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CONSEQUENCES OF SLEEP DEPRIVATION

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Abstract
This paper presents the history of research and the results of recent studies on the effects of sleep deprivation in animals and humans. Humans can bear several days of continuous sleeplessness, experiencing deterioration in wellbeing and effectiveness; however, also a shorter reduction in the sleep time may lead to deteriorated functioning. Sleeplessness accounts for impaired perception, difficulties in keeping concentration, vision disturbances, slower reactions, as well as the appearance of microepisodes of sleep during wakefulness which lead to lower capabilities and efficiency of task performance and to increased number of errors. Sleep deprivation results in poor memorizing, schematic thinking, which yields wrong decisions, and emotional disturbances such as deteriorated interpersonal responses and increased aggressiveness. The symptoms are accompanied by brain tissue hypometabolism, particularly in the thalamus, prefrontal, frontal and occipital cortex and motor speech centres. Sleep deficiency intensifies muscle tonus and coexisting tremor, speech performance becomes monotonous and unclear, and sensitivity to pain is higher. Sleeplessness also relates to the changes in the immune response and the pattern of hormonal secretion, of the growth hormone in particular. The risk of obesity, diabetes and cardiovascular disease increases. The impairment of performance which is caused by 20–25 hours of sleeplessness is comparable to that after ethanol intoxication at the level of 0.10% blood alcohol concentration. The consequences of chronic sleep reduction or a shallow sleep repeated for several days tend to accumulate and resemble the effects of acute sleep deprivation lasting several dozen hours. At work, such effects hinder proper performance of many essential tasks and in extreme situations (machine operation or vehicle driving), sleep loss may be hazardous to the worker and his/her environment.

Key words:
Sleep deprivation, Slow-wave sleep, REM sleep, Sleeplessness, Deterioration of effectiveness, Impairment of performance

INTRODUCTION

Sleep deprivation consists either in a complete lack of sleep during a certain period of time or a shorter-than-optimal sleep time. The most common causes of sleep deprivation are those related to contemporary lifestyle and work-related factors; thus the condition affects a considerable number of people. A chronic reduction in the sleep time or the fragmentation of sleep, leading to the disruption of the sleep cycle [1], may have consequences comparable to those of severe acute sleep deprivation; this referring particularly to the cognitive functions, attention and operant memory [2–4]. The changes in sleep time across the circadian pattern [5], such as during shift work [6–9] or air travel (jet-lag syndrome resulting from changing time zones) [10], prove to be unfavourable as well. Many people also experience mild discomfort while adjusting to the daylight saving time. Sleep deprivation lasting as long as several days usually takes place in extreme situations or under experimental conditions. Sleep deficiency (insomnia) accompanies certain pathological states and may require treatment. Several types of sleep deprivation can be distinguished, as shown in Table 1.

Chronic sleep deprivation in humans

The first attempts at assessing the effects of long-term sleep deprivation date back to 1896. Three American volunteers were subjected to a 90-hour sleep deprivation during which one person experienced hallucinations [11], but it was not until the 1960s that organized series of trials were performed on humans [12,13], yielding sleep deprivation of one week. This type of studies makes it possible to evaluate the influence of progressive sleep loss

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Table 1. Types of sleep deprivation and the causes of insomnia [1–10]

Types of sleep reduction	Causes	Comments/examples
Commonly observed reduction in sleep time	Daily sleep time reduction below the level of optimal individual needs	Sleep time reduction is a common phenomenon resulting from contemporary lifestyle
	Single omission of night sleep (24-h wakefulness)	Being on duty at work, taking care of an ill person, partying
	Shifting sleep period in relation to the circadian pattern (shift work)	In shift work, the sleep time is not concordant with the biological rhythms and is usually shorter than that of the natural sleep. In air travel, rapidly changing the time zones results in the jet-lag syndrome
Considerable reduction in sleep time	Wakefulness prolonged to several days	Experimental conditions, extreme situations (e.g. tortures), tribal shamanic rites
	Selective deprivation (only REM or 4-NREM sleep)	Experimental conditions, with polysomnographic assessment of the sleep stages and phases
	Total sleep deprivation (extreme prolongation of wakefulness)	Only in experimental animals; the rats die after 16–21 days of sleep loss on average, other species show lesser disruption in functioning after a comparable sleep loss
Sleep reduction (insomnia) due to pathological processes	Depression, anxiety disorders	In these disorders, the shallow sleep is delayed and shortened, not providing enough rest
	Addiction (medications, alcohol)	Insomnia is one of the symptoms of physical addiction; paradoxically, continuous intake of sleep-inducing medications makes the sleep pill-dependent; alcohol suppresses the REM sleep
	Somatic, mainly painful diseases	Restless leg syndrome, sleep-related breathing disorders and certain metabolic diseases (thyroid hyperactivity)
	Primary sleep disorders: idiopathic, psychophysiological and subjective insomnia	The causes: genetic determinants intensified by old age and improper sleep hygiene; chronic stress, traumatic experience, difficult life situations; inadequate subjective assessment of the duration and quality of one's sleep

on human wellbeing and behaviour. The characteristics of consecutive nights of forced wakefulness [14] are presented in Table 2.

Generally, the clinical symptoms of sleep deprivation include longer reaction time, distractedness, disturbances in attention and concentration, forgetting known facts, difficulty in memorizing new information, and making mistakes and omissions. A higher level of stress is observed; tiredness, drowsiness and irritability increases; work effectiveness decreases and motivation usually falls down. Reasoning slows down not only during the night of sleep deprivation but also on the following day. Work effectiveness decreases, particularly at the low points of the circadian rhythm and when the subjects perform long, difficult, compulsory, monotonous, sitting activities in an unchanging environment with limited lighting, little supply of sound, and low motivation or little interest on the part of the participants [1]. The longest period of sleep deprivation achieved in a human volunteer study lasted 205 hours (8.5 days) [12,13]. During this period, alpha waves were absent in EEG recording, and during the waking state, the EEG signal resembled the 1 NREM stage. Since no method is available to keep the participants further awake, longer periods of sleep deprivation have not been yielded. A well-documented case of a long period of sleep deprivation is a 17-year-old male from California who endured 264 hours without sleep [15]. He withstood the deprivation exceptionally well, which gave rise to a premature conclusion that long deprivation is relatively harmless to human health. A subsequent world record for the sleep deprivation was reported in May 2007; this time being claimed by a 42-year-old Englishman from Cornwall [16].

Table 2. Symptoms observed during consecutive nights of sleep deprivation in humans [14]

Duration of sleep deprivation	Symptoms
Night 1.	Most people are capable of withstanding one-night sleep deprivation, although a slight discomfort may be experienced. 24-h sleeplessness does not alter behaviour; however, tremor and increased tonus, leading to impairment in precise movements, can be observed.
Night 2.	A feeling of fatigue and a stronger need for sleep is persistent, especially between 3 a.m. and 5 a.m., when the body temperature reaches its lowest value.
Night 3.	Performing tasks that require concentration and calculating may be impaired, particularly if the tasks are dull and repetitious. The volunteers become irritated and impolite in any instance of disagreement. During early-morning hours, the subjects experience an overpowering need for sleep. Remaining wakeful is possible only with the help of the observers who wake the volunteers up if necessary.
Night 4.	Prolonged microepisodes of sleep occur: the subjects discontinue their activities and stare into space; the delta waves are recorded in the EEG output signal, even if the person is awake. Sleep microepisodes impair performance of the tasks that require attention over a period of time. Subjects may also experience perception disorders, illusions, hallucinations, irritation, inaccuracy and the 'hat phenomenon' (a feeling of pressure around the head).
Night 5.	The symptoms become more intense and include disturbances in reasoning and orientation, visual and tactile hallucinations, fatigue, irritability and delusions. The subjects may exhibit distrust: suspecting that someone attempts to murder them is a characteristic syndrome at this stage. Intellectual and problem-solving abilities are considerably impaired.
Night 6.	Participants develop symptoms of depersonalization and they are no longer capable of interpreting reality. This syndrome is known as the sleep deprivation psychosis (very rarely persisting after the termination of the experiment; it usually subsides after a sufficient time of sleeping).

The trial was performed despite the fact that this category had been excluded from the Guinness Book of Records. The result did not differ much from the Californian record (2 hours more), probably constituting the upper limit of human capabilities to withstand sleep deprivation.

The duration and limit of sleep time

Sleep readiness (sleep latency, recorded every two hours from morning to evening) increases after a sleepless night and decreases after a sleep period longer than the daily norm. The tolerated minimum sleep time is approximately 6 hours, although for some individuals, maintaining such sleep time over several days may result in a lower effectiveness of work performance. However, if this sleep time regime is kept for several weeks, no deterioration in the neurobehavioral function, apart from drowsiness, can be seen, which can be regarded as an adaptation to reduced sleep. Interestingly, prolonging the sleep time by 2–3 hours over what is an individual daily norm, does not significantly enhance one's general efficiency. The need for sleep changes with age and to a certain extent depends on gender and chronotype [17]. This demand varies across individuals, as some people need only 3–5 hours of sleep, whereas others need at least 8 hours of sleep per night to maintain work effectiveness. Hence, the term 'deprivation' applies only to the cases when impaired functioning due to sleep loss can be observed. The extent to which one experiences the effects of sleep deprivation depends on individual needs. Most people declare that they need approximately 8 hours of sleep. Nonetheless, during a six-year questionnaire study involving over one million participants of both genders, the lowest mortality was recorded in a group sleeping 6.5–7.5 hours on average [18], which may be attributed to various reasons. Shortened sleep (but also the one that lasts too long) correlates with a probability of developing diabetes [19] and high blood pressure [20]. Notably, however, a higher risk of these diseases is attributed to sleep deficiency. The sleep apnoea deteriorates the quality of sleep and thus contributes to an increase in the sleep time needed. Moreover, such

conditions as depression (both in the shorter or prolonged sleep), heart diseases, poor general health, or even the beginning of lethal processes preceding death, do prolong the sleep time, and at the same time, they may constitute a cause of higher mortality. The psychological profile of the short and long sleepers is also interesting: at the opposite ends of the U-shaped curve showing the death rate variability in relation to sleep time, there are ambitious, active, energetic workaholics, for whom sleep means a waste of time, and the sorrowful, depressive introverts who seek escape from life hardships into sleep. However, a possibility that the sleep duration itself may have influence on the capacity to survive cannot be excluded [18].

Total sleep deprivation in animals

The first report on the total chronic sleep deprivation in rats dates back to 1962 [21]. The animals were kept awake for 27 days, which led to aggressive behaviour, decreased body mass gain and impairment of the startle response. The most detailed analysis of sleep deprivation was based on data deriving from well designed, several-year experiments conducted by Bergmann and Rechtschaffen [22–26]. The experiments were performed using the disk-over-water method, with a rat being placed on a disk over a layer of water, and a polysomnograph signal setting the disk into motion whenever an initiation of sleep was recorded [27]. The sleep deprivation obtained using this procedure made up 70–90% of the experiment time and led to the death of the animals within 2–3 weeks. In the course of the experiment, weight loss was observed despite an increased food intake, as well as pathological skin reactions on the tail and paws and a bad condition of the fur. Initially, body temperature was elevated, but it decreased during the period preceding death. Plasma levels of the thyroid hormones decreased significantly and heart rate increased. At the same time, no stress symptoms, such as stomach ulcers, elevated ACTH or corticosterone levels, or decreased metabolic rate, could be observed during the experiment [26,27]. Rats died within 11–32 days (16–21 days on average) from the onset of deprivation, a period comparable to that of food deprivation with lethal effects (17–19 days). However, histopathological findings did not reveal any cause of death [28–30]. The animals which survived acute deprivation (that were eventually allowed to sleep) showed a dramatic compensatory increase in the REM sleep [31]. The other symptoms subsided within 24 hours, which indicates that the sleep deprivation did not exert destructive effects either on the cells, the neurons or the vital organs. Nonetheless, a complete recovery of the pre-deprivation levels of the particular sleep stages, or of the heart rate and body temperature, lasted several days [32,33].

An interesting exception to the rule can be observed among marine mammals: despite the periodic, significant sleep restriction, they do not experience the recovery sleep that would be a typical reaction to prolonged wakefulness, as well as to 4 NREM or REM sleep deficiency, in terrestrial mammals. The seals, for example, when staying in the ocean, can function well for several weeks despite the fact that they exhibit a considerably low duration of the REM sleep. Their sleep architecture changes immediately after they come back to the land. Unihemispheric slow-wave sleep (characteristic of dolphins and whales) is replaced by alternate NREM and REM phases. The sleep time typical for terrestrial conditions is immediately restored, and no symptoms of developing the recovery sleep can be seen [34]. Similarly, no rebound sleep occurs in infant dolphins and their mothers who refrain from sleeping throughout the period from the delivery till the youngsters achieve some self-sufficiency, which can last several weeks [35]. The ability to withstand sleep deprivation is dependent on the species-related natural sleep characteristics regarding the duration and quality of sleep. For instance, large ungulate herbivores have a short, shallow and intermittent sleep, while predators usually sleep long and deeply.

The relationship between sleep deprivation and the level of stress has not been fully explained, although the latter may have a varying influence on the compensation for sleep deficits. In a study reporting on wakefulness maintained through immobilization for 0.5 to 4 hours, the recovery sleep became significantly shorter when the immobilization period reached its maximal duration [36]. Two-hour immobilization repeated on the consecutive days of the experiment produced similar effects. However,

a single 2-hour immobilization resulted in an 92% increase in paradoxical sleep within the following 10 hours, whereas a 2-hour wakefulness, maintained using standard methods (disk or gentle handling), did not significantly affect the sleep that followed [37].

Rats appear to be particularly vulnerable to sleep deprivation enforced using the moving disk method, since in other animals (pigeons), the changes observed after 24–29 days of this procedure were not as severe as in rats [38]. Other deprivation procedures were not lethal either to rats or other laboratory animals [39], although this may have been due to the significantly shorter periods of deprivation under other experimental conditions or to the difficulties in achieving total sleep deprivation.

Post-deprivation recovery: rebound sleep

Rebound sleep takes place after the sleep deprivation and is longer than the usual sleep time. It is composed of longer periods of the delta-wave sleep and REM sleep, while stage 2 NREM is shortened and stage 1 NREM may be absent [31,40,41]. The duration of the rebound sleep does not correspond to the total duration of sleep loss; the sleep lasting several hours more than usual may provide sufficient recovery even within the first 24 hours post-deprivation. In rats, REM deficiencies after 24 hours of sleep deprivation are compensated mainly during the initial period of recovery, mostly within the light sleep phase, whereas the compensation for NREM deficiency proceeds at a slower pace. The post-deprivation changes in the sleep may be present for several days [32], gradually losing their intensity.

Selective REM sleep deprivation (waking up at the beginning of REM episodes) makes the entry into REM more frequent: the longer the paradoxical sleep (PS) deprivation, the higher the number of interventions necessary to prevent this sleep phase. This finding indicates a progressive increase in PS propensity [42,43]. At the same time, selective REM sleep deprivation leads to the deterioration of cognitive functions. Annoyance, anxiety and difficulty in focusing attention result [44], while drowsiness during daytime does not increase [45]. Other symptoms include increased heart rate [33]. Apart from that, hypersexuality has also been observed in rats [46,47]. During the rebound sleep, the proportion of REM sleep increases (above 50%), mainly due to an increased number of REM episodes [36]. The compensatory period may last several days and is proportional to the period of deprivation. Selective 4 NREM stage deprivation also leads to an increase in the percentage rate of this stage during the post-deprivation period. However, it is difficult to enforce a complete deprivation of the deep sleep since the number of delta waves tends to increase during the remaining sleep stages. Sleep disruption results in a greater need for PS sleep. The polysomnographic recording of PS shows slow-wave episodes (lasting several dozen seconds) with atony and hippocampal theta rhythm [48]. The subjects show a depressive effect reflected by decreased reactivity.

THE CONSEQUENCES OF SLEEP LOSS OR SLEEP RESTRICTION

Tonus, posture maintenance and physical exercise capacity

An increase in muscle tonus compensates for the decreased attention during sleep deprivation and makes it possible to maintain the initial level of the test results [49]. Evidence for this finding comes from the observations concerning tired individuals who, when tested at late hours, showed an increased facial muscle tonus [50]. Higher muscle tonus is accompanied by tremor whose amplitude usually increases under conditions of fatigue [51,52]. Twenty-four hours of sleep deprivation led to the disturbances in postural control which intensified with the duration of sleeplessness [53]. A possible explanation may be the changes in the sensory integration that may be concurrent with the visual deficiencies caused by sleep deprivation [54]. During the sleep deprivation, stimulating the muscles involved in postural control with a 205-second vibration stimulus resulted in a false perception of movement and deterioration in maintaining body balance. Interestingly, the most significant balance disorders occurred after 100–150 seconds of stimulation, which is a period sufficient to develop adaptation to such uncommon proprioceptive stimuli. The disruption was augmented after closing the eyes [55]. Assuming a standing posture instead of the sitting one

during the experiment reduced the number of errors in the tests [56]. This effect, however, could not be seen before the 20th hour of sleep deprivation.

While a 24-hour wakefulness did not alter the maximal oxygen intake, the sleep deprivation lasting 36 hours resulted in a decreased oxygen intake. Furthermore, sleep deprivation leads to decreased amplitude of the anaerobic power parameters across the circadian cycle. This finding could explain why moderate sleep loss is relatively well endured by sportsmen who practice running or the sports involving a brief use of a great force. In contrast, in the sports that require precise movements, attention, concentration and frequent decision making (shooting, sailing, cycling, team sports), prolonged wakefulness results in an increased number of errors [58].

Exteroceptive impairments

Sleep loss results in inaccurate image formation on the retina and, as a consequence, the perceived images become dim, and double vision and the disruption of visual perception may occur [59]. Visual disruption initially results in the tunnel vision [60], but may affect the centre of the visual field as well, if the period of sleep deprivation is long [61,62]. The number of visual errors and hallucinations increases with the duration of wakefulness. Interestingly, the number of auditory errors does not increase significantly even after 72 hours of sleeplessness [59]. After 24 hours of sleep deprivation, the ability to distinguish scents deteriorates. However, paradoxically, the ability is augmented when the subjective drowsiness is higher [63]. Hyperesthesia or limb numbness may occur, as well as an increased sensitivity to pain, whereas the sense of temperature remains unchanged. During the recovery period after sleep deprivation, the perception of pain is temporarily reduced [64,65].

Disruption in the effectiveness and accuracy of cognitive and operant processes

In the course of prolonged wakefulness, the concentration of attention becomes impaired [56], the thoughts are distracted and the microepisodes of sleep are longer [59]. Such effects lead to decreased accuracy and effectiveness of work performance as well as impaired cognitive processing. Work effectiveness decreases during sleep deprivation at consecutive experimental sessions, but also at a single session if the tasks are repetitious and monotonous. Well-rested individuals can obtain similar results in a number of tests in a row, whereas during sleep-deprivation, the accuracy of performance deteriorates with consecutive tasks in a particular series [59]. As reported in literature, one-night sleep deprivation contributed to a 20–32% increase in the number of errors and a 14% increase in the time required to perform an electrocoagulation trial on a surgical laparoscope simulator [66,67]. It is plausible that during a real surgical operation, the surgeon's motivation partially compensates for the effects of weariness [59]. Nonetheless, the problem of insufficient rest among the health care workers seems to have been underestimated.

As far as the speech performance is concerned, the volunteers kept awake for 36 hours showed a tendency to use word repetitions and cliches; they spoke monotonously, slowly, indistinctly, and stammed. Owing to the intonation impairments and poor word choice after prolonged wakefulness, they were not able to properly express and verbalize their thoughts and concepts [68]. Reasoning processes became schematic, which impaired the outcomes in the tasks that required flexible thinking and ability to reschedule plans [69]. Innovation in thinking, as well as proper decision making, were less apparent, while there was an increasing tendency to take up risky decisions [70]. When presented with a series of situations that included a changing element each time, the persons examined tended to choose the same solution even if it did not strictly apply to the new context.

Dermal effects

In the experiments on sleep deprivation, the characteristic alterations of the skin were reported only in rats [38,71]. Considerable idiopathic changes were localized within the tail and the hairless parts of the paws both during the total and selective deprivation of paradoxical sleep. It was postulated that these effects might be linked either to the change in the release pattern of the growth hormone (GH, a hormone promoting anabolic processes), namely,

the absence of the nocturnal maximal GH release in the sleep-deprived animals [72,73], or to a tendency for such animals to become infected with their own migrating bacterial flora [74]. These conjectures are in contradiction with the findings indicating that REM loss does not disrupt the wound healing process [75]. The impaired recovery of the damaged skin is attributed to stress reactions [76], but since no considerable stress symptoms have been reported in the sleep-deprived rats [26,27], this process cannot explain the pathological skin condition after sleep deprivation.

Metabolic alterations, hunger and obesity

In animal experiments, sleep deprivation induced an increased rate of systemic metabolism, which led to reduced body mass despite an increased food intake, even if the animals were provided with food that was rich in proteins and calories [29]. It is disputable whether the animals ate more food during the first few experimental days, since they might scatter or crumble the food pellets more during that time [77]. Nevertheless, the food intake increased by 29% when the sleep deprivation lasted longer than five days [78]. The sleep-deprived pigeons also showed weight loss accompanied by increased food intake and energy expenditure; however, to a significantly lesser extent than did the rats [38]. Considerably increased appetite and hunger were also apparent in the persons who were allowed to sleep only four hours per night [79]. This was attributed to the decreased concentration of leptin, a hormone inhibiting appetite and hunger and inducing higher energy expenditure, and a higher level of ghrelin, acting in an opposite direction to leptin [80]. In contrast to the animal findings, a relationship between reduced sleep and obesity was observed in humans [81–83]. Obesity was accompanied by lower energy expenditure and impaired glucose metabolism leading to diabetic condition [19,80]. The sleep loss-related tendency for weight gain was already apparent in the children and teenagers [84], and the BMI increase was significantly higher among younger children (3–8 years old) than the older ones (8–13 years old). Interestingly, the lower rate of body mass gain in younger children was related to the tendency to go to bed at earlier hours, while in the older ones, to wake up later in the morning.

Studies carried out on a large population of forty-year-olds of both genders [83] corroborated the existence of a U-shaped relationship between sleep duration and BMI or blood concentrations of cholesterol and triglycerides, which indicates that the risk of overweight is considerably more dependent on the reduction of sleep time. The recently published results of a six-year research [85] indicate even more clearly that both the reduced and prolonged sleep time contribute to body mass gain. Among the sleep-deprived individuals, the risk of gaining weight by 5 kg increased by 35% and the risk of obesity by 27% in comparison with the individuals having optimum sleep time. For prolonged sleep time, the risk of a 5-kg weight gain increased by 25% and the risk of obesity by 21%. Thus, both the deficiency and excess in the sleep time are related to the risk of weight gain and development of fatty tissue.

Hormonal changes

Both in the total and selective deprivation of REM sleep in rats, the plasma concentrations of the thyroid hormones, mainly thyroxine and triiodothyronine, decreased considerably [86]. This decline is surprising in view of the increased metabolic rate and body temperature in the sleep-deprived animals. In humans, however, a 24-h sleep deprivation induced an increase in T3, T4 and TSH concentrations [87]. The different duration of the sleep loss investigated in these studies makes it impossible to compare the two sets of data. Nonetheless, the analysis of diagrams illustrating the course of the experiment on rats indicates that the total sleep deprivation caused a decrease in T3 and T4 concentrations from the onset of the experiment. The deprivation of the REM sleep at first led to a slight increase and then to a significant decrease in respective concentrations. Notably, the human studies were performed mainly on depressive patients, and it is doubtful whether these can be regarded as a representative group of the whole population.

In animal experiments, after 72 hours of sleep loss, the level of the corticotropin-releasing hormone (CRH) changed

depending on the brain area: CRH increased in the striatum, limbic structures and hypophysis, while decreased in the hypothalamus [88]. During the late deprivation period at the second half of the experiment, the levels of ACTH and corticosteroids were found to increase. All the sleep-deprived rats showed elevated levels of noradrenaline, which might indicate the deprivation-related augmentation of the sympathetic system. This would partially explain the increased energy expenditure [86]. In humans, a 24-hour sleep deprivation induced a high rate of ACTH secretion between 3 a.m. and 5 a.m. on the following night, while under normal conditions, the ACTH level shows a slight linear increase [89]. 24-hour hour wakefulness resulted in a slight increase in plasma cortisol level, while plasma aldosterone concentration and renin activity decreased and their release peaks were absent [90].

The influence of 24-hour wakefulness on GH secretion is particularly interesting. The typical maximum release peak, normally present during the first sleep cycle, could not be seen, whereas the total GH release remained unchanged [72,73]. The physiological significance of the GH release peak at early nocturnal hours has not been elucidated. It also remains to be shown whether the lack of GH peak in the sleep-deprived subjects might be compensated simply by an increase in the daily release of the hormone. Such considerations are justified by the findings indicating that during the rebound sleep, the GH release peak appeared earlier and achieved a higher level than the values obtained for the controls [89].

Immune system impairment

A relationship between infectious diseases and prolonged sleep time as a symptom of healing has long been intuitively anticipated. It was presumed that cytokines, which are the mediators of the defensive immune response, might also be involved in the sleep regulation processes [91–93]. Interleukin IL-1β potentially acts both as a somnogen and pyrogen, which would explain the prolonged duration of sleep in the course of febrile diseases [94,95]. Classic research conducted by Rechtschaffen and his team does not indicate, however, any mitogen-related changes in the proliferation, number and activity of the spleen lymphocytes, after either total or selective sleep deprivation in rats [96]. However, even the authors themselves have found this outcome surprising.

The sleep-deprived animals develop infections of the lymph glands and other tissues, which are induced by their own intestinal bacterial flora [74]. This can take place only in the state of immunological suppression. In rabbits infected with *Staphylococcus aureus*, the deterioration in the quality and duration of the slow wave sleep correlated with an increased mortality rate [97,98]. Sleep deprivation resulted in lower resistance to bacterial infections (bacterial blood infections), but no fever or tissue inflammation developed [98,99]. The data deriving from the human studies are inconsistent or contradictory [100,101]. While it is evident that sleep loss exerts an influence on the immune system [102], it remains unclear whether the influence is beneficial or detrimental. IgG, IgA and IgM concentrations were found to increase after a 24-hour wakefulness [103], and so was the number of leukocytes and NK cells as well as their activity during a 64-hour sleep deprivation. The number of T helper cells and NK cytotoxicity decreased as well [100,104,105]. Other data show a 37% decrease in the number of NK cells after 48-hour wakefulness [106]. Interestingly, while plasma concentrations of interleukin IL-1β and γ-interferon changed little during a 64-hour sleep deprivation, they decreased significantly on the first day following a 10-hour rebound sleep [100].

Changes in the activity of brain structures

Sleep deprivation attenuates the functions of a number of brain structures. During 72-hour wakefulness, a 6–8% decrease on average in the brain metabolic rate was observed. However, in certain areas of the brain, this decrease could reach as much as 15%. Glucose hypometabolism was apparent mainly in the thalamus, particularly in its dorsal part, as well as in the striatum, hypothalamus, prefrontal and frontal cortex (areas 44/45 and 46), parietal, temporal, cingulate and primary visual cortex, and even in the cerebellum [59,107]. On the second and third day of sleep deprivation, a slight increase in the relative activity was found in certain areas (18 and 19 visual areas as well as 4 and 6 motor areas), although the level remained

below the baseline value. No significant interhemispheric differences were detected. However, the left-sided hypometabolism in 44/45 areas clearly indicated a disruption in the functions of the motor speech centre. This finding was confirmed by behavioural observations. Alertness and cognitive functions weakened, which was attributed to a decreased activity of the connections linking the cortex and the thalamus. However, the functional magnetic resonance revealed that the sleep-deprived participants showed activation of larger brain areas when performing certain types of cognitive tests than did the well-rested subjects. After 35 hours of sleep deprivation [108], the participants doing arithmetic tests showed a bilaterally decreased activity of the prefrontal and parietal cortex, whereas at verbal memory testing, they showed a higher activity in these areas, mainly in the right hemisphere. However, under control conditions, such tests activate mainly the temporal lobe. It is postulated that the activation of the cortex areas, which is not normally associated with a particular function, may help sustain the effectiveness of the testing during prolonged wakefulness. This would explain the paradox of a greater capacity of short-term memory in the sleep-deprived individuals. The short-term memory is associated with the functions of the parietal lobes; therefore, the augmented activation of this area seems to facilitate the memorizing and analysis of information from different parts of the brain. The rate of performance and precision of the verbal tests decreases due to a lower activity in the temporal speech area. The activation of a "substitute" area of the brain during the verbal tests, but not the arithmetic ones, is difficult to interpret at present. A possible explanation is that the function of verbal communication precedes that of the ability to calculate: the sequence of the child development stages supports this view. The increased activity of the prefrontal cortex, on the other hand, may have been connected with an augmented motivation in the course of the experiment [59,108]. After a partial sleep deprivation, the application of the target stimuli induced changes in the evoked potentials within the prefrontal cortex: the P1 component increased in EEG recorded from Brodmann's areas 9 and 10, and the N1 component increased in areas 8 and 9 of the right frontal lobe [109]. Simultaneous monitoring of the mental functions showed only a slight increase in the reaction time, and this finding supports the hypothesis that an increased activity of the frontal lobe may allow one to maintain the testing effectiveness after sleep loss. Another set of data showed that after 36 hours of sleep deprivation, the application of the target stimuli resulted in a decreased amplitude of the P3 component in the frontal and apical skull regions. Applying the novelty stimuli under the same conditions brought about a decreased activity of P3 only in the prefrontal area [110]. The relocation of the cortical functions and the activation of the prefrontal regions, which was noted after sleep deprivation, may also be connected with the ability of these areas to recover within a relatively short time during the rebound sleep. Within the first 30 minutes of the rebound sleep, the delta waves in the EEG recorded from the prefrontal area showed a significantly greater power than those recorded from other areas [111,112].

Changes in EEG signal

EEG recording is used in various experiments on sleep because it provides an objective monitoring of the brain activity. The total power of the delta and theta waves recorded from the frontal, central and occipital regions was found to significantly increase within the first 24 hours of sleep deprivation. However, assuming the standing posture allowed one to maintain the control power values even at the end of the second day of sleep deprivation. This referred mainly to the theta wave band [56,113]. While the total power in the delta and theta bands increased in proportion to the time of wakefulness, the increase in the total power of the alpha waves was not apparent before the 20th hour of staying awake [56]. These findings not only describe the electroencephalographic characteristics of sleeplessness, but they also point to the role that the changing of body posture may have in counteracting the effects of sleep loss. The frontal and prefrontal gamma rhythm (40 Hz), related to the perception of auditory stimuli, was found to be attenuated as early as after 24 hours of sleep deprivation [114]. Another study made it possible to establish a 'functional cluster' of the EEG signal recorded from particular regions [115]. The functional cluster is a group of

brain areas that under specific conditions cooperate with one another more closely than with the remaining areas. In this case, the specific condition of brain functioning is sleep deprivation.

In rested subjects, the symmetrical dominant cluster in the EEG signal included the F7, F8, C3 and C4 locations, whereas after 24 hours of wakefulness, the cluster comprised the C4, F8, F3, F4 and O1 locations, which indicates that after sleep deprivation, the F3/F4 and O1 locations are functionally associated with C4 and F8. The finding that the frontal locations within the functional cluster have changed, and the dominance of the cooperating areas has been shifted to the right hemisphere, may reflect the functional plasticity of the sleep-deprived brain.

During the recovery period after a 24-hour sleep deprivation in rats, the theta band activity (7.25–10.0 Hz) increased both during the REM sleep and active wakefulness [40]. In epileptics subjected to sleep deprivation, the excitability of the cortex increased, which indicates that the sleep deprivation in such patients may lead to an epileptic seizure [116].

Changes in mental functions

A strong relationship was found between sleep time and the intensity of manic symptoms [117]. An animal model of mania could be obtained under conditions of the sleep deprivation experiment. However, since the procedures involve stressful conditions: immobilization on a disk, isolation from other animals, falling into water and soaking the fur, the outcomes would be difficult to interpret. Nonetheless, after 72 hours of wakefulness and before the rebound sleep, rats displayed approximately a 30-min period of symptoms resembling a manic state, namely insomnia, hyperactivity, irritability, aggression, hypersexuality and behavioural stereotypes. The administration of D1 receptor antagonists alleviated the symptoms, while of D1 agonists and opioids, intensified this behavioural pattern, which points to the mesolimbic contribution to developing behavioural changes after sleep deprivation [118]. The relationship between intensified maniacal behaviour and sleep loss is bidirectional: mania episodes may occur after sleep deprivation, but mania may also induce insomnia. After a 50-hour sleep deprivation, healthy volunteers showed decreased emotional intelligence and deteriorated interpersonal relations (lower assertiveness, empathy and positive thinking) with enhanced esoteric reasoning, and they became more superstitious [119]. Fifty-five hours of sleep loss induced intense frustration and aggression, deterioration in interpersonal relations [120], as well as an increase in the subjective perception of affective symptoms of psychopathology (anxiety, depression, mania, insanity) [121]. Survey studies conducted on male teenagers revealed a correlation between sleep deficiency and elevated aggression [122]. Moreover, an improvement in the quality of sleep mitigated the emotional problems.

Therapeutic applications of sleep restriction

In healthy humans, the sleep loss hinders maintenance of their normal functions. However, the situation may be totally different for people with CNS disorders who experience sleep disruption. Depressive disorders are often accompanied by difficulties in falling asleep as well as a shallow and intermittent sleep or waking up too early in the morning. Notably, a complete elimination of such sleep disorders usually alleviates the depressive symptoms in 40–60% of cases. Aggravation of the symptoms concerns only a very low proportion of people (2–7%) [123,124]. First attempts at applying the sleep restriction therapy were reported in 1960s. At night, the patients would spend their time performing organized activities which allowed them to stay awake. Mood improvement was already apparent during early morning hours and continued throughout the day as well. Unfortunately, the subsequent sleep caused a relapse of the depressive symptoms (50–80% of relapses), although in some patients the improved mood would sometimes persist for several days or weeks. For a number of patients (10–15%), it is no sooner than on the second day after sleep deprivation that the therapeutic effects of sleep loss can be observed. Since the improvement does not last long, attempts have been made to combine sleep deprivation with pharmacological treatment or the light therapy, or shifting the sleep time [123]. Nonetheless, due to its simplicity and possibility of being repeated at

certain time intervals, as well as applicability to all age groups, the sleep deprivation therapy has been useful in different types of depressive syndromes. The side effects of sleep deprivation are relatively insignificant and include drowsiness or hypomania (REM deprivation in rats induced episodes of hypomania which is at the opposite end to depression [125]). The sleep deprivation for therapeutic purposes can be applied either as a total deprivation (throughout the night and the following day, which makes up about 40 hours of wakefulness in total) or a selective deprivation (period of sleep of no more than 3 hours during the first or second half of the night). Selective REM deprivation is considered to be even more effective, for its results are comparable to those obtained after administration of imipramine [125]. However, in order to achieve significant mood improvement, selective sleep deprivation must be applied for at least one week and also involve the use of more complicated methods [124]. Examining brain activity with the functional magnetic resonance partially explains why sleep deprivation yields different results in depressive patients. The method indicates increased activity within certain regions of the brain, such as Brodmann's area 32 in the cingulate gyrus, in depressive patients. If a patient reacts positively to the treatment with sleep deprivation, this activity decreases to the level characteristic of healthy individuals, while it does not in the patients whom sleep deprivation did not help [126].

Sleep deprivation can be applied also in the treatment of Parkinson's disease. One-night wakefulness results in an improvement lasting for about one week, which consists in decreased tremor and muscle stiffness. REM sleep restriction may play an important role in this process, as dopamine activity increases and the cholinergic activity decreases [127]. Neuroimaging confirms the existence of a relationship between the synaptic dopamine release within the anterior cingulate cortex and the antidepressive effect of sleep loss [128]. The improvement after sleep deprivation probably takes place also through an augmentation of adenosine activity which inhibits acetylocholine (REM loss increases the density of A_1 subtype of adenosine receptors) [127].

The influence of sleep deprivation

The connection between the learning or memory processes and sleep seems to be well documented [129,130], although there are also reports denying this linkage [131,132]. The stimulating effect of REM sleep on memory in humans is particularly unclear, since the antidepressants subduing REM sleep do not exhibit detrimental effects on memory, even if administered for a long time. Furthermore, there are cases of patients with brainstem injuries that resulted in permanent suppression of the REM sleep but did not disrupt their general functioning or produce memory disturbances.

Nonetheless, a number of data confirm memory impairments due to sleep deprivation, particularly if the deprivation covers a specific time window. During memory consolidation period, which can take from several minutes to days after the learning period, a transition occurs between the short-term and long-term memory. Rats exhibited impaired memorizing in behavioural tests when they were deprived of the REM sleep after the training. In a water maze experiment, either in a spatial version (involving external cues) or enclosed version, a rat learns to find an escape platform immersed in opaque water, which involves the activity of the hippocampal structures. In a maze with a visible platform, the platform is located differently at each trial and the rat learns to find it independently of the hippocampal functions, but the ability may be impaired due to striatal lesions. It has been shown that REM sleep deprivation impairs task acquisition in the spatial version of the water maze. Rats deprived of REM sleep for four hours immediately after the training exhibited a longer latency in finding the platform at the following trial in comparison with the rats deprived of sleep at other periods. Twelve-hour REM deprivation after the training at the visible version of the water maze had no influence on the training results [133,134]. A total sleep deprivation at six hours before the water maze test brought about spatial memory impairments. Although the sleepy rats were capable of learning the task as quickly as the control group, they were far less capable of retrieving the task on the following day [135]. Mice deprived of REM sleep either before or after the training session had worse results

in memory tests: pre-training REM deprivation induced earlier memory deficits, whereas post-training deprivation resulted in the deficits appearing later [136]. Humans, when awoken repeatedly during a night, obtained better results in memorizing pairs of words if the waking took place after 10 minutes of each REM episode than when it happened after 40 minutes of sleep, and disrupted the completion of the sleep cycle [137]. A vast body of literature makes it possible to draw a conclusion that it is not only the REM but also the NREM sleep with all its stages that enhance the long-term memory processes (procedural, semantic and episodic memory, and perceptual representation memory system) [138]. Recent research [139] indicates that a 42-hour total sleep deprivation impairs operational memory in humans. The alterations, varying across individuals, include a decreased memory capacity and impaired concentration.

Gender influence on the effects of sleep deprivation

The effects of sleep deprivation were either assessed mainly in male participants or the gender factor was not taken into consideration. However, it seems natural that the results of sleep deprivation must correlate with gender-specific differences; the anatomical, functional and hormonal in particular. Nonetheless, literature reports include data confirming the gender-related consequences of the sleep loss. Experiments performed on mice did not corroborate the post-sleep deprivation differences between genders [140]. In rats, however, after 4 days of REM sleep deprivation and concurrent 30% loss of NREM sleep, the males exhibited less slow-wave and more REM rebound sleep during the light period than did the females, while during the dark period, the rebound sleep occurred only among the females, was longer than for the males, and depended on the oestrus cycle [141].

In humans, after a 38-hour sleep deprivation, the EEG signal recorded in wakefulness showed different changes in men and women. In resting EEG, the signal power increased in all the frequency bands to the level below 17.5 Hz in men, whereas in women, the signal power decreased in lower alpha bands (7.5–9.5 Hz) as well as in the delta band. During the trials involving attention, the power of the theta and alpha waves as well as of beta waves in the 13–17.5 Hz range was found to increase only in the male subjects. After sleep deprivation, the reaction time among males was by 30% longer than under the control conditions, while the respective parameter among females increased only by 11%. It seems that the effects of sleep deprivation may be milder in women, allowing them to better cope with environmental demands under conditions of sleep loss. However, after a 9-hour rebound sleep, most of the frequency bands did not regain their initial values only in the group of females [142].

However, another set of data shows a reverse relationship regarding the reaction time: it takes a longer time for the women to react (by pushing a button when a red point appears), but they make fewer mistakes than men do [143]. The authors suppose that although they are instructed to respond instantly, the women do not do so until they are certain that the reaction is correct. Such explanation is confirmed by the data indicating that women are more cautious and take fewer risky decisions after sleep deprivation [144], even though the assessment of impulsiveness did not show any differences between genders.

Social aspects of sleep deprivation and fatigue

The reduction in sleep time causes disruption in performing tasks: the sleep-deprived individuals require more time than usual for performance and they make more mistakes. Survey studies revealed a significant relationship between the duration and quality of sleep among car drivers and the number of road accidents [145]. After sleep loss, the subjects taking tests on a driving simulator made more errors (driving over the road axis or too close to the roadside) and what is more, the sleepy drivers tended to increase their average driving speed [146]. It has been confirmed that weariness caused by driving for a long time may intensify the effects of drowsiness, such as prolonged reaction time, whereas weariness itself does not affect the driving capability if the driver has a sufficient sleep time [147]. In the case of motorcyclists, sleep deprivation reduces the difference between the morning and afternoon levels of individual reactivity and deteriorates the testing results from both the periods [148]. The driver's

age is a significant factor which has influence on the number of drowsiness-related accidents and determines the time of the day or night when these accidents occur. Drivers younger than 25 years of age seem to cause twice as many road accidents as the other age groups, although they do not make up the majority of drivers [149]. This is associated not only with the carelessness and overestimating one's abilities that are characteristic of young people but also with the fact that older individuals can sometimes more efficiently cope with sleep deficiency [150,151]. Young drivers cause accidents mainly at night, whereas the older ones mainly in the afternoon [149], which may be connected with the fact that many older drivers refrain from driving at night hours and that the changes in the circadian pattern of activity develop with age.

After one night of sleeplessness, the ability to simultaneously perceive stimuli both in the central and peripheral areas of the visual field is impaired and the deficit intensifies with the driving time, but is also age-dependent. While long-lasting and monotonous driving makes the visual field more narrow, intense drowsiness causes deficits within the whole field [61]. Sleep restriction increases the rate of risky behaviour, due to impaired ability to assess a situation [152], and of aggressive behaviour as well [120]. Prolonged microepisodes of sleep during driving considerably reduce the driving safety [59]. With regard to such parameters as the concentration of attention, reflexes, perceptiveness and accuracy of task performance, the effects of a 24-hour sleep deprivation, or of a 4–5-hour night sleep repeated over a period of one week, are similar to those induced by the 0.5–1‰ level of blood alcohol concentration [153–157].

In most of the European countries, the highest permissible blood level of alcohol in car drivers is 0.5‰, and the Polish law permits only the values below 0.2‰. While there are legal regulations that impose prosecution of drunk drivers, no restrictions apply to the drivers who show a comparable impairment of perceptiveness and reactivity due to sleep deprivation and who also pose a considerable hazard to other traffic participants. The only solution is to appeal to the common sense of such drivers. The most effective remedy for drowsiness is a brief nap: a 5-min nap improves the driver's condition but that of 10–15 min, which does not lead to deep sleep and the resulting sleep inertia, seems to be most beneficial in the shortage of the optimum sleep time. A 10-min nap, particularly in a semirecumbent position, improves the driving capability for 1–2 hours [158–160].

SUMMARY

The first investigations into the effects of sleep deprivation in humans led to the findings indicating relatively safe and transient consequences of sleep loss. However, a growing body of evidence points out that sleep restriction, although inducing relatively small physiological effects (changes in the immune function, increased tendency to gain weight and to develop high blood pressure with all its consequences), not only leads to weariness but also causes a significant disruption in functioning, such as the deterioration of vision and perception, weakened concentration, impaired memory, longer reaction time, increased number of errors, reduced precision of performance, occurrence of sleep microepisodes during wakefulness, schematic thinking, making inaccurate decisions, and emotional disorders. Moderate fatigue after 20–25 hours of sleeplessness impairs task performance to an extent comparable with that caused by alcohol intoxication at the level of 0.10% blood alcohol concentration. The effects of a chronic sleep loss or a shallow sleep maintained for several days tend to accumulate, leading to the disruption of cognitive functions which is comparable to that after severe acute total sleep deprivation of several dozen hours. Such effects hinder the correct performance at work, and in extreme cases (machine operation and vehicle driving), may pose hazard to the workers themselves and their environment.

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