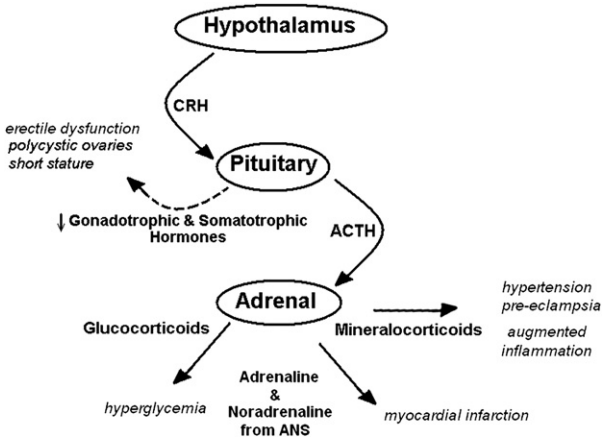


**Fig. 1.** This schematic diagram illustrates Selye's concept of the relationship between the metabolic manifestations of chronic stress and the hormones associated with the hypothalamic–pituitary–adrenal axis (indicated along the arrow shafts). The manifestations, including hypertension, pre-eclampsia, hyperglycemia, myocardial infarction, enhanced immune function, erectile dysfunction, polycystic ovaries and decreased stature in children, have all been described among patients with sleep disordered breathing. CRH – corticotrophin releasing hormone; ACTH – adrenocorticotrophic hormone; ANS – autonomic nervous system.

While our understanding of the relationship between HPA axis activity, FSS and anxiety disorders is incomplete, the relationship of the autonomic nervous system function to these disorders seems clearer. By analyzing heart rate variability, investigators have demonstrated increased sympathetic tone relative to parasympathetic tone among patients with fibromyalgia,[35] Gulf War illness (GWI),[36] IBS[37]and chronic fatigue syndrome.[38] The increased sympathetic tone observed among these patients is appropriate to individuals experiencing activation of the HPA axis with both adrenal medullary epinephrine and autonomic nervous system norepinephrine present.

If FSS and anxiety disorder patients are responding to a chronic allostatic challenge, then one might expect to observe associated disorders related to down-regulation of sexual function and growth among these individuals. There is a limited literature supporting this possibility. Investigators have found evidence of an association between fibromyalgia, IBS, anxiety disorders and polycystic ovarian syndrome in females.[39–41] Moreover, a survey of a large group of female veterans with PTSD found an increased prevalence among them of polycystic ovary disease, IBS, fibromyalgia and chronic pelvic pain.[42] Among males, a recent epidemiologic study has found an association between restless legs syndrome and erectile dysfunction.[43] Growth hormone deficiency has been observed among females with fibromyalgia and IBS[44,45] but it has not been found among chronic fatigue syndrome patients.[46] Therefore, some patients with FSS and anxiety disorders have demonstrated down-regulated sexual function and growth that characterize patients responding to an allostatic challenge.

If the FSS and anxiety disorders are a response to a chronic allostatic challenge, then one might also expect to see evidence of the metabolic consequences, metabolic syndrome, among individuals with FSS and anxiety disorders. Indeed, there is strong evidence for this association based on large epidemiologic studies. A study of nearly 16,000 people of mixed race and gender, The Atherosclerosis Risk in Communities Study, has found an association between microvascular retinopathy (associated with hypertension and predictive of stroke and other cardiovascular outcomes) and migraines.[47] Similarly, in a study of 798 transient ischemic attack (TIA) patients,[48] both migraine headaches and mitral valve prolapse were identified as risk factors for TIA in young individuals. In a population-based case-control study conducted in metropolitan, urban, and rural areas of the state of Georgia (United States), chronic fatigue syndrome was found to be a associated with metabolic syndrome.[48] In a large population-based study conducted in Taiwan (22,000 participants, including 3672 with panic disorder), patients with panic disorder were more likely to have hypertension, hyperlipidemia, diabetes, coronary artery disease, cerebrovascular disease and myocardial infarction.[49] Similarly, a study of over 1900 veterans participating in the Veterans Affairs' Normative Aging Study demonstrated an association between PTSD and coronary heart disease.[50] Thus, considerable data suggest that patients with FSS and anxiety disorders experience not only the functional complaints associated with chronic allostatic challenge, but also the metabolic consequences.

Although the evidence supporting a relationship between chronic allostatic activation of the HPA axis, FSS and anxiety disorders is incomplete, the role of the HPA axis in these disorders has gained credence among investigators[31,34,51,52] and is becoming the paradigm through which these disorders are understood.

## The upper airway in FSS and anxiety disorders

In addition to evidence for chronic activation of the HPA axis, FSS and anxiety disorders also share abnormal upper airway function in common. Fibromyalgia,[53,54] IBS[55] migraine headaches[56] and anxiety disorders[57] are more prevalent among individuals with rhinitis than among controls without nasal pathology. Moreover, among patients with nasal obstruction experiencing body pain and chronic fatigue, relief of nasal obstruction by endoscopic sinus surgery has been found to relieve the symptoms of pain[58] and chronic fatigue,[59] improving the quality of life of fibromyalgia patients.[60] These findings suggest the possibility that increased nasal resistance plays a role in the symptoms of FSS and anxiety disorders.

Narrowing of the maxillary arch with a high arched palate, a factor predicting the severity of sleep apnea,[61] is also very common among individuals with joint hypermobility[62,63] and mitral valve prolapse syndromes.[64] Cistulli and associates have demonstrated that the high arched palate of Marfan's syndrome patients leads to increased nasal resistance while the height of the palate correlates with the severity of sleep apnea in this group.[65]

In addition to the altered upper airway structure/function observed in individuals with FSS and anxiety disorders, epidemiologic studies have associated the symptoms of these disorders with SDB. In two large studies, habitual snoring was more common among chronic headache sufferers than among controls without headaches.[66,67] In an epidemiologic study of a large European population (19,000 participants), respondents with restless legs were twice as likely to be *loud* snorers as those without restless legs. In a large survey of US women conducted by the National Sleep Foundation, those assessed by questionnaire to be at high risk for sleep apnea had a 33% prevalence of restless legs.[68] In an earlier survey by the same foundation, a history of body pain was significantly correlated with the sleep complaints of snoring, insomnia and restless legs.[69] In a recent large study of questionnaire data obtained from New York City rescue/recovery workers exposed to the World Trade Center on 9/11/2001 and during the two-year cleanup that followed, a diagnosis of PTSD was associated with a high likelihood of sleep apnea at baseline (assessed by Berlin Questionnaire) and, among those who were at low likelihood at baseline, with an increased likelihood of developing sleep apnea in the following 1.4 years.[70] In a smaller study of 98 Dutch veterans of the Second World War, 55 of whom had PTSD, the occurrence of anxiety dreams was strongly associated with spousal reports of snoring.[71] Similarly, among 174 children with psychiatric disorders (half were diagnosed with anxiety/mood disorders), the prevalence of snoring was 56% compared to 17% in a control group of healthy children.[72] The association of headache, restless legs, body pain and anxiety with SDB supports a role for SDB in the pathophysiology of FSS and anxiety disorders.

A growing number of polysomnographic studies also support an association between SDB and FSS. Patients with mild sleep apnea and UARS (particularly females) have a high prevalence of FSS symptoms.[73] Furthermore a high prevalence of SDB has been observed in small groups of patients with fibromyalgia,[74–77] IBS[78] and cluster headaches.[79,80] Stabilization of the upper airway during sleep with either nasal CPAP or oral appliances has improved the symptoms of fibromyalgia (fatigue, pain, insomnia and gastrointestinal complaints),[75] cluster headache[80–82] and restless legs syndrome patients.[83] Thus, polysomnographic data and treatment trial data from several small clinical series support a role for SDB in the symptoms of FSS patients.

Although a large amount of circumstantial evidence links the upper airway and SDB to FSS and anxiety disorders, not everyone with SDB experiences the symptoms of FSS or anxiety disorders. In our study of inspiratory airflow dynamics during sleep in lean females with IBS,[78] we found that among females below age 40, lean IBS participants were distinguished from rigorously screened, matched, healthy controls by having mild inspiratory airflow

limitation during sleep. Above age 40, however, the increasing prevalence of inspiratory airflow limitation during sleep among our healthy females resulted in the same inspiratory airflow dynamics in both groups. Even obstructive sleep apnea may be asymptomatic. Pavlova and associates[84] examined the breathing during sleep of non-obese, asymptomatic adults and found an increased frequency of apnea and hypopnea among participants older than 50 years compared to younger individuals. Our findings[78] together with those of Pavlova and associates[84] suggest that while SDB could be *necessary* for the occurrence of the FSS and anxiety disorders, it is not *sufficient* for their occurrence; something more is needed.

## From SDB to FSS and anxiety disorders

To this point, it appears that FSS and anxiety disorders are associated with both a history of allostatic challenge[24–29] and with the presence of upper airway dysfunction/SDB.[65–69,71–73,75,78,85] The cross-sectional character of the studies supporting these associations, however, does not permit one to assess the interaction of allostatic challenge and SDB in the development of these disorders. To investigate such an interaction, one might find a cohort of individuals exposed to an allostatic challenge and then compare the inspiratory airflow dynamics during sleep between individuals who develop FSS and anxiety disorders and those who do not. Furthermore, in individuals with SDB who develop an FSS or anxiety disorder after an allostatic challenge, one might splint the pharynx with nasal CPAP and observe the effect upon symptoms. For both anxiety disorders and FSS, investigators have begun to perform these *longitudinal* studies and the results suggest an interaction between allostatic challenge and SDB in the development of these disorders.

The interaction of allostatic challenge with SDB in the development of anxiety disorders has been studied by Krakow and his group in a series of clinical investigations performed at the University of New Mexico-Albuquerque. In two clinical series, 40 of 44 crime victims with PTSD tested positive for either mild sleep apnea or UARS,[86] and 37 of 39 fire evacuees with PTSD tested positive for SDB.[87] In a comparative study of sexual assault victims, those with SDB had more severe symptoms of PTSD than did victims without SDB.[88] Concerning treatment, a telephone survey of 23 patients with PTSD, nightmares and SDB suggested improvement in nightmares and PTSD symptoms following treatment with nasal CPAP.[89] Similarly, Youakim and associates have reported a decrease in nightmares and anxious arousal in one patient with both PTSD and obstructive sleep apnea treated with nasal CPAP.[90] Although Krakow et al.'s studies lacked controls who were exposed to the allostatic challenge but did not develop PTSD, they corroborate the presence of SDB in individuals who develop PTSD following an allostatic challenge (similar to the survey studies cited above[71,72]), suggest the absence of SDB among those who experience the emotional stress but have milder anxiety symptoms, and (together with Youakim et al.'s case report) suggest improvement of anxiety symptoms in PTSD patients treated with nasal CPAP.

In the realm of war-related illness, a pair of experiments has been conducted by Amin et al. in our sleep laboratory at the DVA Medical Center at Northport, NY. The first Gulf War (1990–1991) presented a variety of allostatic challenges for troops who were engaged. Among these were intense heat, sleep deprivation, combat (the anticipation of SCUD missiles/chemical weapons) and the inhalation of volatile materials from oil well fires. Of the 700,000 troops who were deployed during the first Gulf War, it is estimated that 200,000 returned with symptoms of fatigue, pain, insomnia, cognitive dysfunction and gastrointestinal motility problems known today as GWI.[91] Beginning in 2005, Amin et al. recruited 18 male veterans with persistent GWI and 11 male veterans of the same war matched for age and obesity who remained asymptomatic. Polysomnography revealed SDB among all of the GWI participants with 95% of breaths during continuous N2 sleep being flow-limited. Among the controls, there was little SDB and only 36% of the breaths during continuous N2 sleep were flow-limited.[92] In a randomized, 3-week, sham-controlled trial of nasal CPAP among the 18 veterans with GWI, treatment with nasal CPAP resulted in an improvement in fatigue, pain, sleep, cognitive function and physical/mental health that ranged from 35% to 45%[93] (comparable to the improvement in fibromyalgia symptoms we observed in a previous clinical series[75]). These findings in veterans with GWI suggest that among a cohort of individuals exposed to an allostatic challenge, those with SDB are more likely to develop the symptoms associated with the FSS.

The studies of Krakow et al. and Amin et al. suggest that after an allostatic challenge, the presence of SDB leads to functional consequences that are ameliorated by splinting the upper airway with nasal CPAP. What is unknown, however, is whether SDB was present among the symptomatic individuals prior to the allostatic challenge. For the purpose of this review, I will assume that SDB was present in these individuals prior to the allostatic challenge that resulted in their symptoms. From this perspective, it appears that exposure to an allostatic challenge changes the body's *response* to SDB from *benign neglect* to *mobilization to meet an allostatic challenge*. Thus, for our purposes, understanding the relationship between SDB, FSS and anxiety disorders will require a model that can account for the body's changing response to SDB.

## Multiple chemical sensitivity and neural sensitization

Multiple chemical sensitivity (MCS), an FSS that often co-exists with FSS like fibromyalgia and GWI, provides us with a *model* that can explain how a benign stimulus like mild SDB (snoring or mild sleep apnea) transforms into an allostatic challenge. MCS is an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects.[94] Pesticides, cigarette smoke, paint fumes, wood preservatives, office photocopier fumes, perfumes, and epoxy are among the chemically unrelated compounds that commonly trigger MCS. The symptoms of MCS include fatigue, cognitive problems, dizziness, depression, headache and joint pain.[94] To account for the transformation of a benign odorant into an allostatic challenge, Bell and her associates at the University of Arizona have postulated a paradigm of MCS based upon a process of *neural sensitization*.[95–97]

Neural sensitization of the brain's limbic system (Fig. 2) is a phenomenon that has been studied extensively as a model for substance abuse/addiction, bipolar disorder and anxiety disorders.[98–100] The limbic system is the portion of the brain that recognizes and reacts to novel stimuli.[101] Its main controller, the amygdala, receives input from the external/internal environment and analysis of the input by the hippocampus (which compares it to memories of previous experience), and initiates emotional, hormonal, autonomic, motor and cognitive responses that benefit the organism.[101] Neural plasticity, the brain's capacity to develop new anatomic and physiological connections, enables the limbic system to learn from experience and modify its responses. Therefore, neural plasticity may make the limbic system vulnerable to sensitization to a variety of stimuli.

The limbic system can become sensitized to sedatives, stimulants and electrical stimuli, producing a variety of responses. Repetitive exposure of mice to a fixed dose of alcohol, opiates or

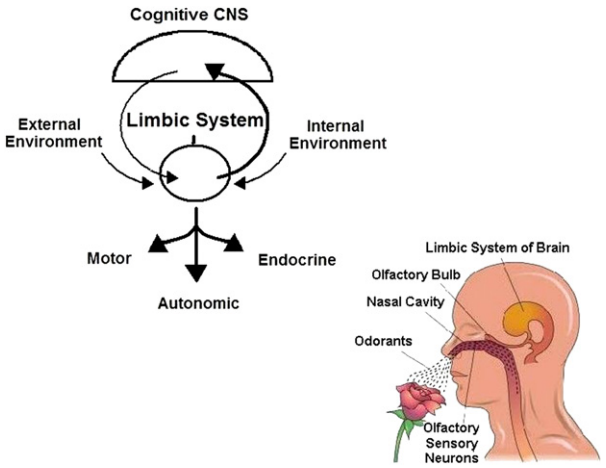


**Fig. 2.** This figure illustrates, schematically, the inputs and outputs of the limbic system. The thin arrows indicate the inputs to the limbic system from the external and internal environments and from cognition. The thick arrows indicate the output of the limbic system initiating responses that involve motor function, the autonomic nervous system and activation of the hypothalamic–pituitary–adrenal axis (endocrine). The lower right hand portion of the figure demonstrates that odorants (external environment) input directly into the limbic system through the olfactory nerve.

amphetamines results in a progressive increase in their locomotor response to the drug, a phenomenon known as *behavioral* sensitization.[102] Repetitive exposure of an animal to focal electrical stimulation of the limbic system large enough to cause a short seizure with little motor accompaniment results in progressive increases in both the duration and motor accompaniment of the seizure, a phenomenon known as *kindling*.[103] Neural sensitization of the limbic system demonstrates a certain degree of non-selectivity with cross-sensitization between stimuli occurring.[104–106] In addition, emotional stress (by maternal separation, restraint or foot-shock) in rodents, without exposure to specific stimuli, induces neural sensitization to ethanol,[107] morphine,[108] amphetamine,[109] cocaine[110] and electrical kindling of the limbic system.[111] Thus, neural sensitization is a somewhat non-selective process characterized by the amplification of the response to a variety of stimuli with allostatic challenge having the ability to sensitize, non-selectively.

Investigators of neural sensitization have identified several attributes in animals and humans that are associated with a predisposition to becoming sensitized. Among these characteristics are female gender,[112] hyper-reactivity to the novel or unfamiliar[113,114] (shyness, in humans[113]) and a preference for sweets.[115] Furthermore, the children of alcoholic fathers (alcoholism being a form of neural sensitization) have increased alpha frequency power in their electroencephalogram (EEG).[116,117] The presence of characteristics predisposing to neural sensitization in a patient population serves as circumstantial evidence for neural sensitization playing a role in the illness.

Bell's paradigm of MCS begins with the observation that individuals complaining of MCS have several of the attributes predisposing to neural sensitization. They are predominantly female[94]; they demonstrate increased alpha frequency power of the EEG[118]; they score higher than healthy controls on validated ratings of shyness and preference for sweet foods.[119] These attributes led Bell and her associates to propose that MCS results from sensitization of the limbic system to a variety of volatile chemical odorants reaching it through the olfactory nerve with the outcome being the recognition of these chemicals as allostatic challenges.[95–97] With a single catastrophic exposure (activating the HPA axis) or repetitive lesser exposures to these chemicals, the symptoms related to these stimuli are amplified. Thus, Bell's paradigm extends neural sensitization beyond amplification of a behavioral response or of the extent of a seizure to amplification of the allostatic response to an odorant.

## Neural sensitization to SDB

The relation of SDB to FSS and anxiety disorders fits Bell's paradigm of MCS very well. Given that MCS is one of the FSS and that it occurs in individuals with other FSS like fibromyalgia and GWI, it is reasonable to conclude that any FSS patient may have attributes that predispose to neural sensitization. FSS and anxiety disorder patients are predominantly female[1,120] demonstrate increased alpha frequency power in their sleeping EEG[121] and an increased prevalence of alcoholic fathers.[122] In addition, shyness and a preference for sweets are both characteristics of anxiety disorder patients. Indeed, the personality trait *shyness* represents the mild end of the spectrum of social phobia,[123] and a preference for sweets is characteristic of females with anxiety disorders,[124] particularly during their associated bouts of sleep-related eating.[125,126] Therefore, FSS and anxiety disorders patients are characterized by attributes that support their being vulnerable to neural sensitization.

Figs. 3 and 4 illustrate a model of how the limbic system may become sensitized to pharyngeal collapse during sleep among patients with FSS and anxiety disorders. Fig. 3 indicates that neural sensitization begins with a large allostatic challenge (a *trigger factor*) that greatly activates the HPA axis.[24–29] The activation of the HPA axis results in the non-specific sensitization of the limbic system predisposing the individual to respond to a variety of odorants *and pharyngeal collapse* as an allostatic challenge with HPA axis activation. The tendency to neural sensitization is promoted by the hereditary factors: female gender, increased EEG alpha power/alcoholic father, shyness and sweet food-preference. Among individuals without pharyngeal collapse during sleep, as the allostatic challenge subsides, HPA axis activity lessens (Fig. 4).

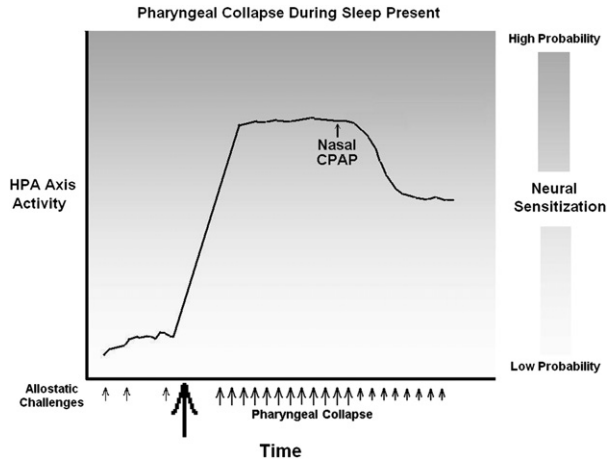


**Fig. 3.** This figure illustrates a model of neural sensitization of the limbic system in an individual with sleep disordered breathing. The sensitization occurs when a strong allostatic challenge (an emotional or physical *trigger* factor; represented as a large arrow beneath the abscissa) leads to marked activation of the hypothalamic–pituitary–adrenal (HPA) axis. Higher levels of HPA axis activity increase the probability of neural sensitization predisposing to the recognition of previously benign stimuli such as odorants and pharyngeal collapse during sleep as allostatic challenges. Following neural sensitization, the nightly occurrence of snoring or hypopnea leads to chronic stimulation of the HPA axis (a *perpetuating* factor represented as a chain of smaller arrows beneath the abscissa) and the symptoms of *chronic stress*, the functional somatic syndromes and anxiety disorders. Using nasal CPAP during sleep (black arrow above), by preventing pharyngeal collapse during sleep, lessens the allostatic challenge and lowers HPA axis activity ameliorating the symptoms of *chronic stress*.

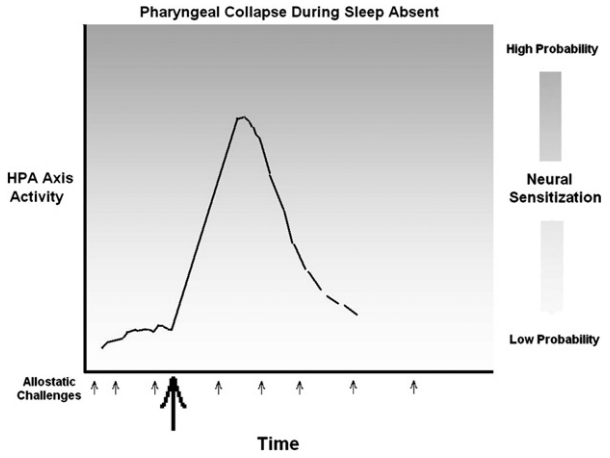


**Fig. 4.** This figure illustrates the model of neural sensitization of the limbic system in an individual without sleep disordered breathing. As in Fig. 3, this individual also undergoes a marked allostatic challenge which *triggers* neural sensitization as detailed in the legend for Fig. 3. In this individual without pharyngeal collapse, the chronic, nightly activation of the HPA axis is absent (the *perpetuating* factor of pharyngeal collapse during sleep is absent) and there is a return toward baseline levels as the allostatic challenge subsides. The figure shows that although episodic allostatic challenges continue, they are not sufficient to lead to the symptoms of *chronic stress* in the absence of pharyngeal collapse during sleep.

Among individuals with SDB, the nightly occurrence of pharyngeal collapse serves as an allostatic challenge (a *perpetuating factor*), chronically activating the HPA axis, causing the symptoms associated with FSS and anxiety disorders. Prevention of SDB with nasal CPAP (the degree of prevention dependent upon CPAP compliance; Fig. 3) reduces the allostatic challenge activating the HPA axis and alleviates the symptoms of FSS and anxiety disorders. Thus, one can model the relationship of SDB to FSS and anxiety disorders as a process of limbic system sensitization to SDB.

Having proposed pharyngeal collapse as a stimulus to which the limbic system can be sensitized, an important issue remains to be addressed. All of the stimuli that have been found to cause neural sensitization are either chemical or electrical and have clear pathways to the limbic system through the blood and olfactory nerve (for alcohol, stimulants, sedatives and odorants) or through neighboring neurons (for kindling). Having modeled the relationship between SDB, FSS and anxiety disorders after Bell's paradigm for MCS, how the limbic system can sense pharyngeal collapse with inspiratory airflow limitation and differentiate it from non-flow-limited breathing remains to be addressed.

## Airflow and the olfactory nerve

In Bell's model of MCS, volatile odorants stimulate the limbic system through the olfactory nerve (Fig. 2). For the limbic system to be sensitized to pharyngeal collapse during sleep, the same olfactory nerve can provide access because the olfactory nerve also senses airflow. The sensation of airflow by the olfactory nerve results in a 40 Hz electrical burst in the olfactory bulb of the limbic system, as well as the medial amygdala, piriform cortex and lateral olfactory stria of waking monkeys that persists in the absence of odorants.[127] This electrical burst, coupled with the respiratory cycle, is enhanced by occlusion of the contralateral nostril and mouth and is eliminated when the olfactory nerve is anesthetized.[127] Recently, researchers have discovered that sensing pressure is a *non-specific* function of the olfactory sensory neuron, the same neuron that senses *specific* odorants.[128] The effect of pressure is to partially depolarize the olfactory sensory neuron making it more sensitive to firing with fewer molecules of its specific odorant. It has been suggested that this is the reason for sniffing when one is trying to detect a faint odor.[128] Thus, the same olfactory sensory neuron that brings odorants in contact with the limbic system has the potential to communicate changes in inspiratory airflow/pressure during sleep.

Olfactory nerve input of airflow/pressure into the limbic system has already been associated with pathological consequences in humans. Among patients with temporal lobe (limbic system) epilepsy, nasal hyperventilation increases the frequency of epileptic electrographic abnormalities while oral hyperventilation tends to suppress them.[129] Locally anesthetizing the olfactory nerve negates the effects of nasal hyperventilation in these individuals.[129] Therefore, temporal lobe epilepsy is a clinical model of the olfactory nerve triggering a limbic system disorder in response to airflow/pressure.

How might flow-limited inspiration and non-flow-limited inspiration differentially stimulate the olfactory nerve? During inspiratory airflow limitation, there is a more rapid decrease in nasal pressure (an increase in nasal airflow) at the start of inspiration with a longer duration of inspiratory airflow (Fig. 5). Although the peak inspiratory airflow (nadir in nasal pressure) during flow-limited breathing is not as high as during breathing in the absence of inspiratory airflow limitation (Fig. 5), the longer duration of inspiratory airflow (and negative pressure) may cause greater stimulation of the olfactory nerve and the limbic system. Thus, the differing relationships between airflow/pressure and time in flow-limited and non-flow-limited inspiration, makes it possible for flow-limited inspiration to provide a unique stimulus to the limbic system through the olfactory nerve. Whether flow-limited inspiration is processed differently from non-flow-limited inspiration by the limbic system remains to be determined.

## The utility of the neural sensitization paradigm and its limits

The neural sensitization paradigm for the relationship of SDB to the FSS and anxiety disorders provides explanations for a variety of observations that have been made concerning SDB, the FSS and

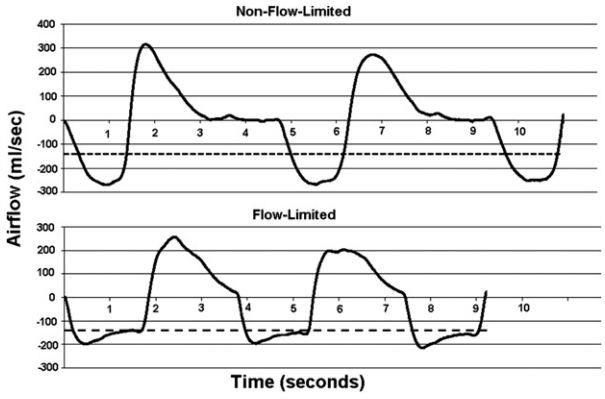


**Fig. 5.** This figure illustrates 3 non-flow-limited and 3 flow-limited breaths in the same individual during continuous N2 sleep at two different times during the night (inspiration is down-going). Both plots mark an inspiratory flow of 140 ml/s with a hatched line for the purpose of comparison. During the period of non-flow-limited breathing, the increase in inspiratory flow is more gradual and inspiratory flows are greater (nasal pressure decreases more) but the period of inspiration is shorter and the olfactory nerve experiences shorter periods of subatmospheric pressure. During flow-limited breathing, maximal inspiratory airflow is not as great (nasal pressure does not fall as much), but inspiratory airflow increases more rapidly and the period of inspiration is longer exposing the olfactory nerve to longer periods of subatmospheric pressure. The prolonged negative nasal pressure can be sensed by the olfactory nerve and transmitted to the limbic system.

anxiety disorders. The examples that follow represent a sampling of reasoning from the paradigm.

The neural sensitization paradigm can explain the association of allostatic challenges that are not chronic events (like a whiplash injury or a viral infection) with the FSS. According to this paradigm, activation of the HPA axis at the time of the *triggering* acute allostatic challenge sensitizes the limbic system to SDB as an allostatic challenge (much as emotional stress in rodents leads to behavioral sensitization to drugs and to the kindling of seizures). SDB then becomes the *perpetuating* allostatic challenge that results in the symptoms of the FSS and anxiety disorders (Fig. 3). This *perpetuating* allostatic challenge can be ameliorated by splinting the upper airway during sleep with nasal CPAP or mandibular advancement.

The neural sensitization paradigm also explains the high prevalence of females and the alpha frequency intrusion into sleep observed among patients with FSS[121] and mild SDB (UARS and mild sleep apnea[73,130]). According to the paradigm, female gender and increased alpha power in the EEG are markers for susceptibility to the neural sensitization[116,117] that creates a chronic allostatic challenge of SDB.

The neural sensitization paradigm can also explain discrepancies we have observed among asymptomatic controls between our studies of inspiratory airflow dynamics during sleep in females with IBS[78] and males with GWI[92] (both studies have been discussed above). Among our IBS controls, females above age 40 demonstrated considerable SDB while among our GWI controls there was little SDB. The paradigm suggests that among our IBS controls, some were asymptomatic because they had no SDB while others were asymptomatic because they had SDB, but had not become sensitized by an allostatic challenge. Among our GWI controls, all had been exposed to the allostatic challenges of the Persian Gulf War. Those with SDB underwent neural sensitization and developed GWI, leaving those without SDB to become our asymptomatic controls.

The neural sensitization paradigm also provides an explanation for the perplexing relationship that has been observed between the prevalence of FSS and anxiety disorders, and the severity of SDB. Among SDB patients, as the apnea/hypopnea index increases, the prevalence of FSS symptoms *decreases*.[73] Similarly, among patients with FSS and anxiety disorders, the apnea/hypopnea index tends to be low. Among 18 females with fibromyalgia for whom we performed polysomnography, the mean apnea/hypopnea index was 2.4/h.[75] The mean apnea/hypopnea index for 18 GWI participants in Amin et al.'s study[92] was 18/hr with 13/18 below 10/hr. Similarly, Krakow et al.'s patients with PTSD had values of apnea/hypopnea index below 20/h.[86–88] If SDB has a causative role in FSS and anxiety disorders, why are these disorders found in those patients with the mildest SDB?

The reason for the paradoxical relationship that exists between the prevalence of FSS and anxiety disorders and the severity of SDB stems from how we understand SDB. According to the existing paradigm as the severity of SDB decreases, the frequency of arousals from sleep and of oxyhemoglobin desaturations also decreases. However, if the prevalence of a disorder related to SDB is increasing should there not be an *increase* in some factor related to SDB? There is. The research characterizing pharyngeal collapsibility using the critical pressure (Pcrit)[131] has demonstrated that with decreasing pharyngeal collapsibility (decreasing Pcrit), there is a decrease in apnea/hypopnea index[132] and a shift from a predominance of apnea to a predominance of hypopnea in disordered breathing events.[133] Thus, as the severity of SDB decreases, the prevalence of hypopnea and snoring increases. While complete apnea isolates the nasal airway from the hypopharynx and results in nasal pressure that is equal to atmospheric pressure, hypopnea and, to a greater extent, snoring lead to prolonged decreases in nasal pressure (Fig. 5). The neural sensitization paradigm postulates that SDB stimulates the limbic system through the effect of subatmospheric pressure in the nasal airway on the olfactory nerve. This effect is likely to be most pronounced among UARS and mild sleep apnea patients with predominantly snoring and hyponea and to decrease as the prevalence of *apnea* increases with increasing apnea/hypopnea index (nasal pressure becoming equal to atmospheric pressure). Thus, by modifying our understanding of how SDB impacts man, we can hypothesize a mechanism for decreasing severity of SDB leading to an increasing prevalence of FSS and anxiety disorders.

In addition to providing a paradigm to explain the relationship of SDB to the FSS and anxiety disorders, the neural sensitization paradigm also explains observations that have been made concerning the treatment of SDB. Those of us who have been practicing Sleep Medicine since before nasal CPAP became available remember the extraordinary first experience of seeing a patient with an apnea/hypopnea index of 80/h go to bed exhausted and wake up refreshed, demanding a nasal CPAP unit of his own, after a nasal CPAP titration study. In the intervening years, poor compliance with nasal CPAP among some patients has complicated our approach to treating SDB. A large prospective, cohort study of factors predisposing to CPAP non-compliance, performed by Pelletier-Fleury and associates,[134] has found that non-compliance is greater among females, among individuals with a body mass index below 30 kg/m$^2$ and among those with an apnea/hypopnea index below 30/hr. The characteristics of the CPAP non-compliant group described by Pelletier-Fleury and associates are found in patients with UARS and mild sleep apnea,[73] patients in whom the neural sensitization paradigm may play a role. Can the neural sensitization paradigm help us to understand why this patient population might be more poorly compliant with nasal CPAP?

To understand why SDB patients susceptible to neural sensitization may be less compliant with nasal CPAP than are other SDB patients, it is first important to recognize that the two paradigms of SDB mentioned in this review, pharyngeal collapse giving rise to apnea/hypopnea, repetitive arousals and oxyhemoglobin desaturation (I will call this the *sleep apnea paradigm*), and the neural sensitization paradigm, are not mutually exclusive. Both can have a role in different patients with SDB. The roles of pharyngeal collapse during sleep in these two paradigms, however, are somewhat different. In the sleep apnea paradigm, pharyngeal collapse is the *immediate* cause of the sleep disturbance. When nasal CPAP is applied, the pharynx is splinted open, hypoventilation does not occur and the repeated arousals from sleep are eliminated. In this paradigm of SDB, the improvement in sleep quality induced by nasal CPAP begins immediately. In the neural sensitization paradigm, it is not pharyngeal collapse, but the activity of the HPA axis that disrupts sleep. The HPA axis and sympathetic nervous system create a state of hyperarousal and insomnia among patients with FSS and anxiety disorders that prevents sleep,[135] enabling them to recognize and respond to a threat. Similarly, the frequent shifts from deeper to lighter sleep stages throughout the night[136–139] (or the unstable sleep of the cyclic alternating pattern[140–143]) and the increased alpha frequency in the EEG[121] of patients with FSS and anxiety disorders can be viewed as an adaptation of sleep to an allostatic challenge. The light, unstable sleep enables the organism to recognize a threat and to respond.[144] In the neural sensitization paradigm of SDB, pharyngeal collapse is the allostatic challenge. When nasal CPAP is applied to the patient, the elimination of pharyngeal collapse is first perceived by the limbic system which deactivates the HPA axis and decreases the level of stress hormones. The

change in metabolic state, over a longer period, leads to normalization of sleep. Thus, the patient for whom SDB is an allostatic challenge leading to poor sleep quality recovers more slowly after starting nasal CPAP. During the first few nights with nasal CPAP, despite his patent airway, his insomnia persists, his sleep remains unconsolidated, and the new mask on his nose can further impair his sleep. This situation can lead to an unwillingness of the patient to use nasal CPAP. If he persists in using nasal CPAP, however, this patient will derive the benefit of decreased HPA axis activity decreasing insomnia and consolidating sleep. This understanding of CPAP non-compliance is supported by the study of Drake and associates[145] who found that the change in sleep efficiency between a patient's diagnostic polysomnogram and his nasal CPAP titration study predicted his compliance during the first 1.5 months of CPAP use. Patients who increased their sleep efficiency *immediately* with nasal CPAP had a 50% greater compliance (6.1 h/night) than patients who decreased their sleep efficiency from the diagnostic polysomnogram to the CPAP titration night (4.1 h/night; their poor sleep during the titration night suggesting little immediate improvement in sleep by nasal CPAP and presaging difficulty adjusting to the treatment). Therefore, the neural sensitization paradigm provides an alternative pathophysiology of SDB that enables us to make sense of the differing responses of patients to treatment.

Although the neural sensitization paradigm provides explanations for a variety of observations concerning patients with SDB, FSS and anxiety disorders, it is only as valid as the 2 paradigms on which it is based: Selye's paradigm of the consequences of chronic *stress* and the *neural sensitization* paradigm of MCS, and the assumption that the presence of SDB precedes the onset of symptoms among FSS and anxiety disorder patients. Selye's paradigm of the consequences of chronic stress has withstood the test of time. While subsequent investigation has added to our knowledge of mediators and mechanisms involved, the consequences attributed to chronic allostatic challenge remain largely unchanged.[146] Bell's neural sensitization model remains one paradigm of MCS. The assumption that SDB is present among FSS and anxiety disorders patients prior to their becoming symptomatic remains to be tested (see Research Agenda 5). Thus, the foundations for the paradigm presented in this review represent reasonable speculation.

## Alternative paradigms

Although the relationship between SDB, FSS and the anxiety disorders is not one of the more extensively reviewed topics in Sleep Medicine, alternative paradigms for the relationship exist.

Krakow and associates, among the original investigators in this field, speculated on the significance of the mild SDB they observed in so many of their patients with PTSD in a review published in 2002[147], before FSS were also recognized to be associated with mild SDB. The essence of their paradigm is that the hyperarousal related to stress in PTSD patients, destabilizes the continuity of sleep and the control of breathing, leading to the SDB that is observed among them. The SDB then further destabilizes sleep leading to the marked insomnia and nightmares experienced by many PTSD patients. It would be reasonable to assume that the SDB created by this mechanism would be relatively mild, as observed in their PTSD patients. A limitation of this paradigm, one recognized by Krakow and associates, is that it does not explain the decrease in *post-traumatic stress* experienced during wakefulness by their patients treated for SDB.[89] They postulated that, perhaps, the SDB contributed to the post-traumatic stress in some way, but they did not address a possible mechanism. Thus, an early paradigm of the relationship between anxiety disorders and SDB was that among patients with both, the SDB was a consequence of the anxiety disorder.

A second paradigm exists for the relationship between SDB, FSS and anxiety disorders that I have heard described, but have not seen published. The essence of this paradigm is that SDB is unrelated to FSS and anxiety disorders, but worsens the symptom severity of these disorders through sleep fragmentation. For pain, a symptom that occurs among many FSS and anxiety disorder patients, there is even supporting evidence for sleep deprivation worsening the symptom.[148] This paradigm helps to explain the improvement in the severity of FSS and anxiety disorder symptoms observed following splinting of the pharyngeal airway during sleep.[75,81,83,93] A limitation of this paradigm is that it does not explain the inverse relationship that has been observed between the prevalence of FSS symptoms and the apnea/hypopnea index[73] nor the predominance of mild SDB among patients with FSS[75,77,92] and anxiety disorders.[86–88] If SDB is unrelated to FSS and anxiety disorders there should be no trend toward mild SDB among the latter patients. Moreover, if sleep fragmentation worsens the symptoms of FSS and anxiety disorders, why don't these disorders predominate among patients with the worst sleep fragmentation, patients with severe SDB? Thus, a paradigm in which SDB is unrelated to FSS and anxiety disorders, but worsens the symptoms of these disorders through sleep fragmentation has limited utility.

Although there are differences in paradigms concerning the relationship of SDB to FSS and anxiety disorders, a larger contrast in paradigms exists in this review that has not yet been addressed. This contrast in paradigms concerns the *consequences of chronic allostatic challenge*. In this review, I have used Selye's paradigm for the *consequences of chronic stress* (Fig. 1, Table 2) to identify those consequences (metabolic and functional) among patients with FSS and anxiety disorders. Among investigators of SDB, however, the paradigm appears to be somewhat different. In the remainder of this review, I will briefly compare and contrast the two paradigms.

Most SDB investigators believe that the metabolic consequences of chronic allostatic challenge may be found among SDB patients.[149] Hypertension,[13] glucose intolerance,[15] hyperlipidemia,[150] increased levels of catecholamines[151] and of inflammatory cytokines,[17] and atherosclerosis[16] have been demonstrated among patients with sleep apnea. SDB is viewed by these investigators as the source of the allostatic challenge[15,149] with some even postulating a feed forward loop in which metabolic syndrome then promotes upper airway collapse during sleep.[149] Although the mechanism by which SDB activates the HPA axis is uncertain to these investigators, they postulate a role for recurrent hypoxemia or sleep fragmentation.[15,149] Thus, regarding the metabolic consequences of chronic allostatic challenge, the paradigm of SDB investigators is similar to Selye's paradigm.

On the issue of down-regulation of growth and sexuality during chronic allostatic challenge, a difference appears between the paradigms of Selye and of SDB investigators. Among children with SDB, investigators have observed a decreased level of growth factors with growth retardation that can be reversed by adenotonsillectomy.[20] Similarly, erectile dysfunction has long been viewed as a consequence of SDB, although factors other than altered testosterone levels may have a role in its development.[18] Polycystic ovarian syndrome, a consequence of decreased gonadotrophic hormone, however, is considered a cause of SDB among females and not viewed as a consequence.[19] The presence of hypertension, insulin resistance, hyperlipidemia and atherosclerosis among women with the polycystic ovarian syndrome supports a role for chronic allostatic challenge in this syndrome.[19] But whether mild pharyngeal collapse during sleep is the chronic

allostatic challenge that promotes polycystic ovarian syndrome in women (and then, with decreased estrogen, feeds forward to more severe SDB) has not been explored. Therefore, among SDB investigators, the paradigm for down-regulation of growth and sexuality during the chronic allostatic challenge of SDB (Fig. 1) does not address polycystic ovarian syndrome as an example of sexual down-regulation.

Finally, regarding insomnia, fatigue, cognitive dysfunction, pain and diarrhea/constipation, symptoms viewed by Dr. Hans Selye as the functional consequences of chronic allostatic challenge (Table 2), the paradigm of SDB investigators is silent. Indeed, until the recent publications of Amin and associates,[93] the literature associating the FSS with SDB makes no mention of chronic activation of the HPA axis by SDB as a potential source of these syndromes.[66–69,73–77,85] Identifying the functional complaints of SDB patients as possible outcomes of chronic allostatic challenge, similar to the metabolic outcomes so readily recognized, would increase their recognition among SDB patients by sleep clinicians and investigators.

Our understanding of the relationships between FSS, anxiety disorders, the upper airway and SDB remains incomplete. As such, there exist a variety of paradigms developed by endocrinologists, mental health professionals and sleep clinicians/investigators that attempt to explain the large amount of data that has been collected about these disorders. At this point, there is no *right* or *wrong* paradigm. Paradigms differ, however, in the spectrum of disorders they address, their capacity to explain existing data, and the questions they lead us to investigate. By continuing to develop new paradigms and to refine existing ones as new data become available, we will eventually reach an authentic understanding of the relationship between FSS, anxiety disorders, the upper airway and SDB.

**Practice points**

1) The endocrinologist, Dr. Hans Selye, bundled the symptoms that characterize functional somatic syndromes and anxiety disorders together with hypertension, pre-eclampsia, hyperglycemia, augmented inflammation, myocardial infarction, polycystic ovarian syndrome, erectile dysfunction and growth retardation as the consequences of chronic activation of the hypothalamic–pituitary–adrenal axis.
2) Studies of patients with functional somatic syndromes and anxiety disorders have demonstrated a history of psychological and physical allostatic challenges that differentiate them from healthy controls.
3) Studies of patients with functional somatic syndrome and anxiety disorders have demonstrated upper airway dysfunction during wakefulness and sleep. In a small number of preliminary studies, normalization of upper airway function has resulted in an improvement of symptoms among functional somatic syndromes and anxiety disorders patients.
4) The limbic system of the brain, containing the hypothalamus, is the brain's *first response system* originating adaptive responses to internal and external stimuli. If the limbic system could learn to recognize pharyngeal collapse during sleep as a threat, the resulting chronic activation of the hypothalamic–pituitary–adrenal axis could predispose to the functional somatic syndromes, anxiety disorders and the variety of metabolic consequences associated with sleep disordered breathing.

**Research Agenda**

1) Functional somatic syndrome and anxiety disorders patients demonstrate not only the functional consequences of chronic allostasis, but also the metabolic consequences. Symptoms of functional somatic syndromes are common in patients with mild sleep disordered breathing and become less common as the apnea hypopnea index increases. Do the metabolic consequences of sleep disordered breathing follow a similar distribution among sleep disordered breathing patients?
2) If sleep disordered breathing is a chronic allostatic challenge predisposing to the functional somatic syndromes and anxiety disorders, then nasal CPAP is a tool that can be utilized to alter the physiology of these disorders. How does treatment with nasal CPAP affect heart rate variability (sympathetic/parasympathetic balance) and functional imaging of limbic system structures among patients with functional somatic syndromes and anxiety disorders?
3) The sensing of inspiratory airflow by the olfactory nerve and its transmission to the limbic system is a piece of the neural sensitization paradigm presented in this review. In an animal model, how does olfactory nerve transmission to the limbic system vary between non-flow limited and flow-limited breathing? Does neural sensitization of the animal (with a drug or emotional stress) alter the limbic system's response to olfactory nerve input under conditions of flow-limited breathing?
4) Dr. Hans Selye's *warning signs of chronic stress* include not only the symptoms of functional somatic syndromes and anxiety disorders, but also substance abuse. Does sleep disordered breathing predispose an individual to substance abuse? Investigating this question is complicated by the possibility that some substances permanently alter the control of breathing, making *cause* and *effect* difficult to separate. Consider comparing inspiratory airflow dynamics during sleep between young, non-drinking offspring of alcoholics and controls.
5) Examine the relationship between sleep disordered breathing, functional somatic syndromes and anxiety disorders prospectively.
   a) Many combat veterans experience war-related illness and post-traumatic stress disorder (PTSD). Does the presence of sleep disordered breathing, pre-deployment, help to predict which combat veterans will experience these disorders? Does nasal CPAP alleviate combat veterans' symptoms of PTSD?
   b) At this time, a large oil decontamination project is beginning in the Gulf of Mexico. Historically, some workers/soldiers experiencing inhalation exposure (the first Gulf War and the post-9/11 WorldTrade Center cleanup) develop functional somatic syndromes with multiple chemical sensitivity. Will the presence of sleep disordered breathing, pre-exposure, identify a group of decontamination workers at high risk for developing functional somatic syndromes, anxiety disorders?

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