REVIEW ARTICLE

Sleep Deprivation and its Consequences

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Sleep deprivation is not a sleep disorder *per se,* but a by-product of several sleep disorders and is implicated in major health issues. Sleep deprivation is a commonplace occurrence of the modern culture. This condition of not having adequate sleep may be either acute or chronic. Sleep deprivation can occur secondary to various sleep or medical disorders, but the major cause in current times seems to be a result of behavioural lifestyle modifications. This self-imposed restriction of sleep may be either due to increased work pressure or social obligations. Few Indian studies have highlighted these issues and have demonstrated the increasing prevalence of sleep deprivation in adolescents as well.

Sleep is needed to regenerate certain parts of the body, especially the brain, so that it may continue to function optimally. After periods of extended wakefulness or reduced sleep, neurons may begin to malfunction, visibly affecting a person's behaviour, adversely affecting the cardiovascular, metabolic and immune status of the body, thus reducing longevity. The effects vary with the duration over which the sleep debt develops. The term *sleep debt* is usually synonymous with chronic sleep deprivation, as it refers to the increased pressure for sleep due to inadequate amount of normal physiological sleep. In this article, we will address the effects of sleep on the human body during acute and chronic sleep deprivation.

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Acute Sleep Deprivation

Experimental studies of the effects of acute sleep deprivation (ASD) date back to animal studies in 1894[1] and human studies in 1896 [2]. Although the results in animal studies have revealed an increased metabolic rate, weight loss with increased appetite, impaired thermoregulation and ultimately death, human studies were associated with changes in physiological and behavioural functions. Furthermore, human studies have reiterated the effects of sleep deficit on performance in mental tasks [3].

Physiological effects of ASD

1. **Neurological**: Subjective measures of sleepiness, fatigue and mood changes are the most consistent and common features seen with sleep deprivation. Other minor neurological changes like mild nystagmus, hand tremors, intermittent slurring of speech and ptosis have been observed with extended sleep deprivation over >205 hours. Longer periods of sleep deprivation have also been associated with sluggish corneal reflexes, hyperactive gag reflex, hyperactive deep tendon reflexes and increased sensitivity to pain. However, all the above changes are seen to revert completely after recovery sleep.

A. **Psychomotor Vigilance**: Most experimental studies have laid emphasis on the effects of sleep deprivation on psychomotor performance. Whatever the task used in assessment of these patients requires attention and working memory. In a sleep-deprived state, individuals have difficulty in sustaining attention and there are intermittent lapses in attention [4], which are probably due to episodes of 'microsleeps' that intrude the conscious state. Besides the lapses in attention, there is a generalised slowing of the cognitive processing, which reflects in the speed of

conducting tasks.

The results of various studies using visual, auditory, cognitive, psychomotor vigilance tasks, etc. have shown varied results. The results of an individual's performance on a particular task depend on the duration of sleep deprivation (worse results with longer sleep-deprived periods), duration of the test and whether the tests are self-paced or externally paced (patients did better on self-paced tasks than on externally faster paced tasks), complexity of the task (eg, performance was poorer in tasks of mental calculation rather than in a simple motor task [5]) and past experience with learned skills. Incentives to the subjects as in immediate intimation of results on a particular test possibly served as an encouragement making the subjects fair better.

B. Memory: On memory testing, deficits in short-term memory have been observed with sleep deprivation. These are probably due to additional difficulty in encoding, as the deficits persisted when subjects were asked to write down the words to be recalled [6].

C. Executive Functioning: ASD has also been observed to affect judgement and decision making, which could result in increased incidence of motor vehicle and work-related accidents in the sleep deprived. An experiment of simulated driving in individuals deprived of sleep for a night, observed impairment in lane-keeping ability, which was equivalent to the deficit observed at a blood alcohol content of 0.07% [7].

D. Electroencephalography: EEG changes have been observed with sleep deprivation with a reduction in alpha activity. A study observed that following 24 hours of sleep loss, subjects could not sustain an alpha activity for >10 seconds. This decline increased linearly with further sleep deprivation [8]. In epileptic patients, sleep deprivation acts as an activation method for epileptiform activity and a sleep-deprived EEG protocol is often used in most neurophysiology laboratories.

E. Functional Imaging: Positron emission tomography (PET) in sleep-deprived individuals shows global depression being more marked in the prefrontal, parietal areas and in the thalamus [9]. Tests requiring greater attention and concentration were associated with increased activity in the prefrontal and parietal areas as long as subjects showed good performance in the task. A decline in performance in sleep-deprived subjects was associated with decreased activity in the parietal area [10].

2. **Autonomic:** Although animal studies were suggestive of prominent changes in appetite, metabolism and thermoregulation with sleep deprivation [11], human studies besides mild reduction in body temperature (0.3-0.4 ^{o}C) and minor reduction in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) with sleep deprivation, have not consistently shown changes in heart rate, blood pressure and body metabolism.
3. **Biochemical:** Thyroid hormone levels seem to increase with greater duration of wakefulness after sleep deprivation. Circadian rhythm-dependent hormones like noradrenaline, prolactin, ghrelin and growth hormones lose their periodic pattern of secretion during periods of sleep deprivation [12]. Rebound increase in the growth hormone and the adrenocorticotrophic hormone has been observed during recovery sleep. No significant changes were observed in other hormones (adrenal and sex hormones) and other parameters, such as plasma glucose, creatinine and haematocrit.
4. **Immune system**: Animal and human studies have shown conflicting results wherein some observed an increased susceptibility to infections, whereas others showed no increase in susceptibility. The effects may be greater with chronic partial sleep deprivation than in acute sleep loss.
5. **Pain sensitivity**: Increased pain sensitivity occurs with sleep deprivation. Although initially observed in total sleep deprivation, it was also observed in studies targeting sleep stage deprivation by fragmenting sleep. Lack of rapid eye movement (REM) sleep has also been found to be associated with reduced tolerance to pain.

Factors affecting response to ASD

Multiple factors has been shown to affect the response to ASD in various studies. Among them, the duration of sleep prior to the period of sleep deprivation, the duration of the sleep-deprived period and the distribution of the sleep-deprived period with relation to the individual's circadian rhythm can have a bearing on the results and tolerance to sleep deprivation in an individual. Other individual characteristics, which can alter the performance during sleep-deprived periods, include age, individual sensitivity and personality of the subject.

Younger individuals show a greater decline in performance compared with baseline, secondary to sleep deprivation as compared with older adults with similar periods of sleep deprivation. The personality of an individual can influence results on various tasks in a sleep-deprived state with motivated individuals performing better than unmotivated ones under similar conditions.

Manoeuvres that may induce arousal can influence performance in sleep-deprived periods. Among these, activity, posture, noise, bright light, ambient temperature, rewards and motivation, drugs (nicotine, caffeine, modafinil), repeated attempts at sleep restriction can all temporarily improve performance. As the sleep-deprived period increases, the duration of the effect of arousal mechanisms reduces.

Subject performance in tests during sleep-deprived periods also depends on test characteristics. These variables have been discussed earlier under psychomotor vigilance.

Chronic Sleep Deprivation

Chronic sleep deprivation may be a result of intrinsic sleep disorders, comorbid chronic medical illnesses, occupational stressors, shift work syndrome and lifestyle mannerisms.

The burden of chronic partial sleep deprivation is immense. In polls of 1000 American adults conducted by the National Sleep Foundation [13], 15% (aged 18-84 years) reported sleeping <6 hours on weekdays, and 10% reported sleeping <6 hours on weekends over the past year. Approximately 20% of more than 1.1 million Americans indicated that they slept ≤6.5 hours each night.

Neurocognitive and physiological effects are cumulative, proportional to deficit of sleep and are not well recognised by the subject as clinical manifestations are variable.

Sleep propensity: Chronic restriction of nocturnal sleep increases daytime sleep propensity. This was demonstrated using the Multiple Sleep Latency Test in studies spanning 7 days. This correlation was also consistent with objective self-reports of chronic sleep deprivation.

Sleep architecture: During chronic periods of sleep restriction, a consistent conservation of slow-wave sleep (SWS) is noted at the expense of other non-REM and REM sleep stages. Dement et al demonstrated that a reduction in total sleep time over several nights resulted in an increased percentage of SWS during recovery sleep. Bennington and Heller suggested that REM sleep propensity accumulates during NREM sleep, and described a linear correlation between the amounts of NREM sleep and the amount of REM sleep. In addition, the amount of REM sleep also appears to be a function of previous REM deprivation.

Effects of Sleep Deprivation in Humans

Most physiological studies are animal model based and translate well to humans.

Cardiovascular Health: A prospective study showed that cardiovascular factors resulted in mortality. Meta-analysis of sleep duration and all-cause mortality by Capuccio et al [14], demonstrated that short and long sleep were associated with greater risk of mortality. Ikehara et al [15] demonstrated a U-shaped relation to duration. Both short and long sleep duration were associated with increased cardiovascular and all-cause mortality risk. Total sleep duration above or below the median of 7 to less than 8 hours per night is associated with an increased prevalence of hypertension, particularly at the extreme of <6 hours per night. Sleep deprivation alters the activity of the hypothalamic–pituitary adrenal axis, with short-term partial sleep deprivation resulting in elevated cortisol levels, which may increase blood pressure.

Cardiovascular risk factors are exacerbated by sleep deprivation such as increased BP, sympathetic drive, CRP levels and pro-inflammatory cytokines. Increased CRP levels have been found in patients with obstructive sleep apnoea, who commonly experience reduced sleep time as well as hypoxia. Increases in CRP levels were reported after both total sleep deprivation and sleep restriction (4 hours in bed for sleep per night) in healthy subjects [16]. Increased leukocyte and neutrophil counts have been shown to be an independent risk factor for cardiovascular mortality. Leukocytes are involved in atherogenesis and in plaque destabilisation through proteolytic and oxidative actions. Neutrophils are known to release proteolytic proteases inducing a desquamation of endothelium, as well as chemotactic agents such as leukotrienes B4 in patients with stable angina and large amounts of inflammatory mediators. Neutrophils also produce superoxide anions in hyperlipidaemic patients. Total sleep deprivation induces increased levels in granulocytes and neutrophil counts after either total sleep deprivation or severe sleep restriction [17].

Sleep Deprivation and Immunity

Sleep loss also alters immune responses. Although the magnitude of changes found in short-term studies was modest, they provide a potential mechanism, whereby long-term sleep restriction may affect health. Sleep deprivation leads to increased CRP, autonomic and inflammatory factors IL-1,6,17 [18,19]. Reduced natural killer cell activity, changes in circulating levels of leukocytes and cytokines (eg, increased TNF, IL-6).

Effect on Vaccination

Antibody titres were decreased by >50% after 10 days in subjects who were vaccinated for influenza immediately after 6 nights of sleep restricted to 4 hours per night, compared with those who were vaccinated after habitual sleep duration. But by 3-4 weeks after the vaccination, there was no difference in antibody levels between the two subject groups. Therefore, sleep loss appeared to alter the acute immune response to vaccination.

Sleep Deprivation and Endocrine

Elevation in evening cortisol, increased sympathetic activation, decreased thyrotropin activity and decreased glucose tolerance have been observed in the restricted as opposed to the extended sleep condition [20]. Changes in the timing of the growth hormone secretory profile associated with sleep restriction to 4 hours per night for 6 nights, with a bimodal secretory pattern evolving, have also been reported [21,22].

Correlation with Diabetes

A U-shaped relationship has been demonstrated between self-reported sleep duration and the risk of type 2 diabetes mellitus with the lowest risk between 7 and 8 hours of sleep. Marked reduction in glucose tolerance was assessed using an intravenous glucose tolerance test along with a blunted acute insulin response after 6 days of sleep restriction to 4 hours per night as compared with 6 subsequent days of 9-hour recovery sleep. In addition to impaired â-cell insulin secretory function, insulin sensitivity was found to be distinctly reduced after 24 h of total sleep deprivation, suggesting that insulin resistance critically contributes to the deterioration of glucose metabolism by sleep loss.

Short durations of SWS, as seen with ageing and obesity, could contribute to the higher risk of type 2 diabetes in these populations.

Sleep Deprivation and Obesity

A U-shaped curvilinear association between sleep duration and BMI was observed, with persons sleeping <8 hours having increased BMI proportional to decreased sleep. Reduced sleep has been associated with obesity in children and adolescents, as well as in the elderly. Endocrine changes could be associated with a higher diurnal food intake and preference for energy-dense foods and reduced adipose weight loss during dieting. Reduced total sleep time and reduced REM sleep periods are associated with elevation in leptin and visfatin. These adipokines have been associated with inflammation and insulin resistance.

The sleep-curtailment condition resulted in decreased leptin levels, increased ghrelin levels and markedly elevated hunger and appetite [23]. Subjects were found to particularly crave sweets, starch and salty snacks after being deprived of sleep. Sleep loss has also been linked to decreased glucose tolerance, a risk factor for obesity. Depriving normal subjects of sleep has been shown to result in insulin responses to hyperglycaemia characteristic of insulin resistance and a pre-diabetic metabolic state.

All these changes could result in a positive energy balance, leading to weight gain and a higher obesity risk in the long term.

Sleep Deprivation and Gastrointestinal System

With prolonged sleep loss, there are elevations in monocytes and natural killer cells, which form the source for secretion of inflammatory cytokines. Thus, disturbed sleep and chronic inflammation in IBD could form a self-perpetuating feedback loop with the chronic inflammation of IBD worsening sleep, and decreased sleep exacerbating the production of inflammatory cytokines and the inflammatory milieu was also demonstrated, suggesting that both factors play a role [24,25]. It has been shown that shift work is associated with increased secretion of gastrin and pepsinogen, and it has been speculated that such increases may mediate the elevated risk for both gastric and duodenal ulcers in shift workers.

The Brain and Behaviour

Effects of chronic partial sleep deprivation are variable depending on the manner in which sleep loss accumulates. Slower accumulation over a period of 2-4 days resulted in smaller magnitude of changes neurobehaviourally than total sleep deprivation. This is consistent with a compensatory adaptive mechanism. In addition, neurobehavioral outcomes demonstrate varying responses to chronic sleep restriction, with cognitive functions showing the least adaptation, subjective sleepiness measures showing more adaptation, and waking EEG measures showing little or no response [26].

Effects of sleep debt are also dependent on the additional wakefulness that results thereof; this neurological parameter also accumulates over time. The effects of nocturnal and daytime sleep restriction also vary, thus reflecting a combined influence of homeostatic and circadian drives. Proposed theories suggest that altered daytime functioning involves extracellular adenosine in the basal forebrain.

The neurobehavioral effects of sleep deprivation are congruent with the de-arousal theories in that if performance is affected, it is generally a gradual decremental effect that can be counteracted by arousing stimulation such as noise, motivation or incentives.

Sleep and Learning

Implementation of a new skill on performance does not improve until an extended period of sleep ensures that the brain is able to complete the full sleep cycle, including REM sleep. REM sleep deprivation after learning trials blocks the expected improvement in performance on subsequent retesting[27]. Sleep deprivation has been reported to impair performance on cognitive tasks, including verbal learning tasks, which are dependent on pre-frontal cortex involvement.

Sleep Deprivation and Psychomotor Vigilance Testing

When the implications of these findings are examined as a whole, they indicate that sleep-deprived individuals are slower to attend to relevant environmental stimuli, exhibit less response to the stimuli, lose interest in stimuli more rapidly, as well as are slower and more variable in their processing of stimuli.

Sleep Deprivation and Emotional Coding

Sleep deprivation selectively impairs the accurate judgement of human facial emotions, especially threat- and reward-relevant subtypes. This was more significant in women. This suggests that sleep loss impairs discrete affective neural systems, disrupting the identification of salient social cues.

Sleep Deprivation and Mood Disorders

Major depression has consistently been linked to sleep abnormalities, and insomnia is a robust risk factor in the initiation and development of depression. Recent neurobiological findings indicate the crucial role of sleep in the affective modulation of brain functioning. Studies have demonstrated that sleep in major depression is characterised by a reduction in SWS, interruptions in sleep continuity, longer periods of REM sleep including a shortening of REM latency (ie, the time between sleep onset and the occurrence of the first REM period), as well as an increase in REM density.

Chronic sleep restriction causes a gradual and persistent desensitisation of the 5-HT1A receptor system. This finding provides a link between chronic sleep loss and sensitivity for disorders that are associated with altered serotonergic neurotransmission.

Sleep deprivation is a powerful antidepressant treatment that shows antidepressant responses within hours in 40-60% of depressed patients. In >80% of responders to sleep deprivation, a relapse into depression occurred after the recovery night. Studies demonstrated that the antidepressant effect of sleep deprivation in depression was associated with a high delta sleep ratio (percentage of time spent in slow wave activity during the first non-REM sleep cycle). From this association, they developed a hypothesis that selective SWS deprivation may produce an antidepressant response.

Sleep deprivation amplifies reactivity of brain reward networks; biasing the appraisal of positive emotional experiences sleep deprivation amplifies reactivity throughout human mesolimbic reward brain networks in response to pleasure-evoking stimuli. REM specialises in handling negative motivational and appetitive states, and thus it should not be surprising that REM deprivation has a potent if temporary anti-depressant effect.

Sleep Deprivation and Pain Threshold: Sleep continuity disturbance impairs brainstem, opioidergic descending

systems, which are implicated in central sensitisation models of hyperalgesia and chronic pain.

Recovery after Sleep Deprivation

Only sleep can help individuals recover following sleep deprivation, be it acute or chronic. The amount of sleep required for recovery is a question of debate, although studies have shown that we do not need to sleep the same amount that we deprived our bodies of. In ASD, the duration of the sleep period taken prior to the sleep-deprived period and the duration of sleep deprivation may determine the duration of recovery sleep. Studies have shown that a good period of sleep prior to an expected sleep-deprived period may improve performance and tolerance to sleep deprivation [28]. In chronic sleep deprivation also, there is no 1:1 correlation about the duration of recovery sleep needed to correct sleep debt. The period is much shorter than the sleep debt as it is observed that the body tends to adapt to chronic sustained sleep restriction [29].

EEG studies of recovery sleep following total sleep deprivation are suggestive of increased total sleep time on the recovery night if the individual is allowed unrestricted sleep. The EEG shows increased duration of SWS in young, middle-aged and older individuals, but this increase in the amount of SWS was more pronounced in young subjects. Elderly individuals normally have reduced amounts of SWS in their baseline pre-sleep-deprived EEG and hence it is observed that there may be an increase in stage 2 and REM sleep in these individuals [30,31]during the recovery night. REM onset latencies were observed to be shorter in recovery sleep when compared with baseline values in elderly patients and some of these patients were even noted to have sleep onset REM on the recovery night.

Effects depending on stage-specific deprivation

Selective SWS or REM sleep deprivation in experimental studies showed no significant difference in performance levels [32]. Moreover, studies in which REM or SWS was selectively restricted on two recovery nights which followed 2 days and nights of total sleep deprivation, subjects did not show a better recovery in either of the two groups. The rate of recovery correlated better with the number of hours of recovery sleep rather than stage-specific restriction.

EEG studies in patients deprived of a particular sleep stage show increases in the amount of that particular stage during recovery. This is often seen in patients with obstructive sleep apnoea following adequate CPAP titration. A significant increase in REM sleep duration is seen after adequate titration as compared with baseline values.

Mechanisms to cope with sleep deprivation

A. Acute

1. Anticipatory naps: This is extending the night sleep prior to an expected period of sleep deprivation.
2. Intermittent daytime naps during short periods of severe sleep restriction.
3. Drugs: Stimulants like amphetamine, caffeine, methylphenidate, modafinil, armodafinil, nicotine and cocaine have been tested in various studies. Commonly used are: caffeine (200-600 mg), a good stimulant but the effect tends to reduce on the second sleep-deprived day when the pressure to sleep increases. Modafinil (100-400mg) has longer-lasting effects, which persist even with longer periods of sleep deprivation. It may be used if caffeine is ineffective [33].
4. Bright light and intermittent activity can help increase arousal.

B. Chronic

Chronic partial sleep deprivation needs good sleep hygiene with a gradual attempt to increase the nocturnal sleep to the amount required by a particular individual. This amount of nocturnal sleep needs to be individualised as it depends on the amount of sleep required to make an individual awaken rested, which differs widely in long and short sleepers.

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