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REVIEW

Sleep, cognition, and neurodegenerative diseases

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Quality and quantity of sleep are undervalued by many, primarily due to the hunger our generation has for increased productivity during the day, as 24 hours is just not enough. Even fewer pay attention to the timing of sleep during the circadian cycle or are even aware of its importance. Studies show that insufficient amounts of sleep, poor sleep quality, and/or improper timing of sleep induce both acute and chronic clinical issues that can be prevented by simply sleeping the recommended amount, with restorative quality, and correct circadian timing. Forfeiting hours that should be dedicated specifically to sleep can lead not only to psychological deficits such as mood disorders, stress and anxiety, but also physiological issues such as cognitive and memory deficits, metabolic syndrome, obesity, neurodegenerative diseases such as Alzheimer's and Parkinson's, and even possibly cancer. This article reviews the relationship between sleep, cognition and neurodegenerative diseases with the latest research progress, providing new research ideas for researchers. The author also analyzes the importance of improving people's sleep quality from a sociological point of view to remind people to improve their awareness of sleep.

Keywords: Sleep, Cognition diseases, Neurodegenerative diseases

Abbreviations:

CDC, centers for disease control; SD, sleep deprivation; REM, rapid eye movement; MCI, mild cognitive impairment.

Competing interests:

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Introduction

With the current state of technology, the average human multitasks many hours of the day and frequently at night as well [1]. Smartphones allow us to be connected to worldwide news, online shopping, our emails, family, friends, and our jobs twenty-four hours a day. This wealth of information and connectivity with others sometimes cuts into our daily sleep. In particular, the use of electronics within the last hour before going to sleep at night, especially the most interactive electronics (cell phones, laptops, video games), causes sleep disturbances and loss of a proper number of hours of sleep [2]. Therefore, with advancements in technology, Americans are exceptionally prone to going to sleep later and later at night, thus sleeping an inadequate number of hours per night, with adolescents being a distinctly susceptible group [3]. With so much to do every day, most people are in the mindset that the fewer hours of sleep they can get by on, the more hours they will have for productivity. Unfortunately, the average person greatly undervalues the importance of sleep for human health. According to the Centers for disease Control (CDC) [4], roughly 30% of Americans surveyed sleep less than the recommended 7 hours per night [5]. This survey also revealed that 35% percent of adults had fallen asleep during the daytime in the previous 30 days. Moreover, 4.2% had fallen asleep behind the wheel of a car during the previous 30 day-period.

Why do we spend so much of our day sleeping? Everyone seems to hold a basic level of understanding of the importance of sleep. When we sleep, information from throughout the day is consolidated into memories in the hippocampus. Thus, lack of adequate sleep is detrimental to memory consolidation [6] (Figure 1). While sleep is essential to regenerate energy and allow one to be able to function to their full potential the next day, it is very common for individuals to have unusual sleeping patterns and consequently experience fatigue throughout the following day. So how is it that one can sleep during the night for a good amount of time, yet still feel absolutely exhausted during the daytime? This is where quality and quantity of sleep come into question. These factors do not solely affect our functionality during the day, but also contribute to mental and physical aberrations that can lead to more chronic health effects. Sleep is an imperative factor to human health. During rest, the cells of our body renew: skin cells rejuvenate, brain cells (hippocampus) consolidate memories, and muscle fibers repair daily activity. Repetitive disturbances to the natural sleep cycle and/or short-term sleep deprivation lead to inauspicious health effects ranging from: 1) increased stress responsivity, 2) emotional distress, 3) mood disorders, 4) cognitive and memory deficits, and 5) slower reaction times [7]. High levels of stress hormones (cortisol and adrenaline) can lead to chronic detrimental health effects: 1) hypertension (increased blood pressure to be able to fight or take flight), 2) hyperglycemia (increased energy supply to react to the stress), 3) obesity, 4) cardiovascular disease, 5) diabetes, 6) metabolic syndrome, 7) inflammation, 8) neurodegenerative diseases, and even to an extent 9) cancer (Figure 2). Prolonged elevated levels of cortisol cause weight gain, as cortisol acts on insulin/blood sugar levels and thyroid hormone conversion, thus slowing metabolism [8]. Therefore, it is safe to deduce that sleep is one of the most crucial contributors to our overall health and quality of life [9].

Although scientists have studied sleep deprivation and prolonged wakefulness for decades, many unanswered questions still remain. There are numerous consequences that sleep deprivation induces on the human body, one of which is the adverse effects on mental capacity. Sleep deprivation (SD) according to the Alhola Lab at the University of Turku [10], was studied in two forms: partial SD and total SD, each with its own contributing deficits on the brain. Scientists in this study concluded that partial sleep deprivation affects attention and vigilance, and is much more demanding as far as recovery compared to total sleep deprivation

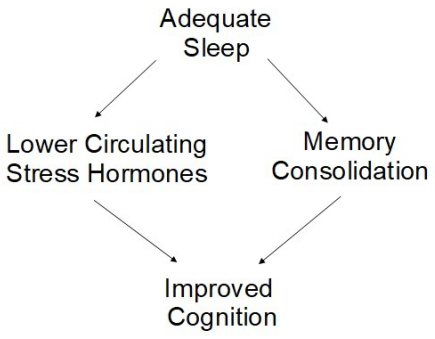

Figure 1 The effect of sleep on cognition

which affects attention and decision making. Thus, a person can actually feel sleepier the following day, if they have only slept for 2–3 hours compared to staying awake all night long. This exemplifies the complexity of sleep, and the balance between sleeping an adequate number of hours while also having restorative sleep quality. Additionally, the quantity of sleep necessary varies between individuals, as do the effects from the lack thereof.

Recent biomedical news has suggested that a genetic subset of the human population only needs approximately 6 hours of sleep daily for maintenance of health and well-being [11]. The gene responsible for this difference is the DEC2 gene, which regulates a hormone known as orexin (responsible for wakefulness and appetite) [11]. However, the average person requires 7 hours or greater of sleep per night, in order to maintain proper health. Not surprising, irregular sleeping habits are most prevalent among college student populations. Considering the amount of "daily" tasks they need to complete in order to stay in the range of an average, competitive student, it is only inevitable for work to gouge into their natural sleeping time. The busyness of the student leaching off of their sleep time may seem to be a productive way to get more work done and be ahead of the game, when in reality it only contributes to a reduced level of productivity, as sleeplessness affects learning and attention, as well as memory consolidation-the most important factors in a student's academic journey.

Scientists have deduced that physiologically-speaking, puberty is associated with changes in preference for a bedtime later than usual. Puberty is also a time when the brain is in a highly "plastic" developmental state with many synaptic connections being formed, modified, or removed. Individuals post-puberty tend to be more nocturnal and have a lower "homeostatic sleep drive" according to Dr. Hershner and Dr. Chervin [12]. Henceforth, sleeplessness can become problematic in individuals as more responsibility is weighed over their shoulders and they gain more access to aspects of life that can keep them busy, and sometimes even too busy to sleep (smart phones, video games, television, studying, work, household chores). There have been numerous studies on how poor quality and quantity of sleep can have an effect on the brain of adults. Adults tested within the age group of 53.9 ± 15.5 years-old displayed reduced cortical volume in the right superior cortex coupled by increased atrophy within their frontal, parietal, and temporal cortices [13]. Additionally, multiple other studies have shown that individuals with poor sleep quality within the age group of 70.7 ± 7 years-old exhibited reduction in bilateral hippocampi and amygdala volumes. Moreover, it has been observed that individuals with poor sleep quality (non-restorative sleep) tend to also exhibit patterns of thinning in the frontal lobes [14], orbitofrontal, middle temporal, thalamus, and posterior cingulate [15]. Additionally, APOE genotype correlated with reduced gray matter volume (including the right hippocampus) in insomniacs, but was associated with higher volumes in non-insomniacs [15]. These studies demonstrate that in the absence of underlying health conditions, sleep disturbances can lead to cognitive decline, executive dysfunction, and memory problems. Therefore, lack of sleep, poor quality of sleep, and timing of sleep represent preemptive therapeutic intervention points for doctors to convey to adolescents, young, middle, and older adults about the crucial nature of sleep and its effects on long-term cognition, memory, execution function, and quality of life. Furthermore, sleep quality, quantity, and timing also represent putative therapeutic targets for clinicians for reducing cognitive decline, memory problems, and potentially neurodegenerative diseases later on in life.

The biological requirement of sleep, in a way serves as a preventative source for potential illnesses. While quantity of sleep is crucial for our body's level of energy, quality of sleep is just as critical for the restorative processes ongoing throughout the human body during rest-memory consolidation, muscle repair, cellular repair (removal of damaged proteins). Lack of quantity or quality of sleep plays a detrimental role in both the short-term and chronic-phases of life. Scientists have found that deep sleep generates a "self-cleaning" system that may serve as a shield against neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. The electrical signals during deep sleep, such as slow waves [16], potentially remove toxins that have previously been linked to Alzheimer's disease [17]. Whereas, rapid eye movement (REM) sleep has been

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shown to be the lightest phase of sleep, in which the brain is in the closest state to wakefulness. Thus the greatest percentage of REM sleep during the night, the less restorative the sleep. This is how it is possible to awaken from 8 hours of sleep and still feel groggy and exhausted throughout the next day. Tiemeier et al. (2002) [18] also found in their study that continuous sleep (non-fragmented) was more crucial than sleep duration, as far as the restorative value of the sleep. Reducing REM sleep and sleep fragmentation are also potential clinical targets for sleep specialists and sleep researchers.

In addition to quality and quantity of sleep, the timing of sleep (relative to our circadian rhythms) is also very important. Someren and colleagues (2015) [19] nicely detailed the subcellular, genetic detrimental effects resulting from mistimed sleep. The most optimal time for sleep is during the night time, when the melatonin levels are the highest (for the day) and the body temperature is the lowest. During this time, protein-coding genes are transcribed, as 43% of genes show circadian rhythmicity [20]. As Someren et al. point out, postponing sleep for an additional 4 hours (until the early morning hours of the following day) can lead to an 84% reduction in circadian transcribed genes [21], which can have profound effects on cellular, tissue-level, and human health. Raising public awareness of the crucial nature of timing of sleep might be even more important than the sleep quantity or quality of sleep, as it seems as though few non-scientists are aware of the importance of circadian rhythms and the profound impact in which an 84% reduction of transcribed genes may have on health and long-term quality of life.

Manousakis et al. (2018) [22] revealed increases in age-related cognitive decline associated with advanced circadian timing (early melatonin release during sleep, leading to sleep fragmentation and shortened sleep) and fragmented sleep (frequent periods of wakefulness throughout sleep). Moreover, since advanced circadian timing is a hallmark of mild cognitive impairment (MCI) and Alzheimer's disease, the authors nicely detail putative therapeutic approaches targeting circadian timing. Doppler et al. (2017) [23] determined that phosphorylated alpha-synuclein deposits (common neuropathological features of Parkinson's disease, dementia with Lewy Bodies, α-synucleinopathies, and multiple system atrophy [24, 25] are present in the skin nerve fibers of Parkinson's patients-thus, likely a good biomarker for detecting early stages of Parkinson's disease. Interestingly, patients suffering from REM sleep behavior disorder (not yet diagnosed with Parkinson's disease) had a 55.6% sensitivity of the test for alpha-synuclein deposits; thus, potential prodromal Parkinson's disease. This study is yet another to exemplify the importance of sleep restoration on health and neurodegenerative diseases. This should provide researchers with an interesting point to target-the prodromal period of Parkinson's disease, to see if the disease onset can be delayed by behavior modifications or REM sleep interventions. In a similar study, Iranzo et al. (2013) [26] also found that patients with REM sleep behavior disorder were in the prodromal phase prior to diagnosis of one of the α-synucleinopathies (Lewy body disorder, dementia with Lewy bodies, or Parkinson's disease). Again, it would be interesting to investigate whether the disease diagnosis can be delayed or disrupted entirely through sleep interventions. While numerous studies have documented sleep disturbances in Huntington's disease [27, 28, 29, 30], it is still not known whether the genetic component of the disease is responsible for the sleep dysfunction. Regardless, the poor quality of sleep in Huntingon's disease patients leads to poorer quality of life and exacerbated cognitive decline. Targeted sleep therapy in Huntingon's disease patients should produce an improved quality of life on a daily basis. While some preclinical studies have examined the relationship between sleep-wake cycles of rodents and the onset of Huntingon's disease symptoms [31], additional studies are needed in order to gain better insight into the potential of long-term sleep disturbances resulting in possible earlier disease onset, exacerbation of disease, or sleep disturbances as a manifestation of the disease itself. Sleep duration (at least 7 hours of sleep per night), sleep quality (restorative versus non-restorative), and timing of sleep (relative to circadian rhythm) are all critical factors in human health and quality of life. Sleep deprivation can lead to increased stress/anxiety, emotional distress, mood disorders, cognitive and memory deficits, and slower reaction times in the short-term. While chronic sleep disruption or deprivation can lead to adrenal fatigue,

hypertension, hyperglycemia, obesity, cardiovascular disease, diabetes, metabolic syndrome, inflammation, neurodegenerative diseases, and cognitive decline (dementia with Lewy bodies, Lewy body disorder, Parkinson's disease, Alzheimer's disease, Huntington's disease), and even potentially cancer (Figure 2). Therefore, in considering all of the things people do to try to improve human health, sleep should definitely be a top priority not only for individuals, but for potential therapeutic targets for clinicians and biomedical research scientists as well.

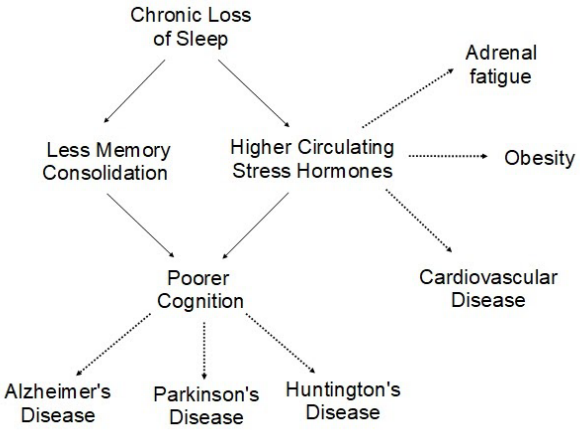

Figure 2 Chronic sleep disturbances can lead to poor cognition and detrimental health effects including neurodegenerative diseases

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