

Role of the Sleeping/Waking Brain in the Pathogenesis of Fibromyalgia, Chronic Fatigue Syndrome, and Related Disorders

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ABSTRACT

This article reviews the epidemiologic, clinical, and experimental evidence that show how perturbations of the sleeping-waking brain are core to the understanding and rational management of the non-restorative sleep, musculoskeletal pain, fatigue, and psychological distress of patients with fibromyalgia syndrome, chronic fatigue syndrome, and related syndromes.

INTRODUCTION

People with fibromyalgia syndrome (FMS) typically complain of unrefreshing sleep, generalized aching in their bodies, and fatigue that interfere with their day-to-day functioning. They describe increased sensitivity to various noxious tactile, environmental, and food stimuli, as well as cognitive and emotional difficulties that include anxiety and depression. Such symptoms are common in medical practice and may be found in patients with other perplexing painful syndromes in which no specific physical pathology has yet been identified.

These syndromes attract diagnostic labels that reflect the beliefs and restricted interests of various medical specialties. For psychiatrists, these symptoms may be considered to be features of a somatoform pain disorder or an underlying major depressive disorder; for allergists, they are features of environmental or chemical hypersensitivities; for neurologists, they may be found in patients with complaints about chronic headaches or migraine; for infectious disease physicians, they may be associated with the label chronic fatigue syndrome

FOCUS POINTS

- Patients with chronic variable musculoskeletal pain, fatigue, and psychological distress typically complain of unrefreshing or nonrestorative sleep and hypersensitivities to various noxious stimuli.
- Clinical and experimental research studies show that there is an interrelationship of nocturnal sleep electroencephalograph physiologic disturbances with poor quality of sleep, pain, tenderness, and fatigue that characterize fibromyalgia syndrome, chronic fatigue syndrome, and comorbid conditions.
- Advances in the understanding of dysfunction of specific neurotransmitters—including central nervous system serotonin, substance P, and neurokinins that affect sleep, pain, and mood—may pave the way for effective treatment of such difficult-to-manage clinical conditions.

(CFS); for gastroenterologists, the diagnosis of irritable bowel syndrome may be offered; for urologists, their concerns may regard irritable bladder syndrome; for cardiologists and emergency physicians, the meaningless label “atypical chest pain” has been given; for dentists, temporomandibular pain and tenderness can involve the joints or regional muscles.

Indeed, FMS patients are more likely than controls to meet lifetime symptomatic and diagnostic criteria for many of these diagnostic labels.¹ Although no specific causative factor or biologic agent is known to account for all the features of FMS and these related diagnoses, the generalized bodily aching and lower than normal pressure pain thresholds (allodynia) are believed to result from central nervous system (CNS) dysfunctions. Such CNS disturbances are intrinsic to

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the sleeping-waking brain where the common symptom elements in all these functional somatic illnesses are poor quality of sleep, nonspecific pain, fatigue, and psychological distress in the absence of known somatic pathology.

Greater than 90% of patients with FMS describe poor quality of sleep. The sleep is often perceived to be light and unrefreshing, irrespective of its duration. The patient may be aware of restlessness with kicking and involuntary leg movements, or sleep-related breathing disorder such as loud snoring and interruptions to breathing. On the rare occasion that restful sleep can be achieved, there is substantial improvement in daytime symptoms. Indeed, unrefreshing or nonrestorative sleep, and not psychological distress, is correlated with the myalgia and tender points (TePs) in FMS.²

Furthermore, because all physiologic functions of the body are intimately linked to the sleeping-waking brain, it would be expected that the perturbations of particular neurotransmitter and neuroendocrine functions that are linked to the sleep-wake functions would contribute to physiologic and behavioral hypersensitivities that occur in people with FMS and its comorbid clinical conditions. In particular, evidence for deregulation of the pituitary-adrenal neuroendocrine axis and autonomic functions have been identified.³ Electrocardiographic methodology has shown that increased overnight sympathetic activity is consistent with the notion of autonomic neurotransmitter dysfunction during the sleep of FMS patients.⁴

This article reviews the epidemiologic, clinical, and experimental evidence that show how such perturbations of the sleeping-waking brain are core to the understanding and management of the unrefreshing sleep, somatic pain, fatigue, and psychological distress of patients with FMS and perhaps with related syndromes.

WHAT IS NONRESTORATIVE SLEEP?

Unrefreshing or nonrestorative sleep differs from sleep problems that are characterized by difficulties in falling and/or staying asleep. Whereas difficulties in falling and/or staying asleep can be assessed using quantitative measures that are derived from standard electroencephalograph (EEG) measures of sleep, nonrestorative sleep is essentially a qualitative phenomenon that has characteristic sleep and waking symptoms. Whether sleep is refreshing or not is not dependent on how long we sleep or when we sleep. Many people have experienced the benefit of a brief daytime “power nap” where upon awakening they feel as though they slept deeply and are refreshed, alert, and energized. On the other hand, a person may sleep for 8–9 hours and

awaken feeling exhausted as though he or she had not slept all night. The qualitative sleep symptoms of nonrestorative sleep include a feeling that sleep has been light or superficial, and that the feeling of being refreshed upon awakening is missing. Wakeful symptoms include a sense of physical and mental fatigue, variable nonspecific bodily pain, increased sensitivity to noxious stimuli, dysphoria, and autonomic disturbances.

PREVALENCE AND SPECIFICITY OF UNREFRESHING SLEEP TO MUSCULOSKELETAL PAIN AND FATIGUE SYNDROMES

Nonrestorative sleep is common and embraces a variety of physical and mental health concerns. The 1991 Canadian General Social Survey of approximately 12,000 Canadians ≥ 15 years of age identified a high prevalence of unrefreshing or nonrestorative sleep.⁵ Twenty-four percent of respondents reported that their sleep is refreshing only sometimes. Three percent reported that their sleep is never refreshing. Increasing pain severity was associated with increasing risk for insomnia and unrefreshing sleep. Other studies have described a similar relationship between disturbed sleep and chronic pain. Nearly all patients attending a pain clinic reported at least one type of sleep disturbance.⁶ In patients with arthritis, there is a high prevalence (estimates approaching 60%) of restless sleep.⁷⁻⁹

A recent survey of >25,000 people in seven European countries (Finland, France, Germany, Italy, Portugal, Spain, and the United Kingdom) provides additional information on the prevalence and significance of unrefreshing or nonrestorative sleep to somatic concerns, fatigue, and emotional distress.¹⁰ This survey found that 10.8% had nonrestorative sleep. The prevalence was highest in the United Kingdom (16.1%), Germany (15.5%), and France (11.4%). The lowest occurred in Spain (2.4%) and Portugal (5.8%). More women than men, especially those <55 years of age, reported nonrestorative sleep. Those with nonrestorative sleep were more likely to have difficulty getting started in the morning, a stressful life, anxiety, bipolar or depressive disorder, and physical illness. They were more likely to seek medical consultations and complain of being impaired because of irritability, physical fatigue, and mental fatigue. Unlike those with insomnia, more people with unrefreshing sleep report being excessively sleepy (approximately 11% versus 33%). This study showed that nonrestorative sleep frequently affected working people and caused greater daytime impairment than those complaining of difficulty initiating or maintaining sleep.

IMPLICATIONS OF NONRESTORATIVE SLEEP TO FMS AND COMORBID CONDITIONS

As in people with FMS, unrefreshing sleep is the most prevalent of the eight CFS case-defining symptoms, being endorsed by 88% to 95% of cases identified in population-based studies^{11,12} and 70% to 80% of cases in clinic-based studies.^{13,14} In order to determine whether there is a specific sleep disorder that commonly occurs in patients who complain of chronic fatigue and musculoskeletal symptoms, the 17-item Sleep Assessment Questionnaire (SAQ) that comprises six sleep factors was used in a recent epidemiologic survey of specific sleep features in CFS.¹⁵ The SAQ showed significantly increased risk of abnormal scores in the non-restorative sleep, and restlessness factors in CFS subjects compared to non-fatigued people. There was no specific increase in prevalence of factor scores for sleep apnea or excessive daytime somnolence. These epidemiologic studies demonstrate how common poor sleep quality is among people with FMS and CFS.

CIRCADIAN VARIATION OF SYMPTOMS

Epidemiologic studies show that nonrestorative sleep is an important component of FMS and related disorders. However, the daytime symptoms are not fixed throughout the day. An examination of circadian sleep-wake-related functions show that the symptoms of FMS vary over the course of the day. Whereas normal subjects have their lowest sensitivity to pain in the morning, patients with FMS have increased tenderness in the morning, or no overnight improvement in pain.¹⁶ Furthermore, as with CFS and in patients with temporomandibular joint disorder, patients with FMS have cognitive impairment that relates to the chronic disturbance in sleep. The pain and fatigue tends to decline from mid morning to mid afternoon, so that after 3PM patients commonly complain that they feel they have hit "a brick wall" with fatigue and are unable to think properly or carry out any meaningful tasks. Although they may believe that they are likely making errors, they are in fact only slowing down in performing a cognitive task.¹⁷ When they go to bed at night they feel no better than when they awaken the following morning. Overall, the disturbances in sleep physiology contribute to this poor quality of sleep and the vicious cycle of unrefreshing sleep, morning aching, stiffness, and fatigue.¹⁸⁻²²

POLYSOMNOGRAPHY IN THE UNDERSTANDING OF THE CONTRIBUTION OF NONRESTORATIVE SLEEP TO THE SYMPTOMS OF FMS

Sleep laboratory assessment typically shows disordered sleep physiology that is thought to be the basis of the unrefreshing sleep experience. Most people with FMS have an arousal disturbance in their sleep EEG, known as the α (7.5–11 Hz) EEG sleep arousal disorder. In 1975, Moldofsky and colleagues¹⁶ described an α EEG non-rapid eye movement (non-REM) sleep anomaly in patients with fibrositis. They proposed that the α EEG sleep anomaly is related to unrefreshing sleep, diffuse myalgia, numerous localized areas of tenderness in specific anatomic areas, and mood symptoms.

Many investigators have reported on the computerized analyses of the α EEG non-REM sleep disorder in patients with FMS.^{19,20,22,23} In particular, the frequency analyses of the sleep EEG demonstrate three varieties of α EEG sleep; namely, phasic (50% of patients versus 7% OF normals), tonic (20% of patients versus 9% of normals), and low α (30% of patients versus 84% of normals).²² Those with the phasic pattern of the α intrusion in slow-wave sleep (SWS) are more likely to have increased post-sleep tenderness and subjective pain, poor sleep efficiency, and less SWS than the other groups. Furthermore, morning stiffness, diffuse pain, and discomfort after awakening commonly occur in FMS patients with phasic α sleep. Although a cause-effect relationship between pain and sleep cannot be established, the data suggest that the phasic α sleep pattern is associated with longer duration of pain symptoms, perception of poor sleep, and morning pain. The finding of the α EEG sleep anomaly in children and their mothers suggests the possibility of a familial or genetic influence in the pathogenesis of the disorder.²³ This requires further study.

Some patients with FMS have fragmented sleep as a result of sleep-related periodic, involuntary, arousal disturbances that occur over the course of the night. These periodic sleep-related disturbances include restless legs and periodic involuntary limb movements, sleep apnea, and an underlying periodic arousal disturbance in the sleep EEG known as sleep-related periodic K- α or frequent cyclic alternating EEG sleep pattern.²⁴

One variety of these periodic arousal disturbances in sleep that occur at approximately 20–40-second intervals is accompanied by movements of the limbs, especially of the lower limbs. These periodic limb movements may extend into the waking daytime and manifest as restless legs syndrome (RLS).

Sometimes sleep may be disrupted by another periodic disturbance involving respiration, where there are interruptions to the breathing, or sleep apnea. While FMS is uncommon in male sleep apnea patients,²¹ greater nocturnal sleep-related reduction in arterial oxygen saturation occurs in sleepy female FMS patients versus control subjects.²⁵ Moreover, such patients are reported to have a lower transfer factor for carbon monoxide from the lungs, and that periodic breathing correlated with the transfer factor for carbon monoxide, number of oxygen desaturations, and carbon dioxide tension in arterial blood.²⁶ Those who complain of daytime sleepiness have more TePs, approximately twice as many arousals per hour of sleep, and lower sleep efficiency than those patients who do not report sleepiness. This sleepy subgroup of FMS has more periodic breathing and greater impairment in the transfer factor for carbon monoxide from the lungs. In another study, women with FMS were found to have a reduction to inspiratory air-flow dynamics during sleep that were suggested to play a role in the development of the syndrome.²⁷ There are currently no reported studies on whether specific treatment of sleep-related breathing disorders influences the symptoms of FMS.

Overt respiratory disturbances or limb movements may not accompany another variety of periodic arousal disturbance that is seen in the EEG sleep. This EEG sleep periodic phenomenon is termed the cyclic alternating pattern (CAP), where one type comprises periodic K α EEG sleep. That is, the typical non-REM stage two EEG K-complex is not followed by a sleep spindle as occurs normally, hence the finding of a lower frequency of sleep spindles.²⁸ The EEG K complex is followed immediately by a burst of α activity lasting <5 seconds (A phase). This indicator of EEG arousal within the non-REM sleep is followed by a quiescent periodic of non-REM sleep (B phase). Then, in approximately 20–30 seconds, the cycle is repeated.²⁹ In fact, a high prevalence CAP has been confirmed to occur in FMS. This periodic CNS arousal disturbance in the sleep EEG is accompanied by less efficient and unrefreshing sleep, and is correlated to the severity of clinical symptoms in FMS patients (ie, TePs).³⁰

Topographic EEG localization known as low-resolution electromagnetic tomography has identified maximum increases in electrical current density of the delta (δ) and theta (τ) sleep EEG frequency components of the A Phase of CAP. These EEG frequency components are localized in the medial frontal gyrus. For the α EEG band, the current density is localized in the middle temporal gyrus.³¹ Such localized functional sleep-related EEG changes are consistent with the findings employing a variety of brain-imaging techniques for localizing pain perception in FMS.³²

Once again, there is the question of the specificity of such sleep-related CNS changes for FMS and CFS. Although the tonic α EEG sleep, phasic α (α - δ) EEG sleep, and CAP may be found in non-complaining people,³³ and is not specific to FMS, it is unknown whether magnification of these sleep EEG disturbances may predispose to the emergence of FMS and CFS symptoms. One hypothesis that requires consideration is whether a specific noxious event or agent may alter CNS functions where these EEG sleep arousal phenomena emerge to become a feature of the final common neurophysiologic pathway of CNS hypersensitivity and the hyperalgesic state. Various noxious events have been considered. For example, the α EEG sleep disorder has been found in FMS patients who report the onset of symptoms following a psychologically traumatic event such as a non-physically injurious motor vehicle or industrial accident. Some FMS and CFS patients with similar sleep disturbances claim to have had the onset of symptoms following a febrile event,³⁴ but no specific infectious agent has been identified. However, many FMS and CFS patients do not report any specific event that heralds the onset of symptoms. This lack of clear evidence for a specific triggering etiologic agent has led to the hypothesis that there may be a combined genetic and environmental predisposition to these syndromes, where specific genes may be activated affecting sleep disturbances that are involved in the evolution of these syndromes.³⁵⁻³⁷

ANIMAL AND HUMAN EXPERIMENTS ON THE INTERRELATIONSHIPS OF SLEEP AND MUSCULOSKELETAL PAIN

Animal Studies

Nociception and Sleep Physiology

Both animal and human studies have demonstrated the specificity of abnormal sleep to the development to pain and fatigue. The animal studies show that sleep deprivation (ie, REM sleep deprivation) promotes an increase in pain sensitivities and behavior.³⁸⁻⁴¹ REM deprivation of rats reduces pain threshold as long as 96 hours after termination of the REM deprivation.³⁹

Experimental studies of persistent nociception produced by formalin injection into the tibialis anterior of freely moving cats showed not only pain behavior, but also increased wakefulness, reduced light, and deep SWS.⁴² With abatement of the formalin pain stimulation and decline of pain behavior, light sleep appears, but slow wave (deep)

sleep and REM sleep are greatly decreased. This research suggests that stages of sleep are differentially affected by acute painful stimulation from muscles. Moreover, sleep physiology differentially affects the pain pathways from the periphery to the brain. The electrophysiologic activity of spinoreticular pain pathways in cats is reduced during REM sleep.⁴³ Similar sleep state-dependent changes in nociception are observed in humans. Additional research shows that the excitability of spinal polysynaptic nociceptive reflexes is reduced in stage 4 sleep and especially during REM sleep.⁴⁴ In summary, these studies show that the perception of pain is influenced by sleep-state conditions. REM sleep differentially affects the physiologic properties of pain pathways from the periphery. However, the comparative effects on nociception of REM sleep, partial sleep deprivation (ie, REM versus SWS), and of total sleep deprivation need to be clarified.

CNS Neurotransmitters, Pain, and Sleep Physiology

Recent research suggests that specific neurotransmitter functions influence CNS hypersensitivity that alters sleep and promotes pain. In particular, inhibition of CNS serotonin (5-HT) synthesis by p-chlorophenylalanine induces insomnia and a hyperalgesic state in animals and humans.⁴⁵ Furthermore, elevated levels of CSF Substance P (SP) are known to occur in FMS.⁴⁶ Andersen and colleagues⁴⁷ hypothesized that the substance P operating through a neurokinin pathway would influence nociception and sleep. Whereas neurokinins have been implicated in modulating pain and mood, little is known about their effect on sleep-wake behavior. Intracerebral ventricular administration of SP in sufficient quantities that did not induce nociceptive response in mice was sufficient to reduce their sleep efficiency, increasing latency to the onset of sleep and provoking awakenings from sleep. A neurokinin-1 (NK1) receptor antagonist reversed the interfering effect upon sleep by SP. This study demonstrates that blocking the SP-induced insomnia by prior treatment of mice with NK1 receptor antagonist provides support for the arousing effect of SP on the sleeping-waking brain. This research provides an animal model for studying sleep disturbances and pain in FMS. Furthermore, this model could be employed to determine the interrelationship of CNS 5-HT and SP, with the hypothesis that 5-HT deficiency results in increased levels of SP in the CNS, leading to sensitivity to sensory stimuli and sleep disturbances. If such experiments support this hypothesis then there would be a rationale to reducing nonrestorative sleep and hypersensitivity with specific drugs that augment CNS 5-HT and inhibit aspects of SP metabolism.

Human Studies

In human subjects, the type of experimental pain stimulus during sleep affects the features in the sleep EEG and the stages of sleep.²⁰ For example, muscle stimuli when applied during sleep cause a decrease in δ (0.5–3.5 Hz) and σ (sigma; 12–14 Hz), and increases in α_1 (8–10 Hz) and β (14.5–25 Hz) brain wave frequencies. During joint pain stimulation the δ , τ (3.5–8 Hz) and α_1 EEG frequency bands in sleep are decreased. The higher EEG frequencies (α_2 [10–12 Hz], σ , and β bands) are increased. Cutaneous stimuli do not affect the background EEG. Sleepiness does not modulate experimental joint pain. Another experimental study employed to determine whether specific stages in (EEG) sleep are affected by pain showed that all stages of sleep are disrupted by noxious stimulation of muscles and that quality of sleep was impaired.⁴⁸

As expected, painful stimuli during sleep interfere with sleep physiologic functions. However, the converse is also true. The experimental introduction of noise during specific stages of sleep in the early 1970s by Moldofsky and colleagues¹⁶ and Moldofsky and Scarisbrick⁴⁹ showed that the disruption of stage 4 non-REM in normal sedentary people by noise stimuli resulted in complaints of unrefreshing sleep, variable aching, and fatigue. Furthermore, they showed increased sensitivity to the application of a pressure gauge to specific anatomic regions that had been identified in FMS patients. Other researchers have replicated many of these seminal findings. Older and colleagues⁵⁰ confirmed that noise-induced disruption of SWS was followed by generalized aching and fatigue in healthy military recruits, but they did not demonstrate significant changes in pressure-pain thresholds. However, Lentz and colleagues⁵¹ confirmed the induction of increased tenderness, diffuse myalgia, and fatigue over 3 nights of noise-induced disruption of SWS in normal middle-aged women. These studies of sleep disruption are shown to produce a generalized reduction in pressure-pain threshold (allodynia). Localized effects on muscular function, ie, jaw muscle activity, masseter pain, and tenderness, were not induced using a similar experimental design, but there was a substantial reduction in SWS on the second and third night of sleep deprivation. Moreover, there were no changes in the duration of sleep time and of EEG stages 1 and 2 sleep.⁵² Onen and colleagues⁴¹ employed a variable design where total sleep deprivation for 40 hours was followed by 2 nights of either REM or SWS deprivation, and then by 1 night of recovery. Total sleep deprivation and both REM and SWS deprivation reduced pressure pain tolerance thresholds. Only SWS on the recovery night was related to an increase in pain

tolerance thresholds. In an attempt to determine whether general somatosensory functions were affected by sleep deprivation, subjects were assessed for heat or cold sensations after either 2 nights of sleep deprivation or 2 night of undisturbed sleep. The research showed that overnight heat-induced pain thresholds and cold-induced pain thresholds were decreased with sleep deprivation, but that warmth- and cold-detection thresholds remained unaffected. This research confirmed that sleep deprivation has a specific effect on inducing allodynia, but does not alter somatosensory functions.⁵³ As with the animal studies, REM deprivation and the loss of 4 hours of sleep induces a hyperalgesic state on the following day.⁵⁴

The arousal disturbance in sleep, pain, and fatigue symptoms that are artificially induced in healthy people and also observed in patients with FMS and CFS may reflect a vigilant state during sleep with daytime symptoms of nonrestorative sleep. However, the symptoms were not induced by the disruption of SWS in a small group of physically fit long-distance runners⁴⁹ or vigorously active military recruits.⁵⁰ Although cardiovascular fitness programs reduce tenderness and increase muscle strength, once again, the mechanisms whereby fitness programs modulate sleep and reduce susceptibility to allodynia are unknown.

CONCLUSION

Clinical studies show that there is an interrelationship of pain and nonrestorative sleep in the evolution of FMS. However, research is required to further understand the emerging information on the prevalence and specificity of the physiologic components of unrefreshing sleep to musculoskeletal pain and fatigue syndromes in FMS, CFS, and related conditions. The advances in sleep EEG technology is expected to enhance knowledge about regions of the sleeping brain that are involved in the periodic arousal disturbances that contribute to nonrestorative sleep and the symptoms of FMS and comorbid disorders. Although various periodic EEG arousal disturbances during sleep have been identified in patients with FMS, it is unknown whether current treatments known to benefit such primary sleep disorders as RLS with periodic limb movement disorder or sleep apnea syndrome will improve the sleep quality and symptoms of FMS. Confirmation is required of the preliminary research findings that showed that reduction in the α EEG sleep arousal disturbances and augmentation of slow wave (deep) sleep by γ -hydroxybutyrate result in improvement in the daytime symptoms of FMS.⁵⁵ Advances in experimental techniques that employ specific alterations in sleep in humans and animals are expected to advance current understanding of the

CNS neurotransmitter mechanisms responsible for nociception and nonrestorative sleep in determining the etiology and rationale for treatment of FMS and comorbid conditions. **PP**

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