JCSM
Journal of Clinical Sleep Medicine

COMMENTARY

Searching for the Brain Bases of Insomnia

Sean P.A. Drummond, Ph.D.

Department of Psychiatry, UCSD/VA San Diego HCS, San Diego, CA

Commentary on Nofzinger EA; Nissen C; Germain A et al. Regional cerebral metabolic correlates of WASO during NREM sleep in insomnia. J Clin Sleep Med 2006;2(3):316-322.

Abstract: Insomnia, daytime sleepiness, and napping are all highly prevalent among the elderly, reflecting changes in sleep architecture, sleep efficiency, sleep quality, and circadian sleep-wake cycles. Insomnia is sometimes associated with subjective daytime sleepiness, as well as other clinical and socioeconomic consequences. The daytime sleepiness will at times lead to napping. Although napping is viewed as a common age-related occurrence, little is known about its benefits or consequences. Factors reported to be contributors to daytime napping include sleep-maintenance difficulty and sleep fragmentation with consequent daytime sleepiness, nighttime use of long-acting sedating agents, daytime use of sedating medications, and dementia. However, a correlation between sleep disturbance and daytime napping has not been consistently observed. Whether napping is beneficial, neutral, or detrimental is an important issue, in light of conflicting findings regarding the impact of daytime napping on nighttime sleep and recent reports of an association between napping and adverse clinical outcomes, including increased mortality risk. Further research is needed to determine whether there is a cause-and-effect relationship between napping and insomnia, and between napping and adverse clinical outcomes, and to explore the clinical implications of improving insomnia and reducing daytime napping. Clinical evaluations of hypnotic agents should assess efficacy for both improving insomnia symptoms (particularly sleep-maintenance difficulty, in the case of elderly patients) and reducing daytime sleepiness thatwould lead to inadvertent napping.

Keywords: Elderly, insomnia, daytime sleepiness, napping
Citation: Drummond SPA. Searching for the brain bases of insomnia. *J Clin Sleep Med* 2006;2(3):323-324.

The need to better understand the neuropathophysiologic underpinnings of insomnia is of critical importance in sleep disorders research and medicine. Gaining such knowledge will help validate, repudiate, or refine current competing models of the etiology and pathophysiology of insomnia.[1-4] Studies aimed at understanding the neurobiology of insomnia should also shed light upon the similarities and difference among insomnia clinical phenotypes. The ultimate outcome of all of this may be to provide insights into the relationship between insomnia and its numerous common comorbid conditions, as well as to improve both behavioral and pharmacologic treatment strategies. Nofzinger and colleagues have been at the forefront of both arguing for the need to better understand the neurobiology of insomnia and conducting the necessary research.

In the current issue of SLEEP, Nofzinger et al report a study using relative glucose metabolic rates to investigate the cerebral correlates of objective and subjective wake after sleep onset (WASO) in a group of 15 patients with insomnia.[5] Subjective WASO was reported prospectively for 1 week on sleep diaries, objective WASO was recorded in the laboratory during an overnight polysomnogram, and glucose metabolism was measured during early non-rapid eye movement sleep on the next night. The authors report increased subjective and objective WASO that were both related to greater amounts of stage 2 sleep and less slow-wave sleep during the glucose uptake. Additionally, both measures of WASO were correlated with glucose metabolic rate during sleep in a wide spread set of brain regions.

The effort to elucidate the neuropathophysiology of insomnia by examining the specific clinical symptoms of the disorder is a logical choice, and the Nofzinger et al paper is an initial attempt at doing that. It is clear, however, that at least 2 methodologic issues will need to be resolved in future studies before this line of work can make a substantial contribution to our understanding of insomnia.

First, Nofzinger et al chose to examine a common symptom of insomnia, WASO, but one that presents significant analytic challenges. Although the authors were interested in cerebral correlates of what is essentially abnormal wake phenomenon, they hoped to find those correlates during sleep. Indeed, they took great pains to show that their results reflected sleep and were not influenced by wakefulness during data collection. The proper interpretation of such indirect evidence for the neural correlates of WASO is unclear. At the most basic level, this study reports that individuals with higher levels of subjective WASO also have higher levels of objective WASO and stage 2 sleep and lower levels of slow-wave

Disclosure Statement
Dr. Drummond has received research support from GlaxoSmithKline and Sanofi-Aventis.

Address correspondence to: Sean P.A. Drummond, Ph.D., Department of Psychiatry 9116A, UCSD/VA San Diego HCS, 3350 LaJolla Village Drive, San Diego, CA 92161; Tel: (858) 642-1274; Fax: (858) 458-4201; E-mail: drummond@ucsd.edu

sleep. Therefore, the comparison across the continuum of WASO (higher to lower amount) was actually a comparison across shallower to deeper stages of non-rapid eye movement sleep. Not surprisingly then, the results conformed to the well-replicated pattern of increased glucose metabolism throughout almost the entire brain in those subjects with shallower sleep. The exact same relationship with WASO would almost assuredly be shown in normal controls, suggesting it is not disease specific.

It is not clear, therefore, what this result really tells us about the neurobiology of sleep or wake in insomnia. The critical comparisons to make are within a state of consciousness (i.e., wake or a specific sleep stage) and between subject groups (e.g., insomnia vs controls or primary vs comorbid insomnia), not the other way around (i.e., within a group across states). This would more specifically inform us on how the waking brain, or the brain in a specific sleep stage, is different in insomnia and how that may contribute to the etiology or maintenance of the disorder. Likewise, studies should focus on those aspects of sleep and wake central to the disorder of insomnia (e.g., subjective-objective discrepancy in WASO or in sleep latency) and on determining any differences between clinical phenotypes. These comparisons will likely require greater specificity in, and shorter duration of, scan periods (e.g., collect data only during the sleep-latency period, or during specific periods of WASO, or only during stage 2 sleep), as well as larger sample sizes and multiple scans within subjects to boost statistical power.

The second major area that will help advance this line of work is a more-thorough conceptual grounding in, and specific tests of, 1 or more of the prevailing theories regarding the neurobiology of insomnia.[1-4] This should be done in both the design and the interpretation phases. For the former, specific experimental manipulations (e.g., of the homeostat) or, again, more specific contrasts can be made. For the latter, functional neuroimaging techniques with finer spatial resolution and/or measuring other aspects of brain function, as well as hypothesis-driven analyses (e.g., functional connectivity and network-based approaches), would likely produce more anatomically focused differences. The key then would be to make explicit the connections between brain regions showing abnormalities and those functions that bear directly on the symptoms and defining characteristics of insomnia.

Functional neuroimaging offers much promise for insomnia researchers. One could argue, though, that this promise will not be fully realized until a number of investigators use a variety of imaging techniques to characterize the neuropathophysiology of both waking and sleeping insomnia, thereby producing several lines of converging evidence. I am confident that this work will be done and the knowledge gained will help produce better treatments for insomnia and will possibly even deepen our understanding of sleep itself.

REFERENCES

1. Espie CA, Broomfield NM, MacMahon KMA, Macphee LM, Taylor LM. The attention-intention effort pathway in the development of psychophysiologic insomnia: invited theoretical review. Sleep Med Rev 2006:Jun 27 [E Pub ahead of print]
2. Spielman A, Caruso L, Glovinsky P. A behavioral perspective on insomnia treatment. Psychiatr Clin North Am 1987;10:541-53.
3. Perlis ML, Giles DE, Mendelson WB, Bootzin RR, Wyatt JK. Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. J Sleep Res 1997;6:179-88.
4. Nofzinger EA. Regional cerebral metabolism in insomnia: hierarchical levels of arousal. INSOM (International News on Sleep and its Optimized Management) 2005;6:4-21.
5. Nofzinger EA, Nissen C, Germain A, et al. Regional cerebral metabolic correlates of WASO during NREM sleep in insomnia. J Clin Sleep Med 2006;2:316-322.