The significance of the sleeping—waking brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes

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Abstract

The clinical focus of rheumatologists on the widespread pain and numerous tender points in specific anatomic regions in their patients who show no evidence for disease pathology has lead to the characterization of such peripheral symptoms as a specific disorder of the musculoskeletal system, now commonly known as fibromyalgia. This rheumatologic diagnostic entity has resulted in relative inattention to an understanding of their patients’ common complaints of unrefreshing sleep, chronic fatigue and psychological distress. Experimental evidence from humans and animal studies indicate that there is an inter-relationship of disturbances in the physiology of the sleeping—waking brain with the widespread musculoskeletal pain, chronic fatigue, and psychological distress in patients with hitherto unexplained pain/fatigue illnesses, e.g., fibromyalgia and chronic fatigue syndromes. The emerging knowledge of the dysfunction of the nervous system in such patients has lead to the study of novel medications that affect neurotransmitter functions, e.g., pregabalin, serotonin/noradrenaline compounds and sodium oxybate that are shown to improve many of the symptoms of such patients.

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While considerable interest in patients with Fibromyalgia Syndrome (FMS) grew out of the publication in 1990 of the American College of Rheumatology criteria [1], the clinical focus on widespread pain and tenderness in specific anatomic regions has not lead to improved understanding and management of such afflicted people. Indeed, the criteria-seeking method that was employed by Wolfe et al. was essentially tautological [2]. That is, the rheumatologist co-authors identified patients in their practices with diffuse musculoskeletal pain and compared them to their patients with other rheumatic diseases, e.g., rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus who also had pain, but in specific joints. It is not surprising that their findings of widespread pain and tenderness differentiated such people from those with known rheumatic disease. In our initial studies in the mid 1970s that attempted to characterize such patients who did not have any known rheumatic or connective tissue disease we considered that their widespread pain and tenderness in specific anatomic regions were only components of the collection of various poorly understood complaints of such patients. These complaints included disturbed unrefreshing sleep, chronic fatigue, and psychological distress that interfered with work and social functional capabilities [3]. Therefore, it is not surprising that the statistical methodology of the Wolfe et al. group [1] would permit exclusion of these other features because these symptoms may affect patients with known rheumatic or connective tissue disease. In subsequent investigations of anatomic regions of tenderness, authors have pointed out that they are nonspecific for characterizing such patients with diffuse pain [4]. Indeed among the many features...
of patients with the label of FMS, unrefreshing or nonrestorative sleep ranks with pain and fatigue as the most common of all symptoms. Furthermore, among the various elements of fibromyalgia, problems with sleep, low energy, emotional distress, and poor health are independent predictors of chronic widespread pain [5]. Therefore the key question is how do these specific elements contribute to widespread pain. The purpose of this paper is to review the animal and human experimental evidence that implicate disordered sleep/wake physiology in the etiology of musculoskeletal pain and fatigue problems. Such an understanding of the disturbances in circadian sleep/wake-related biological and behavioural functions advance our understanding and their potential importance to the management of the various problems posed by patients with widespread pain and tenderness.

1. Nonrestorative sleep in FMS: features and clinical assessment

From a clinical perspective, the patient perceives their nightly sleep to be light and unrefreshing irrespective of its duration. In addition, some patients may be aware of the discomfort that is especially troublesome in the lower limbs. This discomfort may be accompanied by an uncomfortable urge for restlessness, uncontrollable kicking and involuntary leg movements before and during sleep. Or, some may have received complaints from their bed partner about their loud snoring and disturbances of breathing during the night. These are the clinical features of patients with the co-morbid primary sleep disorders: Restless Legs Syndrome (RLS) and Obstructive Sleep Apnea Syndrome (OSAS), respectively. On the rare occasion that sleep is restful, there is substantial improvement in daytime symptoms.

While the generalized myalgia, fatigue, unrefreshing sleep and psychological distress are common in patients with FMS, such symptoms are also features of patients with another diagnostic label that has no defined disease pathology, i.e., chronic fatigue syndrome (CFS). These symptoms may be co-morbid with other pain syndromes without known disease pathology, i.e., migraine headache, irritable bowel syndrome, and temporomandibular joint disorder. Moreover, these FMS symptoms and sleep disturbances also occur in patients with defined rheumatic disease pathology, such as, osteoarthritis, rheumatoid arthritis, primary Sjögren’s syndrome [6] and S.L.E. [7].

A variety of clinical rating scales have been employed to assess the sleep disturbances.

The sleep symptoms may be a component of a general questionnaire on functional disability in patients with FMS, e.g., Fibromyalgia Impact Questionnaire, where sleep disturbance is one of 30 items [8]. Aspects of sleep have been assessed with a sleep behavioural rating scale e.g., Pittsburgh Sleep Quality Index (PSQI). The PSQI has not been validated with polysomnography. Despite its designation, PSQI describes both quality and quantity of sleep. It has been used in small-scale studies where greater sleep disturbance is associated with increased pain sensitivity. Patients with FMS more commonly rate delay in falling asleep, sleep disturbances, and impaired daytime function than normal controls [9]. In a large-scale epidemiological study of chronic fatigue, the brief 17-item Sleep Assessment Questionnaire (SAQ) proved to be an excellent screening questionnaire for identifying people with FMS and CFS. The nonrestorative sleep factor of the SAQ, which is based on both polysomnographic evidence of an arousal disorder in the sleep EEG and clinical evidence, has high sensitivity and specificity for FMS and CFS [10].

2. EEG sleep physiological abnormalities in FMS

2.1. Sleep EEG arousal disturbances are typically present in patients with FMS

Traditionally, most studies rely on polysomnographic recordings of the sleep EEG where the alpha EEG sleep frequency (7—12 Hz) EEG is obtained by C3, C4, and occipital EEG electrode leads. The alpha EEG sleep anomaly consists of minimum peak-to-peak amplitude of 5 µV, which occurs prominently during NonREM stages 2, and/or 3 and 4 sleep. Alpha EEG sleep that occurs during slow wave stages 3 and 4 sleep was first described in a group of 9 patients with varying psychiatric diagnoses but with a common clinical feature of general feeling of malaise and fatigue [11]. This EEG sleep phenomenon was termed alpha—delta sleep. Initially, alpha—delta sleep was defined as a mixture of 5—20 delta waves (>75 µV, 0.5—2 c/s) combined with relatively large amplitude, alpha-like rhythms (7—10 c/s). These alpha rhythms are usually 1—2 c/s slower than waking alpha frequency, which typically occurs over the occipital region.

Subsequently, the alpha EEG sleep, which is not confined to slow wave sleep, but also occurs in stage 2 sleep, became classified by its frequency of occurrence in standardized observer raters, with high inter-rater reliability [12]. Normal presence of alpha in the sleep EEG (7.5—11.5 Hz, using C3, C4 electrode leads) occurs in less than 40% of NonREM sleep. High ratings of more than 40%, or abnormal alpha EEG in NonREM sleep occur with 30-s epoch, sleep stage or overall ratings in NonREM sleep.

Computerized EEG analysis provides a more objective analysis of EEG frequencies. Such automated analyses substantiate the presence of elevated amounts of the alpha EEG NonREM sleep disorder in patients with FMS [13—17]. In one study [20], the analyses of the sleep EEG indicate 3 varieties of alpha EEG sleep: phasic (50% of patients vs. 7% normals), tonic (20% of patients vs. 9% of normals), and low alpha occurs in 30% of patients vs. 84% of normals. Those with the phasic pattern of the alpha intrusion in slow wave sleep (alpha—delta EEG sleep) are more likely to have increased post sleep tenderness and subjective pain, poor sleep efficiency and less slow wave sleep than the other groups. Morning stiffness, diffuse pain and discomfort after awakening commonly occur in FMS patients with phasic alpha sleep. Although a cause—effect relationship between pain and sleep is not definitively established in this research, the data suggest that the phasic alpha sleep pattern is associated with longer duration of pain symptoms, perception of poor sleep and...
The finding of the alpha EEG sleep anomaly in children and their mothers suggests the possibility of a familial or genetic influence in the pathogenesis of an altered sleep pattern in the disorder [18].

Some patients with FMS have fragmented sleep, which is associated with involuntary sleep-related periodic disturbances during the night. These periodic disturbances include: Periodic Limb Movements (PLMs), sleep apnea, and an underlying periodic arousal disturbance in the sleep EEG known as sleep-related periodic K-alpha [19] or frequent cyclic alternating EEG sleep pattern (CAP) [20].

PLMs accompanied by movement arousals occur at approximately 20–40 s intervals. These periodic limb movements, which often involve the lower limbs, may extend in the daytime waking and manifest as Restless Legs Syndrome (RLS). Approximately 20% of FMS patients have this sleep disorder.

OSA and hypopneas are other periodic disturbances that affect the sleep of FMS patients. While FMS is uncommon in male sleep apnea patients [21], greater nocturnal sleep-related reductions in arterial oxygen saturation occur in sleepy female FMS patients [22]. Moreover, such patients have a lower transfer factor from the lungs for carbon monoxide. Their periodic breathing correlates with the transfer factor for carbon monoxide, number of oxygen desaturations and carbon dioxide tension in arterial blood [23]. Those who complain of daytime sleepiness have more tender points, about twice as many arousals per hour of sleep and lower sleep efficiency, than those patients who do not report sleepiness. This sleep 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 showed a reduction to inspiratory airflow dynamics during sleep [24]. In yet another study, 23 women with FMS and poor sleep had frequent apnea—hypopneas and many EEG sleep arousals. Arterial oxygen desaturations were common, with half the patients having nadir oxygen saturation less than 87% [25]. Thus far, there are no systematic studies on whether specific treatments of sleep-related breathing disorders or PLMs/RLS benefit the symptoms of FMS.

Overt respiratory disturbances or limb movements may not accompany another variety of periodic arousal disturbances in the EEG sleep. This periodic phenomenon is termed “CAP”. Periodic K-alpha EEG sleep is one such variety of CAP. That is, the typical NonREM stage 2 EEG K-complex is not followed by a sleep spindle as occurs normally, hence the finding of a lower frequency of sleep spindles in FMS patients [26]. Rather, a burst of alpha frequency activity lasting less than 5 s (A phase) follows the K-complex. A quiescent period of 20–30 s of NonREM sleep (B phase) follows the K-alpha. Then, the cycle is repeated [19]. In fact, a high frequency rating of CAP in NonREM sleep occurs in FMS [20] and in CFS [27]. This intrinsic periodic arousal disturbance in the sleep EEG is accompanied by less efficient sleep, unrefreshing sleep, and is correlated to the severity of clinical symptoms in FMS patients [20].

Topographical EEG localization known as low-resolution electromagnetic tomography (LORETA) provides analyses of the distribution of these sleep anomalies. In alpha—delta sleep, the alpha band source differs from the quiet wakefulness where the alpha EEG pattern is normally localized over the occipital region. LORETA analysis shows the “alpha−delta sleep” to be situated in the anterior cingulate cortex, Brodmann area 32. The LORETA technology shows that the high frequency of CAP in FMS patients has a maximum electrical current density of the delta and theta sleep EEG frequencies’ components of the A phase in the medial frontal gyrus. For the alpha EEG band the current density is localized in the middle temporal gyrus [28]. Thus localized functional sleep-related EEG changes are consistent with the findings employing a variety of brain imaging techniques for localizing pain perception during wakefulness in FMS [29].

Once again, there is the question of the specificity of such sleep-related brain functional changes for FMS/CFS. Although the tonic alpha EEG sleep, phasic alpha (alpha−delta) EEG sleep and CAP may be found in non-complaining people, and is not specific to FMS, we do not know whether these sleep EEG disturbances may be a component of the biological predisposition to the emergence of FMS/CFS symptoms.

3. Animal and human experiments on the inter-relationships of sleep and musculoskeletal pain

3.1. Animal studies

3.1.1. Rheumatic pain causes disordered sleep physiology

The studies of the physiological disturbances associated with disturbed sleep employ animal experimental models of muscle pain. For example, experimental studies of persistent nociception produced by formalin injection into the tibialis anterior of freely moving cats show not only pain behaviour, but also increased wakefulness, reduced light and deep, slow wave sleep. With abatement of the formalin pain stimulation and decline of pain behaviour, light sleep appears, but slow wave sleep and REM sleep remain decreased. This research suggests that acute painful stimulation from muscles differentially affects the stages of sleep [30]. Moreover, sleep physiology affects the pain pathways from the periphery to the brain. During REM sleep the electrophysiological activity of spinoreticular pain pathways in cats is reduced [31]. Similar sleep state-dependent changes in nociception occur in humans. Additional research shows that the excitability of spinal polysynaptic nociceptive reflexes is reduced in stage 4 sleep and especially during REM sleep [32]. REM sleep differentially affects the physiological properties of pain pathways from the periphery.

In summary, these studies show that the perception of pain not only has an adverse effect on circadian sleep/wakefulness, but also pain neural transmission during wakefulness differs from that seen during specific sleep states.

3.1.2. Disordered sleep physiology causes musculoskeletal pain

Both animal and human studies have demonstrated the specificity of abnormal sleep to the development of pain and
fatigue. The animal studies show that REM sleep deprivation, promotes increase in waking pain sensitivities and pain behaviour [33,34]. REM deprivation of rats reduces pain threshold as long as 96 h after termination of the REM deprivation [34]. However, further research is required on the comparative effects of nociception of REM sleep, partial sleep deprivation, i.e., REM vs. SWS, and of total sleep deprivation.

3.1.3. CNS neurotransmitters, pain and sleep physiology

Experimental studies indicate that specific neurotransmitter functions affect hypersensitivity that alters sleep and promotes pain. For example, inhibition of serotonin (5-HT) synthesis by p-chlorophenylalanine induces insomnia and a hyperalgesic state in animals and humans [35]. Furthermore, the high levels of CSF substance P (SP) that occur in patients with FMS [36] led Andersen et al. [37] to hypothesize that SP, operating through a neurokinin (NK) pathway, would influence nociception and sleep. Intracerebral ventricular administration of SP in sufficient quantities that did not induce nociceptive response in mice reduced their sleep efficiency, increased the time to onset of sleep and provoked awakenings from sleep. An NK1 receptor antagonist reversed the interfering effect upon sleep by SP. This study demonstrates that blocking the SP-induced insomnia by prior treatment of the 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 musculoskeletal pain as found in FMS. Furthermore, this model could be employed to determine the inter-relationship of CNS 5-HT and SP, where 5-HT deficiency is hypothesized to increase levels of CNS SP causing sleep disturbances and hypersensitivity to sensory stimuli. If such experiments support this hypothesis then there would be a rationale to improve nonrestorative sleep and neural hypersensitivity with specific drugs that augment CNS 5-HT and inhibit aspects of SP metabolism.

3.2. Human studies

3.2.1. Noxious muscle stimuli cause disordered sleep physiology

In human subjects the type of experimental pain stimulus during sleep affects the features in the sleep EEG and the stages of sleep. For example, noxious muscle stimuli when administered during sleep cause a decrease in delta (0.5–3.5 Hz) and sigma (12–14 Hz) and increases in alpha-1 (8–10 Hz) and beta (14.5–25 Hz) brain wave frequencies. During joint pain stimulation there is a decrease in the delta, theta (3.5–8 Hz) and alpha-1 EEG frequency bands in sleep. The higher EEG frequencies [alpha-2 (10–12 Hz), sigma and beta 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 pain affects specific stages of EEG sleep showed that all stages of sleep are disrupted by noxious stimulation of muscles and that quality of sleep is impaired [38].

3.2.2. Disordered sleep physiology causes generalized myalgia and fatigue

As expected, painful stimuli during sleep interfere with sleep physiological functions. However, the converse is also true. In the early 1970s Moldofsky et al. showed that the experimental induction of noise caused disruption of stage 4 NonREM in normal sedentary people. The slow wave (deep) sleep (SWS) disturbance resulted in complaints of unrefreshing sleep, fatigue and variable aching with increased tenderness in specific anatomical areas that had been identified in patients with FMS [39]. The arousal disturbance in sleep and the pain, and fatigue symptoms that were artificially induced in healthy people, are also observed in patients with FMS and allied syndromes. Moldofsky et al. hypothesized that the arousal physiological disturbances in nocturnal sleep reflect a vigilant state during sleep that contributes to the daytime fatigue, pain and hypersensitivity symptoms associated with nonrestorative sleep [3,39]. However, disruption of SWS in a small group of physically fit long distance runners did not induce the pain and fatigue symptoms [39]. This observation suggests that the physiology associated with aerobic fitness is a factor affecting the emergence of FM symptoms. Although a cardiovascular fitness program reduces tenderness, and increases muscle strength, the mechanisms are unknown whereby fitness programs, behaviour, and mood states modulate sleep and CNS hypersensitivity to noxious stimuli.

Other researchers have confirmed that disruption of SWS produces a generalized hyperalgesic state [15,16]. In another study of nights of either REM or SWS deprivation and a night of recovery both REM and SWS deprivation reduced pressure pain tolerance thresholds. An increase in SWS on the recovery night is associated with an increase in pain tolerance thresholds [40]. In an attempt to determine whether general somatosensory functions were affected by sleep deprivation, subjects were assessed for heat or cold sensations either after 2 nights of sleep deprivation or after 2 nights of undisturbed sleep. This research confirmed that sleep deprivation has a specific effect on inducing a hyperalgesic state but does not alter somatosensory functions [40]. Furthermore, as shown in animal studies REM deprivation, the loss of 4 h of sleep, which interferes with emergence of REM sleep in humans, induces a hyperalgesic state on the following day [41]. Four hours of sleep vs. 8 h of sleep over 12 consecutive nights causes a 15% reduction in psychosocial behaviour and a 3% increase in generalized body pain, back pain, and stomach pain [42].

4. Disordered diurnal sleep/wake physiology and behaviour in patients with FMS

In the search for objective evidence for structural or functional changes to the body that indicate a specific disease entity, studies on the pathogenesis of FMS have attempted to determine whether a noxious agent triggers the generalized myalgia, unrefreshing sleep, fatigue and psychological distress. Various noxious events are reported to trigger such a response; the studies suffer from being retrospective and vulnerable to patient or investigator interpretive bias. For example, the alpha
EEG NonREM sleep disorder may be 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 [43].

No studies as yet have evaluated whether disturbing thoughts emanating from sleep, i.e., recurrent nightmares following a psychologically traumatic event, have an influence on musculoskeletal pain, fatigue, and psychological distress symptoms. This notion is suggested by the epidemiological observations of an increased prevalence of FMS in U.S. female veterans with post-traumatic stress disorder (odds ratio = 3.0, 95% confidence interval (1.98–4.45)) [44], and in a large-scale polysomnographic study of PTSD in a civilian population have found an increased number of brief arousals from REM sleep [45].

Some FMS/CFS patients with a similar sleep anomaly claim to have the onset of symptoms following a febrile event [46] even though no specific infectious agent is identified. On the other hand, FMS and CFS patients may report no specific event that heralds the onset of symptoms. This lack of clear evidence for a specific triggering etiological agent has lead 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 [47]. Despite the absence of specific structural pathology, there is evidence for disordered metabolic functions that involve the sleep—waking brain. These include elevation of cerebral spinal fluid substance P [48], decrease in growth hormone and its metabolites [48], and disturbances in the hypothalamic—cortical adren al axis [49]. Increased overnight sympathetic activity using electrocardiographic methodology is consistent with the notion of circadian autonomic metabolic dysfunction associated with an arousal disturbance during the sleep of patients with fibromyalgia [50]. In addition to the chronobiological physiological abnormalities, there are diurnal changes in behaviour. FMS subjects with light unrefreshing sleep have diurnal impairment in speed of performance on complex cognitive tasks, which are accompanied by sleepiness, fatigue, and negative mood [51]. Such psychological impairment could account for the functional disabilities that are encountered in a work environment and in social behaviour.

5. Drugs, sleep and FMS

While improvement in the quality of sleep is associated with improvement in the symptoms of fibromyalgia, to date no specific treatment has been shown to have long lasting remedial benefits. The treatments are empirical. Most studies are for short-term periods and are reported to be beneficial for the self-ratings of sleep and pain symptoms, but in a small proportion of the patients who complete the studies or who can tolerate the treatments. The treatments include behavioural measures, e.g., cognitive behavioural therapy, hypnotherapy, and electrocardiographic biofeedback methods, exercise, acupuncture, and various analgesic-anti-inflammatory, psychotropic and tricyclic drugs, e.g., cyclobenzaprine and amitriptyline. Some studies directly measure changes in sleep physiology. In a double blind, parallel one-week study, 100 mg chlorpromazine but not 5 gm L-tryptophan increased SWS and reduced alpha EEG sleep physiology and symptoms [52]. The nonspecific and potential adverse effects of chlorpromazine do not make this a desirable drug for the long term management of the disorder, whereas cyclobenzaprine 10–30 mg decreased evening fatigue and increased total sleep time, it had no beneficial effect on pain measures, mood ratings, and alpha NonREM sleep [53]. A similar tricyclic drug, amitriptyline has short-term remedial effects on symptoms, but long term treatment with this drug over two months did not result in lasting benefit on the symptoms of the disorder or in any changes in the alpha NonREM sleep [54].

L-tryptophan facilitates sleep, but there is no effect on alpha EEG sleep, pain, or mood symptoms in patients with FMS [52]. However, 5-hydroxytryptophan, a direct precursor of brain serotonin, tends to improve pain and sleep quality [55], although its effect on the sleep physiology of patients with FMS is unknown. Gabapentin, pregabalin, carbamazepine that were originally classified as anticonvulsants also have sedative properties and antinociceptive effects. Pregabalin, which is an alpha-2–delta ligand that causes increased cellular expression of calcium channels, reduces the expression of substance P and noradrenaline. Recent studies show that this drug improves the pain, quality of sleep and fatigue in FMS [56]. As yet, such alpha-2–delta ligands have not been assessed for their effects on the sleep physiology of FMS patients. Serotonin–noradrenaline receptor inhibitors i.e., duloxetine and milnacipran, which are known to be helpful for pain in animal studies and possibly sleep, benefit many of the symptoms of FMS [57], but have not been studied to determine their effects on EEG sleep arousal patterns in FMS. A dopamine agonist, pramipexole is claimed to be helpful for pain, fatigue, and overall function in a subset of FMS patients, half of whom were also taking narcotics [58]. Further properly controlled studies of dopamine agonists are required because these agents substantially reduce RLS/PLMs, as do narcotics, so that their effects on sleep and symptoms in FMS patients need to be determined. Gamma hydroxybutyrate or sodium oxybate reduces alpha EEG sleep, increases SWS, improves the quality of sleep and reduces pain and fatigue in FMS patients [59]. If confirmed in large-scale studies, such findings are consistent with the importance of the sleeping—waking brain in the pathogenesis and hence management of the syndrome.

References


