Journal of Neural Transmission
https://doi.org/10.1007/s00702-019-02067-z

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Sleep and pain: recent insights, mechanisms, and future directions in the investigation of this relationship

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Received: 2 July 2019 / Accepted: 16 August 2019

Abstract

Sleep disturbances and chronic pain are considered public health concerns. They are frequently associated, and the direction of its relationship and possible mechanisms underlying it are frequently debated. The exploration of the sleep–pain association is of great clinical interest to explore in order to steer potential therapeutic avenues, accommodate the patient's experience, and adapt the common practice of health professionals. In this review, the direction between sleep–pain in adult and pediatric populations will be discussed. Moreover, the possible mechanisms contributing to this relationship as endogenous pain modulation, inflammation, affect, mood and other states, the role of different endogenous substances (dopamine, orexin, melatonin, vitamin D) as well as other lesser known such as cyclic alternating pattern among others, will be explored. Finally, directions for future studies on this area will be discussed, opening up to the addition of tools such as brain imaging (e.g., fMRI), electrophysiology and non-invasive brain stimulation techniques. Such resources paired with artificial intelligence are key to personalized medicine management for patients facing pain and sleep interacting conditions.

Keywords Sleep disturbance · Chronic pain · Insomnia · Obstructive sleep apnea · Pain modulation

Abbreviations

IL-6	Interleukin 6
CRP	C-reactive protein
NAc	Nucleus accumbens
A2A	Adenosine 2 receptor
PAG	Periaqueductal gray
EEG	Electroencephalogram
EMG	Electromyogram
25OHD	25-Hydroxyvitamin D

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Introduction

Sleep is a complex physiological and behavioral process that partially allows the individual to isolate from the external environment, which is thought to be essential for the psychological and physical recuperation, memory consolidation, emotional modulation, performance, and learning (Siegel 2005; Walker and Stickgold 2006). Sleep can be broadly separated into two main phases: non-rapid eye movement (NREM) and rapid eye movement (REM). Each of these phases is categorized by different physiological, behavioral, neurochemical and electrophysical attributes. According to electroencephalogram (EEG) parameters, NREM sleep can be further subdivided into three different stages: N1 and N2, characterized by lower arousal thresholds and often referred to as "light sleep"; and N3 (formerly 3 and 4, now merged into a single stage) or "deep sleep", characterized by higher arousal thresholds and dominance of slow-wave brain activity. While NREM sleep is associated with stable decrease of mental and physical activity, heart rate, blood pressure, and breathing (Siegel 2005; Ogilvie 2001), REM or "paradoxical" sleep, which follows the NREM phase in the sleep cycle, is characterized by an increase of mental activity while muscles remain paralyzed or inactive. During

Published online: 26 August 2019

REM phase, EEG patterns are more variable and physiological parameters such as heart rate, blood pressure or breathing frequency are unstable. Dreams occur in all sleep stages but REM is characterized by more vivid or creative dreams (Siegel 2011). In healthy adults, sleep onset usually occurs within 20–30 min of going to bed. A typical night of sleep encompasses 3–5 NREM to REM ultradian cycles (90 min on average, except for the first cycle which lasts about 120 min), where lighter sleep turns into deep sleep, which is then followed by a REM phase. As the night advances, duration and frequency of stage N3 decrease, stage 2 becomes more predominant, and REM phases become longer (Chokroverty 2010).

It has been reported that sleep difficulties (initiating and maintaining sleep, and experiencing inadequate sleep) can affect approximately 20–30% of the Western population on a daily to weekly basis (Hillman and Lack 2013), and as much as 45% according to a survey performed in Australia (Adams et al. 2017). Sleep loss impairs cognition, decision making, psychomotor function, mood, and immune function (Dinges et al. 1997; Killgore et al. 2006). In addition, poor sleep quality is considered a risk factor for cardiovascular disease, dementia, obesity, diabetes, depression, pain and mortality, among others (Yin et al. 2017; Shi et al. 2018; Fatima et al. 2016; Cappuccio et al. 2008; Gangwisch et al. 2007; Zhai et al. 2015). These physical and psychological changes can significantly affect health, well-being, and quality of life, sometimes leading to suicidal ideation (Pigeon et al. 2012; Bishop et al. 2018; Liu et al. 2019; Afolalu et al. 2018). Moreover, inadequate sleep leads to a significant decrease in productivity and substantial financial and nonfinancial costs, becoming an important social and economic burden (Hillman et al. 2018) (Fig. 1).

Pain was defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Treede 2018). Although this definition is probably the most frequently used, there is not a clear consensus about its utilization and recent efforts have been made in updating and reaching a more comprehensive definition of pain. Lately, the following definition was proposed: "Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components" (Williams and Craig 2016). In fact, pain is recognized as a very complex process generated by neural activity in a network composed of several different structures in the brain, called neuromatrix, where its different components may be associated with the anticipation of pain, the discrimination of pain, or with the unpleasant affective manifestations of pain (Melzack 1990; Price 2000). Broadly speaking, pain can be classified into three main categories: nociceptive; inflammatory; and pathological. (1) Nociceptive, considered a normal physiological response and an early-warning protective system in order to minimize contact with damaging or noxious stimuli. (2) Inflammatory, when the immune system gets activated by tissue injury or infection, and pain assists in the healing of the injury by discouraging physical contact and movement, thereby promoting recovery. As they are adaptive and protective in nature, these two types of pain are considered functional. The third pain category is (3) pathological, which is maladaptive as opposed to protective. It can be further subdivided into (a) neuropathic, resulting from a lesion in the peripheral or central nervous systems; or (b) dysfunctional, when there is no such damage or inflammation (fibromyalgia, temporomandibular disorders, or irritable bowel syndrome).

Pain is considered as "acute" when lasting for a duration that does not exceed the expected healing period (usually nociceptive or inflammatory), or as "chronic" when pain

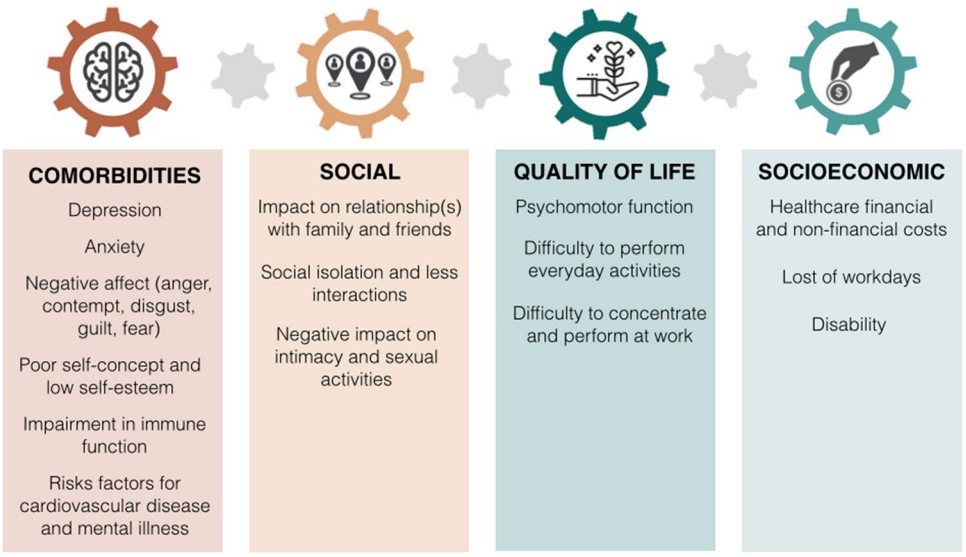

Fig. 1 Consequences of chronic sleep–pain interaction

outlasts or recurs beyond the expected 3- to 6-month healing period (often pathological) (Treede et al. 2019; Woolf 2010). It is reported that chronic pain affects nearly 20% of people worldwide, and that 15–20% of all physician visits are intended to address pain-related issues (Treede et al. 2015). Annual estimates of the direct and indirect costs linked to chronic pain reach 635 billions dollars strictly in the US (Gaskin and Richard 2012), which represents a staggering economic and social burden. Beyond costs, chronic pain has a significant impact on patients' well-being and quality of life, affecting their mood, coping resources, expectations, sleep quality, physical function, and daily activities, being highly related with disability and suicidal risk (Racine 2018; Duenas et al. 2016; Turk et al. 2016) (Fig. 1). Given the considerable suffering associated with pain, access to pain treatment is considered a basic human right by the World Health Organization (International Pain Summit of the International Association for the Study of P 2011; Web statement on pain management guidance 2019).

In this review, an overview of studies that have examined the relationship between sleep and pain will be provided. The direction of this relationship will be discussed and the potential mechanisms underlying this relationship will be addressed. Finally, directions for future studies in the area of sleep and pain will be discussed.

The relationship between sleep and pain: what direction?

Numerous cross-sectional studies have shown a high comorbidity between chronic pain and sleep impairments. A recent meta-analysis estimated a pooled prevalence of sleep disorders in 44% of adult chronic pain patients; insomnia (72%), restless leg syndrome (32%) and obstructive sleep apnea (32%) being the most common diagnoses (Mathias et al. 2018). The latter investigation also established that adult patients with chronic pain had worse measures for sleep onset latency and efficiency, time awake after onset and recurrent awakenings (large effects) when compared to controls. Moreover, chronic pain patients also exhibited worse scores on sleep-related measures such as total sleep time, light sleep duration (NREM 1), number of stage shifts, respiratory-related events and periodic limb movements, even though the effect sizes were small to medium (Mathias et al. 2018). Although the association between poor quality and chronic pain seems obvious, its directionality has been debated for several years. Earlier, it was thought to be bidirectional, where sleep impairments were thought to exacerbate pain and pain was thought to contribute to sleep instability or disturbances. However, recent qualitative analyses of longitudinal (less time points, usually far apart in time) and micro-longitudinal (more time points, close in time) studies point toward a stronger and more consistent unidirectional effect of sleep causing pain exacerbation in adult populations, especially in experimental and acute pain models (Andersen et al. 2018; Lavigne and Sessle 2016; Finan et al. 2013; Lautenbacher et al. 2006; Schuh-Hofer et al. 2013). For instance, it has been shown that sleep deprivation protocols can induce hyperalgesic responses (i.e., abnormally increased sensitivity to pain) that correlate with electrophysiological measures (e.g., decrease in laser evoked potentials) in healthy individuals (Schuh-Hofer et al. 2013, 2015) and that some of those responses can be reversed by napping or short sleep, regardless of vigilance status (Faraut et al. 2015). Recent comprehensive literature reviews and a commentary have been published lately on the bidirectionality of sleep–pain in adults (Andersen et al. 2018; Haack et al. 2019; Lautenbacher 2018). For more information on this topic, the reader may refer to them.

Among pediatric populations, the bidirectionality of this relationship is also unclear. A systematic review of 56 studies that included different pain conditions supported a bidirectional relationship between sleep and pain intensity, where besides sleep problems predisposing to pain, studies based on behavioral assessments and polysomnography (PSG) generally detected a relationship between intense pain and disrupted sleep (Valrie et al. 2013). In addition, the majority of these studies indicated that even after controlling for confounding variables, intense pain was found to be predictive of disrupted sleep patterns, and more frequent headaches predicted sleep disorders symptoms such as parasomnias, sleep walking, and bruxism (Valrie et al. 2013). Nevertheless, findings from recent studies are more contradictory. On one hand, in keeping with evidence from the adult population, a more linear relationship between pain intensity and sleep disturbances was observed in several investigations. In a study, 67 children between the ages of 10 and 17 diagnosed with acute musculoskeletal pain (< 1 month duration) underwent 8 nights of sleep monitoring actigraphy and completed pain diaries twice a day. Generalized linear models were used in order to test nighttime sleep as a predictor of morning pain, and evening pain as a predictor of nighttime sleep. The authors found that shorter sleep duration and poorer sleep quality predicted higher morning pain intensity. However, evening pain did not predict nighttime sleep, suggesting that sleep deficiency, as opposed to late-night pain, is more related to next-day pain (Lewandowski Holley et al. 2017). Furthermore, another study conducted in 60 children (10–18-year-olds) who underwent a major surgery used a multi-methods sleep assessment (electronic diaries, subjective ratings, validated questionnaire measures, and ambulatory actigraphy monitoring; therefore, objective and subjective assessments). Findings indicated that at an individual level, sleep quality and efficiency were significantly reduced at 2 weeks after the surgery, and that

poorer sleep quality was associated with greater next-day pain intensity (Rabbitts et al. 2017). In contrast, two studies conducted with sickle cell disease children ($n = 88$ aged 8–17 years; $n = 30$ African American 8–18 years) showed a bidirectional relationship, where poor subjective sleep quality and efficiency during the night were related to worse pain intensity the next day, and intense pain was related to poor sleep subjective sleep quality and efficiency that night (Valrie et al. 2019; Fisher et al. 2018).

The sections above highlight the complexity of the sleep–pain relationship as well as the potential factors that might underlie the direction and magnitude of this relationship. Caution in the interpretation of these studies is necessary as many of them did not control for confounding variables such as pain comorbidities or mood disorders, which are known to account for some of the pain and sleep quality variability (Dubrovsky et al. 2017). Another factor that should receive attention is the role of expectation and placebo/nocebo effects during sleep, as studies have shown that: (1) analgesic expectations induced before sleep produced a reduction in cortical arousals evoked by noxious stimuli during REM sleep (Laverdure-Dupont et al. 2018); (2) induction of analgesic expectations before sleep led to a reduced nocturnal pain perception, subjective sleep disturbances, and activated brain processes that modulate incoming nociceptive signals differentially according to sleep stage (Chouchou et al. 2018); (3) REM sleep appears to moderate the relationship between pain relief expectations and placebo analgesia (Chouchou et al. 2015); and (4) although nocebo effects (expectations of higher pain levels) can increase sensitivity to electrically induced pain, they do not explain sleep restriction-related hyperalgesia, as they appear to be mediated by different cortical mechanisms than sleep restriction (Ree et al. 2019).

The possible variation between subjective or objective sleep measures needs to be considered as well, as it has been suggested that each of them may measure different aspects of sleep (Landry et al. 2015; Wu et al. 2017) and, finally, more refined methodological modeling approaches to capture directionality are warranted for future investigations.

Possible mechanisms underlying the sleep and pain relationship

Sleep is an active process; it is not coma neither anesthesia. In fact, processing of sensory inputs could be preserved under particular circumstances (Mazza et al. 2012). Brain-evoked potentials to painful laser stimuli, which reflect cortical activity, have been recorded during all sleep stages (Bastuji et al. 2008). Research has shown that nociceptive stimuli can interrupt sleep (more easily in stage 1 or 2 when compared to deep sleep or REM), and produce significantly more arousals than non-nociceptive ones (Mazza et al. 2012; Bentley et al. 2003; Lavigne et al. 2000). Moreover, electroencephalographic (EEG) thalamic signals seem to vary according to the nature of the awakenings (i.e., "spontaneous" vs "nociceptive-induced") (Peter-Derex et al. 2015).

Although the link between sleep and pain is widely established, the mechanisms underlying this relationship have yet to be fully elucidated. Different reports have pointed toward the potential role of endogenous pain modulation, inflammatory markers, affect, mood and other states such as emotional distress or catastrophizing as possible mediators. Moreover, we will also discuss the potential importance of different endogenous substances and the role of other mechanisms such as brain anatomical areas or cyclic alternating pattern (Fig. 2).

Endogenous pain modulation (EPM)

EPM can be defined as the array of actions of several central nervous system (CNS) mechanisms that affect nociceptive signal processing. Deficient EPM can be represented by increased pain facilitation or impaired pain inhibition. Pain facilitation can be measured through temporal summation paradigms, by delivering suprathreshold noxious stimuli repeatedly in frequencies ≤ 0.33 Hz that lead to increased pain perception (Price et al. 1977) and it is considered a clinical correlate of the wind-up phenomenon (Herrero et al. 2000). Pain inhibition can be assessed through conditioned pain modulation (CPM), offset analgesia, or a combination of both. CPM paradigms are the clinical equivalent of "pain inhibits pain" testing in animal models, which triggers diffuse noxious inhibitory controls, and it is usually induced by presenting two noxious stimuli in distant body sites simultaneously or sequentially (Nir and Yarnitsky 2015). Alternatively, offset analgesia is another paradigm that represents a temporal filtering of nociceptive information, where a disproportionately large decrease in pain perception after a brief, temporary increment of thermal pain stimulus occurs (Grill and Coghill 2002; Moana-Filho et al. 2019). The presence of increased pain facilitation and impaired pain inhibition has been implicated in the development and maintenance of various chronic pain conditions, including musculoskeletal, visceral, and neuropathic pain (Edwards 2005; Staud 2012; Lewis et al. 2012; O'Brien et al. 2018; Moana-Filho et al. 2018; Arendt-Nielsen et al. 2008). In addition, it has been suggested that EPM testing can be used to predict pain onset and also pain treatment outcomes (Yarnitsky et al. 2014; Yarnitsky 2015; Moana-Filho and Herrero Babiloni 2018).

The effects of sleep on EPM mechanisms have been investigated in different studies. Although both pain facilitation and inhibition mechanisms have been found to be altered in an insomnia population ($n = 17$) when compared

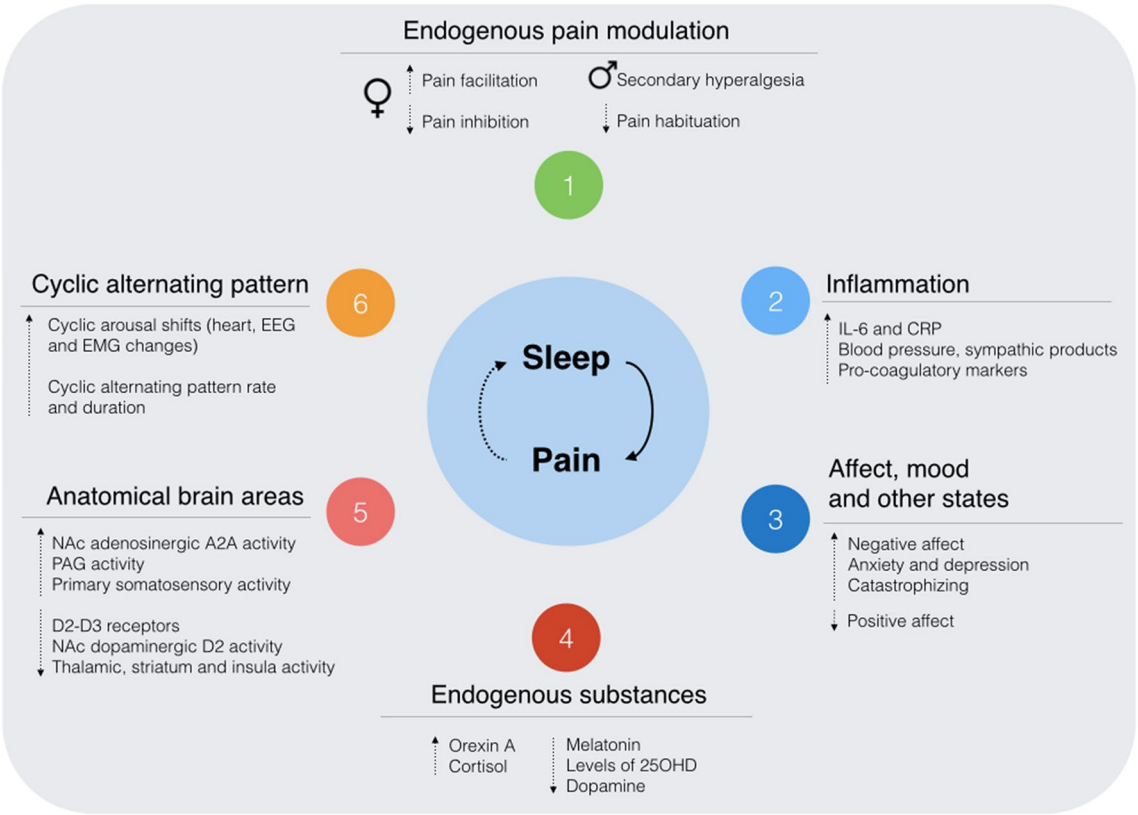

Fig. 2 Possible mechanisms underlaying the sleep–pain relationship in sleep and awake models

to controls (Haack et al. 2012), it has been suggested that pain inhibition could be more affected by sleep disruption than pain facilitation. Females were also found to be more susceptible to sleep deprivations effects in EPM than males (Finan et al. 2013; Tiede et al. 2010; Eichhorn et al. 2018). A cross-over balanced study (i.e., one night of total sleep deprivation was contrasted with one night of habitual sleep) showed that the endogenous capacity to inhibit pain was only reduced in sleep-deprived females, further pointing toward a sex-dependent effect of total sleep deprivation on descending pain pathways (Eichhorn et al. 2018). In another study conducted among healthy females in which partial sleep deprivation was induced by forced awakenings, a significant loss of pain inhibition and an increase in spontaneous pain were observed, suggesting that sleep continuity disturbance can impair EPM inhibitory function (Smith et al. 2007). On the contrary, other studies have shown absent-to-mild effects of partial sleep restriction and sleep alterations in CPM and temporal summation measures, the latter being at odds with previous findings. However, no sex-specific effect was assessed (Matre et al. 2016; Karmann et al. 2018).

Although conjectural, a recent study conducted among 79 healthy adults showed that the association between sleep disruption and central sensitization [pain amplification by central nervous system (CNS) mechanisms] involved distinct action mechanisms according to the sex. In males, sleep disruption induced secondary hyperalgesia, whereas sleep disruption increased temporal summation in females (Smith et al. 2019). Another study followed 14 healthy individuals undergoing both a 3-week protocol involving restricted sleep with limited recovery (5 nights of 4 h sleep per night followed by 2 nights of 8 h sleep per night) and a control protocol involving 3 consecutive weeks of normal sleep (8 h sleep per night). Spontaneous pain, heat-pain thresholds, cold-pain tolerance and habituation, and temporal summation were measured at multiple points during each protocol. Compared to participants exposed to the control protocol, participants in the sleep restriction protocol experienced mild increases in spontaneous pain, decrease in time of heat-pain thresholds, decreased pain habituation, and increased temporal summation in the last 2 weeks of sleep restriction. These results suggest that exposure to chronic insufficient sleep may increase vulnerability to chronic pain by altering processes of pain habituation and sensitization (Simpson et al. 2018). Interestingly, other study showed that one night of sleep deprivation resulted in an attention-dependent enhancement of habituation to noxious laser stimuli, which could be interpreted as a homeostatic self-protective mechanism produced by sleep deprivation (Schuh-Hofer et al. 2015; Valeriani 2015).

Subjective sleep quality has been related to CPM efficacy in both fibromyalgia and acute low back pain patient populations (Klyne et al. 2018; Paul-Savoie et al. 2012). Moreover, in a PSG study of patients experiencing chronic TMD pain, decreased sleep efficiency was significantly associated with diminished pain inhibition or CPM efficacy (Edwards et al. 2009). Likewise, self-reported sleep disturbances in chronic rheumatoid arthritis patients were related to reduced CPM efficacy (Lee et al. 2013). In sum, alterations in EPM appear to be a potent mechanism underlying the sleep and pain relationship. However, longitudinal studies are needed to ascertain the importance of EPM in new onset and chronification of pain. Moreover, the effects of sleep in other EPM testing such as offset analgesia could provide different lines of valuable research (Ligato et al. 2018; Niesters et al. 2011).

Inflammation

Inflammation itself, as in many other chronic pain conditions, has been an essential constituent in the relationship between sleep and pain (Watkins et al. 2003). Pro-inflammatory cytokines (i.e., IL-1β, IL-6 and TNF-α) are known to be part of the development of inflammatory and neuropathic pain (Zhang and An 2007) and are primarily involved in the regulation of sleep through the central nervous system (Mullington et al. 2010). The immune system is also characterized by variations modulated by the sleep–wake cycle. For example, some immune cells are at their lowest point in the morning, while others reach their peak level at night (Simpson and Dinges 2007; Redwine et al. 2000; Born et al. 1997). An increase of cytokines secretion has been observed in a context of sleep deprivation (Simpson and Dinges 2007; Vgontzas et al. 1999), and morning IL-6 concentrations were negatively associated with impaired sleep quality among healthy adults (Hong et al. 2005). Interestingly, a meta-analysis of cohort studies and experimental sleep deprivation models indicated that sleep disturbance and long sleep duration, excluding short sleep duration, were associated with increases in markers of systemic inflammation (CRP and IL-6) (Irwin et al. 2016). It has been reported that sleep deprivation can also exert important effects on the host defense including immune memory (i.e., the ability of the immune system to respond more rapidly and effectively to pathogens that have been encountered previously), thus increasing the risk for infections (Everson 1993). Chronic sleep deficiencies, as seen in insomnia, could increase low-grade inflammation (i.e., the chronic production, but in a low-grade state, of inflammatory factors) through different mechanisms, such as intestinal dysbiosis, impairment of HPA axes, circadian sleep disruption, obesity, or physical inactivity among others. On the other hand, inflammation/immune response can affect sleep as well, through cytokines, prostaglandins, or other sleep regulatory substances, such as components and/or decomposition products of pathogens (Mullington et al. 2010; Besedovsky et al. 2019).

Autonomic activation and resistance to insulin are other theorized mechanisms involved in the sleep inflammation pathway (Mullington et al. 2010; Besedovsky et al. 2019). It has been shown that blood pressure, sympathetic products and pro-coagulatory markers were increased in healthy participants after sleep deprivation (Besedovsky et al. 2019) and that the experience of acute and physical stress force along with the increase of blood pressure triggers inflammatory mediators (Chae et al. 2001; Sauvet et al. 2010). Alternatively, resistance to insulin and reduction of glucose metabolism have been linked to impaired vascular function and increased inflammation (Gonzalez-Ortiz et al. 2000; Knutson et al. 2007). Thus, parameters such as sympathetic activation, stress, metabolism and sex need to be accounted when making assumptions about this relationship.

In sum, the sections above highlight the importance of inflammation in the sleep and pain relationship, as sleep alterations may lead to an alteration of the immune response that could worsen chronic pain disorders and inflammation products could dysregulate sleep mechanisms.

Affect, mood, and other states

Negative affect (NA) is a personality variable that involves the experience of negative emotions such as anger, contempt, disgust, guilt, fear and also poor self-concept, while positive affect (PA) is characterized by emotions such as enthusiasm, energy, confidence, activeness, and alertness. Although NA and PA are negatively correlated, they are not completely opposite constructs (Larsen et al. 2017), being actually psychometrically different (Smith and Zautra 2008). The relationship of these affective states and sleep has been firmly demonstrated, with some studies showing the effect of sleep disruption on PA/NA and vice versa (Finan et al. 2017; Konjarski et al. 2018). The same concept has also been observed with chronic pain (Wiech and Tracey 2009). Higher NA is thought to increase arousal and hypervigilance to pain, causing sensitization to pain, avoidance, and functional disability (Janssen 2002). On the contrary, it is believed that higher PA attenuates both the perception of pain and the negative affective response to pain, increasing the resilience of the individual, whereas the absence of PA exposes vulnerable patients to poor pain-related outcomes (Finan and Garland 2015; Arewasikporn et al. 2018).

NA/PA is considered one of the most important mediators in the sleep and pain relationship in non-clinically depressed samples. A cross-sectional study conducted in 213 children and adolescents presenting with chronic pain indicated that 74% of children reported altered sleep and that poor sleep quality was significantly associated with increased pain, disability, higher NA, and decreased PA. NA (but not PA) was

considered as a mediator of the relationship between poor sleep and increased pain, and both NA and PA mediated the relationship between poor sleep and increased functional disability (Evans et al. 2017). In the latter study, affect did not modulate the relationship between poor sleep and increased pain. Another cross-sectional study was conducted in 948 mid-to late-life individuals with chronic pain. Mediation analyses revealed that sleep disturbance indirectly predicted pain interference via NA and PA and that both mediated the total sleep time and pain interference relationship (Ravyts et al. 2018). A longitudinal study conducted in 220 patients with fibromyalgia involved completion of electronic diary records for 21 consecutive days assessing both pain levels and subsequent activity interference and levels of PA and NA. Multilevel structural equation modeling showed that pain and PA mediated the relation between sleep quality and activity interference, that early-morning reports of poor sleep quality the previous night predicted elevated levels of pain and lower levels of PA at late morning. In turn, PA levels measured at the late-morning time point also predicted elevated end-of-day activity interference. PA levels were also found to be a stronger mediator than pain between sleep quality and subsequent activity interference, while NA was not a significant mediator in this study (Kothari et al. 2015).

These reports highlight NA and PA as essential contributing factors to consider if we are to understand the relationship between sleep and pain. Further longitudinal research on this matter, incorporating objective sleep measures and perhaps also neuroimaging, may help to further clarify the exact role of NA and PA in this relationship. The pivotal role played by affect as a mediator of the sleep and pain association also has important clinical implications. More specifically, there is reason to believe that treatment interventions designed to improve sleep quality might improve patients' affective states (i.e., by lowering negative affect and/or enhancing positive affect), which in turn could lead to reductions in pain. Treatment studies involving cognitive-behavioral treatment approaches designed to improve sleep quality, chronic pain, or both, have proven effective in improving sleep symptoms, patients' affective states and pain-related outcomes (Finan et al. 2014; Koffel et al. 2015; McCrae et al. 2018).

Other comorbidities frequently associated with deteriorated sleep and chronic pain are mood disorders such as anxiety and depression. Studies have shown that depressive symptoms partially mediate the relationship between insomnia/short sleep and chronic pain development and that anxiety symptoms partially mediated the relationship between insomnia symptoms and incidence of pain (Generaal et al. 2017; Dunietz et al. 2018). Additionally, elevated emotional distress and greater catastrophizing have also been considered mediators of the association between sleep disturbance and chronic pain intensity (Burgess et al. 2019). When referred to pain, catastrophizing has been defined as the tendency to magnify the threat value of pain stimulus and to feel helpless in the context of pain, and by a relative inability to inhibit pain-related thoughts in anticipation of, during or following a painful encounter (Quartana et al. 2009). A cross-sectional study conducted in 214 participants with TMD showed that pain catastrophizing was associated with greater sleep disturbance, and that a significant portion of the variance of clinical pain severity and pain-related interference attributed to pain catastrophizing, especially through rumination, was mediated by sleep disturbances (Buenaver et al. 2012). Another longitudinal study conducted in 50 consecutive chronic non-malignant pain patients concluded that pain was the mediator in the relationship between sleep and pain catastrophizing (Wilt et al. 2016). Nevertheless, one should note that the tested models did not include pain as an antecedent to poor sleep quality or catastrophizing as a moderator.

Endogenous substances (dopamine, orexin, melatonin, vitamin D)

Dopamine (DA) is a neurotransmitter and also a hormone involved in several functions of the body. In the brain, DA is well known for playing a major role in the sleep–wake cycle, in the reward motivation system, and for its involvement in movement control. In the sleep–wake cycle, more DA is associated with more time awake and less DA with a sleep inductor state. It is currently thought that dopamine neurons are a heterogeneous population of neurons that respond to both appetitive and aversive stimuli to mediate motivated behavior (Taylor et al. 2016).

Release of dopamine after an acute painful stimulus acts as a salience cue and is critical for approach or avoidance behavior. It has been theorized that chronic pain may lead to significant impairment of the mesolimbic dopaminergic system (i.e., reward pathways), which in turn could interfere with motivation (Taylor et al. 2016). Moreover, animal models showed that acute sleep deprivation is associated with downregulated D2/3 receptors activity, which could at least partially explained reduced alertness after sleep deprivation (Volkow et al. 2012). Downregulation of D2/3 receptors activity may also affect other systems where DA is involved, including the reward motivation and pain modulation systems (Finan and Remeniuk 2016). DA has also been related with antinociceptive effects and with motivated behavior despite chronic pain (Finan and Remeniuk 2016; Moradi et al. 2015; Schwartz et al. 2014), and some authors have hypothesized that this "lack" of DA may lead to a decreased protection toward pain, which then facilitates nociception (Finan and Remeniuk 2016). For instance, in fibromyalgia patients, one of the most common chronic pain conditions, a dysfunction of the dopaminergic system has been observed

(Wood et al. 2007). Moreover, patients with Parkinson's disease, a neurodegenerative disease where DA projections are progressively abolished, also present frequent pain and sleep complaints (Lee et al. 2006).

Orexin, also known as hypocretine, is a neuropeptide involved in the regulation of arousal, wake–sleep cycle, and appetite among others, which has become very popular in recent years for its involvement in multiple central nervous system processes. Two types of orexin peptides (orexin 1 and 2) and two types of receptors, orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R) have been identified. The orexinergic system has different projections to various areas in the CNS, and the latter system is thought to be involved in different physiological functions and conditions such as feeding and metabolism, cardiovascular homeostasis, hormone secretion, reproduction, sleep/wake cycle, reward and addiction, anxiety and stress, seizures, and recently pain modulation (Gotter et al. 2012; Razavi and Hosseinzadeh 2017; Roohbakhsh et al. 2018). To date, the bulk of evidence on the various roles of orexin in pain comes from animal models and suggests a contribution of the orexin system to neuropathic and visceral nociception, headaches, orofacial pain, rheumatoid arthritis, and stress-induced analgesia among others. It appears that the effects of orexin-A on pain are more potent than orexin-B and that these orexin subtypes can regulate thermal, mechanical and chemical antinociceptive effects at spinal and supraspinal levels (Cady et al. 2014). Despite having their main cell bodies located in the hypothalamus, regions such as the cerebral cortex, basal ganglia, nucleus accumbens (NAc), hippocampus, hypothalamic and thalamic nuclei, dorsal and medial raphe, locus coeruleus (LC) and regions involved in pain modulation, such as periaqueductal gray (PAG) and reticular formation, also receive projections from the orexin system. However, the exact action mechanism of this system in nociception and pain modulation is not fully understood.

Other important substance is melatonin (5-methoxy-*N*-acetyltryptamine), a neurohormone secreted in the pineal gland and regulated by the suprachiasmatic nucleus. It is synchronized to the light/dark cycle of the environment and is involved in circadian rhythms, which control its timing, quantity, and quality. Melatonin acts through melatonin 1 (MT1) and MT2 receptors in mammals, located in the hypothalamus, thalamus, anterior pituitary, dorsal horn of the spinal cord, spinal trigeminal tract, and trigeminal nucleus (Ng et al. 2017; Kaur and Shyu 2018). Besides participating in circadian rhythms, melatonin is also involved in other physiological functions, such as mood states and pain regulation. Additionally, melatonin has been related to the pathogenesis of a number of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and Huntington's disease (Ng et al. 2017; Kaur and Shyu 2018). It appears that melatonin also has free-radical activity and interacts with different pathways involved in pain, including *N*-methyl-D-aspartate (NMDA) and GABA, opioid, extracellular signal-regulated kinase (ERK/MAPK), and nitric oxide systems. Thus, melatonin could decrease pain improving sleep through circadian rhythms normalization, but also in an independent manner through its action on melatonin receptors and several neurotransmitter systems (Danilov and Kurganova 2016). Animal models have also demonstrated that the suppression of melatonin secretion due to sleep deprivation can increase glial activation and aggravate neuropathic pain (Huang et al. 2014). Moreover, disrupted melatonin secretion has been related to clinical symptoms in major depression and fibromyalgia patients (Caumo et al. 2019).

Vitamin D is another essential substance that can be obtained through sunlight exposure or diet, available in different types. Vitamin D plays a major role in calcium metabolism and bone mineralization among others (Holick 2004). Its status is based on the serum levels of 25-hydroxyvitamin D (25OHD), the metabolite found in the human body in higher concentration. Vitamin D is also related to the sleep–wake cycle and with the nociceptive process, mainly due to its role on inflammation (Shipton and Shipton 2015; de Oliveira et al. 2017; Wu et al. 2018). Different studies have speculated about the importance of vitamin D in sleep disorders, as it appears that vitamin D receptors have been found in different sleep–awake cycle areas such as the hypothalamus, and that lower levels of 25OHD have been correlated with shorter sleep duration, less sleep efficiency, and with the presence of sleep disorders such as obstructive sleep apnea (OSA) in adults and pediatric patients, restless leg syndrome or narcolepsy (de Oliveira et al. 2017). In an OSA study, along with clinical symptoms, 25OHD levels increased with continuous positive airways pressure (CPAP) treatment, mainly in an obese group (Liguori et al. 2017). Vitamin D and its modulating role on the immune system and the inflammatory cascade have been emphasized, suggesting possible neuroimmunomodulatory properties (de Oliveira et al. 2017). As with sleep conditions, lower levels of 25OHD (frequently defined as lower than 20 ng/mL) have been found in fibromyalgia, rheumatoid arthritis, osteoarthritis, or sickle cell disease among others (de Oliveira et al. 2017; Wu et al. 2018). Decreased 25OHD has also been associated with a higher consumption of opioids in a cancer pain population and with exacerbated central sensitivity in a chronic musculoskeletal pain sample (Bergman et al. 2015; von Kanel et al. 2014).

Finally, attention should also be directed toward the role of other neurotransmitters, such as serotonin, noradrenaline or oxytocin, which are commonly implicated in sleep and chronic pain pathways (Boakye et al. 2016; Schuh-Hofer et al. 2018).

Anatomical brain areas

A recent study, using a controlled laboratory sleep deprivation model in 21 healthy subjects, evaluated the acute effects of experimental sleep disruption on pain-related activation of the NAc with functional MRI (fMRI). The NAc is a brain area involved in pain modulation and reward motivation, receiving multiple dopaminergic inputs from different brain structures also involved with pain and cognition. The results of this study demonstrated that sleep disruption can attenuate NAc function and increase reward-related connectivity with the anterior midcingulate cortex (aMCC), a region commonly associated with the use of cognitive resources to regulate pain (Seminowicz et al. 2019). Furthermore, there is evidence showing that sleep deprivation increases pain by increasing NAc adenosinergic A2A activity and by decreasing NAc dopaminergic D2 activity and that chronic sleep restriction increases pain sensitivity over time in the PAG area (primary control center for descending pain modulation) and NAc in a dependent manner (Sardi et al. 2018a, b).

Other recent fMRI study investigated thermal pain thresholds in 25 healthy participants undergoing one night of sleep and one night of sleep deprivation (Krause et al. 2019). After a PSG night of normal sleep or sleep deprivation (enforced wakening period with non-stressful activities), thermal pain thresholds were assessed outside the fMRI scanner, which was followed by an in-scanner thermal pain sensitivity task. The latter involved a pseudo-randomly ordered sequence of painful hot and non-painful warm stimuli. The authors observed that sleep deprivation significantly increased pain reactivity within the right primary somatosensory cortex (the pain was induced over the left side of the body) and that the extent of sleep deprivation amplified somatosensory pain reactivity positively, which significantly predicted the lowering of pain thresholds. Moreover, following sleep deprivation, significant decreases in activity were observed in the thalamus and other brain areas involved in decision-making such as the striatum, insula, and NAc. The reduction of thalamic activity also significantly and negatively predicted lowering of pain thresholds across individuals. The authors concluded that sleep loss triggering hyperalgesia involves complex brain processes, as the impact of insufficient sleep on pain likely involves both an amplification of primary cortical pain processing, potentially due to thalamic disinhibition, and a shift in affective valuation and decision making involving the insula and NAc (Krause et al. 2019).

Cyclic alternating pattern

As mentioned above, sleep is an active process, where the individual is not completely isolated from external and internal stimuli. During NREM sleep, a process called cyclic alternating pattern (CAP) is present (Parrino et al. 2014). CAP is considered a visualization method and a physiological phenomenon representing the balance between sleep quietness and sleep arousal. Thus, there are frequent brief brain, heart, and muscle reactivations or microarousals called "windows" that last 3–15 s. These windows occur approximately 5–15 times per hour, allowing the individual to reposition or to recognize any harmful situation (Parrino et al. 2012). The sleep arousal is part of a protective "flight or fight mechanism" that remains present during NREM sleep to preserve body integrity (sleep positioning, adjustments in heart rate, etc.) and to react to threatening event. This process does not occur in an "abrupt binary way", as it appears that it may represent to some extent a transition between wakefulness and sleep, to preserve the continuity of sleep over the possibility to react in life-threatening situations (Peter-Derex et al. 2015). CAP is divided into two phases: an active and a quiet phase. The active A phase is further subdivided in A1 (high dominance of slow-wave sleep/promotor of sleep restoration), in A2 (a transition phase) and A3 (an arousal-dominant phase that is essential for our survival). The high rate of A2 and A3 phase represents sleep fragmentation, which is associated with higher number of arousals and decreased sleep efficiency (Parrino et al. 2012, 2014). During the quiet phase, corresponding to the B phase, sleep is very stable and quiet (Parrino et al. 1998). CAP phases are in the minute's domains and their rate rise with age or in the presence of disease. Therefore, it seems that CAP represents a possible "window" for arousal and, in fact, CAP is considered by many as a marker of sleep instability (Parrino et al. 2012).

Despite the fact that CAP has not been widely investigated in chronic pain populations, some studies have been conducted among patients with fibromyalgia. These patients have been found to present 50% more cyclic arousal shifts (heart, EEG and EMG changes) during their sleep and that CAP rate and duration were significantly increased in these patients when compared to controls. This activity pattern suggests a possible autonomic dysfunction and an alteration in sleep microstructure. It is to note that these results have yet to be reproduced in other studies. CAP was also associated with less sleep efficiency and more clinical symptoms such as pain intensity, and recent speculations suggested that sleep may cause the same effect as a stressing test in chronic pain patients (Rizzi et al. 2004, 2017). Moreover, CAP has also been strongly associated with the onset of sleep bruxism (Carra et al. 2011). More investigations about this marker in pain populations could better illustrate its role in the sleep and pain relationship, perhaps clarifying the relative weight of this possible mechanism.

Other sleep–pain mediators

Other identified mediators for the relationship between impaired sleep and higher pain intensity are fatigue, activation of HPA axis measured through cortisol (Bonvanie et al. 2016; Goodin et al. 2012) and, although inconclusive, several authors have identified the need to further investigate the role of physical activity, frequently associated with sleep disturbances and chronic pain (Banno et al. 2018; Kichline et al. 2019). Caffeine, alcohol or nicotine intake, other comorbidities, and the use of medications such as opioids can also have direct influence on sleep quality and pain instability (Marshansky et al. 2018; Whibley et al. 2019).

Future directions

Although more longitudinal, micro-longitudinal and mediation studies using subjective and objective outcomes have emerged in the past few years, additional studies using brain imaging (e.g., fMRI), electrophysiology, or human adaptation of other techniques (e.g., optogenetics, chemogenetics) will be needed to shed light on the neural underpinnings underlying the sleep and pain association (Dinh et al. 2019; Venner et al. 2019). The use of non-invasive techniques, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), may also be of great value to further investigate the mechanisms underlying the sleep–pain association. Research will be needed to determine whether non-invasive techniques such as TMS or tDCS could represent an effective therapeutic alternative for patients with pain with comorbid sleep problems. For instance, both techniques have been used to treat different chronic pain and sleep conditions (O'Connell et al. 2018; Herrero Babiloni et al. 2018a; Huang et al. 2018; Frase et al. 2019; Jodoin et al. 2017), and TMS was also used to assess cortical excitability of OSA, restless leg syndrome (RLS), and chronic insomnia patients (Salas et al. 2014; Herrero Babiloni et al. 2018b). Finally, novel modeling techniques will be needed to thoroughly assess potential relationships between sleep and pain phenotypes. Machine learning, for instance, is a mathematical approach that can help to identify patterns or clusters in variables to characterize phenotypes and observe more precise characteristics of vulnerability among patients. For example, it could be used to evaluate: (a) the influence of pain and use of management strategies (medication, CBT, etc.) on sleep, which is not solidly confirmed with usual statistical method, and (b) to further assess the impact of poor sleep or sleep disturbances on next-day functioning, pain, or quality of life (Lotsch and Ultsch 2018; Shahin et al. 2017). Such tools could reveal to be a major addition to personalized medicine diagnosis and treatment for patients facing pain and sleep conditions.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

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