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Sleep, Respiration, and Pain: A Potential Nexus for Chronic Pain Risk?

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“[This study presents] the possibility that nocturnal hypoxemia and sleep fragmentation are distinct sleep disordered breathing phenotypes that may exert potentially differential effects on pain sensitivity and symptom expression.”

The bidirectional interaction between sleep and pain is now a well-recognized clinical phenomenon supported by experimental studies and large-scale epidemiological investigations, which convincingly demonstrate that sleep disruption induces hyperalgesia and that poor sleep is a risk factor for the development chronic pain, *e.g.*,¹⁻³. Despite decades of work demonstrating that pain and sleep systems mutually influence each other, the mechanisms accounting for these associations remain largely a mystery. Doufas *et al.*'s naturalistic study⁴ in the Journal, reporting that nocturnal hypoxemia is associated with sleep-related pain, highlights the possibility that brainstem regions regulating both sleep and respiration may provide an underappreciated, regional nexus to guide future experimental investigations seeking to unravel the mechanisms for sleep-pain interactions.

In the Doufas *et al.* study⁴ published in the Journal, nocturnal hypoxemia was found to be correlated with self-reported morning headache, headache disrupting sleep, and chest pain while in bed. Importantly, these effects were independent of sleep fragmentation, which has been shown in numerous experiments to induce hyperalgesia, *e.g.*⁵. The Doufas *et al.* findings⁴ are consistent with recent work demonstrating that positive airway pressure therapy decreases laboratory measures of pain sensitivity in pain free patients with severe sleep apnea⁶, as well as, a study demonstrating that low nocturnal oxygen saturation levels were associated with the presence of morning headache in patients with moderate to severe sleep apnea⁷.

Intriguingly and perhaps even critically important, the findings seem to conflict with work demonstrating that patients with chronic temporomandibular joint disorder pain and mild sleep apnea have diminished laboratory pain sensitivity compared to temporomandibular joint disorder patients without sleep apnea⁸. Another study of patients with suspected sleep disordered breathing, similarly found that those meeting formal criteria for a headache

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disorder exhibited higher mean nocturnal SpO₂ values and lower apnea hypopnea indices compared to patients not meeting criteria for headache disorder⁹. Even recent work by the authors of the current article in the Journal reported that hypoxemia during sleep was associated with decreased sensitivity to cold pain during remifentanyl infusion in patients at risk for sleep apnea¹⁰. This study also found that IGFBP-1 levels, a marker of hypoxia, were associated with decreased baseline pain sensitivity. The reasons for the seemingly conflicting findings are unclear and will require subsequent research, but perhaps the extant data suggest the possibility that pain chronicity and / or sleep disordered breathing severity may moderate the direction of the association between sleep-related hypoxemia and pain.

With respect to chronic pain, this type of effect has precedent, as pain chronicity has similarly been found to moderate the association between blood pressure and pain sensitivity¹¹. Specifically, resting blood pressure is inversely associated with pain sensitivity in individuals free of chronic pain, but this relationship is absent in patients with chronic pain. This suggests a dysfunction of these interacting systems as pain becomes chronic. It should be noted, however, that pain duration was not reported in the Doufas *et al.*⁴ study in the Journal and therefore, it is unclear whether pain in this sample might best be classified as acute or chronic. Moreover, the pain reported is episodic and highly specific to the sleep period, making it rather atypical. It is also unclear from the prior sleep apnea studies that reported a positive association between sleep disordered breathing and pain / hyperalgesia whether patients with other episodic and / or persistent chronic pain were included in the samples. We suspect that since the samples were not pre-selected to include chronic pain disorders that they were not comprised predominantly of patients meeting criteria for a specific chronic pain disorder. One interesting possibility to consider regarding the apparent reversal of the association between hypoxemia and pain sensitivity in chronic pain samples, is that this reversal might serve as potential biomarker for the transition between acute and chronic pain. Testing this hypothesis, of course, would require longitudinal studies measuring sleep in acute pain patients as they transition to chronic pain disorders.

In addition to the possibility that the association between SaO₂ and pain sensitivity might be altered as a function of pain chronicity, the severity of sleep-disordered breathing might also moderate the relationship. All three studies⁸⁻¹⁰ demonstrating a positive association between SaO₂ during sleep and pain / pain sensitivity, involved samples of minimal to mild sleep disordered breathing, whereas studies reporting an inverse association between nocturnal SaO₂ and clinical pain / pain sensitivity included patients with moderate to severe apnea / hypopnea indices. The implications of Doufas *et al.* findings⁴ published in the Journal, therefore, would be enhanced by determining if a subset of subjects reporting at least some pain and only mild or no sleep apnea, demonstrated positive correlations between pain frequency and SaO₂. Interestingly, recent longitudinal work has found that symptoms suggestive of sleep apnea, *e.g.*, loud snoring and daytime sleepiness predicted the development of chronic temporomandibular joint pain disorder¹². Unfortunately, this study did not measure the severity of sleep-disordered breathing or associations between sleep-related hypoxemia and pain sensitivity, but it does underscore the importance of considering nocturnal hypoxemia as a potential mechanism for neuroplastic changes that lead to the development of persistent pain.

Aside from contributing to an emerging literature linking pain to sleep-related hypoxemia, one of the most important contributions of the Doufas *et al.* study⁴ in the Journal is the emphasis on the possibility that nocturnal hypoxemia and sleep fragmentation are distinct sleep disordered breathing phenotypes that may exert potentially differential effects on pain sensitivity and symptom expression. Researchers studying sleep-pain interactions have rarely considered this possibility. To disentangle the effects of sleep fragmentation from the effects of sleep-related hypoxemia and inflammation, Doufas *et al.* studied the effects of nocturnal SaO₂ indices on clinical pain report while controlling for six polysomnographic parameters: 1) a respiratory disturbance index associated with no change in SaO₂, 2) overall arousal index, 3) % REM sleep, 4) % S1, 5) %S2, and 6) %S3. They also controlled for inflammatory markers, using a data reducing principle components analysis. Methodologically, the data reduction procedure may be a quite useful approach for subsequent studies involving models with many potential multiple confounders. It is unclear, however, why total sleep time, wake after sleep onset time and sleep efficiency were not included in the models. Many studies demonstrate that these traditional sleep continuity variables are robustly linked with hyperalgesia, and perhaps to a greater extent than brief electroencephalographically recorded arousals without frank wakefulness^{13;14}. Future studies attempting to tease apart the unique effects of hypoxemia from sleep continuity should include measures of fragmentation (arousals) and sleep duration (total sleep time), wake after sleep onset time, and / or sleep efficiency.

Although the reasons for the seemingly conflicting findings between sleep-related oxygen saturation and pain are unclear and perplexing at present, the answers may lie in brain stem regions, such as the nucleus tractus solitarius, that regulate both nociception and breathing, *e.g.*¹⁵. Future work in this regard is needed and likely to inform the pathophysiology of both chronic pain and sleep disordered breathing. Continued study of these relationships will also contribute to a better understanding of the complex symptomatology and morbidity associated with these commonly co-occurring disorders.

Reference List

1. Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep*. 2007; 30:494–505. [PubMed: 17520794]
2. Roehrs TA, Hyde M, Blaisdell MS, Greenwald M, Roth T. Sleep Loss and REM sleep loss are hyperalgesic. *Sleep*. 2006; 29:145–51. [PubMed: 16494081]
3. Gupta A, Silman AJ, Ray D, Morriss R, Dickens C, Macfarlane GJ, Chiu YH, Nicholl B, McBeth J. The role of psychosocial factors in predicting the onset of chronic widespread pain: Results from a prospective population-based study. *Rheumatology (Oxford)*. 2007; 46:666–71.
4. Doufas AG, Tian L, Davies MF, Warby SC. Nocturnal intermittent hypoxia is independently associated with pain in subjects suffering from sleep-disordered breathing. *Anesthesiology*. 2013; XXX:XXX–XXX.
5. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev*. 2004; 8:119–32. [PubMed: 15033151]
6. Khalid I, Roehrs TA, Hudgel DW, Roth T. Continuous positive airway pressure in severe obstructive sleep apnea reduces pain sensitivity. *Sleep*. 2011; 34:1687–91. [PubMed: 22131606]
7. Goksan B, Gunduz A, Karadeniz D, Agan K, Tascilar FN, Tan F, Purisa S, Kaynak H. Morning headache in sleep apnoea: Clinical and polysomnographic evaluation and response to nasal continuous positive airway pressure. *Cephalalgia*. 2009; 29:635–41. [PubMed: 19187338]

8. Smith MT, Wickwire EM, Grace EG, Edwards RR, Buenaver L, Peterson S, Klick B, Haythornthwaite JA. Sleep disorders and their association with laboratory pain sensitivity in temporomandibular joint disorder (TMD). *Sleep*. 2009; 32:779–90. [PubMed: 19544755]
9. Lovati C, Zardoni M, D'Amico D, Pecis M, Giani L, Raimondi E, Bertora P, Legnani D, Bussone G, Mariani C. Possible relationships between headache-allodynia and nocturnal sleep breathing. *Neurol Sci*. 2011; 32(Suppl 1):S145–8. [PubMed: 21533732]
10. Doufas AG, Tian L, Padrez KA, Suwanprathes P, Cardell JA, Maecker HT, Panousis P. Experimental pain and opioid analgesia in volunteers at high risk for obstructive sleep apnea. *PLoS One*. 2013; 8:e54807. [PubMed: 23382975]
11. Olsen RB, Bruehl S, Nielsen CS, Rosseland LA, Eggen AE, Stubhaug A. Hypertension prevalence and diminished blood pressure-related hypoalgesia in individuals reporting chronic pain in a general population: The Tromso study. *Pain*. 2013; 154:257–62. [PubMed: 23245863]
12. Sanders AE, Essick GK, Fillingim R, Knott C, Ohrbach R, Greenspan JD, Diatchenko L, Maixner W, Dubner R, Bair E, Miller VE, Slade GD. Sleep apnea symptoms and risk of temporomandibular disorder: OPPERA cohort. *J Dent Res*. 2013; 92:S70–7.
13. Smith MT, Haythornthwaite JA. The relationship between sleep disturbance and chronic pain: Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev*. 2004; 8:119–32. [PubMed: 15033151]
14. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep Med Rev*. 2006; 10:357–69. [PubMed: 16386930]
15. Lewis JW, Baldrighi G, Akil H. A possible interface between autonomic function and pain control: Opioid analgesia and the nucleus tractus solitarius. *Brain Res*. 1987; 424:65–70. [PubMed: 3319042]