American Pain Society
RESEARCH
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TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 16, No 5 (May), 2015: pp 478-490
Available online at www.jpain.org and www.sciencedirect.com

Disrupted Sleep Is Associated With Altered Pain Processing by Sex and Ethnicity in Knee Osteoarthritis

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Abstract: **Studies indicate that improving sleep decreases reported pain in patients with knee osteoarthritis, but it is unclear if this association extends to experimentally induced pain responses. A community-based sample of 88 African American and 52 non-Hispanic white adults (45–76 years) with knee osteoarthritis completed the Insomnia Severity Index and the arousal subscale of the Sleep Hygiene and Practices Scale. Participants underwent quantitative sensory testing, including measures of pain sensitivity and facilitation at the knee, and pain inhibition. Outcomes were analyzed with multiple Tobit hierarchical regression models, with adjustment for relevant covariates. Ethnicity and sex by sleep interactions were also entered into the models. After covariate adjustment, main associations were not observed. However, sex interacted with insomnia severity to predict greater temporal summation of heat and punctate pressure pain among women and lower heat temporal summation among men. Men and women who engaged in frequent arousal-associated sleep behaviors demonstrated higher and lower heat temporal summation, respectively. Non-Hispanic whites with greater insomnia severity displayed lower pressure pain thresholds and pain inhibition. Our findings are the first to demonstrate that disrupted sleep is associated with altered pain processing differentially by sex and ethnicity/race among people with knee osteoarthritis.**

Perspective: ***This article presents the association between insomnia severity, maladaptive sleep behaviors, and experimentally induced pain responses among people with knee osteoarthritis. Disrupted sleep was associated with altered pain processing by sex and ethnicity/race. Offering sleep interventions may help ameliorate pain, but treatment may need to be tailored by sex and ethnicity/race.***

Key words: *Quantitative sensory testing, knee osteoarthritis, insomnia, sleep, ethnicity.*

Received September 15, 2014; Revised January 21, 2015; Accepted February 8, 2015.

Support provided by the National Institutes of Health/National Institute on Aging (grant number R01AG033906) and the University of Florida Clinical and Translational Science Institute (grant number UL1TR000064, R.B.F., primary investigator), and the University of Alabama at Birmingham Clinical and Translational Science Institute (grant number UL1TR000165).

M.E.P. received support from the Agency for Healthcare Research and Quality (5 T32 HS013852-09) and the National Institute on Minority Health and Health Disparities (3 P60 MD000502-08S1). T.L.G. received support from the John A. Hartford Foundation (2011-2013) as a Building Academic Geriatric Nursing Capacity Scholar and a Mayday Fund grantee (grant number AAN 11-116). K.T.S. received support from the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (K23AR062099). E.J.B. is supported by a National Institute of Neurological Disorders and Stroke training grant T32NS045551 to the University of Florida Pain Research and Intervention Center of Excellence.

The authors have no conflicts of interest to declare.

Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.

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1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2015.02.004

Osteoarthritis (OA) is the most common form of arthritis and the leading cause of disability and work limitations in the United States,[10] with the knee being the most frequently affected joint. More than half of patients with OA experience pain during the night[21] and suffer from some form of sleep disruption, including poor sleep quality, sleep fragmentation, and frequent shifts between sleep stages.[29,31,39,53,61] Importantly, sleep disruption is also associated with significant daytime fatigue[26] and reduced quality of life.[62] Further, about a third of OA sufferers report both clinically significant pain and insomnia.[35] Hence, comorbid insomnia and pain in OA represent a major deterrent to patient well-being.

Interactions between pain and sleep disturbance in pain populations were previously thought to be cyclical.[24,25,51,52,58] However, a recent review suggests that, more consistently than pain causes sleep disruption, sleep disruption may be a predictor of the incidence and augmentation of pain severity.[20] A possible explanation for these observations is that sleep disturbance may engage multiple pain modulatory circuits within the central nervous system through inflammatory mediators or *N*-methyl-D-aspartate receptor activation.[13,54] Consequently, activation of these mechanisms is associated with reductions in pain thresholds, pain inhibition, and enhanced temporal summation of pain (ie, enhanced pain in response to repeated noxious stimuli) as measured with laboratory-based quantitative sensory testing (QST). However, the nature of the association between sleep disruption and pain modulation is unclear among individuals with knee OA. The first paper in this area reported that among persons with knee OA, those with diagnosed insomnia, relative to those without insomnia, display significantly greater increases in interleukin-10 evoked by QST procedures, suggesting support for the inflammatory mediation hypothesis.[42]

To better understand the relationship between sleep disruption and pain modulation, additional QST studies are needed. QST is a clinically relevant method of pain assessment because the responses produced are related to clinical pain reports and treatment outcomes,[3,32,34] and it provides mechanistic information on abnormal pain processing that can be used for more accurate diagnosis and tailored treatment.[11,18] QST responses are also associated with moderate to severe knee OA–related symptoms in comparison to patients with mild symptom severity and persons with no knee OA.[27] The substantial relationship between QST measures and clinical pain reports among persons with knee OA is likely related to the finding that increases in clinical pain and QST procedures evoke enhanced activity in the same brain regions (ie, thalamus, cingulate cortex, amygdala).[28] It should also be noted that among persons with knee OA, ethnic differences between African Americans and non-Hispanic whites in self-reports of pain intensity disappear after covariates (eg, body mass index [BMI], socioeconomic status) are controlled.[1,12] However, ethnic differences on QST pain measures remain significant after these covariates are entered in analyses.[12,27] Thus, QST measures are particularly preferable to self-reports of pain in studies of ethnic differences in pain.

Only a few studies have implemented QST to examine whether sleep disruption is associated with pain facilitation in samples of relatively healthy persons and persons with chronic pain.[25,46,49] Schuh-Hofer and colleagues found that 1 night of sleep deprivation was unrelated to changes in temporal summation in healthy participants,[49] whereas Haack and colleagues reported lower temporal summation of heat pain in participants with insomnia compared to participants without insomnia.[25] Despite these mixed findings, there is reliable evidence that experimental sleep deprivation and poor sleep efficiency are related to reduced pain inhibition in healthy persons and those with chronic pain.[17,30,40,51] Thus, it is possible that sleep disruption is associated with increased pain sensitivity and enhanced pain facilitation in addition to reduced pain inhibition in persons with chronic pain such as knee OA.

Identifying the relationships between sleep and pain in knee OA is important because sleep is a highly modifiable behavior that may potentially alter pain. Evidence from a community-based study of patients with heterogeneous pain conditions revealed that patients with comorbid sleep disturbance engaged in more maladaptive behaviors for pain and sleep management (eg, catastrophizing and activity avoidance) that, in turn, were associated with greater comorbid disease severity.[33] Alterations in maladaptive sleep-related behaviors are the cornerstone of cognitive-behavioral interventions for insomnia. Additionally, a recent outcome study of a cognitive-behavioral intervention for insomnia revealed improvements in sleep and decreases in clinical pain severity among elderly patients with comorbid insomnia and OA.[60] However, this study did not address whether specific, maladaptive sleep behaviors are associated with experimental pain responses in persons with knee OA.

The aim of the present study was to determine the relationships of self-reported insomnia severity and maladaptive sleep behaviors on QST measures of pain sensitivity, inhibition, and facilitation among persons with knee OA. We hypothesized that reports of greater insomnia severity and maladaptive sleep behaviors would be associated with lower pain thresholds and inhibition and with greater temporal summation of pain. Furthermore, both clinical pain and QST pain responses are known to differ by ethnicity/race and sex, such that ethnic minorities and women report heightened pain experiences.[8,9,12,14-16,19,45] There are also known sex and ethnic/racial differences in reports of sleep disruption[47,66]; however, these differences have not been investigated among persons with knee OA. Therefore, perceived sleep disturbance may be related to abnormal pain processing differentially by sex and ethnicity/race. As an exploratory aim of our study, we investigated the interactions of ethnicity/race and sex with the sleep parameters on pain outcomes. Given the exploratory nature of this aim, no directional hypotheses were stated.