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Sleep Medicine 9 Suppl. 1 (2008) S29–S34

SLEEP MEDICINE

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Original article

Cognitive consequences of sleep and sleep loss

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Abstract

Although we still lack any consensus function(s) for sleep, accumulating evidence suggests it plays an important role in homeostatic restoration, thermoregulation, tissue repair, immune control and memory processing. In the last decade an increasing number of reports continue to support a bidirectional and symbiotic relationship between sleep and memory. Studies using procedural and declarative learning tasks have demonstrated the need for sleep after learning in the offline consolidation of new memories. Furthermore, these consolidation benefits appear to be mediated by an overnight neural reorganization of memory that may result in a more efficient storage of information, affording improved next-day recall. Sleep before learning also appears to be critical for brain functioning. Specifically, one night of sleep deprivation markedly impairs hippocampal function, imposing a deficit in the ability to commit new experiences to memory. Taken together, these observations are of particular ecologic importance from a professional and education perspective when considering that sleep time continues to decrease across all age ranges throughout industrialized nations.

Keywords: Memory encoding; Memory consolidation; Sleep deprivation; Slow wave sleep; Hippocampus

1. Introduction

Although sleep constitutes a large proportion of the human life time, fundamental questions still remain about its role in physiological function. Many hypotheses have been proposed, including homeostatic restoration, thermoregulation, tissue repair, immune control and memory processing. Indeed, the paramount role of sleep in human physiology and health is exemplified by the fact that sleep deprivation has been shown to have a negative impact on metabolic parameters such as glucose tolerance and insulin sensitivity [1], and places individuals at a greater risk of serious disease, such as diabetes [2]. One of the most exciting hypotheses is that sleep makes an important contribution to processes of learning, memory and brain plasticity [3].

2. Sleep and memory

The notion that sleep plays an important role in learning and memory has been around for over two centuries – in 1801 David Hartley proposed that dreaming may alter the strength of neural associative memory links [4]. Following this hypothesis, the first systematic assessment of sleep and memory was conducted over a century later in 1924, when it was shown that, compared with time awake during the day, memory retention was better after a night's sleep [5]. Sleep-dependent memory processing as a specific concept, however, is a relatively new theory for which a large number of studies over the last 10 years, spanning most of the neurosciences, have provided supportive evidence [3,6].

The development of a concise, singular description of sleep-dependent memory processing is made more difficult by the complexity of what constitutes "sleep" and "memory". Sleep is frequently described in two broad states: rapid eye movement (REM) sleep and non-REM (NREM) sleep (NREM sleep is classified into progressively deeper stages, numbered from 1-light to 3-deep). Similarly, memory is not considered a single phenomenon but broadly split into memory *types* and memory *stages*. Memory types are separated into declarative (consciously accessible memories of fact-based information which include episodic and semantic memory) and nondeclarative (procedural memories of habits, actions or skills, which includes procedural, implicit, non-associative and conditioning memory). Memory stages (or the various steps of memory evolution) include several phases, including acquisition/encoding, consolidation, integration, recall and even erasure [7].

Because there are a number of different sleep stages and memory stages, the number of dynamic ways that various sleep states may interact and influence different aspects of memory is considerable [7]. The specifics of this relationship still remain an active focus of research: understanding

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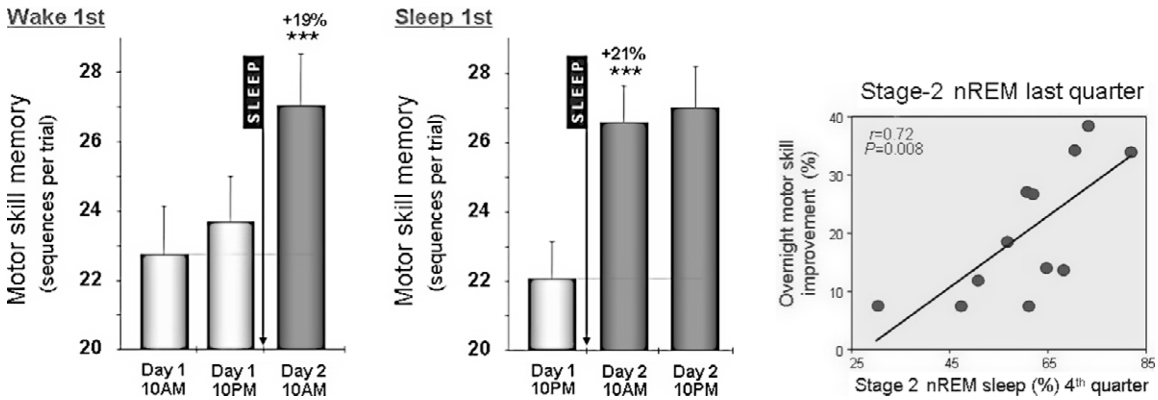

Fig. 1. Sleep-dependent motor memory enhancement [9]. ***$P < 0.002$. *Wake first* group: participants were trained at 10 a.m., retested at 10 p.m. after 12 hours awake, and again at 10 a.m. the next morning after a night of sleep. *Sleep first* group: participants were trained at 10 p.m., tested at 10 a.m. the next morning after a night of sleep, then retested again at 10 p.m. after 12 hours awake. Reprinted from Neuron, Vol. 35, Walker MP et al., Practice with sleep makes perfect: sleep-dependent motor skill learning, p205–11, Copyright © 2002, with permission from Elsevier.

how sleep affects memory and/or vice versa, and whether this relationship is uni- or bi-directional. The aim of this article is to briefly examine the current knowledge of sleep-dependent memory processing. It is beyond the scope of this article to explore all interactions exhaustively, therefore, the focus will be on REM and NREM sleep and how they impact acquisition/encoding and consolidation of episodic and procedural memory.

3. Learning and sleep

Interesting results from a study examining learning efficiency and sleep have shown that learning can affect the structure of sleep. In a study by De Koninck and colleagues, polysomnographic analysis before and after an intensive language course indicated that changes in sleep structure take place during learning and that these changes are correlated with knowledge acquisition [8]. In this study, the authors found a significant positive correlation between language learning efficiency and increases in proportion of REM sleep from before the 6-week language course and during the course [8]. These results indicate that the act of learning can affect sleep and produce changes in the structure of subsequent sleep. With this in mind, does the relationship work both ways, that is, does sleep affect learning?

4. Sleep after learning

While the old adage "practice makes perfect" has an irrevocable truth to it, the results of many studies have indicated that time can have an important influence on motor skill learning. In addition, many studies have demonstrated that sleep after learning improves memory performance [3].

In a computerized sequential finger-tapping task, sleep after learning resulted in consolidated and enhanced motor skill memories (Figure 1). In the study, motor skill performance (number and accuracy of key-press sequences completed) was tested following offline time delays: all participants were trained and retested, but variations in sleep conditions between the groups were imposed to determine the consolidation benefit of (1) wake-time, (2) wake-time followed by sleep, and (3) sleep then wake-time. No significant improvements in motor performance were seen after 12 hours of wake-time. However, large and significant enhancements in motor performance (19–21%) were observed after a night of sleep; improvements in performance were observed in individuals who slept immediately after training and in those who initiated sleep up to 12 hours after training. Analysis of the sleeping individuals revealed a significant relationship between total percentage of stage 2 NREM sleep and the percentage of overnight motor skill improvement [$r(10) = 0.66$, $P = 0.01$], but no correlation for other sleep stages [9,10]. Further analysis of the motor improvements and sleep stages revealed that, when the night of sleep was divided into quarters, overnight motor skill improvement was correlated to the proportion of stage 2 NREM sleep in the 4th quarter of the sleep period (Figure 1) [9].

Based on evidence that motor skill memories are consolidated across a night of sleep and correlate with stage 2 NREM, the influence of daytime naps on memory consolidation has recently been explored [11]. Two groups of participants were trained on a motor skill task using their left hand – a paradigm known to result in overnight plastic changes in the contralateral, right motor cortex [12]. Both groups trained in the morning and were tested 8 hours later, with one group obtaining a 60–90 min intervening midday nap, while the other group remained awake. At testing, individuals who did not nap showed no significant performance improvement, yet those who did nap expressed a highly significant consolidation enhancement. Within the nap group, the amount of offline improvement showed a significant correlation with the global measure of stage 2 NREM sleep. However, topographical sleep-spindle analysis revealed more precise correlations (Figure 2). Specifically, when spindle activity (sigma power in the 12–16 Hz range) at the central electrode of the non-learning hemisphere (left) was subtracted from that in the learning hemisphere (right)

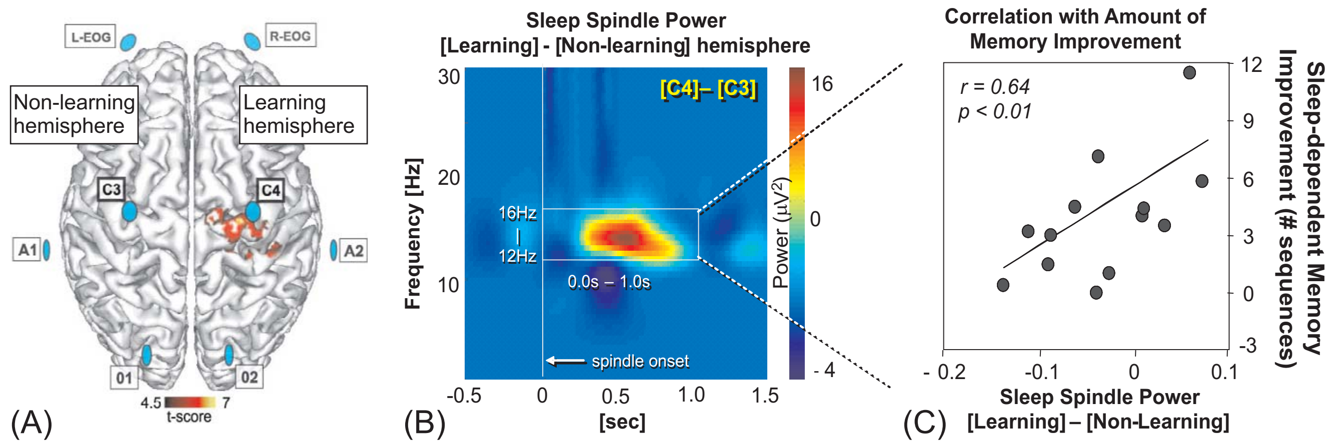

Fig. 2. Association between regionally specific sleep-spindles and motor-memory consolidation: (A) Sleep-EEG array (blue discs) superimposed on the known overnight plastic reorganization of motor-memory [12], including the right motor cortex; (B) difference in sleep-spindle activity (power) in central electrodes of the Learning (relative to Non-learning) hemisphere, which (C) accurately predicts the amount of post-sleep memory improvement across subjects.

(Figure 2B), representing the within subject, between hemisphere homeostatic difference in spindle activity following learning, strong positive relationships with offline memory improvement emerged (Figure 2C) – correlations that were not evident for either hemisphere alone. These results demonstrate that motor memories are dynamically facilitated across daytime naps, and are uniquely associated with electrophysiological events expressed at local, anatomically discrete locations of the brain.

Other studies have also demonstrated sleep-dependent benefits for declarative memory. Several reports by Born and his colleagues have shown actual improvement on a paired word associates test after early night sleep, rich in SWS [13], and modification of sleep characteristics following intensive learning of word pairs [14]. In addition to classically defined slow delta waves (1–4 Hz), the very slow cortical oscillation (<1 Hz) also appears to be important for memory consolidation. Marshall and colleagues showed that experimentally boosting human slow oscillations in the prefrontal cortex results in improved memory performance the following day [15]. Following learning of a word-pair list, a technique called Direct Current Stimulation (DCS) was used to induce these slow (in this case, 0.75 Hz) oscillation-like field potentials during early delta-rich sleep. The DCS not only increased the amount of SWS sleep during the simulation period (and for some time after), but also enhanced the retention of these hippocampal-dependent factual memories, suggesting a causal benefit of SWS sleep neurophysiology.

These findings are striking in the face of earlier studies that showed no effect, but this discrepancy may well reflect the nature of the word pairs used. While older studies used unrelated word pair, such as dog–leaf, Born has used related word pairs, such as dog–bone. The nature of the learning task thus shifts from forming and retaining completely novel associations (dog–leaf) to the strengthening or tagging of well-formed associations (dog–bone) for recall at testing. Thus, sleep's role in declarative memory consolidation, rather than being absolute, might depend on more subtle aspects of the consolidation task.

The breadth of these reported correlations between different stages of sleep and learning exercises and memory contributes further to the notion that the connection between sleep and learning is complex and multi-faceted. This aside, what is clear is that sleep after learning performs a preferential, if not necessary, role in offline memory consolidation.

4.1. The neural basis for the role of sleep after learning

The underlying neural basis for the role of sleep in specific forms of learning improvement has been increasingly investigated. For example, it appears that a systems-level alteration in neural representation of a learned motor memory takes place during sleep, an alteration that does not appear to take place to the same extent during a period of wakefulness [12,16]. Using functional magnetic resonance imaging (fMRI), it has been demonstrated that, following sleep, there is differential activation of brain regions and a reorganization of motor memories: regions of increased activation were expressed in the right primary motor cortex, medial prefrontal lobe, hippocampus and left cerebellum (Figure 3) [12]. These changes were postulated to facilitate faster motor output and more precise mapping of keypress movements. Conversely, reductions in activity signals were recorded in parietal cortices, the left insular cortex, temporal pole and fronto-polar region potentially associated with a decreased need for conscious spatial monitoring due to automated performance, post-sleep. This suggests that overnight, plastic reorganization of memory within the brain may result in a more refined storage representation of information, such that the access and availability of memory recall is more efficient the next day. Therefore, it appears that sleep after learning of certain tasks is required for

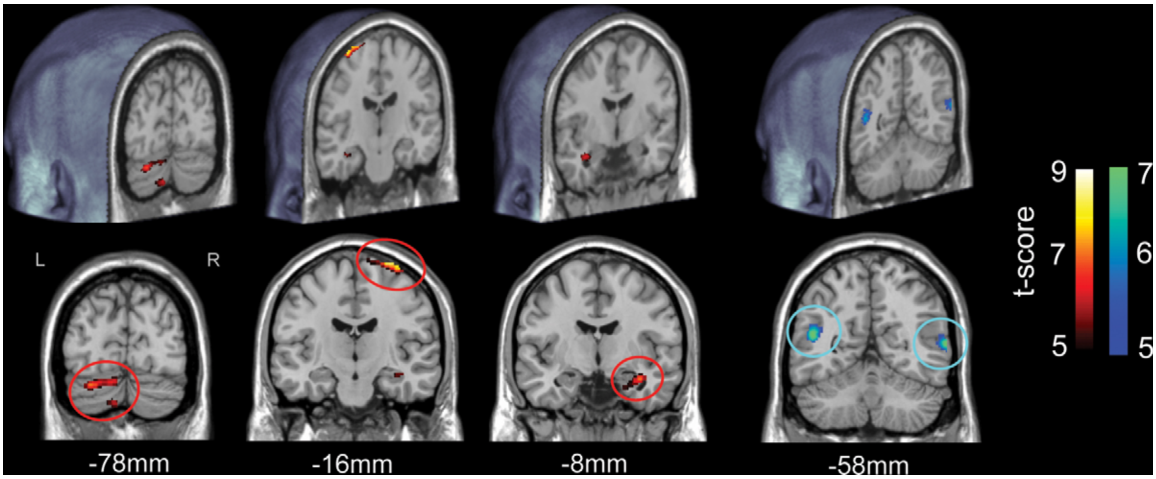

Fig. 3. Overnight, sleep-dependent reorganization of human motor memories [12]. Following sleep, there is differential activation of brain regions and a reorganisation of motor memories. Enhanced activity in the cerebellum & primary motor cortex (M1) are thought to result in faster and more accurate motor output while hippocampal changes correct temporal sequential ordering of finger movements. In contrast, reduced parietal lobe activity suggests a decrease in the need for conscious control due to greater memory automation. Reprinted from Neuroscience, Vol. 133, Walker MP et al., Sleep-dependent motor memory plasticity in the human brain, p911–7, Copyright © 2005, with permission from Elsevier.

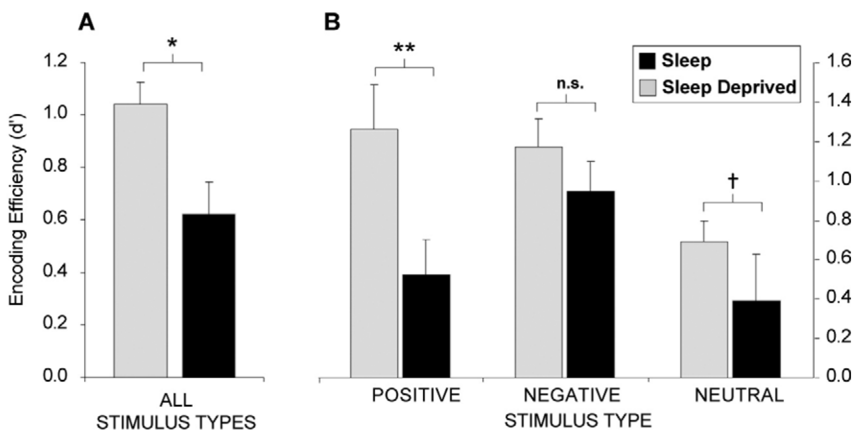

Fig. 4. Sleep deprivation induced emotional and neutral memory encoding impairments [3,18]. $*P \leqslant 0.05$, $**P \leqslant 0.01$. Reprinted, with permission, from the Annual Review of Psychology, Volume 57. © 2006 by Annual Reviews www.annualreviews.org

the subsequent neural reorganization needed to consolidate memory.

5. Sleep before learning

While the merits of sleep after learning have been clearly demonstrated, it has become apparent that sleep before learning is also critical for brain functioning. Animal studies have shown that sleep deprivation leads to changes at a cellular and molecular level that inhibit hippocampal functioning and impair subsequent performance on a hippocampus-dependent spatial learning task [17]. The importance of sleep before learning has also been demonstrated in humans [18]. Yoo and colleagues examined the functional relationship between the hippocampal deficits produced by sleep deprivation and memory encoding. Study participants were either deprived for one night (sleep-deprived) or allowed to sleep normally (sleep-control) on the evening before the memory-encoding task. A pilot study [Walker, unpublished] involved viewing positive, negative and neutral words presented to subjects, followed by a recognition test two days later after recovery sleep.

When combined across all stimulus types, individuals in the sleep deprived condition exhibited a striking 40% reduction in the ability to form new human memories (Figure 4A). However, when these data were separated into the three affective categories (negative, positive or neutral), the magnitude of encoding impairment differed across categories (Figure 4B). In those who had slept, both positive and negative stimuli were associated with superior retention levels relative to the neutral condition, consonant with the notion that emotion facilitates memory encoding. However, there was severe disruption of encoding and hence later retention deficit for neutral and especially positive emotional memory in the sleep-deprived group. In contrast, a relative resistance of negative emotional memory was observed in the deprivation group. These data suggest that, while the

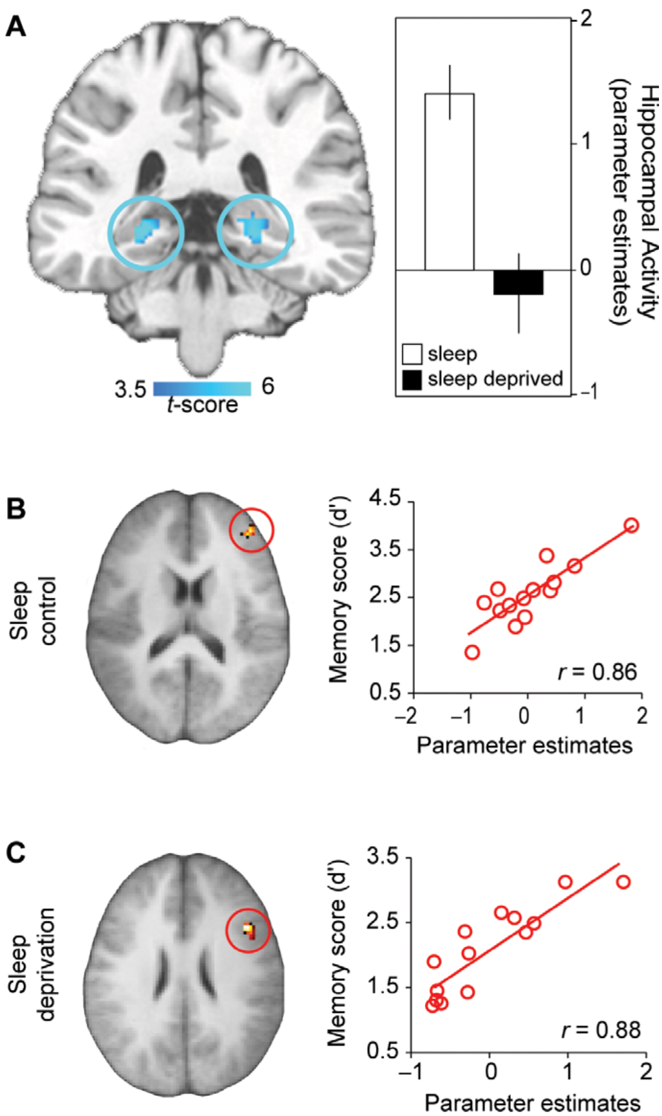

Fig. 5. Sleep-deprivation induced changes in episodic memory encoding activity. (A) Deficit in hippocampal encoding activation in the sleep deprivation group, relative to control group (respective hippocampal signal for each group shown in right panel); (B) association between the effectiveness of memory encoding (d′ score) and dorso-lateral prefrontal cortex across individuals in the sleep control group, yet (C) a different regional association (inferior frontal gyrus) in the sleep deprivation group [18]. Adapted by permission from Macmillan Publishers Ltd: Nature Neuroscience, Yoo SS et al. 2007 Mar;10(3):385–92. Copyright © 2007.

effects of sleep deprivation are directionally consistent across emotional sub-categories, the most profound impact is on the encoding of positive emotional stimuli, and to a lesser degree, emotionally neutral stimuli; yet negative stimuli appear to be more resistant to the effects of prior sleep loss. Intriguingly, these data may offer novel insights into affective mood disorders that express co-occurring sleep abnormalities [19]. Indeed, if one compares the two profiles of memory encoding in Figure 4 it is clear that those who have slept encode and retain a balanced mix of both positive and negative memories. In contrast, however, those in the deprivation group express a skewed distribution of encoding, resulting in an overriding dominance of negative memories, combined with a marked retention deficit of positive and neutral memories. This selective alteration in memory encoding may provide an experimental explanation for the higher incidence of depression in populations expressing impairments in sleep, which, due to these specific deficits, may suffer a negative remembering bias, despite experiencing equally positive and negative reinforcing past events.

The impact of sleep deprivation on the neural dynamics associated with encoding of new declarative memories has been revealed using event-related fMRI [18]. In addition to performance encoding impairments at a behavioural level, a highly significant and selective deficit in encoding activation was revealed in bilateral regions of the hippocampus in the sleep deprivation condition – a structure known to be critical for learning new episodic information (Figure 5). While these findings indicated that, at a group level, sleep deprivation markedly impairs hippocampal memory function, when examined within each group separately, the success of encoding, from low to high, was further determined by different regions of the prefrontal lobe. The right dorsal/middle lateral prefrontal cortex had a strong positive relationship with increasing memory performance in those who had slept normally prior to learning. In contrast, a region in the right inferior frontal gyrus (IFG) displayed a significant positive, potentially compensatory, relationship with memory performance in the those who were sleep deprived (Figures 5B, 5C).

Taken together, this collection of findings indicate the critical need for sleep before learning: without adequate sleep, hippocampal function is markedly disrupted, resulting in a decreased ability to encode new experiences, the extent of which appears to be further governed by alterations in prefrontal encoding dynamics. Thus, sleep is not only important after learning for the subsequent consolidation of memory, but sleep before learning appears equally critical in preparing key brain structures for efficient next-day memory formation.

6. Conclusions

By virtue of the diversity of sleep states and memory types and stages, there are an intriguing number of possible interactions between these two entities. It is apparent that there are specific and extensive relationships between certain sleep states and memory processes, our understanding of the full complexity of which is still growing. However, what is fundamental in our understanding is that sleep plays a critical role in modulating and regulating memory processes, both before and after the learning episode: sleep before learning is necessary for initial encoding of certain memories, while sleep after learning is required for subsequent consolidation of numerous forms of memory. This relationship is of significant importance given that we live in a time when work hours and cognitive demands are increasing; while sleep patterns are changing, total sleep time is decreasing and a good night's sleep is perhaps more elusive than ever.

Acknowledgements

The author wishes to thank Robert Stickgold, Edwin Robertson and Ninad Gujar for their thoughtful insights. This work was supported in part by grants from the National Institutes of Health (MH069935) and the American Academy of Sleep Medicine. The author would like to thank Matt Weitz, from Wolters Kluwer Health, who provided medical writing support on behalf of sanofi-aventis.

Disclosures

None.

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