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Critical Review

The Association of Sleep and Pain: An Update and a Path Forward

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Abstract: Ample evidence suggests that sleep and pain are related. However, many questions remain about the direction of causality in their association, as well as mechanisms that may account for their association. The prevailing view has generally been that they are reciprocally related. The present review critically examines the recent prospective and experimental literature (2005–present) in an attempt to update the field on emergent themes pertaining to the directionality and mechanisms of the association of sleep and pain. A key trend emerging from population-based longitudinal studies is that sleep impairments reliably predict new incidents and exacerbations of chronic pain. Microlongitudinal studies employing deep subjective and objective assessments of pain and sleep support the notion that sleep impairments are a stronger, more reliable predictor of pain than pain is of sleep impairments. Recent experimental studies suggest that sleep disturbance may impair key processes that contribute to the development and maintenance of chronic pain, including endogenous pain inhibition and joint pain. Several biopsychosocial targets for future mechanistic research on sleep and pain are discussed, including dopamine and opioid systems, positive and negative affect, and sociodemographic factors.

***Perspective:** This critical review examines the recent prospective and experimental research (2005–present) on the association of sleep and pain in an attempt to identify trends suggestive of directionality and potential mechanisms. An update on this literature is needed to guide future clinical efforts to develop and augment treatments for chronic sleep disturbance and chronic pain.*

***Key words:** Chronic pain, sleep, insomnia, longitudinal, sleep deprivation.*

Pain is a physical and emotional signal of bodily harm that strongly motivates behavior. Sleep is a behaviorally regulated drive that broadly serves to maintain homeostasis and optimize function across multiple physiologic systems. Humans require both pain and sleep for survival; however, chronic impairments in the systems regulating pain and sleep can have a broad negative impact on health and well-being. Sleep complaints are present in 67 to 88% of chronic pain disorders,[70,102] and at least 50% of individuals with insomnia—the most commonly diagnosed disorder of sleep impairment—suffer from chronic pain.[116] Across most medical interventions, the development of pain as a side effect coincides with the development of sleep disturbance, and vice versa.[20] Further, both chronic pain and sleep disturbances share an array of physical and mental health comorbidities, such as obesity,[45] type 2 diabetes,[18,50] and depression.[34,126]

In the backdrop of this accruing evidence in support of a sleep–pain association, 2 fundamental questions continue to linger: 1) Are pain and sleep reciprocally or unidirectionally related? and 2) What mechanisms account for the associations between sleep and pain? The vast expanse of research on the association of sleep and pain necessitates that we narrow the scope of the present review. Prior reviews on the subject have examined evidence from prospective[102] and experimental[54] studies to determine if sleep and pain are reciprocally

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related or better characterized through unidirectional models. The steadily emergent view supported by those reviews has been that pain and sleep are reciprocally related and that acute experimentally induced sleep loss increases pain sensitivity. However, early evidence informing those views was limited by methodologic inconsistencies across a relatively small number of studies, and newer data suggest that a more complex and textured characterization is warranted. As methods of prospective and experimental design have advanced in recent years, our intention is to provide an updated review of prospective and experimental studies conducted in the past decade to clarify what we currently know about the issue of reciprocality/directionality. Additionally, we discuss several promising targets for future research on potential mechanisms underlying the association of sleep and pain. Although we have not exhausted the list of possible mechanisms, we focus on 3 mechanistic possibilities (affective systems, brain neurotransmitter systems, and sociodemographic factors) that have received considerable attention in the separate fields of sleep and pain research but have received less integrative attention as mechanisms of the sleep–pain association. The pharmacologic[6] and cognitive-behavioral[115] treatment outcome literature have been recently reviewed elsewhere. Therefore, we will not review these studies and will refer readers to those papers.

Methods

The purpose of this paper is to critically review longitudinal and experimental studies that have been published since prior comprehensive reviews on this topic. Smith and Haythornthwaite[102] discussed longitudinal studies published in the years prior to and including 2004. Therefore, we searched the PubMed and Google Scholar databases for longitudinal studies, restricting the search to studies published from 2005 to present, and employing the following search terms individually and in combination: "pain," "chronic pain," "sleep," "insomnia," "longitudinal," "prospective," and "daily diary." Lautenbacher et al[54] discussed experimental studies published in the years prior to and including 2006. Therefore, our search for experimental studies was conducted in PubMed and Google Scholar, restricting the search to studies published from 2006 to present, and employing the following search terms individually and in combination: "pain," "pain sensitivity," "hyperalgesia," "quantitative sensory testing," "sleep deprivation," "total sleep deprivation," "partial sleep deprivation," "sleep fragmentation," and "experimental."

In addition to those database searches, reference sections of relevant studies were scanned for additional articles not identified by the original search. All prospective and experimental sleep deprivation studies identified were included in this review. Further, any additional article appearing in the synthesis of the prospective and experimental studies was chosen for review based on its relevance, in our judgment, for addressing the questions of directionality and mechanisms of the association of sleep and pain. Articles were neither included nor excluded based on the statistical significance, or lack thereof, of the results.

We first review the key findings from studies identified in our search procedure. Subsequently, we raise several directions for future research, organized under 2 broad headings: 1) biobehavioral mechanisms of the association of sleep and pain and 2) sociodemographic moderators of the association of sleep and pain. Although these categories by no means exhaust the potential supply of future studies to enhance our understanding of sleep and pain, we have selected them because they represent large gaps in the current knowledge base and may be incorporated into existing programs of research with relative ease.

Results

Directionality or Reciprocal Influence?

Overview of Prior Work

Early longitudinal evidence reviewed by Smith and Haythornthwaite[102] suggested a reciprocal relationship between sleep and pain. In that review, a pain→sleep directional effect was observed in 5 of 6 applicable longitudinal studies,[1,21,73,92,93] and evidence for a sleep→pain directional effect was observed in 4 of 6 applicable studies[1,21,92,111] involving patients with fibromyalgia, rheumatoid arthritis, burn injury, and orofacial pain. Since then, the literature has matured in several key facets that improve the strength of inferences that can be made. First, there are more than twice as many prospective studies (Table 1) that include a variety of novel clinical samples, including patients with tension headache, migraine, primary insomnia, primary depression, and pediatric chronic pain. Second, there is now a greater mix of longitudinal (eg, few time points, far apart) and microlongitudinal (eg, many time points, close together) studies, providing greater texture in the temporal analysis of sleep and pain. Third, several studies examine new instances of pain complaints and/or sleep disturbance predicted by prior symptoms. Fourth, there are now several very large epidemiologic studies from which one may more firmly draw population-level conclusions.

We broadly categorized the recent prospective studies into those that only assessed the sleep→pain directional effect and those that assessed a bidirectional association. We did not find any recent prospective studies that have exclusively evaluated the unidirectional pain→sleep directional effect.

Recent Prospective Studies Assessing the Unidirectional Effect of Sleep on Future Pain (2005–2012)

Three large longitudinal studies have demonstrated that elevated insomnia symptoms increase the risk of exacerbating existing headache and developing new incident headache at long-term follow-up, ranging from 1 to 12 years.[10,62,77] Specifically, Danish individuals with infrequent, episodic tension-type headache were more likely to develop chronic tension-type headache

Table 1. Longitudinal and Microlongitudinal Studies, 2005 to 2012

Reference	*Study Sample*	*Pain Measures*	*Sleep Measures*	*Pain→Sleep*	*Sleep→Pain*
Lyngberg et al[62]	Tension headache (n = 549) and migraine (n = 160)	Chronic headache (12-year follow-up)	Self-report sleep problems (baseline)	N/A	Yes*
Boardman et al[10]	Headache-free general population (N = 455)	Headache incidence (1-year follow-up)	Self-report severe sleep problems (baseline)	N/A	Yes‡
Hamilton et al[43]	Fibromyalgia and rheumatoid arthritis (N = 49)	1) Correlation of daily pain and negative affect 2) Correlation of daily pain and positive affect	1) Sleep quality 2) Sleep duration (both baseline)	N/A	1) Yes† 2) Yes*
Davies et al[17]	Chronic widespread pain (N = 679)	Resolution of chronic widespread pain (15 months' follow-up)	Self-report restorative sleep (baseline)	N/A	Yes*
Bigatti et al[8,§]	Fibromyalgia (N = 492)	Self-report pain (baseline; 1 year)	Self-report sleep quality (baseline; 1 year)	N/S	Yes*
Edwards et al[29]	General population (N = 971)	Daily self-report pain	Daily self-report sleep duration	Yes† (weaker)	Yes† (stronger)
Smith et al[104]	Burn injury (N = 333)	Self-report pain (baseline; 2-year)	Self-report sleep-onset insomnia (baseline; 2-year)	Yes†	Yes†
Quartana et al[88]	TMD (N = 53)	Biweekly pain ratings	Biweekly insomnia severity	N/S	Yes*
Dzierzewski et al[24]	Older adults with insomnia (N = 50)	Daily self-report pain	Actigraphy	N/A	Yes*
Chung and Tso[16]	Major Depression (N = 82)	Self-report pain (baseline; 3 month)	Actigraphy (baseline; 3 month)	N/A	Yes*
O'Brien et al[76]	Fibromyalgia (N = 22)	Daily self-report pain	1) Daily self-report sleep quality 2) Actigraphy	1) Yes† 2) N/S	1) Yes† 2) N/S
Lewandowski et al[59]	Adolescents with chronic pain (N = 39)	Daily self-report pain	Actigraphy	N/S	Yes†
Odegard et al[77]	General population (N = 15,268)	Headache incidence (11-year follow-up)	Self-report insomnia (baseline)	N/A	Yes†
Bromberg et al[12]	Adolescents with juvenile polyarticular arthritis (N = 51)	Daily self-report pain	Daily self-report sleep quality	N/S	Yes†
Mork and Nilsen[71]	General population (N = 12,350)	Fibromyalgia incidence (11-year follow-up)	Self-report insomnia (baseline)	N/A	Yes†
Jansson-Frojmark and Boersma[47]	General population (N = 1,746)	1) Pain incidence 2) Pain persistence (baseline; 1-year)	1) Insomnia incidence 2) Insomnia persistence (baseline; 1-year)	1) Yes* 2) Yes*	1) N/S 2) Yes†
Tang et al[114]	Comorbid heterogeneous chronic pain and insomnia (N = 119)	Daily self-report pain	Daily self-report sleep quality, efficiency	Yes* (weaker)	Yes* (stronger)

Abbreviations: TMD, temporomandibular disorder; N/A, not assessed; N/S, not significant.
NOTE. *Stronger* and *weaker* refer to the relative strength of the general directional effect across multiple data analytic models tested.
*$P < .05$.
†$P < .01$.
‡P value not reported.
§This study tested various sequential models with path analysis, and only reported the statistics for the best-fitting model in which sleep quality predicted pain.

at 12-year follow-up if insomnia symptoms were present at baseline.[62] Insomnia symptoms, however, were not predictive of migraine prognosis in that sample. In contrast, baseline insomnia symptoms in a headache-free, population-based Norwegian sample predicted new incident cases of both tension-type and migraine headache at an 11-year follow-up.[77] A headache-free, population-based British sample were significantly more likely to develop new incident cases of headache (diagnostic type not specified) at 1-year follow-up if insomnia symptoms were present at baseline.[10] In the same study, individuals with headache were more likely to remit at 1 year if insomnia symptoms were absent at baseline.[10]

A large population-based study of Norwegian women found that women who endorse frequent "sleep problems," defined as frequent difficulty falling asleep or having a sleep disorder, were significantly more likely to develop fibromyalgia 10 years later.[71] The authors estimated that two-thirds of the incident cases of fibromyalgia in their sample were explained by sleep problems.[71] These findings are supported by a separate population-based study that found that insomnia symptoms at baseline significantly increased the risk of developing chronic musculoskeletal pain (both widespread and regional) at 17-year follow-up.[74] Quality sleep has also been shown to predict chronic widespread pain symptom resolution over 15 months.[17]

In addition to the longitudinal studies, recent micro-longitudinal studies have shown that sleep disruption linearly predicts next-day pain reports in patients with depression[16] and older adults,[24] and next-day affective responses to pain in rheumatoid arthritis and fibromyalgia patients.[43]

Together, these prospective studies indicate that sleep disturbance increases the risk for new-onset cases of chronic pain in pain-free individuals, worsens the long-term prognosis of existing headache and chronic musculoskeletal pain, and influences daily fluctuations in clinical pain. Furthermore, good sleep appears to improve the long-term prognosis of individuals with tension-type headache, migraine, and chronic musculoskeletal pain.

Recent Prospective Studies Assessing Bidirectional Effects of Sleep and Pain (2005–2012)

Evidence for Temporal Precedence of Sleep Over Pain. Across the studies investigating bidirectional linkages, a trend has emerged suggesting that sleep disturbance may predict pain to a greater degree than pain predicts sleep disturbance. A 1-year longitudinal cohort study of fibromyalgia patients revealed through structural equation modeling that sleep disturbance temporally preceded increases in pain, whereas pain at time 1 was not significantly associated with sleep disturbance 1 year later.[8] Cross-lagged panel modeling of biweekly insomnia severity and pain ratings in temporomandibular disorder (TMD) patients found a similar effect.[88] Across 3 months of measurement (6 biweekly assessments), within-month fluctuations in insomnia severity predicted next-month changes in pain ratings, whereas fluctuations in pain were not predictive of future changes in insomnia severity. In the general population, sleep and pain evidenced lagged day-to-day interdependencies.[29] However, the magnitude of the effect was stronger for the sleep→pain direction than for the opposite direction, such that decreased sleep on a given day predicted increased pain on the subsequent day.[29]

Evidence favoring the temporal precedence of sleep over pain was also presented in 3 subsequent studies of daily sleep and pain. In 1 study of adolescents with heterogeneous chronic pain complaints, including headache, abdominal pain, back pain, and other musculoskeletal pain, daily actigraphy assessments revealed significant associations of total sleep time and wake after sleep onset on next-day pain reports.[59] Pain did not prospectively predict any sleep measure. In another study of adolescents with juvenile polyarticular arthritis, daily self-reported poor sleep quality predicted daily pain, but the reverse association was not significant.[12] Similar effects were observed in adult pain clinic patients with a wide range of chronic pain etiologies and comorbid insomnia.[114] In that study, self-reported sleep quality and actigraphically measured sleep efficiency reliably predicted next-day pain reports. In contrast, pain was removed from final models predicting sleep parameters because of its relatively weak predictive validity compared to cognitive variables.

It is worth noting that in addition to these prospective studies, a large cross-sectional cohort study of cancer patients utilized structural equation modeling to suggest directionality in the sleep–pain association.[110] In a series of analyses involving associations between depression, fatigue, sleep, and pain, the best-fitting structural equation model included a path in which sleep predicted pain; inclusion of the reverse path—pain predicting sleep—produced a poorer fitting model that was dropped from final analyses. These findings provide suggestive evidence that the influence of sleep on pain symptoms may be stronger than the influence of pain on sleep symptoms in cancer patients.

Evidence for Bidirectionality. Other recent longitudinal studies have offered data consistent with a bidirectional association of sleep and pain. A large longitudinal study of acute burn injury patients employed linear mixed modeling and demonstrated that acute insomnia symptoms observed at hospital discharge predicted attenuated recovery and elevated pain severity over a 2-year follow-up period.[104] The reverse relationship was also observed: pain severity at discharge predicted insomnia severity at the 2-year follow-up. A reciprocal relationship between chronic pain and chronic insomnia symptoms was observed over a 1-year time frame in a population-based study of Swedish adults.[47] However, insomnia at baseline did not significantly predict new incidents of pain at follow-up after adjusting for age, sex, and depression symptoms. On a daily time scale, a bidirectional association of pain and sleep disturbance was observed in a sample of women with fibromyalgia.[76] In that study, multilevel modeling revealed that poor self-reported subjective sleep quality

predicted increased next-day pain, and increased pain predicted poor next-night sleep quality.

Summary of Recent Prospective Studies

As experimental and data analytic methods have been refined over the past decade, a trend in the literature suggests that the temporal effect of sleep on pain may be stronger than that of pain on sleep. Out of 9 recent prospective studies that have tested both directional effects, 6 found stronger evidence for the temporal precedence of sleep over pain.[8,12,29,59,88,114] Each of these studies employed sophisticated measurement (eg, microlongitudinal) and analytic techniques, including multilevel modeling and cross-lagged panel modeling, whereby time-based dependencies in repeated measures and random error variance are controlled, and sequential relationships can be inferred with a greater degree of confidence than is possible with ordinary least squares regression or analysis of variance techniques. Notably, 2 of the studies that reported relatively equivalent bidirectional effects[47,104] were limited by their reliance on basic self-report instruments to assess sleep and pain. Thus, when assessed in broad strokes, sleep and pain may appear to be reciprocally related, whereas finer-grained analyses suggest that poor sleep may exert a stronger and perhaps more durable toll on the experience of chronic pain (see O'Brien et al[76] as a notable exception). Further, several large prospective studies suggest that sleep problems increase the risk of developing future chronic pain, and good sleep increases the chance that chronic pain will remit over time.[10,17,62,71,74,77] These studies provide a sound basis from which to hypothesize that sleep has a causal influence on pain. From a clinical standpoint, these findings strongly suggest that sleep disruption may hold significant promise as an intervention target in efforts to prevent and treat chronic pain. However, it is important to note that it is not clear if different mechanisms are at play in the development of new incident pain as opposed to exacerbation of existing pain as a result of sleep disturbance. Future work should investigate if the mechanisms are identical, or if the sleep disturbance input required to provoke a new incident case is of greater magnitude or duration than that required to provoke a flare of an existing condition.

Going forward, prospective studies should also include more objective measures of sleep and pain. Several studies reviewed here employed actigraphy, which provides an objective assessment of activity versus inactivity to quantify sleep parameters, including total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency. Given its increasing affordability and minimal subject burden, actigraphy should become a standard assessment tool in prospective studies of sleep and pain. In addition, ambulatory polysomnography is becoming more widely available and user-friendly, providing a unique opportunity to repeatedly assess within-person electrophysiological sleep parameters. Little is known about the longitudinal association of objective sleep disturbance and quantitative sensory tests of pain sensitivity or pain modulation. All of the prior studies relied on self-reported clinical pain. These questions should be taken up in future studies with both clinical and nonclinical samples.

Experimental Sleep Deprivation and Pain

Overview of Prior Work

Whereas recent advances in prospective studies have shed new light on the temporal relationship of sleep and pain, advances in sleep deprivation studies have provided deeper insights into the mechanisms by which sleep and pain are related. By manipulating specific aspects of a person's typical sleep opportunity period, these studies inform us of the impact of sleep loss on acute analgesic responses to nociceptive stimuli, as well as any spontaneous changes in clinical pain. This topic has been the subject of a previous review,[54] the results of which provided tentative support for the notion that sleep deprivation increases pain sensitivity. Out of 8 studies reviewed, 5[52,58,66,67,80] found evidence in favor of a hyperalgesic effect of sleep deprivation and 3[2,22,79] failed to find evidence for sleep deprivation–induced hyperalgesia. The findings from those initial studies were limited in several respects. First, sample sizes were all quite low (N ranging from 9 to 20) and were restricted to healthy subjects, thereby limiting generality to clinical populations. Second, the sleep deprivation techniques were limited to total sleep deprivation and selective sleep-stage deprivation. The former tells us what happens when the brain and body are completely deprived of sleep. The latter assesses the effects of disrupting specific sleep stages, such as slow-wave sleep or rapid eye movement. Notably absent from the early studies reviewed by Lautenbacher et al[54] were partial sleep deprivation techniques, which may offer novel and more ecologically valid insights on how sleep and pain are related in both the general population and clinical samples. Partial sleep deprivation approaches involve curtailing sleep or disrupting sleep. Finally, the quantitative sensory testing (QST) modalities of early studies were limited to tests of thermal and mechanical threshold and tolerance and did not assess the influence of sleep deprivation on descending pain modulatory processes such as pain inhibition or facilitation. Recent experimental studies have addressed some of these gaps, though many remain. Here, we review recent studies that have employed partial sleep deprivation techniques in the investigation of sleep disturbance–induced hyperalgesia. Additionally, we review several recent experimental sleep studies that have included clinical samples.

Recent Studies of Partial Sleep Deprivation and Pain Sensitivity

Most people with clinical sleep impairments achieve some measure of sleep throughout a typical sleep opportunity period. Therefore, partial sleep deprivation paradigms, which restrict sleep for part but not all of the sleep opportunity period, may come closer than total

sleep deprivation designs to approximating the effects of common sleep problems on pain sensitivity. Indeed, healthy subjects (N = 22) report spontaneous bodily pain after 2 nights of partial (4 hours) sleep deprivation, and this effect increases as the number of nights of partial sleep deprivation increases.[40] A small within-person study of healthy subjects (N = 7) found that 4-hour continuous sleep restriction for 2 consecutive nights significantly decreased finger withdrawal latency to a noxious suprathreshold thermal stimulus,[95] suggesting that partial sleep deprivation may produce hyperalgesia. A recent partial sleep deprivation study of rheumatoid arthritis patients underscored the clinical relevance of those findings.[46] In a relatively large sample of healthy subjects (N = 27) and rheumatoid arthritis patients (N = 27), continuous 4-hour sleep restriction for only 1 night resulted in elevations in self-reported pain, fatigue, depression, and anxiety in rheumatoid arthritis patients but not controls. Importantly, disease-specific measures of pain severity and painful joint counts were elevated in the rheumatoid arthritis patients following partial sleep deprivation.[46]

A small within-person partial sleep deprivation experiment provided evidence suggesting differential effects of partial sleep deprivation on subjective pain reports versus cortical activation during QST.[117] Subjects were instructed to restrict themselves to 4 hours or less of sleep in their home environment for 1 night, and sleep duration was verified with actigraphy. The next day, subjects arrived at the laboratory for QST involving laser pulses of radiant heat (the same protocol was administered on a separate occasion following uninterrupted sleep). Noxious stimuli were rated as significantly more painful following partial sleep deprivation compared to uninterrupted sleep, whereas cortical electroencephalographic activity in the insular and cingulate regions was attenuated. These results might suggest that the hyperalgesic effect of partial sleep deprivation is mediated by impairments in the descending pain modulatory systems, rather than an amplification of the ascending sensory pathways, though further research is needed to confirm this possibility.

Partial sleep deprivation paradigms that disrupt sleep continuity, rather than maintain wakefulness continuously for a specified period (eg, 4 hours), may provide an even closer experimental analog to sleep disturbance in chronic pain. The predominant sleep complaint reported by patients with chronic pain is multiple nocturnal awakenings due to pain-related arousals throughout the night.[116] Smith et al[101] developed a forced awakenings (FA) sleep continuity disruption paradigm to enhance the predictive validity of hypotheses regarding sleep disturbance–induced hyperalgesia. FA is a partial sleep deprivation paradigm through which individuals are awakened pseudorandomly each hour during an 8-hour sleep opportunity period. Seven awakenings are for a 20-minute interval, and 1 awakening is for an entire 60-minute interval. In total, subjects are awake for 200 minutes and permitted to sleep for 280 minutes. Results from the initial FA study[101] demonstrated that disruption of sleep continuity resulted in next-day spontaneous pain reports in otherwise healthy women (n = 10) compared to a group receiving restricted sleep opportunity (n = 10) who slept continuously for an equivalent amount of time as the FA group, and healthy controls who slept continuously for 8 hours (n = 12). Additionally, conditioned pain modulation (CPM)—a measure of endogenous opioid-mediated pain inhibition[128]—was significantly reduced following the sleep continuity disruption relative to both other groups.[101]

The deleterious effect of sleep continuity disturbance on pain inhibitory function has since been replicated in several clinical studies. In a polysomnography study of TMD patients, poor sleep efficiency was significantly associated with diminished CPM efficacy, or impaired pain inhibition.[28] Self-reported sleep efficiency was also inversely correlated with CPM efficacy in fibromyalgia patients.[82] Further, CPM efficacy is reduced in rheumatoid arthritis patients relative to healthy controls and appears to be mediated by self-reported sleep disturbance in that patient group.[56]

Recent Studies of Experimental Sleep Deprivation in Clinical Samples

The majority of experimental sleep deprivation studies continue to rely on healthy samples in order to minimize error variance and establish basic causal effects. However, several recent studies have advanced the science by examining the hyperalgesic effects of sleep deprivation in clinical samples. As described above, Irwin et al[46] demonstrated that partial sleep deprivation altered both psychosocial symptoms and disease-specific markers of rheumatoid arthritis. Comparable effects have been reported in patients with gastroesophageal reflux disease (GERD) who were exposed to partial sleep deprivation.[98] Relative to healthy controls, GERD patients showed significantly greater increases in symptom intensity ratings following an acid perfusion test designed to evoke GERD-like symptoms. The authors interpreted changes in symptom intensity as clinically relevant evidence of hyperalgesia following partial sleep deprivation.

Kundermann et al[51] conducted the first study of sleep deprivation–induced hyperalgesia in a sample of patients with major depressive disorder. Patients demonstrated reductions in heat pain threshold following total sleep deprivation, whereas detection thresholds (eg, touch) remained unchanged. These findings replicated effects from nonclinical studies[52] and suggest that total sleep deprivation selectively augments the activity of nociceptive pathways without altering the perception of nonnociceptive somatosensory stimuli. This study is limited, however, by the absence of a control group against which to compare the increases in hyperalgesia following sleep deprivation.

Finally, Busch et al[14] recently reported that clinical pain complaints increased but thermal and pressure pain thresholds were unchanged following total sleep deprivation in patients with chronic somatoform disorder. In contrast—and similar to Kundermann et al's study[51] with depressed patients—mood significantly improved

following sleep deprivation. The findings suggest that in patients with somatoform disorder, mood and pain symptoms may be differentially affected by sleep disturbance and that the hyperalgesic nociceptive responses observed in sleep deprivation studies involving healthy subjects may not translate to this patient population.

A recent experimental study suggests that the extension of sleep in individuals with mild chronic sleep loss attenuates baseline pain sensitivity levels.[94] Individuals with an average sleep onset latency on the Multiple Sleep Latency Test of less than 8 minutes were randomized to 4 nights of an extended 10-hour bedtime or 4 nights of habitual bedtimes. Compared to habitual sleep, extended sleep increased tolerance to a radiant heat stimulus. Further, increased pain tolerance (ie, reduced pain sensitivity) significantly correlated with changes in the Multiple Sleep Latency Test. As individuals with mild chronic sleep loss may be at risk for elevated pain sensitivity, these findings suggest that early intervention to increase sleep time may prevent chronic deficits in pain regulatory function.

Summary of Recent Experimental Sleep Deprivation Studies

A variety of sleep deprivation paradigms have been employed to test the direct effect of sleep disturbance on pain sensitivity. Across studies, it is evident that experimental disturbance of sleep, even after a single night, has the potential to increase both clinical pain and responses to quantitative sensory tests, although effects may vary between healthy and clinical populations. Hyperalgesic effects following experimental disruption of sleep continuity may be particularly relevant to patients with chronic pain, as they have been shown to functionally alter key endogenous pain modulatory pathways known to increase vulnerability to central sensitization and persistent pain.[101] A next step, modeled elegantly by the Irwin et al[46] study, will be to disrupt sleep continuity in a clinical population to determine its effect on disease-specific measures of pain and disability.

Discussion

Future Directions: Biobehavioral Mechanisms of the Association of Sleep and Pain

The focus of research on the association of sleep and pain is beginning to shift to mechanisms. Whereas early work was principally concerned with establishing *whether* sleep and pain were consistently associated, future work will undoubtedly become more concerned with *how* sleep and pain are associated. Here we highlight 3 broad areas that we believe hold great promise in explaining how sleep and pain are related.

Dopaminergic Signaling

Dopamine (DA) is the principal neurotransmitter of the forebrain reward system, a complex network of mesolimbic and nigrostriatal circuitry underlying the human behavioral drive to pursue pleasure. DA is also integral to the promotion and maintenance of arousal states[68] (for reviews, see[69]) and is, therefore, intimately tied to the regulation of sleep and wake.[25,83,87] DA receptors are abundant in the ascending reticular activating system, including aspects of the raphe nuclei in the brain stem, a critical sleep modulation region.[3,61] Foo and Mason[37] postulated that serotonergic raphe cells signaling alertness may become dysregulated in the course of chronic pain and contribute to prolonged periods of sleep loss and greater disruption of sleep continuity. Given the abundance of DA receptors in that region of the brain stem, and the well-known interaction of serotonergic and dopaminergic neurotransmission,[49] it is possible that pain-induced alterations in DA signaling may influence the raphe nuclei modulation of sleep and wake.

This possibility is underscored by evidence indicating that patients with chronic facial pain and fibromyalgia, respectively,[55,63] have reduced DA metabolite concentrations in the cerebrospinal fluid[11,57,96] and a reduced phasic DA response to noxious stimuli.[99,127] But basic mechanistic studies are needed to establish how sleep disturbance alters the function of DA, and how that alteration may consequently influence pain sensitivity. For example, Volkow et al[123,124] conducted 2 total sleep deprivation experiments with positron emission tomography imaging that found evidence for reduced [^{11}C]raclopride binding to D_2/D_3 receptors in the striatum and thalamus of healthy human subjects. The authors initially interpreted these results to indicate that sleep deprivation *enhanced* endogenous DA tone in order to combat the primary drive to sleep and postulated that the suprachiasmatic nucleus, which innervates the striatum and mesencephalon, may regulate this homeostatic process. However, a more recent sleep deprivation experiment from their group[122] found that the effects of methylphenidate on D_2 receptor binding were no different following sleep deprivation compared to uninterrupted sleep. As methylphenidate is known to block the dopamine transporter receptor, this finding suggests that sleep deprivation may downregulate D_2/D_3 receptors, rather than enhance endogenous DA tone. Clearly, more research is needed to clarify the exact manner in which sleep deprivation alters DA, and whether those changes are correlated with concurrent changes in pain sensitivity. In addition, more clinical studies are needed to establish the behavioral consequences of sleep disturbance on reward processing, and how those changes influence coping with chronic pain.

Opioidergic Signaling

An abundance of transdisciplinary research suggests that opioid peptides play a critical mediating role in descending pain modulatory systems.[5,7,48] Compromised pain inhibitory capacity has been demonstrated in many idiopathic clinical pain conditions with prominent sleep disturbance components,[53,84,108] such as fibromyalgia. Preclinical studies indicate that sleep deprivation dysregulates endogenous opioid systems and attenuates the analgesic efficacy of μ-opioid receptor agonists.[72,120] Several pathways could contribute to diminished opioid

analgesia following sleep disruption. Opioid receptors are located in multiple nuclei that actively regulate both sleep and pain,[37] including the preoptic suprachiasmatic nuclei, which controls sleep–wake cycles,[19] and the periaqueductal gray, which plays a major role in descending pain inhibition.[97] Animal studies have found that sleep deprivation alters μ- and δ-opioid receptor function in mesolimbic circuits,[31] diminishes basal endogenous opioid levels,[86] and downregulates central opioid receptors.[32] A recent study with humans supports these preclinical findings by demonstrating that diminished codeine analgesia is correlated with daytime sleepiness.[109] Sleep, however, was not assessed. At the epidemiologic level, sleep disturbance cross-sectionally correlates with opioid use,[132] but most of these studies focused on sleep apnea and cannot address directionality. Two diary studies of burn injury survivors provide preliminary evidence that a night of poor sleep predicts next-day increases in opioid consumption.[91,92] One way to probe the mechanisms underlying sleep-dependent impairment to opioid pathways is to determine whether sleep disturbance reduces the effectiveness of exogenously administered opioids. Efforts to that end are under way in our laboratory.

Negative and Positive Affect

Mediation analyses have revealed that elevations in negative affect (eg, moods or emotions) may explain a significant portion of variance in the directional associations between sleep disturbance and pain in nonclinically depressed samples. However, studies have varied with respect to how the sleep–pain pathways were specified, requiring clarification in future research. One study found that negative mood mediates the relationship between sleep and pain in a heterogeneous sample of patients with back pain, fibromyalgia, and facial pain.[75] A separate study of fibromyalgia patients treated sleep as a mediator of the pain–depression pathway, finding that sleep quality mediates the relationship between pain and symptoms of depression.[64] Finally, another study of fibromyalgia patients found evidence in support of a model in which pain was a mediator of the pathway from sleep impairment to depressive symptoms.[44] This set of findings suggests that sleep, pain, and negative mood share variance but provides little clarity regarding the temporal dynamics of their associations. Prospective research could help resolve this dilemma by comparing several competing mediational models involving sleep, negative affect, and pain in multiple samples of patients with chronic pain and sleep disturbance.

Chung and Tso[16] reported that pharmaceutical treatment of depression did *not* attenuate the effects of self-reported and polysomnographic sleep disturbance on pain symptoms observed during an acute depressive episode, suggesting that sleep and pain vary beyond the influence of depression. This possibility is supported by several studies showing that the association of insomnia symptoms and chronic pain remains after controlling for depression symptoms.[9,121,126] Going forward, studies should strive for consistency in the measurement of negative affect and depression symptoms, as findings may vary as a function of assessment instrument. In general, there has been relatively little attention directed toward distinctions in measurement of affective states within the context of studies on sleep and pain. Affect may be considered an umbrella term that comprises both moods, which are longer-duration, lower-intensity affective states, and emotions, which are shorter-duration, higher-intensity affective states.[38] Both moods and emotions are discrete feeling states and are distinct from depression and other clinical disorders, which indicate frank mental health impairment. Thus, measures that target affective states, such as the Positive and Negative Affect Schedule,[125] or discrete emotions,[4] may be more appropriate for delineating mechanisms of the association of sleep and pain than depressive symptom inventories, which tend to be diffuse and nonspecific.

In a similar vein, the maladaptive cognitive coping style known as pain catastrophizing may also be an interesting target in mechanistic research. Pain catastrophizing is generally modestly correlated with negative affect but is distinct from clinical anxiety or depression.[113] A recent study from our group demonstrated that sleep disturbance partially mediated the associations of pain catastrophizing and pain, and pain-related interference in a sample (N = 214) of TMD patients.[13] In this study, the tendency to report ruminative catastrophizing thoughts when experiencing pain was associated with poorer self-reported sleep and increased self-reported pain. Entered together, sleep disturbance significantly attenuated the association between pain catastrophizing and both pain and pain-related interference with function. Thus, these findings raise the possibility that treatments targeting pain catastrophizing may have "cross-pollinating" effects on both sleep and pain-related outcomes. The mechanism by which sleep disturbance mediates the association of pain catastrophizing and pain remains to be determined. One possibility supported by previous research is that high pain catastrophizers may have generally poorer sleep because of an inability to silence intrusive pain-related thoughts prior to bedtime.[103]

Although many studies investigating the association of sleep and pain have incorporated negative or depressed affect into their investigation, none have evaluated the potentially important role of positive affect. Positive affect is psychometrically distinct from negative affect[100,125] and has been shown to buffer, or attenuate, the relation of negative affect and chronic pain.[129-131] Although the gold standard cognitive-behavioral interventions for chronic pain and insomnia are primarily focused on reducing negative affect,[26,119] a nascent but growing body of work has demonstrated that positive affect promotes resilient physical and psychosocial functioning among individuals with chronic pain[30,81,112,118] and insomnia.[135] Positive affect has been identified as a unique contributor to the variance in pain reports in patients with fibromyalgia, for whom sleep disturbance is highly prevalent.[130] A study of rheumatoid arthritis and fibromyalgia patients found that sleep duration uniquely moderated the association of pain and positive affect.[43] Specifically, patients reporting 8 or more hours of sleep maintained positive affect through fluctuating pain states, whereas patients

reporting 7 or fewer hours of sleep per night were more likely to have reduced positive affect when pain was elevated.[43] The extent to which positive affect, independent of negative affect, contributes variance to the association of sleep and pain is unclear and should be investigated in future longitudinal and experimental studies.

Future Directions: Sociodemographic Moderators of the Association of Sleep and Pain

A wealth of data suggests that sleep and pain vary according to the most prominent sociodemographic factors. Out of a large literature on individual differences in sleep and pain, the most salient findings are that both sleep disturbance[35,36,78] and pain[85] tend to increase with age; African Americans exhibit worse objective and subjective sleep impairments[23,42,106] and greater clinical and experimental pain sensitivity than Caucasians[27,90]; and females exhibit worse objective and subjective sleep impairments[15,60,133] and greater clinical and experimental pain sensitivity than males.[33,65,89] It will be important to determine whether the effect of sleep on pain, and vice versa, is moderated by key demographic variables, such as age, race, or sex. There is limited recent evidence that such interactions may reveal important sources of variance in the relation of sleep and pain.

Zhang et al[134] investigated insomnia, pain, and somatic symptoms in a large sample of male and female adolescents (n = 259) and adults (n = 256). Moderation analyses revealed that females with insomnia reported significantly greater pain and somatic symptoms than females without insomnia, whereas no such effect for insomnia was observed among males. In fact, females without insomnia were comparable to males without insomnia, suggesting that insomnia may be a mechanism for the oft-noted sex differences in pain sensitivity.[134] Further, although a similar pattern was observed as a statistical trend for adolescents, the effect was much stronger in adults, suggesting that sex differences associated with pain and insomnia may evolve with age. These findings highlight the rich opportunities for enhancing our understanding of the association of sleep and pain that emerge through sociodemographic moderation analyses. For example, given that African Americans report both greater sleep impairments and greater pain sensitivity, it is possible that the deleterious effects of sleep disturbance on pain are magnified in African Americans compared to Caucasians. Alternatively, it is possible that the increased clinical and experimental pain sensitivity in African Americans is better attributed to elevated sleep disturbance than to putative sociocultural influences on pain sensitivity. Such hypotheses should be tested in future studies by modeling interactions akin to those reported by Zhang et al.[134]

General Summary and Conclusions

This review summarizes the recent longitudinal and experimental data on the association of sleep and pain. Because of the diversity of studies and methods, we chose to conduct a narrative review in order to compare and contrast across a wide range of studies. Still, as a result of the breadth of literature on sleep and pain, it was necessary to limit the scope of this review, which prevented us from discussing interesting studies on related topics, such as the role of sleep in inflammation.[39,41] Our review is further limited by its inability to generate objective quantitative summary statistics, which are typically obtained within a more narrow and rigid scope of studies than we elected to review here. That being said, our review has revealed several important findings regarding the state of the science on sleep and pain.

First, over the past decade, the volume of studies investigating the association of sleep and pain has sharply risen. At the same time, methodologic advances in study design, measurement, and analysis have unveiled a rich landscape of longitudinal and experimental effects. Large, longitudinal cohort studies with basic subjective assessments of sleep and pain generally support a reciprocal relationship between sleep disturbance (eg, insomnia symptoms) and clinical pain reports. However, several longitudinal studies convincingly demonstrate that insomnia symptoms significantly increase the risk of developing future chronic pain disorders in previously pain-free individuals, whereas existing pain is not a strong predictor of new incident cases of insomnia.[10,62] Furthermore, deeper assessments of sleep disturbance and pain across multiple temporal sequences (eg, microlongitudinal vs longitudinal) tend to suggest that sleep disturbance is a stronger predictor of future pain than pain of sleep disturbance. These findings should encourage future investigators to incorporate a diverse set of pain and sleep assessments when feasible. Additionally, the longitudinal and microlongitudinal findings suggest that efforts to prevent and treat chronic pain may be well served to target sleep disturbance as a point of primary prevention and intervention.

It remains to be determined if the association of sleep and pain varies across different chronic pain disorders. The present review synthesizes findings from a wide range of disorders, including neuropathic, musculoskeletal, headache/migraine, and idiopathic pain disorders. The extent to which sleep disturbance differentially influences pain across disorder types may best be determined through mechanistic studies that identify reliable substrates of the sleep–pain dynamic. For example, current efforts in our lab and elsewhere to explicate the role of inflammation in the association of sleep disturbance and pain may yield data that are relevant for identifying which disorders are more likely to be differentially affected by sleep disturbance.

The experimental literature has expanded to include several studies of partial sleep deprivation and sleep continuity disruption that offer greater ecological validity than prior experimental designs. Combined with advances in QST, these studies demonstrate that sleep disturbance may impair pain processing at multiple levels of the neuraxis, including those that regulate descending pain modulation.

Investigating the influence of biopsychosocial variables, such as positive and negative affect, brain dopamine and opioid systems, age, ethnicity, and sex on the

relationship of sleep and pain may reveal mechanisms that can be targeted in novel treatments of patients with comorbid insomnia and chronic pain. The biopsychosocial model provides an excellent framework through which to integrate these and other potential mechanisms of the association of sleep and pain, such as inflammation[105] and neuroendocrine factors.[107] Experimental studies that manipulate both sleep and pain are needed to isolate real-time changes in dopaminergic and opioidergic neurotransmission (eg, through positron emission tomography and pharmacologic challenge). Likewise, we are in need of a greater volume of microlongitudinal studies that take advantage of the increasingly feasible smartphone applications and ambulatory electroencephalogram technologies. Such studies are ideally suited for evaluation of biopsychosocial hypotheses of the association of sleep and pain, given their ability to assess dynamic changes in sleep architecture, transient pain flares, affect regulation, and cognitive coping, both within-person and across diverse social and ethnic community structures.

By testing mediation and moderation models of the biopsychosocial antecedents and sequelae of the association of sleep and pain, we may come closer to realizing the ultimate goals of research in this arena: improved clinical care of patients with sleep disorders and comorbid chronic pain. Integral to the optimization of clinical care is a better understanding of symptom trajectories that define not only *who* is most likely to develop poor outcomes but *when* transitions to poor health are most likely to occur. Such a multilevel framework is critical to solving some of the most vexing clinical problems of our time, including the development of chronic pain following surgery and the experience of pain in relapsing/remitting conditions such as rheumatoid arthritis, lupus, and multiple sclerosis. Many of the tools required to pursue these questions are currently available, but we need to be asking the right questions in order to implement them effectively. The past decade of research has allowed us to move past the question of whether sleep and pain are related. Now, we must turn our attention to the biological, psychological, and social contingencies that qualify their association.

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