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Subchronic Sleep Fragmentation-Associated Memory Deficit: Absence of Changes in Hippocampal Neurogenesis

Subkronik Uyku Fragmantasyonuna Bağlı Hafıza Bozukluğu: Hipokampal Nörogenezde Değişiklik Yoktur

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Abstract

Objective: Sleep fragmentation (SF) is a hallmark of sleep-related disorders such as obstructive sleep apnea and is strongly associated with impairments in attention, learning, and memory. However, the neurobiological basis of this effect is unclear. This study investigated the effects of 14 days of treadmill-induced SF on memory and hippocampal alterations in adult male Wistar rats.

Materials and Methods: Rats were divided into three groups (n = 8): treadmill control (TC), activity control (AC), and SF (SF; treadmill-induced). The TC group was exposed to a stationary treadmill, while the AC group received a 10-minute ON–30-minute OFF treadmill routine, and the SF group received a 30-second ON–90-second OFF treadmill routine. Cognitive performance was assessed on day 14 using a modified elevated plus maze. Subsequently, hippocampal neurogenesis and gliosis were analyzed by measuring doublecortin, Ki67, and glial fibrillary acidic protein expression in the dentate gyrus.

Results: Rats in the SF group demonstrated significant impairments in modified elevated plus maze test compared to the AC and TC groups ($p < 0.001$). However, no significant differences were observed between

Öz

Amaç: Uyku bölünmesi (UB), obstrüktif uyku apnesi gibi uyku ile ilişkili bozuklukların temel özelliklerinden biridir ve dikkat, öğrenme ve bellek bozukluklarıyla güçlü biçimde ilişkilidir. Ancak bu etkinin nörobiyolojik temeli tam olarak açıklığa kavuşmamıştır. Bu çalışmada, yetişkin erkek Wistar sıçanlarında koşu bandı ile oluşturulan 14 günlük uyku bölünmesinin bellek ve hipokampal değişiklikler üzerindeki etkileri araştırılmıştır.

Gereç ve Yöntem: Sıçanlar üç gruba ayrıldı (n = 8): koşu bandı kontrolü (TC), aktivite kontrolü (AC) ve uyku bölünmesi (SF; koşu bandı ile indüklenen). TC grubu hareketsiz koşu bandına maruz bırakılırken, AC grubuna 10 dakika AÇIK–30 dakika KAPALI koşu bandı protokolü, SF grubuna ise 30 saniye AÇIK–90 saniye KAPALI koşu bandı protokolü uygulandı. Bilişsel performans, 14. günde modifiye yükseltilmiş artı labirent kullanılarak değerlendirildi. Daha sonra dentat girusta doublecortin, Ki67 ve glial fibriler asidik protein ekspresyonları ölçülerek hipokampal nörogenez ve gliozis analiz edildi.

Bulgular: SF grubundaki sıçanlar, AC ve TC gruplarıyla karşılaştırıldığında modifiye yükseltilmiş artı labirent testinde anlamlı düzeyde bozulma

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the groups in terms of hippocampal neurogenesis or gliosis ($p > 0.05$).

Conclusion: These findings suggest that subchronic SF can negatively impact learning and memory without significant structural changes. These memory impairments likely arise from functional rather than structural hippocampal alterations.

Keywords: Sleep fragmentation, hippocampus, neurogenesis, cognitive functions, memory

gösterdi ($p < 0,001$). Bununla birlikte, hipokampal nörogenez veya gliozis açısından gruplar arasında anlamlı bir fark gözlenmedi ($p > 0,05$).

Sonuç: Bu bulgular, subkronik uyku bölünmesinin belirgin yapısal değişikliklere yol açmaksızın öğrenme ve belleği olumsuz etkileyebileceğini göstermektedir. Bu bellek bozukluklarının, yapısal değişikliklerden ziyade hipokampustaki fonksiyonel değişikliklerden kaynaklanması olasıdır.

Anahtar Kelimeler: Uyku bölünmesi, hipokampus, nörogenez, bilişsel fonksiyonlar, hafıza

Introduction

Sleep is an essential biological process for maintaining cognitive function, regulating synaptic plasticity, and supporting overall brain homeostasis. Disruption of sleep continuity, particularly sleep fragmentation (SF) is a hallmark of sleep-related disorders such as obstructive sleep apnea (OSA) and is strongly associated with impairments in attention, learning, and memory (1). Notably, cognitive deficits caused by fragmented sleep may arise independently of total sleep duration (i.e., sleep deprivation), suggesting that both sleep continuity and architecture are critical for hippocampal function (2). Slow-wave sleep in particular plays a significant role in hippocampus-dependent learning and memory, supporting synaptic restructuring and memory consolidation (3,4). Despite the crucial role of intact sleep architecture, the neurobiological mechanisms by which SF impairs cognition remain incompletely understood (2).

The dentate gyrus (DG) of the hippocampus, a major site of adult neurogenesis, contributes to learning and memory through the proliferation, differentiation, and integration of neural progenitor cells into existing circuits. These processes can be evaluated using markers such as Ki67 and doublecortin (DCX) (5). Various types of sleep disruption can modulate hippocampal neurogenesis, potentially affecting synaptic plasticity and memory formation (6). Subchronic sleep deprivation in adolescent mice has also been linked to lasting deficits in hippocampus-dependent long-term memory, likely through reduced astrocyte function and neurogenesis (7). Alterations in glial fibrillary acidic protein (GFAP) expression, an indicator of reactive gliosis, may influence synaptic plasticity and memory (8). Modifications in synaptic plasticity and neurotransmitter balance can contribute to cognitive deficits even in the absence of major structural changes in neurogenesis or gliosis (9). However, the effects of subchronic SF have not been thoroughly investigated, particularly regarding whether memory impairment develops in the presence or absence of detectable cellular changes in the hippocampus (10).

The aim of this study was to investigate the effects of subchronic SF on memory performance and hippocampal neurogenesis in rats.

Materials and Methods

Animals

Male Wistar albino rats (180–210 g) were obtained from the Military Medical Academy breeding facility in Belgrade, Serbia. Animals were housed in transparent Plexiglas cages (55 × 35 × 30 cm) with ad libitum access to standard chow and tap water. Environmental conditions were maintained at 22–24 °C and 50 ± 5% relative humidity, under a 12:12 h light/dark cycle (lights on 08:00–20:00). Rats were acclimated to laboratory conditions for 9 days prior to the experiments. Each animal was used only once.

All animal experiments were performed following the principles of the European Directive 2010/63/EU for animal research and were approved by the Ethics Council for Animal Welfare of the Republic of Serbia (approval no: 323-07-05290/2017-05, date: January 25, 2018). All efforts were made to minimize animal suffering and to reduce the number of animals used.

Experimental Design and Sleep Fragmentation

SF was induced using a motor-driven treadmill system for small laboratory animals (NeuroSciLaBG-Treadmill, Elunit, Serbia) during the first six hours of the light phase of a 12:12 h light/dark cycle and applied daily for fourteen consecutive days, in order to mimic the frequent arousal patterns observed in patients with OSA (11,12).

Using a computer-generated sequence, adult male Wistar rats ($n = 24$) were randomly assigned at a 1:1:1 ratio ($n = 8$ per group) to three groups: the SF group, subjected to repeated treadmill activation cycles of 30 seconds ON / 90 seconds OFF during the first six hours of the light phase; the treadmill control (TC) group, in which animals were placed on the stationary treadmill without belt movement; and the activity control (AC) group, exposed to treadmill activity for six hours per day using 10-minute ON / 30-minute OFF cycles to match the total locomotor distance of the SF group without inducing SF.

Prior to the experiment, all animals underwent a two-day habituation period on the treadmill consisting of one-hour daily sessions with alternating five-minute ON and OFF phases. Cage location and behavioral testing order were counterbalanced to minimize potential confounders, and only healthy adult male rats within the specified weight range were included. No animals were excluded.

Memory retention, the primary outcome measure, was assessed by transfer latency (TL2) in the modified elevated plus maze (mEPM) to evaluate the effects of SF on cognitive performance after 14 days (Figure 1). Investigators conducting behavioral assessments and immunohistochemical analyses were blinded to group allocation. Sample size was based on previous studies using similar behavioral and histological endpoints, without formal a priori power calculation.

Modified Elevated Plus Maze Test

Rats placed individually at the end of an open arm, facing away from the memory-related behavior was assessed using the mEPM as previously described (13). The apparatus comprised a central platform (5 × 5 cm), two open arms (5 × 30 cm), and two enclosed arms (5 × 30 × 15 cm) arranged in a plus configuration, elevated 50 cm above the floor. The test exploits rodents' natural aversion to open and elevated spaces, requiring them to remember the spatial arrangement of the arms. Each rat was placed central platform.

The test consisted of two trials separated by a 24-hour interval to evaluate memory retention over a standard consolidation period. In the first trial (acquisition), latency to enter an enclosed arm (TL1) was recorded, with a maximum of 90 seconds. Rats that did not enter within this time were guided into an enclosed arm for 60 seconds, and their TL1 was recorded as 90 seconds. The second trial (retention) was conducted 24 hours later following the same procedure, and latency to enter an enclosed arm (TL2) was recorded, also capped at 90 seconds.

TL2 served as the primary outcome measure of learning and memory performance, while TL1 was used as a baseline. Behavioral scoring was performed by investigators blinded to group allocation, and the order of testing was randomized to prevent order effects.

Immunohistochemical Protocol and Quantification

At the end of the 14-day intervention, the animals were euthanized, and brain hemispheres (alternating left or right) were harvested, fixed in 4% buffered paraformaldehyde, and processed for paraffin embedding following standard procedures. Coronal sections (4 μm) were cut, dried, dewaxed in xylene, rehydrated, and subjected to antigen retrieval using citrate buffer (pH 6.0) in a microwave. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide, and nonspecific binding was prevented by a one-hour incubation with normal rabbit serum for DCX or normal goat serum for Ki67 and GFAP. Sections were then incubated overnight at room temperature with goat polyclonal anti-DCX (1:100, Santa Cruz Biotechnology, USA), rabbit polyclonal anti-Ki67 (1:3500, Abcam, UK), or rabbit polyclonal anti-GFAP (1:500, DAKO, USA) antibodies. Following washes, biotinylated secondary antibodies were applied for one hour (rabbit anti-goat for DCX; goat anti-rabbit for Ki67 and GFAP), followed by avidin-biotin–horseradish peroxidase complex (Vector Laboratories, USA). Immunoreactive sites were visualized using 3,3'-diaminobenzidine (DAB). The sections were then counterstained with Mayer's hematoxylin, dehydrated in ethanol, and mounted with DPX.

Immunohistochemical analyses were performed with each rat as the experimental unit, and the mean number of immunoreactive cells per animal was used for statistical comparisons. DCX- and Ki67-positive neurons were quantified along the subgranular zone (SGZ) of the DG, defined as the boundary between the hilus and granular cell layer, and expressed per 1 mm of SGZ. GFAP-positive areas were analyzed using the Color Picker Threshold Plugin in Icy software, with positive (brown DAB-stained) and negative (blue or light brown) areas defined to

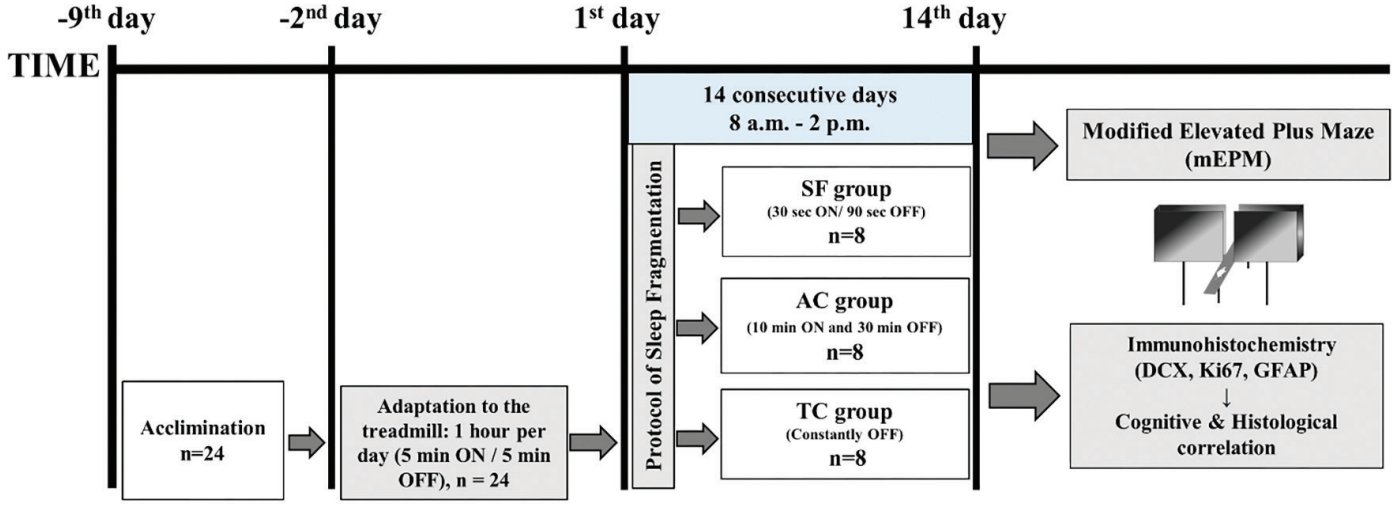

Figure 1. Study design. Sleep fragmentation (SF) was induced using a motorized treadmill system during the first 6 h of the light phase of a 12:12 h light/dark cycle and applied daily for 14 consecutive days. Animals were habituated to the treadmill prior to the intervention. Rats were randomly allocated into three experimental groups: SF group, subjected to repeated treadmill activation cycles for 6 h/day with 30 s ON / 90 s OFF intervals during the light phase; the treadmill control group, in which animals were placed in the treadmill apparatus for 6 h/day without belt movement; and the activity control group, exposed to treadmill activity for 6 h/day consisting of 10 min ON / 30 min OFF cycles to match the total locomotor distance of the SF group without inducing SF. Cognitive performance was assessed using the modified elevated plus maze on day 14. At the end of the 14-day experimental period, all animals were euthanized, and brain tissues were collected for immunohistochemical analyses.

AC: Activity control, DCX: Doublecortin, GFAP: Glial fibrillary acidic protein, mEPM: Modified elevated plus maze, SF: Sleep fragmentation, TC: Treadmill control.

calculate the relative GFAP-positive area as a percentage of the total region of interest.

All analyses were performed by two independent investigators blinded to group allocation, with high inter-rater reliability (Pearson's r = 0.95). The sample size for each immunohistochemical analysis was n = 8 per group (TC = 8, AC = 8, SF = 8).

Statistical Analysis

Data distribution was assessed using the Shapiro-Wilk test, supplemented by visual inspection of Q–Q plots. All test variables met the assumptions of normality. Differences in outcome variables among the experimental groups were analyzed using one-way analysis of variance (ANOVA), followed by the Tukey-Kramer post hoc test when appropriate. All animals were included in the analyses (n = 8 per group), and investigators performing statistical analyses were blinded to group allocation. Statistical significance was set at $p < 0.05$, and exact p-values are reported. All statistical analyses were performed using STATISTICA 10 (StatSoft Inc., Tulsa, OK, USA).

Results

Modified Elevated Plus Maze Test Revealed Cognitive Decline in the SF Group

Acquisition values (TL1) did not differ between the groups (SF: 80.37 ± 6.80 s; TC: 74.37 ± 9.62 s; AC: 70.87 ± 10.92, p = 0.143) (Figure 2A). In the subsequent test trial (TL2), SF rats exhibited significantly longer latency to enter the enclosed arms compared with the TC and AC groups (SF 66.87 ± 9.20 s vs. TC 20.12 ± 4.08 s and AC 21.25 ± 4.20 s; $p < 0.001$), indicating impaired learning and memory (Figure 2B). Furthermore, the change in transfer latency between TL1 and TL2 (ΔTL) was significantly smaller in SF rats compared with both control groups (SF 13.50 ± 7.91 s vs. TC 54.25 ± 6.82 s and AC 49.62 ± 11.58 s; $p < 0.001$) (Figure 2C).

Immunohistochemistry Staining Revealed No Significant Changes in DCX, Ki67, or GFAP in the Dentate Gyrus

No significant differences were observed in DCX, Ki67, or GFAP expression in the DG among the groups ($p > 0.05$) (Figure 3). Data are shown in Table 1.

Discussion

In the present study, 14 days of treadmill-induced subchronic SF resulted in significant impairments in learning and memory in adult male Wistar rats, as evidenced by increased TL2 and a reduced difference between acquisition and retention latencies in the mEPM. Rats exposed to SF exhibited longer retention latencies and diminished improvement between acquisition and recall trials compared with both control groups, indicating disrupted memory consolidation (Figure 2). Notably, these behavioral deficits were not accompanied by significant alterations in hippocampal neurogenesis (DCX- or Ki67-positive cell density) or astrocytic reactivity (GFAP) within the DG (Figure 3). These findings suggest that moderate subchronic SF can impair hippocampus-dependent cognitive function in the

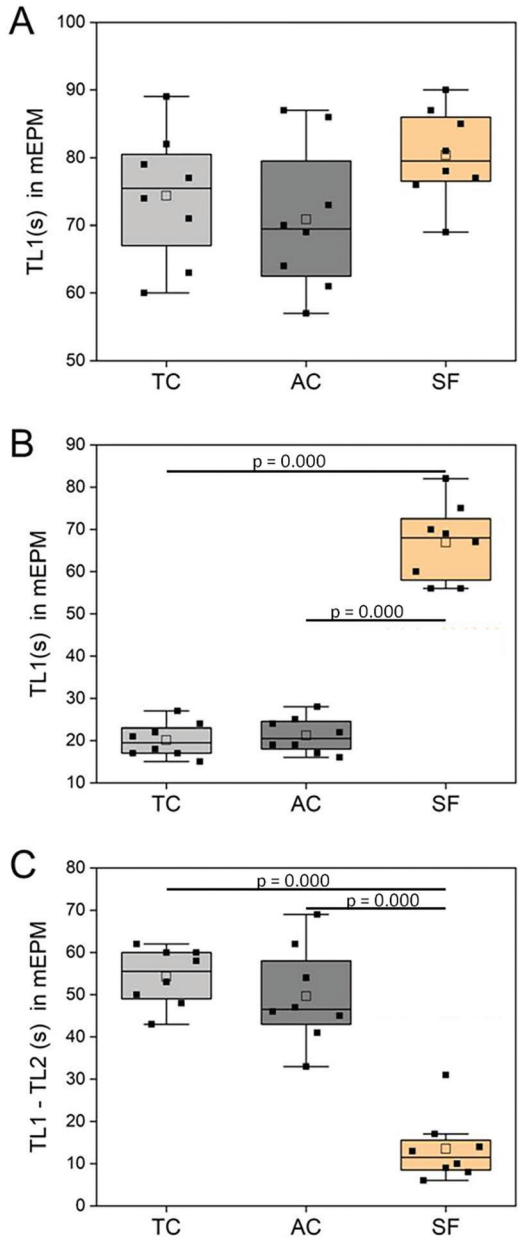

Figure 2. The effects of subchronic sleep fragmentation on memory function in the modified elevated plus maze (mEPM) test. Transfer latencies during the acquisition trial (TL1, A), retention trial (TL2, B), and the changes in transfer latency (ΔTL, C) in the treadmill control (TC), activity control (AC), and sleep fragmentation (SF) groups. Data are presented as mean ± SD (n = 8 animals per group). No significant difference was observed for TL1 (p = 0.143). TL2 was significantly increased in the SF group compared with both the TC and AC groups (overall ANOVA, $p < 0.001$). Likewise, ΔTL differed significantly among groups (overall ANOVA, $p < 0.001$). Statistical analyses were performed using one-way ANOVA followed by the Tukey-Kramer post hoc test.
AC: Activity control, mEPM: Modified elevated plus maze, SF: Sleep fragmentation, TC: Treadmill control.

absence of detectable structural changes in classical markers of neuroplasticity, resembling early-stage conditions such as OSA.

Transfer latency in the mEPM is a well-established measure of hippocampus-dependent memory recall and consolidation, though performance can be influenced by anxiety, fatigue, or locomotor activity (14). In this study, intact TL1 performance with impaired TL2 performance in the SF group reflects memory consolidation deficits induced by subchronic SF. This effect is consistent with prior rodent studies showing that sleep disruption can selectively impair 24-hour retention without affecting acquisition (15,16). However, the potential influences of anxiety or motor activity cannot be fully ruled out, which represents a limitation of the present study.

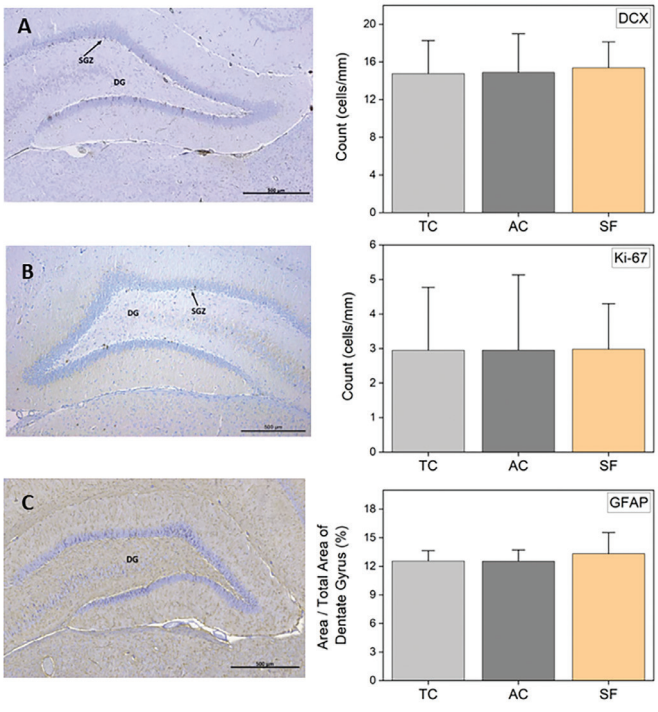

Figure 3. Immunohistochemical staining of the hippocampal dentate gyrus. Representative quantitative analysis of DCX (A), Ki67 (B), and GFAP (C) immunoreactivity in the dentate gyrus of the treadmill control, activity control, and sleep fragmentation (SF) groups. Data are presented as mean ± standard deviation (n = 8 animals per group). No statistically significant differences were observed among the groups for any marker (one-way ANOVA, all $p > 0.05$).
AC: Activity control, DCX: Doublecortin, DG: Dentate gyrus, GFAP: Glial fibrillary acidic protein, SF: Sleep fragmentation, SGZ: Subgranular zone, TC: Treadmill control.

Previous research has shown that the impact of total sleep deprivation on hippocampal neurogenesis and cognition depends critically on its severity and duration. Chronic or prolonged deprivation clearly reduces neurogenesis and impairs spatial learning (17) and can suppress adult hippocampal neurogenesis independently of stress hormones (18). By contrast, the moderate SF applied in the present study may have disrupted synaptic function and network organization without inducing evident structural changes, suggesting that functional deficits may precede measurable morphological alterations. This dissociation may be explained by early alterations in synaptic proteins such as postsynaptic density protein 95 and synaptophysin, impaired brain-derived neurotrophic factor signaling, mitochondrial dysfunction, or subtle neuroinflammatory processes that were not evaluated in the present study. These molecular and functional alterations could impair hippocampal information processing despite preserved neurogenesis and astrocytic morphology. Therefore, cognitive impairments may emerge before overt cellular damage, emphasizing the sensitivity of hippocampal networks to sleep disturbances.

Emerging evidence indicates that memory impairments caused by SF result from multiple, interacting mechanisms. Key drivers include disruptions in synaptic plasticity and cortical state dynamics. Reductions in slow-wave and REM sleep further compromise system-level memory consolidation by impairing hippocampal-cortical communication (19,20). Importantly, neuromodulatory pathways, particularly orexin signaling, also modulate hippocampal excitability and memory encoding, with functional deficits emerging even in the absence of overt structural changes (21,22). These findings support a multilevel model in which network- and neuromodulator-level disturbances drive cognitive deficits. Collectively, these studies demonstrate that sleep continuity and architecture are critical for hippocampus-dependent memory.

Glial activation and neuroinflammation have been proposed as contributors to SF-related cognitive deficits (23,24). However, the lack of significant GFAP changes in the present study suggests that moderate SF may be insufficient to elicit a robust glial response, in contrast to longer or more severe protocols that trigger microglial activation and inflammation (25-27). Consistent with our findings, it was reported that SF could

Table 1. Changes in DCX, Ki67, and GFAP in the dentate gyrus.

Groups	Hippocampus		
	DCX	**Ki67**	**GFAP**
TC	14.76 ± 3.48	2.95 ± 1.83	12.55 ± 1.08
AC	14.88 ± 4.10	2.95± 2.18	12.52 ± 1.19
SF	15.35 ± 2.72	2.83 ± 1.29	12.46 ± 2.51

No significant difference was observed in DCX (number of positively stained cells), Ki67 (number of positively stained cells) and GFAP (% of stained area) expression in the hippocampal dentate gyrus ($p > 0.05$). Data are presented as mean ± standard deviation. Differences among the groups were evaluated using one-way ANOVA with Tukey-Kramer LSD post hoc test. AC: Activity control, DCX: Doublecortin, GFAP: Glial fibrillary acidic protein, SF: Sleep fragmentation; TC: Treadmill control, LSD: Least significant difference.

impair memory consolidation by disrupting hippocampal energy metabolism and network activity, even when neurogenesis markers were unaffected (28,29).

Clinical evidence shows that fragmented sleep impairs memory, attention, and executive function in elderly individuals, even without significant neurodegenerative changes (2,30,31). Similarly, OSA is strongly associated with cognitive deficits, with imaging and neuropsychological studies revealing hippocampal structural and functional alterations (31,32). Furthermore, continuous positive airway pressure therapy improves cognitive performance and partially restores hippocampal networks, demonstrating that the cognitive consequences of SF are at least partially reversible (33,34). In this context, the experimental SF model employed in the present study provides a relevant translational framework for investigating the neural mechanisms underlying cognitive impairments observed in OSA.

Study Limitations

Several limitations of the present study should be acknowledged. First, only adult male Wistar rats were used, which may limit the generalizability of the findings to females or other strains. Second, the duration of SF was moderate (14 days), and longer-term effects on cognition and underlying neurophysiology were not assessed. Third, only three immunohistochemical markers (DCX, Ki67, and GFAP) were evaluated. Although these markers provide important information regarding neurogenesis and astrocytic activation, they may not detect subtle alterations in synaptic plasticity, neurotrophic signaling, mitochondrial function, or electrophysiological activity. Finally, evidence from human studies indicates that SF and poor sleep quality are associated with broader cognitive dysfunction and altered neurophysiological correlates of cognitive fatigue, underscoring the need for models that integrate both structural and functional outcomes (35,36). Future studies including both sexes, longer exposure durations, and a broader range of molecular, electrophysiological, and functional analyses are warranted to more fully elucidate the mechanisms underlying cognitive deficits induced by disrupted sleep.

Conclusion

Subchronic SF (14 days) impaired hippocampus-dependent memory in adult male Wistar rats without detectable changes in DG neurogenesis or astrocytic activity. This dissociation suggests that moderate sleep disruption primarily affects synaptic and network-level processes rather than cellular plasticity. These results highlight the importance of sleep continuity for memory consolidation and point to synaptic, neuromodulatory, and network-level mechanisms as potential contributors to cognitive vulnerability under fragmented sleep.

Ethics

Ethics Committee Approval: All animal experiments were performed following the principles of the European Directive 2010/63/EU for animal research and were approved by the Ethics Council for Animal Welfare of the Republic of Serbia (approval no: 323-07-05290/2017-05, date: January 25, 2018).

Informed Consent: Animals were healthy and handled to minimize stress and discomfort, and the study design aimed to use the minimum number of animals necessary to achieve reliable results.

Footnotes

Authorship Contributions

Concept: Z.G., A.R.M., O.S., D.H., Design: N.Š., N.P., M.V., A.E.C., D.H., Data Collection or Processing: Z.G., N.P., M.V., D.M., E.Đ., A.G., A.R.M., Analysis or Interpretation: Z.G., D.M., J.B.M., D.H., Literature Search: Z.G., N.E., N.Š., N.P., A.R.M., O.S., D.H., Writing: Z.G., N.E., N.Š., N.P., M.V., D.M., E.Đ., J.B.M., A.G., A.E.C., A.R.M., O.S., D.H.

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