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# Disturbed Sleep in Preclinical Cognitive Impairment: Cause and Effect?

Commentary on Hita-Yañez et al. Polysomnographic and subjective sleep markers of mild cognitive impairment. SLEEP 2013;36:1327-1334.

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Cognitive decline in old age, particularly impairments associated with neurodegenerative dementias such as Alzheimer disease (AD), represents one of the largest public health and economic challenges of the 21st century. The current annual societal cost of dementia outstrips the cost of heart disease and cancer.[1] With 10% of adults over 65 now suffering from dementia,[1,3] and this number projected to double over the next forty years,[3,4] understanding the factors responsible for cognitive decline is of critical importance. Dementia neuropathology, such as AD-linked β-amyloid aggregation and cerebral infarcts affiliated with vascular dementia, are important causal factors that are present even in relatively healthy elderly populations.[5-9] However, recent evidence suggests that these factors do not directly explain the majority of the variance in cognitive decline.[10] This means additional factors must contribute to cognitive decline or mediate the effects of neuropathology on cognitive decline. Identifying those factors is an important step towards the alleviation of cognitive impairment in the elderly.

New findings from Hita-Yañez and colleagues in this issue of *SLEEP* suggest that sleep may be one of those factors.[11] Traditionally, disturbed sleep and circadian rhythms were described as symptoms of neurodegenerative disorders such as AD.[12-16] Hypotheses that disturbed sleep either contributes to the progression of cognitive decline, or can be used to detect patients at risk for developing cognitive disorders at a preclinical stage[11,17-24] are only beginning to be proposed. One of the unique challenges to evaluating these hypotheses is determining the appropriate populations to test these associations. Once patients have developed AD, we do not know if sleep disruption contributes to AD progression, if AD progression contributes to sleep disruption, or if a vicious cycle emerges where each exacerbates the effects of the other. To address this challenge, Hita-Yañez and colleagues[11] focused on a preclinical population likely to develop AD: patients with mild cognitive impairment (MCI).[25,26] In their study, objective and subjective measures of sleep were compared between healthy elderly individuals and patients with MCI. Sleep disturbances were observed in MCI patients in both objective and subjective measures. Specifically, MCI patients had more fragmented SWS and reduced REM sleep, consistent with other reports.[13,24,27] Further, REM sleep disruption was exacerbated in apolipoprotein E4 (ApoE4) carriers—a genetic marker associated with early onset AD[28]—relative to noncarriers. Collectively, their findings suggest that even at a preclinical stage, significant sleep disturbances are present in those at risk for developing AD.[11] While only correlational, two clinically relevant interpretations can emerge from these data. Either sleep is particularly sensitive to dementia pathology at an early stage, or sleep disturbance is itself a contributor to disease progression. If the former is the case, then specific measures of sleep may assist in the detection of preclinical AD. If the latter is the case, sleep is one of those currently unrecognized factors contributing to cognitive decline.

Given that sleep disturbance is greater in MCI patients, symptoms of sleep disorders may be more prominent as well. To that end, a novel strength of the report by Hita-Yañez and colleagues is in their comparison of subjective measures of sleep disturbance collected at home with objective sleep measures. MCI patients had significant subjective sleep complaints, specifically reporting greater difficulty in falling asleep, staying asleep, and returning to sleep upon awakening. These findings are consistent with animal studies linking amyloid pathology to sleep fragmention.[21,27,29] This suggests that patients suffering from preclinical AD may also experience canonical symptoms of insomnia,[30] perhaps explaining, in part, the increased prevalence of insomnia in older adults.[31,32] Congruent with this possibility, patients with MCI exhibited another symptom of insomnia: sleep misperception.[11] Sleep onset latency was overestimated, and the group with MCI was less able to accurately estimate arousals, suggesting that the sleep they obtained was less restorative. In light of these findings, it is important to consider evaluating sleep in patients presenting with memory complaints, as they may be at risk for developing sleep disorders. An exciting avenue for future research would be investigating whether amyloid pathology promotes hyperarousal similar to some forms of insomnia, contributing to the increased prevalence of insomnia in later life.[33]

Beyond the findings of Hita-Yañez and colleagues,[11] sleep disturbance may also proactively contribute to cognitive decline. This possibility remains one of the most important and yet understudied areas in sleep and aging research. A few reports have linked sleep and cognition in healthy aging[17,22,23,34,35] and preclinical AD populations,[24,36] but little is known regarding the underlying mechanisms of this link. Is cognitive impairment exacerbated by the acceleration of neuropathology due to sleep disruption? It has been reported that sleep restriction increases β-amyloid plaque formation in rodent models of AD.[21] Does neuropathology disrupt sleep-dependent memory? Amyloid pathology is associated with shortened and fragmented sleep.[21,27,29] It is also possible that healthy sleep may promote an independent neural resilience in the face of accumulating neuropathology, or disturbed sleep may cause independent neural dysfunction that increases susceptibility to neuropathology. Some or all of these hypotheses may be true, and future

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research is needed to determine exactly how sleep and its disorders are tied to cognitive decline.

Complicating matters further, sleep disturbance takes on a variety of forms, and each form may herald specific neurobehavioral and neurodegenerative consequences. For example, prospective studies have linked REM sleep behavior disorder with Parkinson disease,[37,38] insomnia with cognitive decline,[39] and sleep apnea with MCI and dementia.[40] Characterizing the mechanisms linking sleep disruption, neurodegeneration, and cognitive decline will pave the way for novel therapeutic targets that could minimize or delay the progression of cognitive decline. Building on these findings, known methods for SWS enhancement and sleep disorders treatment will need to be employed to aid determining whether sleep should be a viable intervention in these populations. However, if we can successfully characterize the role of sleep in cognitive decline, we may yet prove that while aging is an inevitable part of life, if healthy sleep is obtained, the negative consequences associated with it do not have to be.

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## DISCLOSURE STATEMENT

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## REFERENCES

1. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. N Engl J Med 2013;368:1326-34.
2. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. JAMA 1989;262:2551-6.
3. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003;60:1119-22.
4. Norton S, Matthews FE, Brayne C. A commentary on studies presenting projections of the future prevalence of dementia. BMC Public Health 2013;13:1.
5. Driscoll I, Resnick SM, Troncoso JC, An Y, O'Brien R, Zonderman AB. Impact of Alzheimer's pathology on cognitive trajectories in nondemented elderly. Ann Neurol 2006;60:688-95.
6. Jack CR Jr., Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119-28.
7. Mormino EC, Kluth JT, Madison CM, et al. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. Brain 2009;132:1310-23.
8. Schneider JA, Arvanitakis Z, Yu L, Boyle PA, Leurgans SE, Bennett DA. Cognitive impairment, decline and fluctuations in older community-dwelling subjects with Lewy bodies. Brain 2012;135:3005-14.
9. Wilson RS, Leurgans SE, Boyle PA, Schneider JA, Bennett DA. Neurodegenerative basis of age-related cognitive decline. Neurology 2010;75:1070-8.
10. Boyle PA, Wilson RS, Yu L, et al. Much of late life cognitive decline is not due to common neurodegenerative pathologies. Ann Neurol 2013. Jun 24. [Epub ahead of print].
11. Hita-Yañez E, Atienza M, Cantero JL. Polysomnographic and subjective sleep markers of mild cognitive impairment. Sleep 2013;36:1327-34.
12. Montplaisir J, Petit D, Lorrain D, Gauthier S, Nielsen T. Sleep in Alzheimer's disease: further considerations on the role of brainstem and forebrain cholinergic populations in sleep-wake mechanisms. Sleep 1995;18:145-8.
13. Prinz PN, Vitaliano PP, Vitiello MV, et al. Sleep, EEG and mental function changes in senile dementia of the Alzheimer's type. Neurobiol Aging 1982;3:361-70.
14. Reynolds CF 3rd, Kupfer DJ, Taska LS, et al. EEG sleep in elderly depressed, demented, and healthy subjects. Biol Psychiatry 1985;20:431-42.
15. Weldemichael DA, Grossberg GT. Circadian rhythm disturbances in patients with Alzheimer's disease: a review. Int J Alzheimers Dis 2010;2010.
16. Witting W, Kwa IH, Eikelenboom P, Mirmiran M, Swaab DF. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. Biol Psychiatry 1990;27:563-72.
17. Backhaus J, Born J, Hoeckesfeld R, Fokuhl S, Hohagen F, Junghanns K. Midlife decline in declarative memory consolidation is correlated with a decline in slow wave sleep. Learn Mem 2007;14:336-41.
18. Fogel SM, Martin N, Lafortune M, et al. NREM sleep oscillations and brain plasticity in aging. Front Neurol 2012;3:176.
19. Hita-Yanez E, Atienza M, Gil-Neciga E, Cantero JL. Disturbed sleep patterns in elders with mild cognitive impairment: the role of memory decline and ApoE epsilon4 genotype. Curr Alzheimer Res 2012;9:290-7.
20. Hornung OP, Danker-Hopfe H, Heuser I. Age-related changes in sleep and memory: commonalities and interrelationships. Exp Gerontol 2005;40:279-85.
21. Kang JE, Lim MM, Bateman RJ, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 2009;326:1005-7.
22. Mander BA, Rao V, Lu B, et al. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. Nat Neurosci 2013;16:357-64.
23. Scullin MK. Sleep, memory, and aging: the link between slow-wave sleep and episodic memory changes from younger to older adults. Psychol Aging 2013;28:105-14.
24. Westerberg CE, Mander BA, Florczak SM, et al. Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. J Int Neuropsychol Soc 2012:1-11.
25. Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. Lancet Neurol 2003;2:605-13.
26. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303-8.
27. Roh JH, Huang Y, Bero AW, et al. Disruption of the sleep-wake cycle and diurnal fluctuation of beta-amyloid in mice with Alzheimer's disease pathology. Sci Transl Med 2012;4:150ra22.
28. Selkoe DJ, Podlisny MB. Deciphering the genetic basis of Alzheimer's disease. Annu Rev Genomics Hum Genet 2002;3:67-99.
29. Gerstner JR, Chan MT, Lenz O, Pfeiffenberger C, Pack A. Amyloid-beta induced sleep fragmentation is rescued by fatty-acid binding proteins in drosophila. Sleep 2013;36(Abstract supplement):A22-3.
30. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4:487-504.
31. Ancoli-Israel S. Sleep and its disorders in aging populations. Sleep Med 2009;10:S7-S11.
32. Vitiello MV. Recent advances in understanding sleep and sleep disturbances in older adults: growing older does not mean sleeping poorly. Curr Dir Psychol Sci 2009;18:316-20.
33. Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 2004;161:2126-9.
34. Blackwell T, Yaffe K, Ancoli-Israel S, et al. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 2006;61:405-10.
35. Spencer RM, Gouw AM, Ivry RB. Age-related decline of sleep-dependent consolidation. Learn Mem 2007;14:480-4.
36. Westerberg CE, Lundgren EM, Florczak SM, et al. Sleep influences the severity of memory disruption in amnestic mild cognitive impairment: results from sleep self-assessment and continuous activity monitoring. Alzheimer Dis Assoc Disord 2010 Jun 29. [Epub ahead of print].
37. Boot BP, Boeve BF, Roberts RO, et al. Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. Ann Neurol 2012;71:49-56.
38. Postuma RB, Bertrand JA, Montplaisir J, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. Mov Disord 2012;27:720-6.
39. Cricco M, Simonsick EM, Foley DJ. The impact of insomnia on cognitive functioning in older adults. J Am Geriatr Soc 2001;49:1185-9.
40. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 2011;306:613-9.