Healthy Brain Aging: What Has Sleep Got To Do With It?

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- Sleep • Memory • Dementia • Cognition
- Insomnia • Sleep apnea

For centuries, sleep was considered a passive activity, perhaps even a period of time in life that was a hindrance or barrier to getting more things accomplished. Although the exact function of sleep is still being explored, experts now believe it plays a valuable role in maintaining health. Recent research has begun to focus on its importance to cardiovascular health, longevity, mood, and immune function, although ever since scientists began to study sleep, there has been a belief in its vital role in learning, memory, and overall central nervous system homeostasis. Despite new awareness of the consequences of sleep loss, over the past 100 years, the population's total sleep time has diminished. On average, Americans are sleeping 6.8 hours per night, as reported in 2005 (National Sleep Foundation Sleep in America poll). Twenty two percent of Americans believe they are not getting the amount of sleep they need. Whether or not they are deciding to voluntarily deprive themselves of adequate sleep or are not obtaining good quality sleep secondary to a sleep disorder, there is increasing evidence of the immediate and long-term consequences, especially relating to the brain. As described in this article, sleep deprivation and sleep disruption may not only have transient effects on cognition but also result in permanent and long-standing effects on processes of memory and brain plasticity.

Sleep deprivation and sleep disorders are common in the general population. The Institute of Medicine in 2006 estimated that 50 to 70 million Americans chronically suffer from a disorder of sleep or wakefulness, hindering daily functioning.

Although many effective treatments for sleep disorders exist, the majority of patients remain

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SLEEP AND ITS EFFECT ON COGNITION

Sleep and Memory

Sleep has been implicated in the encoding and consolidation of memory. In a group of healthy adults deprived of sleep for 36 hours continuously, significant impairments in retention of new information were evident compared with controls who were not sleep deprived, even in a subgroup that received caffeine to overcome nonspecific effects of lower alertness. Furthermore, the sleep-deprived subjects displayed significantly worse insight into their performance, resulting in lower predictive ability of performance. Inadequate sleep before learning produces bidirectional changes in episodic encoding activity, involving the inability of the medial temporal lobe (the primary center for encoding) to engage normally during learning, combined with potential compensation attempts by prefrontal regions, which in turn may facilitate recruitment of parietal lobe function. Thus, optimal prefrontal function may be necessary for adequate compensatory strategies to overcome encoding problems due to sleep deprivation. For individuals with pre-existing prefrontal lobe dysfunction (e.g., individuals with depression or cerebrovascular disease affecting the frontal lobe), the impact of sleep deprivation on memory encoding may be even greater. Sleep deprivation has also been found to markedly impair hippocampal function, and the hippocampus is critical for learning new episodic information.

There is robust, consistent literature demonstrating the need for sleep after learning in the subsequent consolidation and enhancement of implicit memories. Recent research has also revealed a strong beneficial effect of sleep on the consolidation of declarative memory. Several studies have suggested a critical role for slow wave sleep (SWS) neurophysiology in the offline consolidation of episodic facts. Memories tested after a night of sleep are significantly more resistant to interference, whereas across a waking day, memories are far more susceptible to interference. Functional imaging (e.g., functional MRI) studies contrasting sleep-deprived and well-rested brains provide substantial evidence that sleep is important for optimal cognitive function and learning. One mechanism proposed as underlying these effects on hippocampal-dependent learning tasks is the reactivation of memory representations during SWS and possibly rapid eye movement (REM) sleep.

Stage 2 non-REM (NREM) sleep (marked by sleep spindles or K-complexes on electroencephalogram) has also been implicated in memory consolidation. Increased spindle density after intensive training on a pursuit motor skill task and increased spindle density after combined training on several simple procedural motor tasks have been reported. The mechanistic benefit of sleep spindles may be related to their faster stimulating frequency, a range suggested as facilitating long-term potentiation, a foundational principal of synaptic strengthening in the brain and essential for memory consolidation.

REM sleep may play an important role in emotional memory processing. Experiences that evoke emotions not only encode more strongly but also seem to persist and even improve over time as the delay between learning and testing increases. A consistent relationship between REM sleep and emotional processing has been identified. Increased activity within limbic and paralimbic structures (including the hippocampus and amygdala) during REM sleep offers the ability for reactivation of previously acquired affective experiences. REM sleep (characterized by dominant theta oscillations within subcortical and cortical nodes) may offer large-scale network cooperation at night, allowing the integration and, as a consequence, greater understanding of recently experienced emotional events in the context of pre-existing neocortical stored semantic memory. The process of REM sleep mental activity may aid in the resolution of previous emotional conflict, resulting in improved next-day negative mood.

Sleep and Creativity

Sleep is also involved in the association and integration of new experience into pre-existing networks of knowledge. Research involving laps in infants has shown that sleep allows the reinterpretation of prior experience and supports the ability to detect a general pattern in new information. Human memory integration takes time to develop, requiring slow, offline associative processes. In an elegant study, sleep after exposure to a problem was found to more than double the likelihood of solving it. Thus, during sleep, the brain may also replay collections of memories to discover patterns and thus help find meaning in what has been learned.

Sleep and Neuroplasticity

Rapidly growing experimental evidence supports the notion that sleep plays an active role in modulating synaptic plasticity in the brain. Several neural level mechanistic models of sleep-dependent neuroplasticity have been described. Emerging evidence has suggested a role for sleep in regulating the synaptic connectivity of the brain, principally the neocortex. There is evidence indicating local sleep-dependent neural pruning by SWS, the goal of which may be to regulate neural architecture at a highly specific anatomical level, mapping onto corresponding locations of memory representation. Thus, SWS selectively downregulates synaptic strength back to baseline levels, preventing synaptic overpotentiation, which would result in saturated brain plasticity. In doing so, this rescaling leaves behind more efficient and refined memory representations the next day, affording improved recall. In humans, NREM SWS dominates early in the night, and stage N2 (stage 2) and REM sleep prevail later in the night. From a memory consolidation perspective, the predominance of hippocampal-neocortical interaction takes place in the early SWS-rich phase of the night, leaving corticocortical connections on offer for later processing during stage N2 and REM sleep. Such a cooperative mechanism produces a network of stored information that is not only more efficient but also, for those representations remaining, more enhanced. Sleep deprivation inhibits adult neurogenesis possibly by elevating corticosterone. Such a suppression of adult neurogenesis and synaptic plasticity may underlie some of the cognitive deficits associated with prolonged sleep deprivation.
These changes are gradual over a lifetime. The percentage of SWS (or delta sleep) that a person has at night decreases with age, especially for men.53 The elderly (over age 65) also have more awakenings during sleep.54 This leads to older adults being significantly sleepier than younger adults when measured objectively.53 Despite these changes with age, sleep need remains the same throughout adulthood. Sleep complaints are more common in the elderly, partly due to more comorbid psychiatric and medical conditions that disrupt sleep and concomitantly affect cognition.

COGNITIVE IMPAIRMENT/IMPROVEMENT FROM MEDICATIONS USED FOR SLEEP

Table 1 lists commonly used hypnotics, their potential risks, and safer alternatives. Drugs commonly used to treat insomnia (eg, benzodiazepines and drugs with high anticholinergic properties, such as diphenhydramine) have a particularly high risk of cognitive impairment in older adults.56,58 The risk of hypnotic medication-induced cognitive impairment may be minimized by several strategies, including avoidance of unnecessary medications; use of nonpharmacologic insomnia treatments, such as cognitive-behavioral therapy; and selection of hypnotics least likely to cause cognitive impairment.59 In people over age 60, the benefits of sedative hypnotics (eg, improvements in sleep latency and total sleep time) may not justify the increased risk, particularly if patients have additional risk factors for cognitive or psychomotor adverse events.57 Based on limited data, zolpidem, zaleplon, eszopiclone, and ramelteon represent modestly effective and generally well-tolerated treatments for insomnia in older adults.60 The 2005 National Institutes of Health State-of-the-Science Conference on Insomnia concluded there is no systematic evidence for the effectiveness of many medications, including antihistamines, antidepressants, antipsychotics, and anticonvulsants used off label for the treatment of insomnia, and warned that the risks of use outweighed the benefits.60 Trazodone, a frequently prescribed antidepressant for insomnia in older persons, is sedating but can cause orthostasis and has no published evidence of sustained efficacy.71 Benzodiazepine receptor agonists (eg, zolpidem, zaleplon, and eszopiclone) have lower frequency of adverse effects (eg, falls and cognitive impairment) than those found in the older benzodiazepines approved as hypnotics (eg, triazolam and temazepam) and are thus preferable for use in older adults in whom short-term therapy of hypnotics is indicated for treatment of insomnia (NIH 2005). In the adult nonelderly population, use of melatonin agonist ramelteon has not been well studied in geriatric populations, although one study did show there was less balance difficulty in the middle of the night in the elderly with use of ramelteon as compared with zolpidem.72 Table 2 lists some practical rules to follow when prescribing sedative hypnotics to older individuals for insomnia.

Treatment of excessive daytime sleepiness associated with sleep disorders, such as OSA and narcolepsy, may be treated with modafinil, armodafinil, or stimulants (methylphenidate, d-amphetamines, methylphenidates, or amphetamines). These drugs may also be useful for treatment of idiopathic hypersomnia, hypersomnia related to medications (eg, opioids), and hypersomnia due to a medical condition.71 These wake-promoting drugs may improve cognitive performance by reducing daytime sleepiness and improving daytime alertness.71,72,75 (Table 3).

RESEARCH GAPS

Despite the explosion of research recently on the effects of sleep disorders on cognition and the healthy aging brain, many significant questions remain. Much of the current data on sleep and memory are in younger adults and have not included the elderly. Some of the findings in younger subjects (eg, increase in sleep spindle density after motor learning) may not be seen in older adults.76 It will also be crucial to learn if there is a particular stage of sleep (eg, SWS) that is more important than other stages of sleep in memory processing or influencing cognitive function. Finding this vital piece of information would assist in developing treatments targeting this stage of sleep. Mechanisms linking sleep disorders (eg, OSA) to cognitive impairment in older adults need to be better characterized and identified, especially if they are leading to permanent central nervous system damage. There needs to be more research showing that

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**Table 1**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Indication</th>
<th>Safe Alternatives</th>
<th>Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>Insomnia</td>
<td>Nondrug interventions, BRA, MRA</td>
<td>CI, DS</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Insomnia</td>
<td>Nondrug interventions, BRA, MRA</td>
<td>Orthostasis, DS</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Insomnia</td>
<td>Nondrug interventions, BRA, MRA</td>
<td>DS, falls, CI</td>
</tr>
<tr>
<td>Quazepam</td>
<td>Insomnia</td>
<td>Nondrug interventions, BRA, MRA</td>
<td>DS, falls, CI</td>
</tr>
<tr>
<td>Estazolam</td>
<td>Insomnia</td>
<td>Nondrug interventions, BRA, MRA</td>
<td>DS, falls, CI</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Insomnia</td>
<td>Nondrug interventions, BRA, MRA</td>
<td>Falls, CI</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Insomnia</td>
<td>Nondrug interventions, MRA</td>
<td>Falls</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>Insomnia</td>
<td>Nondrug interventions, MRA</td>
<td>Falls</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Insomnia</td>
<td>Nondrug interventions</td>
<td>Falls</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Insomnia</td>
<td>Nondrug interventions</td>
<td>Falls</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>Insomnia</td>
<td>Nondrug interventions</td>
<td>Not well studied in older adults</td>
</tr>
</tbody>
</table>

**Table 2**

**Basic principles in pharmacologic treatment of insomnia**

1. After a thorough assessment, establish a clear diagnosis of insomnia by differentiating it from specific sleep disorders causing insomnia, such as restless legs syndrome, REM sleep behavior disorder, or OSA.
2. Consider discontinuing unnecessary medications, medications that are inappropriate for use in the older individual, and medications that may be contributing to insomnia (eg, stimulants).
3. Encourage evidenced-based effective nondrug interventions to treat insomnia, such as cognitive behavioral therapy for insomnia.
4. Take into account chronic conditions leading to cognitive impairment, balance and gait difficulties.
5. Take into account concomitant prescriptions of central nervous system active agents (especially psychotropics and anticholinergic drugs) that may increase the risk of cognitive toxicity that may occur with use of sedative hypnotics.
6. Discuss risks and benefits of sedative hypnotics thoroughly.
7. Start low (eg, half the recommended adult dosage) and go slow (slower titration to final lowest possible therapeutic dose).
Table 3
Potential cognition-improving drugs used for sleep disorders

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Indication</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
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<td>Modafinil</td>
<td>EDS due to narcolepsy</td>
<td>May improve alertness and cognition</td>
</tr>
<tr>
<td></td>
<td>EDS despite treated OSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EDS due to shift work disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiopathic insomnia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medication-induced hypersomnia</td>
<td></td>
</tr>
<tr>
<td>Armodafinil</td>
<td>EDS due to narcolepsy</td>
<td>May improve alertness and cognition</td>
</tr>
<tr>
<td></td>
<td>EDS despite treated OSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EDS due to shift work disorder</td>
<td></td>
</tr>
<tr>
<td>Stimulants*</td>
<td>Narcolepsy</td>
<td>May improve alertness and cognition</td>
</tr>
<tr>
<td></td>
<td>Medication-induced hypersomnia</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: EDS, excessive daytime sleepiness.
* Methylphenidate and amphetamine derivatives.

Treating sleep disorders leads to improved cognitive function or halting cognitive decline in patients with progressive dementia. Comparative pharmacovigilance studies focusing on the impact of different sedative hypnotics on cognition are needed, including a better understanding of the risks involved with these medications in the elderly.

SUMMARY

Sleep may have a crucial role in molecular, cellular, and systems-level processes that convert initial, labile memory representations into more permanent ones that are available for continued reactivation and recall over extended periods of time. Optimal sleep before learning is necessary to prepare key neural structures for efficient next-day learning. Without adequate sleep, hippocampal function becomes markedly disrupted, resulting in a decreased ability for recording new experiences, the extent of which seems to be further governed by alterations in prefrontal encoding dynamics. Sleep also protects memory from being lost due to interference (i.e., learning disruption). Besides memory, sleep has a role in problem solving, creativity, and regulating emotional brain reactivity. The final goal of sleep-dependent memory processing may be integration of memories into a common schema and consequently the development of universal concepts, a process that forms the basis of generalized knowledge and creativity.

Assessing the quality of a person’s sleep is frequently overlooked during routine physician visits. Many common sleep disorders continue to remain undiagnosed, although they have been associated with neurocognitive dysfunction and frequently respond to treatment. Permanent brain changes may result from sleep disorders, such as OSA, as evidenced by many imaging modalities. It is time for all health care providers to wake up and routinely assess sleep quality and duration in their patients. This is especially important in assessing adults who complain of new-onset memory and cognitive problems.

REFERENCES


Endocrine Aspects of Healthy Brain Aging

Nazem Bassil, MD, John E. Morley, MB, BCh, BSc,

KEYWORDS
• Hormones • Cognition • Metabolic alteration

The concept that hormones can alter behavior is not new; Aretaeus the Cappadocian stated that hypogonadism in men was related to altered (effeminate) behavior.1–3 The original description of Graves disease (hyperthyroidism) in the nineteenth century included a description of associated anxiety. Myxedema madness associated with goiter was also recognized. Behavior changes have been reported in Addison and Cushings disease. Depression has commonly been considered a symptom of various endocrinopathies

This review does not concentrate on these well-known psychiatric manifestations of endocrine diseases, but concentrates on the more subtle effects of hormones and metabolic alteration seen in many older persons. The article focuses predominately on the role of hormones in cognition, as dementia and mild cognitive impairment are major problems in the older individual.4–8

DIABETES MELLITUS AND INSULIN RESISTANCE

Studies9–13 from various populations have consistently shown an association between diabetes and cognitive decline or dementia. Hyperglycemia leads to cognitive decline in animals and humans.14–16 Diabetes is associated with a 50% to 100% increase in risk of Alzheimer disease (AD) and of dementia overall and a 100% to 150% increased risk of vascular dementia.17 Higher postprandial plasma glucose levels were associated with greater declines in cognitive performance.18 An inverse correlation has been noted between some cognitive measures and hemoglobin A1C levels, suggesting that worse glycemic control may be associated with greater cognitive decline.19

The relationship between diabetes and dementia of the Alzheimer type is not clear.20 The mechanism by which diabetes may increase dementia risk is uncertain:

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