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THE IMPACT OF SLEEP DEPRIVATION ON THE BRAIN

Tatjana Trošt Bobić[1], Ana Šečić[2], Iris Zavoreo[3], Valentina Matijević[2], Branimir Filipović[1], Željka Kolak[4], Vanja Bašić Kes[3,6], Dubravka Ciliga[1] and Dubravka Sajković[5]

[1]Faculty of Kinesiology, University of Zagreb; [2]Clinical Department of Rheumatology, Physical Medicine and Rehabilitation, [3]Clinical Department of Neurology, Sestre milosrdnice University Hospital Center, Zagreb; [4]Department of Physical Medicine and Rehabilitation, Vinkovci General Hospital, Vinkovci; [5]Clinical Unit for Rehabilitation of Traumatology Patients, Clinical Department of Rheumatology, Physical Medicine and Rehabilitation, Sestre milosrdnice University Hospital Center, Zagreb, Croatia; [6]Faculty of Medicine, University of Osijek, Croatia

SUMMARY – Each sleep phase is characterized by specific chemical, cellular and anatomic events of vital importance for normal neural functioning. Different forms of sleep deprivation may lead to a decline of cognitive functions in individuals. Studies in this field make a distinction between total sleep deprivation, chronic sleep restriction, and the situation of sleep disruption. Investigations covering the acute effects of sleep deprivation on the brain show that the discovered behavioral deficits in most cases regenerate after two nights of complete sleep. However, some studies done on mice emphasize the possible chronic effects of long-term sleep deprivation or chronic restriction on the occurrence of neurodegenerative diseases such as Alzheimer's disease and dementia. In order to better understand the acute and chronic effects of sleep loss, the mechanisms of neural adaptation in the situations of insufficient sleep need to be further investigated. Future integrative research on the impact of sleep deprivation on neural functioning measured through the macro level of cognitive functions and the micro molecular and cell level could contribute to more accurate conclusions about the basic cellular mechanisms responsible for the detected behavioral deficits occurring due to sleep deprivation.

Key words**:** *Sleep deprivation; Cognition; Brain*

Introduction

In human life, the periods of activity and rest alternate. In order to survive, human beings need to work, and in order to be able to perform everyday activities properly they need sleep. For this reason, nature has designated cyclic (circadian) alternation of waking and sleeping periods. Being too occupied with everyday life, people nowadays frequently neglect their need for sleep, which can lead to a number of disorders in various body systems and subsystems. Modern society often makes it imperative to increase productivity, even at the cost of sleep deprivation. However, research has shown that it is not wise because a longer period of sleep deprivation or chronic shortening of its duration will necessarily lead to a decline of cognitive functions in individuals, thus also leading to a decline in the quality of their productivity[1-4]. Sleeping is a natural state of the human body, which involves cyclic alternation of two main stages, non-rapid-eye movement (NREM) sleep and rapid-eye movement (REM) sleep. NREM sleep consists of stages 1 (N1) and 2 (N2) light sleep, which is followed by stages 3 and 4, during which deeper, slow-wave-sleep (SWS) occurs. A night of sufficient sleep consists of five to six major phasic changes (cycles). Despite the fact that each major sleep cycle lasts for 90 minutes, the duration of individual phases within the cycle changes during the night in such a way that the REM phase gradually deepens,

Correspondence to: *Prof. Tatjana Trošt Bobić, MD PhD*, Faculty of Kinesiology, University of Zagreb, Horvaćanski zavoj 15, HR-10000 Zagreb, Croatia
E-mail: ttrostbobic@gmail.com
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whereas the NREM phase shortens. The sleep cycle is clearly structured, considering that each sleep phase is characterized by specific chemical, cellular and anatomic events[1].

Methodology of Sleep Deprivation Studies

In human life, different forms of sleep deprivation may occur. Studies in this field make a distinction between total sleep deprivation (absence of sleep)[2], chronic sleep restriction[3], and the situation of sleep disruption/sleep fragmentation[4]. Total sleep deprivation denotes a lack of sleep for a specific period of time (one night at least) extending to a longer period of wake (in some studies even more than 72 h)[5,6]. Chronic sleep restriction implies long-term shortening of the usual duration of sleep in an individual, or shortening of the duration of sleep compared to the expected physiological duration for a given age. The basic need for sleep in a healthy adult is roughly 7.5 to 8.5 hours of sleep daily[5]. Fragmented sleep signifies interrupted sleep. Fragmented sleep chiefly occurs in cases of sleep disorders such as apnea, but it is also present in individuals who live in noisy streets, whose usual sleep dynamics is interrupted by frequent excitation (due to external disturbances). In studies that use sleep fragmentation it is necessary to carefully define the changes provoked in the architecture of sleep, that is, which sleep/dream stage is specifically targeted (for instance, SWS or REM sleep, or whether the researchers plan random fragmentation, such as in the case of sleep disorder). This is of great importance because different sleep fragmentation techniques can affect cognitive abilities of an individual in various ways[5]. Sleep fragmentation, total sleep deprivation and long-term chronic sleep restriction will all have a virtually equal negative impact on cognitive functioning in humans[5,6]. However, there are slight differences. Those individuals whose regular sleep duration has been reduced by 4 h/night over a period of 14 days show roughly the same decrease in cognitive functions as those who have experienced two days of total sleep deprivation. However, the individuals subjected to sleep deprivation subjectively report feelings of sleepiness, fatigue and pain, while the individuals subjected to chronic sleep deprivation do not report it. Hence, after a longer period of chronic sleep restriction, the person is unable to subjectively evaluate his/her objective lack of cognitive skills[5]. This shows that sleep quantity, continuity and quality are equally important factors in maintaining neural functions at an optimal level and that it is possible to study the impact of each of these factors on the brain functioning.

The Impact of Sleep Deprivation on the Brain

Sleep deprivation can affect human abilities and neural functioning in various ways. The occurrence of these different effects of sleep deprivation has been observed in previous studies by tracking changes at the macro, meso and micro levels[6]. The macro level describes the effect of sleep deprivation on human behavior, including cognitive functions, emotional processes, muscular activity, kinematics, as well as a range of behaviors that involve crude changes in large brain regions such as the prefrontal cortex, thalamus and hippocampus[7]. The meso level entails studying the effect of sleep deprivation at the level of neural activity from larger areas of the brain all the way down to smaller clusters of cells. Cell clusters at the meso level still manage to form more or less well defined functional units in terms of structure (e.g., the hypercolumn in the visual cortex) and in terms of activity (e.g., neural synchrony)[7]. Finally, the micro level deals with the molecular and cell level, i.e. the level of ion channels, gene expression and protein synthesis[7].

Besides the fact that studies on sleep deprivation use various forms of sleep deprivation and look at variables at different levels of neural functioning, it is also important to mention that they are conducted on human volunteers or by means of experimental animal models[1,5,8]. In this regard, direct evidence for sleep deprivation in humans has mostly been looked for in indicators of the macro level functioning[5,6]. The meso level is also relatively well researched in human beings[6], while changes at the molecular and cell level have been researched mainly by using experiments on animals[1,9]. In review articles, the results gathered from human subjects at the macro level of functionality (e.g., reduced ability of cognitive tasks or changes in electroencephalography (EEG) rhythm) are often explained by cellular mechanisms studied in rats (e.g., increased amounts of adenosine in certain parts of the brain)[6]. Such an approach in solving the problem of the effect of sleep deprivation on neural functioning in humans is incomplete; however, for now, it offers an

accessible manner of researching the problem, as well as a possible basis for targeted search for specific mechanisms in human subjects in future studies (within the realm of possibility).

The results of research into the effect of sleep deprivation on neural functions as monitored on macro-level variables show significant reduction of cognitive abilities, but they also reported negative moods[1,5,6] following the period of sleep deprivation, which may vary from 24 to 72 h, and less commonly beyond that[5,6]. Total sleep deprivation for longer than 36 h can in human beings reduce the ability to perform cognitive tasks, such as executive decision making, categorizing, spatial memory, fluid verbal expression, creativity, planning tasks, detecting changes in the environment, etc.[1,6]. Additionally, it leads to a strong subjective experience of fatigue, sleepiness and pain, and in some cases to bad moods and stress[1,5,6,10]. After a prolonged period of sleep deprivation, humans demonstrate a significantly diminished ability of detecting changes in the environment around them, as well as slowed-down reactions to external stimuli[5]. Under extreme conditions, hallucinations can also occur, and in animal studies even cases of death have been reported[1,6]. The previously mentioned behavioral data indicate the possibility of the involvement of neural structures which are linked to attention and excitation. Researchers often mention the possibility of sleep deprivation having a negative impact on the functioning of the prefrontal cortex, which is a large neocortical net connecting the perceptual motor and limbic region in the brain and which plays the key role in making executive decisions and in attention[6]. Similarly, weaker memory after sleep deprivation is linked to the impact on the hippocampus, an important structure involved in learning processes and consolidation of new study material in memory.

The results of the research on the impact of sleep deprivation on neural functions, as observed in variables at the meso level, indicate reduced cortical response to external stimuli, which has been proven by the reduced N1 amplitude and P300 components observed during EEG recording of the sleep deprivation period[6]. It is important to stress that in clinical trials, N1 is linked with the processing of auditory, visual or tactile information in the primary sensory area, but also with the ability to focus attention[6]. Contrary to the N1 signal, which is registered above the sensory cortex, the P300 signal is situated above the frontal part of the skull and is linked to the frontal lobe function. Thus, late emission of the P300 signal, with reduced amplitude, after sleep deprivation, is linked with a reduced ability to detect unpredictable stimuli, as well as the inability to anticipate them[6]. Neuroimaging studies, which used positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), predominantly point to a reduced activity in the area of the prefrontal cortex and thalamus after a period of sleep deprivation. Both structures are involved in the neural network responsible for maintaining focus during executive performances[6,11,12]. Furthermore, these studies also showed lower frequencies of EEG activity, as well as spatial shift of the signals in frontal regions, which most probably indicates reduced cortical excitation of frontal regions[6], thereby also indicating a reduced ability to perform the functions under their control.

Although the data obtained by using fMRI and EEG point to the predominant effect of sleep deprivation on the prefrontal cortex, the exact mechanisms at the cellular level, which are responsible for these findings, have not been fully researched yet. Most researchers agree with the assumption that the ascending nuclei in the reticular system are essential for the physiological wake-sleep state transitions, and that they are most probably affected by sleep deprivation[6]. The reticular system consists of several noradrenergic, dopaminergic and cholinergic nuclei, which project through the cortex and have a key role in maintaining attention and states of excitement[6]. The reduction or blockage of the cholinergic neurons reduces or fragments the N1 and P300 components of the EEG signal. Considering that the cholinergic neurons excite the thalamocortical network, which plays an important role in creating the theta cortical rhythms, this cholinergic activity is most probably related to the modification of theta rhythms, visible in the sleep cycle after the period of sleep deprivation. Furthermore, in several studies, a significant increase in adenosine was observed, especially in the area of the basal forebrain during sleep deprivation, where adenosine has an inhibitory effect on the activity of the cholinergic nuclei[1,6]. Such findings support the idea that adenosine is a modulator of sleepiness, which appears after longer periods of wake. In these situations, extracellular adenosine is selectively accumulated in the basal forebrain and cortex and promotes the transition from wake to slow-wave sleep

by inhibiting the cholinergic neurons in the basal forebrain[6]. However, there is a high probability that it is not the only molecular mechanism that is affected by sleep deprivation; hence in this regard it is necessary to conduct further research at the cellular level in order to discover the other kind of mechanisms of brain adaptation to the conditions of sleep deprivation.

Studies so far have mainly researched the acute effects of sleep deprivation on the brain, stressing how the detected behavioral deficits in most cases regenerate in a relatively short period of time (two nights of complete sleep at most)[5,6,13]. However, some studies done on mice emphasize the possible chronic effects of long-term sleep deprivation or chronic restriction on the occurrence of neurodegenerative diseases such as Alzheimer's disease and dementia. Namely, if an individual constantly finds in a situation of sleep loss, β-amyloid and other waste products could accumulate in the brain and contribute to the destruction of neurons, leading to dementia[14]. In short term, substances like caffeine and nicotine, but physical activity, too, can reduce the acute effects of sleep deprivation[1]; however, their ability to affect the possible chronic negative effects of sleep deprivation need to be further examined.

Even though a sufficiently long period of sleep deprivation, chronic sleep restriction, or sleep fragmentation undoubtedly has negative impacts on neural functioning in individuals, it is important to stress that there are also studies which did not show a clear negative impact of different kinds of sleep deprivation at the behavioral level (measured by solving various cognitive tasks)[5,6]. Considering that it has been demonstrated on many occasions that regular and correct progression of the sleep cycle is of vital importance in a large number of mammals, such findings are most commonly attributed to errors in the methodological approach of the research. Additionally, it is of great importance that the duration of sleep deprivation, chosen sleep fragmentation techniques, chosen cognitive test, the number of animals used in animal study designs, as well as the entire experimental protocol are planned correctly[1,6].

Conclusion

Finally, whereas short-term sporadic exposure to sleep deprivation over the course of life most probably will not have grave long-term consequences on neural functions in humans, a relatively long and constant period of sleep deprivation, chronic sleep restriction or fragmentation can lead to serious acute and chronic damage to neural functioning. In order to prevent this, it is of vital importance to thoroughly research the mechanisms of neural adaptation in the situations of insufficient sleep. In further studies of these mechanisms, integrative research on the impact of sleep deprivation on macro, meso and micro levels within the scope of the same study could contribute to more accurate conclusions about the basic cellular mechanisms responsible for the detected behavioral deficits occurring due to sleep deprivation.

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Sažetak

UTJECAJ GUBITKA SNA NA MOZAK

T. Trošt Bobić, A. Šečić, I. Zavoreo, V. Matijević, B. Filipović, Ž. Kolak, V. Bašić Kes, D. Ciliga i *D. Sajković*

Svaku fazu sna opisuju određeni kemijski, stanični i anatomski procesi koji su iznimno važni za održavanje fiziološke neuralne funkcije. Različiti oblici gubitka sna mogu kod čovjeka uzrokovati pad kognitivnih funkcija. Istraživanja u ovom znanstvenom području razlikuju situaciju potpunog gubitka sna, kronične restrikcije (ograničavanja) sna te stanje isprekidanog sna. Proučavanje akutnih učinaka neispavanosti na moždanu funkciju ukazuje na činjenicu da se otkriveni deficiti kognitivnih funkcija u većini slučajeva regeneriraju nakon dvije noći potpunog sna. Ipak, studije na miševima naglašavaju mogućnost utjecaja dugotrajne neispavanosti na nastanak nekih neurodegenerativnih bolesti kao što su Alzheimerova bolest i demencija. Kako bismo bolje razumjeli akutne i kronične učinke gubitka sna potrebno je dodatno istražiti mehanizme neurološke adaptacije na situacije neispavanosti. Buduća bi istraživanja o utjecaju gubitka sna na neurološke funkcije trebala pratiti makro razinu fenomena mjerenjem kognitivnih funkcija, ali i mikro razinu kroz molekularne i stanične procese. Takav bi pristup mogao doprinijeti točnijim zaključcima o osnovnim staničnim mehanizmima odgovornima za otkriveni kognitivni deficit uslijed nedostatka sna.

Ključne riječi: *San, deprivacija; Spoznaja; Mozak*