Cognitive Impairment and Depression in Sleep-Deprived Individuals: A Systematic Review

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ABSTRACT

Introduction: Sleep-deprivation is a state of combined absence of sleep and extended wakefulness. Notoriously known to be associated with slowing of cognitive processes like attention, working memory, and executive functions, it is also a consequence of insomnia which in turn is an infamous symptom of depression. Depression has adverse effects on social functioning, which further shape its course and outcome.

Material and Methods: This systematic review is based on a systematic search of electronic database PubMed and provides an overview of literature defining cognitive impairment and depression, followed by their associations with sleep deprivation, entailing possible mechanisms of these inter-relationships along with the networks in the human brain which are susceptible or resilient towards the effects of insufficient sleep. A total of 47 such articles and studies considering all these aspects were reviewed.

Results: Reductions in functional MRI signals in the dorsolateral prefrontal cortex in sleep deprivation are thought to account for attention deficits. Impaired working memory seconded by an overall increase in reaction times were observed, while scanning efficiency was claimed to remain unaffected,by some authors. Long term potentiation was seen to decrease due to sleep deprivation. Alterations in the HPA axis, stress and high cortisol levels, low brain-derived neurotrophic factor levels were also interlinked with both sleep deprivation and depression.

Conclusion: Sleep deprivation interrupts physiological functions, neurocognitive processes, and worsens depression. Hence sleep for upto six to eight hours each night is recommended on the lines of this review.

Keywords: Cognitive Impairment, Depression, Sleep-Deprivation

INTRODUCTION

Cognition entails the ability to learn, understand and solve problems, remember imbibed information and also use it appropriately. The DSM-V (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) recognizes five cognitive domains, mainly attention, memory, language, fluency and visuospatial skills.[1] Impaired attention results in normal tasks taking longer, especially when there are competing stimuli, easy distractability, tasks needing oversimplification, difficulty holding information in mind to do mental calculations or while dialing a phone number. Impaired memory manifests as difficulty while recalling recent events, repeating self, misplacing objects, losing track of actions already performed, and an increasing reliance on lists and reminders. Impaired language causes word-finding difficulty, use of general phrases or wrong words, grammatical errors, difficulty with comprehension of others' language or written material; while impaired visuospatial skills lead to getting lost in familiar places, more use of notes and maps, and difficulty using familiar tools and appliances.[2] Mild cognitive impairment(MCI) has also been called mild neurocognitive disorder (NCD) while dementia is referred to as major NCD.[3] The latter also includes in addition to features of MCI, a hindrance to performance of routine activities in an independent manner.[4] MCI is further classified into two categories: amnestic MCI (a-MCI) if performance on neuropsychological tests of episodic memory is poor, and non-amnestic MCI (na-MCI) in case of poor performance on neuropsychological tests covering cognitive domains apart from memory, such as executive functions, language or visuospatial skills. Depending on it's confinement to a single or multiple domains, MCI can have four possible clinical subtypes:

a-MCI–single domain, a-MCI–multiple domain, na-MCI–single domain and na-MCI–multiple domain.

Assessment of MCI/dementia

MCI/ dementia can be screened by a multitude of neuropsychological tests, some of which explore a particular domain in detail. Examples of tests assessing multiple domains include Mini-Mental State Examination (MMSE), Addenbrooke's Cognitive Examination III (ACE-III), Montreal Cognitive Assessment (MoCA), Rowland Universal Dementia Assessment Scale (RUDAS), Rapid Cognitive Screen (RCS), St. Louis University Mental State Examination(SLUMS) while the Memory Impairment Screen (MIS) focuses solely on memory. The specificity and sensitivity of some of these tests have been compared in previous studies.[2]

Depression

Depression is a mood disorder manifesting as physical as

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well as mental symptoms, the most distinguishable ones being anhedonia and a negative cognitive triad (negative view of self, negative view of current life experiences, and negative view of the future). Insomnia is also a key symptom of depression, possibly due to the associated psychological stress. Depression has an adverse effect on social functioning, with patients having difficulties in maintaining social relationships. Social dysfunction further influences the course and outcome of depression. Such dysfunction can place additional stress on relationships, to the extent of social boycott, creating a negative cycle that contributes to the recurrence of depressive episodes.[5] Depressed patients with sleep difficulties also have higher rates of suicidal behavior in comparison to depressed patients without sleep disturbances.[6]

Sleep deprivation

Sleep is generated and attuned by several neural systems located mainly in the anterior hypothalamus, reticular activating system, suprachiasmatic nucleus, and pineal gland.[7] It can be either rapid eye movement(REM) sleep (paradoxical, desynchronized) or slow-wave sleep (non-REM sleep). The latter accounts for most of the sleep during each night. NREM sleep (especially slow-wave sleep (SWS)) helps in the consolidation of declarative memories[8]; REM sleep benefits procedural and emotional aspects of memory [9] and NREM stage 2 sleep is associated with the consolidation of motor sequence memories in humans. [10]

Sleep-deprivation is a state of combined absence of sleep as well as extended wakefulness. It has profound effects on the human brain. MCI patients were seen to have significantly worse outcomes in overall sleep quality as assessed by the Pittsburgh Sleep Quality Index. [11]

MATERIAL AND METHODS

This systematic review is based on a systematic search of electronic database PubMed and provides an overview of literature defining cognitive impairment and depression, followed by their associations with sleep deprivation, entailing possible mechanisms of these inter-relationships along with the networks in the human brain which are susceptible or resilient towards the effects of insufficient sleep. A total of 47 such articles and studies considering all these aspects were reviewed.

Search strategy included the different combinations of headings and terms "cognitive impairment", "attention and sleep deprivation", "memory and sleep deprivation", "depression in sleep deprivation" and "depression and social functioning". All searched articles were full text articles only.

Study Selection: Studies that fulfilled defined inclusion and exclusion criteria were included in the systematic review.

Inclusion criteria

1. Articles defining cognitive domains, depression and sleep deprivation.
2. Studies presenting changes in attention, working memory, memory processing and consolidation, executive functions in sleep deprived individuals.
3. Studies presenting specific data on depression in sleep deprived individuals, due to shift work, organic neurological disorders or insomnia secondary to stress.
4. Full text articles with English language only.

Exclusion criteria

1. Limited access articles.
2. Articles published as editorials, letters.

Data extraction: From most studies, author name, subject selection criteria and the results of the tasks or scaling systems were extracted. The data from comparable studies was also compared in a tabular manner.

RESULTS

Attention in sleep deprivation

A remarkable feature of both acute sleep deprivation (SD) and chronic partial sleep restriction was seen to be a dose-dependent attention deficit, directly proportional to the duration of SD and attributable to the increasing sleep pressure over time.[12] The result is unstable task performance, with the impairments being known as 'lapses' or 'microsleeps'.[13] However, the inter-individual variability of these impairments remains high.

There is radiological evidence of reductions in functional MRI (fMRI) signals in the dorsolateral prefrontal cortex (DLPFC) and intraparietal sulcus while performing attentional tasks after SD. The diminished activity has also been seen in the extrastriate visual cortex during visuospatial attention tasks.[14] Two separate meta-analyses of SD effects on cognition have found that most of the effects of SD are obtained on relatively simple attentional tasks that require vigilance, with substantial effects on more complex tests of attention and working memory (WM).[15,16]

The domains of attention, working memory(WM) and executive function are interrelated. The psychomotor vigilance test (PVT) examines lapses of sustained attention, while in choice reaction time (RT) tasks, subject focuses attention on a stimulus and extracts information quickly in order to choose one response over another, e,g, while choosing between two numerical values.[17] Choice RT measures referred to as tests of *complex attention or decision making* involved asking subjects to decide quickly whether one of the two given stimuli match on some dimension, for example whether two figures are visually identical. [18]

Working memory in sleep deprivation

These are problems in higher-order cognition and are thought to be due to a general decline in the speed of processing. Lim and Dinges [15] found in their meta-analysis that SD effects on the digit symbol substitution task tend to be small. This is indicative of a sparing of complex tasks remaining unaffected even in SD.

Many studies have investigated SD effects on WM using memory-scanning tasks, short-term recall tasks and the N-back task.[19,20] Example of a classic WM task is the Sternberg task, [21]wherein the subject is given a memory set with digits

Test	Executive functions	Non-executive components
Wisconsin Card Sorting Test	Set shifting, inhibition	Encoding, attention, vigilance, visual-spatial processing
Verbal Fluency	Cognitive flexibility, inhibition	Encoding, attention, semantic memory
Stroop test	Inhibition	Encoding, attention, word processing speed
Tower of London	Planning, inhibition	Encoding, attention, short-term memory; visual-spatial processing
Iowa Gambling Task	Emotional decision making	Encoding, attention, reversal learning, memory

Table-1: Some neuropsychological tests of executive function

Authors	Aim	Sample	Instruments	Results
Rusch et al.[35]	Determine the relationship between increased sleep quality and improvement of depressive symptoms	44 Individuals with insomnia	Health-Related Quality of Life (HRQOL) Pittsburgh Sleep Quality Index (PSQI) Blood Analysis	The promotion of sleep quality is an effective way to improve depression and quality of life.
Vallières A, et al[36]	To determine the impact of insomnia on the perceived physical and psychological health of adults working on night and rotating shift schedules compared to day workers.	A total of 418 adults, including 51 night workers, 158 rotating shift workers, and 209 day workers	Beck Depression Inventory (BDI-II). This measure is widely used to assess symptoms of depression	Individuals with insomnia symptoms had significantly more stress, and more depressive symptoms than did good sleepers.
Shimizu et al.[37]	Determine how BDNF levels are related to treated and untreated depressive conditions and how these levels differ between individuals with MDD and controls.	Patients were assessed using the Hamilton Scale for depression (HAMD). BDNF levels were assessed through the ELISA method.	Hamilton Depression Rating Scale (HAMD)	Low levels of BDNF were found in untreated depressive patients when compared to the treatment group and the control group.
Giese et al.[38]	Investigate whether the level of stress influences the association of sleep and BDNF levels.	7 Individuals without insomnia and with restless leg syndrome(RLS)/ periodic limb movement(PLM) 24 controls; 11 Individuals with subclinical insomnia and with RLS/ PLM 8 Individuals with insomnia and with RLS.	Insomnia Severity Index (ISI) Perceived Stress Scale (PSS)	Sleep is a mediator in the relationship stress and BDNF. Sleep disturbance may explain how some people cope well with stress and other people get sick.

Table-2: Studies assessing the relationship between sleep quality in depression, the impact of insomnia on depression in shift workers, BDNF levels in depression and between stress and BDNF levels

or letters as stimuli, with memory set sizes typically between two to six. The memory set is then removed from view and a probe stimulus is presented, after which the subject needs to decide as quickly as possible whether the probe item belongs to the memory set. RTs on the task were seen to be a linear increasing function of the size of the memory set, and the slope of RT functions versus set size denoted the efficiency of scanning WM. The conclusion was that WM is substantially impaired by SD. However, Tucker et al.[22] decomposed the function relating RT to set size into memory scanning (slope) and non-WM (intercept) components and ascertained that working memory scanning efficiency and resistance to proactive interference were not significantly affected by SD; however they maintained that SD does produce an overall increase in reaction times regardless of set size or probe recency.

Hippocampal memory processing in sleep deprivation and consolidation

In rodents, SD substantially decreases the ability to induce hippocampal long-term potentiation (LTP; an electrophysiological measure of neuroplasticity). In case it is induced, the enhancement is seen to decay more rapidly. [23] Supplementary to these findings in animal studies, it was established in humans that one night of SD impairs learning and encoding-related activity within the medial temporal lobe,[24] specifically the hippocampus.[25]

Moreover, selective deprivation of non-rapid eye movement (NREM) slow-wave sleep using auditory stimulation, which preserves total sleep time, also lowers encoding-related activity in the hippocampus and associated learning. [26]In humans, on one hand, SD has been seen to attenuate sleep benefits on declarative memory consolidation [27] and on the

other, increase the formation of false memory. [28]

Executive functions in sleep deprivation

These encompass higher cognitive processes that coordinate more basic aspects of cognition, enabling purposeful, goal-directed behavior. Goal maintenance, set-shifting, mental flexibility and inhibition are examples of cognitive abilities that are considered executive functions.[29] In almost all related studies, [30,31].researchers have chosen subjects with damage to the PFC. A variety of neuropsychological tests of executive function are used in SD research. [Table 1]

Results from SD studies of executive function are quite mixed, with reports of substantial detrimental effects of SD[32,33] as well as reports of no effect of SD. [30,34]

Depression in sleep deprivation

As discussed before, there seems to be a link between depression and SD, with each influencing the other. Sleep deprivation can be broadly categorized into three categories: as part of the shift worker disorder(SWD), secondary to organic neurological diseases or as a result of insomnia in diseases like depression. Some of the studies reviewed are summarized below. [Table 2]

DISCUSSION

Working memory (WM) is closely intertwined with executive control functions of cognition since the information that is actively maintained in WM largely determines the next set of cognitive actions that are executed. [39]

The hippocampus operates in a broad network of anatomically and functionally connected cortical regions during memory encoding, such as the DLPFC and posterior parietal regions, which are also required for directed attention.[40] Inadequate sleep reduces hippocampal synthesis of proteins associated with neuroplasticity and impairs hippocampal neurogenesis[41] and alongwith extracellular accumulation of high levels of adenosine during extended wake also affects plasticity, by disrupting intracellular cAMP signaling in rodents and decreasing hippocampal AMPA and NMDA receptor signaling; all of which are necessary for stable LTP.[42] Since adenosine is cleared from the brain during sleep, these effects on plasticity may be the consequence of abnormally extended wake or a loss of sleep.

In case of depression, one possible mechanism could be changes in the hypothalamus-pituitary-adrenal(HPA) axis due to stress. This is a regular biological finding in more severe depression with melancholic features, leading to excess cortisol release.[43] Stress naturally leads to insomnia, which may further influence the course of depression, as discussed before. Another plausible mechanism is Brain-derived neurotrophic factor(BDNF) mediated. It has also been found to have a link with both insomnia and depression. BDNF is a human brain neurotrophin, essaying a role in neuroplasticity by influencing axonal and dendritic growth and remodeling, neuronal differentiation, synaptic growth and transmission, neurotransmitters' modulation and long-term potentiation.[44,45] It also promotes the development and stability of neuronal connections, with the hippocampus being an important site for its action.[46] It also assists in development and survival of GABAergic neurons, and action of cholinergic and serotonergic antidepressants.[47]

Correlating these and similar such findings, it may be concluded that the increased chances of depression in sleep-deprived individuals may partly be due to their reduced BDNF levels.

CONCLUSION

Sleep is definitely very crucial for proper cognitive functioning, which is in turn essential for a good quality of life. It's deprivation interrupts physiological functions, disturbs circadian rhythms, neurocognitive processes, and contributes to the worsening of depression. Therefore adequate sleep, for upto six to eight hours each night is recommended on the lines of this systematic review.

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