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FOCUS REVIEW

Polysomnographic characteristics in nonmalignant chronic pain populations: A review of controlled studies

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SUMMARY

Sleep and pain are critical homeostatic systems that interact in a bidirectional manner. Complaints of sleep disturbance are ubiquitous among patients with chronic pain disorders, and conversely, patients with persistent insomnia symptoms commonly report suffering from chronic pain. Sleep deprivation paradigms demonstrate that partial or complete sleep loss induce hyperalgesia, possibly due to shared mechanistic pathways including neuroanatomic and molecular substrates. Further, chronic pain conditions and sleep disturbances are intertwined through comorbidities, which together cause detrimental psychological and physical consequences. This critical review examines 29 polysomnography studies to evaluate whether nonmalignant chronic pain patients, as compared to controls, show differences in objective measures of sleep continuity and sleep architecture. Whereas these controlled studies did not reveal a consistent pattern of objective sleep disturbances, alterations of sleep continuity were commonly reported. Alterations of sleep architecture such as increases in light sleep or decreases in slow-wave sleep were less commonly reported and findings were mixed and also inconsistent. Methodological flaws were identified, which complicated interpretation and limited conclusions; hence, recommendations for future research are suggested. Knowledge of abnormalities in the sleep process has implications for understanding the pathophysiology of chronic pain conditions, which might also direct the development of novel intervention strategies.

Introduction

Sleep and perception of pain both play important roles in the health and survival of a human being. A growing body of evidence, derived from experimental and prospective longitudinal studies, implies a bidirectional relationship between these essential homeostatic systems, with a stronger causal influence of sleep on pain, than pain on sleep [1,2]. Mechanistically, regulation of wake, sleep and nociception share common neuroanatomic and molecular substrates, but the contribution of possible neurotransmitters, endogenous opioid systems and inflammatory cytokines, in the regulation of the interaction between sleep and pain remains largely unknown [1,3]. Research in this area is challenging due to the heterogeneity in the mechanisms that contribute to different chronic pain conditions, as well as the expression of sleep problems in relation to chronic pain. Understanding this relationship is a first step in the development of treatments that target either sleep or pain, which might have salutary effects on either sleep or pain perception.

About 50% of people with persistent insomnia disorder report suffering from chronic pain, and conversely, the same percentage of people with chronic pain meet criteria for persistent insomnia disorder [4]. Complaints of sleep disturbance are ubiquitous among patients with chronic pain disorders (67–88%) [1], and have been correlated not only with increased pain, but also to daytime dysfunction, mood disturbance, impaired cognition and fatigue [5–7]. The connection between chronic pain conditions and sleep disturbances is further strengthened through several shared comorbidities, which possibly create vicious cycles to contribute to a multitude of detrimental psychopathological and physical consequences [4,8]. For example, cardiovascular disease, neurologic disease, affective disorders, cognitive impairment, decreased quality of life, and elevated all-cause mortality are all associated with chronic sleep complaints and insomnia [4,9,10]. Besides the direct impact of pain and its comorbidities on sleep, some widely

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Glossary of terms

AHI	apnea/hypopnea index
ArI	arousal index
BDNF	brain-derived neurotrophic factor
CNS	central nervous system
CRPS	complex regional pain syndrome
CSF	cerebrospinal fluid
CWP	chronic widespread pain
EEG	electroencephalography
FM	fibromyalgia
HC	healthy controls
IL	interleukin
MFP	myofascial pain
NREM	non-rapid-eye-movement
NSM	non-sleep migraine
OA	osteoarthritis
PHN	postherpetic neuralgia
PLMS	periodic limb movements during sleep
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
RA	rheumatoid arthritis
REM	rapid-eye-movement
RLS	restless legs syndrome
SE	sleep efficiency
SM	sleep migraine
SOL	sleep onset latency
SWS	slow-wave sleep
TIB	time in bed
TMD	temporomandibular disorders
TNF	tumor necrosis factor
TST	total sleep time
TTH	tension-type headache
WASO	wakefulness after sleep onset

used pain medications, such as opioids, may exert direct negative effects on sleep profiles [11–13]. In the United States, the combined direct and indirect societal costs for chronic pain and insomnia are staggering, possibly exceeding $700 billion annually [14,15].

Reviews of studies utilizing various sleep deprivation paradigms have clearly demonstrated that disturbance of sleep continuity induces increased pain perception and hyperalgesic effects [1,16]. Research aiming to elucidate the pathophysiological mechanisms underlying these effects is emerging, and has implicated decreased activity in descending inhibitory monoaminergic or opioidergic pathways that inhibit nociception at the spinal level [17,18]. However, the variability in pain response is complex and influenced by other factors, such as, for example, alterations in cognitive function associated with concomitant fatigue and mood disturbances, with other mechanisms also implicated [1,16]. Furthermore, sleep complaints and patterns of sleep disturbances in chronic pain populations are diverse and multifaceted – the type of sleep disruption most detrimental to development and maintenance of pain is currently not known, and experimental sleep deprivation studies do not provide a definite answer to this question as such strategies have routinely targeted only sleep duration [16].

Although there is yet no unequivocal explanation to why we sleep, it is clear that sleep is of crucial importance for restorative processes and energy metabolism, neural plasticity, and the immune system [19–21]. Good sleep is thus thought to be a prerequisite for both physical and mental health. Regulation of sleep homeostasis is incompletely understood, and current hypotheses implicate a myriad of molecules, including cytokines (particularly tumor necrosis factor (TNF) α, interleukin (IL) 1β), serotonin, adenosine, nitric oxide and brain-derived neurotrophic factor (BDNF) [19,20,22,23]. Inflammatory cytokines are pivotal mediators involved in CNS neuroimmune activation pathways. Given their role in both creation and maintenance of pain in various chronic pain models, as well as regulation of sleep, this review will discuss the relationships between sleep and inflammatory cytokines, although it is beyond the scope of this review to systematically evaluate the role of inflammatory cytokines [22,24].

Polysomnography (PSG), comprising electroencephalography (EEG), electromyography and electrooculography (additionally often respiration, heart rate and body temperature) is the gold standard method for the assessment of measuring sleep, and sleep disturbances. Specifically, both macro- (sleep continuity, sleep architecture) and microstructure (EEG power spectral analysis) of sleep can be analyzed, which is a great advantage compared to actigraphy data, for example, that provides only an estimate of sleep amounts [25]. Despite its utility in the assessment of sleep, controlled PSG studies in chronic pain populations have to date been relatively limited, in contrast to the high prevalence of sleep complaints in this population. Nevertheless, despite the complexity and high cost of such PSG investigations, several studies have been conducted, but no prior review has systematically evaluated this research to clarify the generalizability and significance of objective sleep disturbances in patients suffering from chronic pain, taking into account methodological quality. This review will extract and analyze PSG data on sleep continuity, sleep architecture, and, when available, EEG power spectral analysis, across adult human chronic pain populations, and identify confounding and limiting factors. The sleep EEG constitutes an electrophysiological correlate to the processes of brain metabolism; thus, knowledge of abnormalities in the sleep process might improve understanding of the pathophysiology of chronic pain conditions. Implications for future research and treatment of chronic pain and sleep disturbances will be outlined.

Basic architecture and physiology of sleep

The dynamic, cyclic process of sleep is divided into non-rapid-eye-movement (NREM) sleep, traditionally stages 1–4 with the deepest stages 3–4 referred to as slow-wave-sleep (SWS) or N3, and rapid-eye-movement (REM) sleep (Table 1) [26]. SWS predominates during the first third of the night, whereas REM sleep predominates during the last half of the night. Each NREM to REM sleep cycle lasts about 80–110 min, and over the course of the night these cycles are repeated three to six times. The conventional staging of sleep is done through visual inspection of the EEG. To achieve a quantitative analysis, a mathematical approach called EEG power spectral analysis is utilized [27]. Spectral analysis describes the frequency content of an EEG signal, which provides a continuous and exact evaluation of the power spectrum density. This method enables detection of trends in EEG power density throughout the night, and also detection of faster frequencies superimposed on slow-waves.

Search methods

A review of the literature was conducted, using the PubMed search engine, Google Scholar, and a manual search of all identified pertinent references. The database searches were performed in