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Altered brain-derived neurotrophic factor levels and oxidative stress in REM sleep deprivation: a rat model study

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Abstract

Background Brain-derived neurotrophic factor (BDNF) is among the modulators associated with cognition and sleep that play a role in sleep disorders. This study aimed at investigating the effects of chronic sleep deprivation and REM sleep deprivation on BDNF levels and oxidative stress markers.

Methods A total of 24 healthy male Wistar albino rats were separated into 3 groups as REM sleep deprivation group, control sleep deprivation group and control group. To create models of 21-day REM sleep deprivation and control sleep deprivation, we used the platform technique. After 21 days blood BDNF, brain tissue BDNF, brain tissue malondialdehyde, glutathione, ascorbic acid, nitrite and nitrate were evaluated.

Results Compared with the control group, control sleep deprivation group showed a significant increase in brain tissue levels of BDNF ($p=0.038$), whereas a significant decrease was observed in the levels of glutathione (GSH) and nitric oxide (NO) (p:0.036). No statistical difference was observed between the blood levels of BDNF in either group (p: 0.795).

Conclusion Our results showed decreases in GSH and NO levels and increases in malondialdehyde levels in the sleep deprivation models, reflecting oxidative stress in the brain. Additionally, we observed increases in brain BDNF levels in the control sleep deprivation model.

Keywords Brain-derived neurotrophic factor, Chronic sleep deprivation, Oxidative stress, REM sleep deprivation

Background

Sleep is an essential biological process crucial for physical and mental health. It is characterized by distinct stages, including non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. These stages play vital roles in various physiological functions, including memory consolidation, emotional processing, and cellular repair. Disruption of sleep can have significant negative consequences [1].

Chronic sleep deprivation is a prevalent concern, with detrimental effects on immunity, cognitive function, and overall health [2, 3]. The multitude of stressors inherent to modern life negatively impact both sleep quality and

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sleep duration [4]. Sleep disruption is linked to alterations in inflammatory and synaptic plasticity-related molecules, including brain-derived neurotrophic factor (BDNF). Studies suggest a complex relationship between BDNF and sleep. BDNF plays a crucial role in cognition and sleep and is implicated in the mechanisms underlying sleep disorders [3].

BDNF is a neurotrophin essential for neuronal development and plasticity. BDNF protects brain tissue from hypoxic damage by providing neural plasticity and preventing and reducing neural death [5]. Deficiencies in BDNF both hinder the prevention of neuronal damage and apoptosis caused by reactive oxygen species in chronic intermittent hypoxia and compromise long-term synaptic plasticity [6].

Studies with animal and human subjects with obstructive sleep apnea syndrome (OSAS) have demonstrated that sleep deprivation leads to increased oxidative stress [7]. Imbalance between the production and removal of reactive oxygen and nitrogen species disrupts cellular function and contributes to the development of various diseases, including cancer, immunodeficiency, neurological disorders, and cardiovascular diseases [8]. Chronic intermittent hypoxia and sleep fragmentation, as observed in OSAS, are associated with systemic and neuronal inflammation, ultimately leading to impairment in neurocognitive function [5]. In this context, BDNF appears to exert a protective role against the results of chronic intermittent hypoxia.

This in vivo study investigated the effects of REM sleep deprivation on BDNF levels and oxidative stress markers. By measuring BDNF levels in a living organism under controlled sleep manipulation conditions, we hoped to elucidate the specific impact of each sleep disruption on this vital neurotrophic factor. Understanding the influence of specific sleep disruptions on BDNF levels could provide valuable insights into the neurobiological underpinnings of sleep disorders and their associated cognitive impairments, potentially paving the way for future therapeutic interventions targeting sleep disorders and related cognitive decline.

Methods

This study was carried out in Giresun University, Giresun, Turkey. The study protocol was approved by the Giresun University Animal Research Local Ethics Committee (18.12.2018/17) and performed in accordance with the principles of The Declaration of Helsinki. The rats used in this study were obtained from Saki Yenilli Experimental Animals Inc. in Ankara, Turkey. We confirm that informed consent regarding use of animals in our study was obtained from the laboratory's authorized personnel from which we obtained animals.

Animals

Twenty-four healthy male Wistar albino rats weighing 200–250 g were included. The rats were randomly divided into three groups (n = 8 per group): REM sleep deprivation, control sleep deprivation and control group. One animal in the control group died after one week of acclimatization. It was decided to continue the experiment with the remaining 7 animals in the control group to maintain the integrity of the experimental design and to avoid confounding variables.

Sleep deprivation model

The platform technique, originally described by Jouvet et al. [9] in 1964 for inducing sleep deprivation in cats and adapted for rats by Cohen and Dement [10], was used to create REM sleep deprivation model.

- **Control Group**: Control rats were housed in a tank assembly, devoid of platforms. A stainless-steel grid, elevated 15 centimeters above the tank base, prevented direct water contact during sleep.
- **REM Sleep Deprivation Group**: A multi-platform water tank was utilized to induce REM sleep deprivation. The tank featured 14 platforms, each 16 cm high and 6.5 cm in diameter, spaced 10 cm apart. Animals were positioned on the platforms, and the tank was filled with water to a depth of 15 cm. During the REM sleep phase, animals experience atonia, leading to a loss of postural control and partial or complete slippage from the platform into the water. This forced them to stay in contact with the water, preventing REM sleep without completely restricting sleep.
- **Control Sleep Deprivation Group**: Rats were placed on wider metal plates (14 cm wide) over the water tank. Similar to the REM sleep deprivation group, they had contact with the water. This group was included in the study design to assess the effect of environmental differences and the effect of different cage configurations and disk sizes.

Housing and habituation

Animals were housed under a standard 12-hour light/dark cycle (lights on at 7:00 AM, lights off at 7:00 PM) in a temperature-controlled room (24 °C) with ad libitum access to food and water. Following a one-week acclimatization period, all animals were introduced to their respective tanks for 30 min daily for five days to minimize experimental stress.

Experimental procedure

On the first day of the experiment, all animals were placed in their designated setups at 4:00 PM and remained there for 18 h. They were then returned to their

home cages at 10:00 AM the following day and allowed to rest until 4:00 PM. This procedure continued for 21 days.

Tissue collection

After 21 days, to achieve general anesthesia in all animals, we administered Xylazine hydrochloride (Rompun®-BAYER; 7.5–15 mg/kg) and Ketamine hydrochloride (Ketalar®, Pfizer, NY, NY; 40–60 mg/kg) via intravenous injection. Subsequently, intracardiac blood samples were obtained. Following decapitation, brain tissues were immediately extracted and flash-frozen in liquid nitrogen. Both the excised tissues and blood samples were then stored at -80 °C until biochemical analyses were conducted.

Determination of BDNF levels

We collected 2–3 mL of blood from each rat in a flat tube and allowed the blood to clot for 30 min at room temperature before centrifugation at 1000× *g* for 20 min at 4 °C. Serum and brain tissue samples were stored at − 80 °C until analysis.

Brain tissues were rinsed using ice-cold phosphate-buffered saline to completely remove excess blood. Tissue samples were cut into small pieces and homogenized in 1 mL of fresh lysis phosphate-buffered saline using a glass homogenizer on ice. The resulting suspension was centrifuged at 10,000× *g* for 5 min. Subsequently, 1 mL of supernatant was taken into an Eppendorf tube and stored at 4 °C for 24 h. The serum and brain tissue levels of BDNF were determined using enzyme-linked immunosorbent assay (ELISA) (Wuhan USCN Business CO., Ltd., China); the test principle used in this kit was the sandwich enzyme immunoassay. BNDF levels in the serum samples are expressed as pg/mL and those in the brain tissue samples are expressed as pg/mg. All assays were performed in duplicate.

Determination of malondialdehyde

Brain tissue was homogenized in a 9:1 v/v ratio in ice-cold 10% trichloroacetic acid solution. The homogenate was centrifuged at 3000 rpm for 15 min, and the level of malondialdehyde (MDA) in the supernatant was determined according to the formation of thiobarbituric acid reactive species (TBARS) [11]. The supernatant was transferred to glass test tubes containing 0.375% (w /v) thiobarbituric acid and 0.02% (w/v) butyl hydroxytoluene to prevent further peroxidation of lipids in later stages. The samples were heated to 100 °C for 15 min in a boiling water bath, cooled, and centrifuged to remove the precipitate. The absorbance of the samples was measured at 532 nm.

Determination of glutathione levels

Glutathione (GSH) levels were determined using the modified Elman method [12]. Tissue samples were homogenized in ice-cold trichloroacetic acid (1 g tissue + 10 mL 10% trichloroacetic acid) in a tissue homogenizer. After centrifugation at 3000 rpm for 10 min, 0.5 mL of the supernatant was added to test tubes containing 2 mL of 0.3 mol/L $Na_2HPO_4 \cdot 2H_2O$ solution. Then, 0.2 mL of dithiobis nitrobenzoic acid solution (0.4 mg/mL, 1% sodium citrate) was added to the test tubes and mixed. The absorbance was measured at 412 nm immediately after mixing. GSH levels per unit were calculated by using an extinction coefficient of 13.600 mol/cm.

Determination of total nitrite/nitrate levels

The Griess method [13] is used to measure nitrite and nitrate (NOx) levels as indicators of nitric oxide (NO) in the tissue, and we applied it to determine total nitric oxide (NOx) levels. Brain tissues were homogenized in five volumes of phosphate-buffered saline (pH = 7.5) and centrifuged at 3000 rpm for 5 min. Then, 0.25 mL of 0.3 M NaOH was added to 0.5 mL of the supernatant. After incubation for 5 min at room temperature, 0.25 mL of 5% (w/v) zinc sulfate ($ZnSO_4$) was added for deproteinization. This mixture was centrifuged at 14,000 rpm for 5 min, and the supernatants were used for the experiment.

Nitrate levels in the tissue homogenates were determined spectrophotometrically based on the reduction of nitrate to nitrite with vanadium chloride (VCl_3). Nitrite levels were measured using the Griess reaction. Sodium nitrite and nitrate solutions (1, 10, 50, and 100 µL) were used as standard.

Determination of levels of ascorbic acid in tissues

Total ascorbate content was determined using the Roe and Keuther method modified by Berger [14]. Brain tissues were weighed and homogenized on ice in nine volumes of 35% perchloric acid with 0.1 mg of ethylene diamine tetraacetic acid/mL (PCA/EDTA). Samples were centrifuged at 12,000 rpm for 3 min at 4 °C and supernatants were obtained. Standard and 200 µL of the sample were combined with 50 µL of colored reagent (1:1:20 0.6% copper sulfate at v/v/v, 5% thiourea, and 2,4-dinitrophenyl hydrazine). Samples were kept in a water bath at 37 °C for 3 h and then cooled to 0 °C, and 300 µL of 65% (v/v) sulfuric acid was added. The samples were vortexed, and optical density was measured using a spectrophotometer at 515 nm.

Statistical analysis

The Number Cruncher Statistical System (NCSS; Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard

Table 1 Evaluation of serum BNDF measurements

	N	BDNF (pg/mL)	
		Min–Max (Median)	**Mean ± SD**
Control Group	7	105.6–251.1 (167.1)	177.17 ± 54.67
REMSD Group	8	1128.7–494.1 (170.6)	205.56 ± 119.38
CSD Group	8	99.5–483.3 (151.2)	205.77 ± 135.66
	p	***[a]0.795***	
Control– REMSD		***[b]1.000***	
Control– CSD		***[b]1.000***	
REMSD– CSD		***[b]1.000***	

[a]Kruskal–Wallis Test [b]Bonferroni (Dunn) Test

BDNF, brain-derived neurotrophic factor; CSD, control sleep deprivation; REMSD, rapid eye movement sleep deprivation; SD, standard deviation

deviation, median, frequency, ratio, minimum, and maximum) were used in evaluating the study data. The Kruskal–Wallis test was used for comparisons of three or more groups that did not show normal distributions, and the Bonferroni–Dunn test was used for pairwise comparisons. Analysis of variance (ANOVA) and the Mann–Whitney *U* test were used to determine differences between groups. Significance was evaluated at the $p < 0.05$ level.

Results

Total serum BDNF levels ranged from 99.5 to 494.1 pg/mL with a mean of 196.99 ± 106.70 and a median of 161.55 pg/mL.

The control group displayed a mean serum BDNF concentration of 177.17 ± 54.67 pg/mL, with a median of 167.1 pg/mL. Rats in the REM sleep deprivation group had a mean serum BDNF level of 205.56 ± 119.38 pg/mL and a median of 170.6 pg/mL. The control sleep deprivation group exhibited a mean BDNF concentration of 205.77 ± 135.66 pg/mL and a median of 151.2 pg/mL. Statistical analysis revealed no significant differences ($p > 0.05$, p: 0.795) in serum BDNF levels among the control, REM sleep deprivation, and control sleep deprivation groups (Table 1).

Brain tissue BDNF and biomarkers of oxidative stress and neuroprotection

The control group had a mean brain tissue BDNF level of 161.95 ± 40.99 pg/mg. REM sleep deprivation group had a mean brain tissue BDNF level of 176.43 ± 43.25 pg/mg. The control sleep deprivation group had a mean brain tissue BDNF concentration of 280.76 ± 52.40 pg/mg. Both the REM sleep deprivation and control sleep deprivation groups showed higher BDNF levels compared to the control group. However, a statistically significant difference was only observed between the control sleep deprivation group and the control group ($p = 0.038$) (Fig. 1). There were no statistically significant differences when comparing the REM sleep deprivation group with the control and control sleep deprivation groups (respectively; $p = 0.065$, $p = 0.056$) (Table 2).

Brain tissue levels of malondialdehyde (MDA), a marker of lipid peroxidation and oxidative stress, were significantly elevated in both the REM sleep deprivation and the control sleep deprivation groups compared to the control group (Fig. 2). Conversely, both groups exhibited significantly decreased levels of GSH (Fig. 3), an endogenous antioxidant, and NO, a signaling molecule with antioxidant properties, compared to controls (Fig. 4).

Brain tissue ascorbic acid (vitamin C) levels were significantly lower only in the control sleep deprivation group compared to controls (Fig. 5). Interestingly, brain tissue BDNF levels were statistically higher in the control sleep deprivation group compared to the control group.

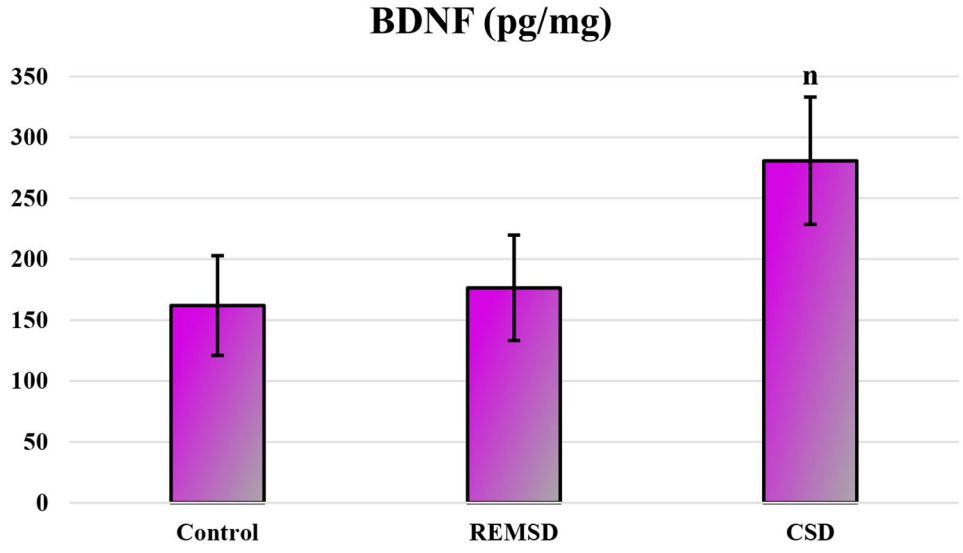

Fig. 1 Comparison of brain BDNF levels in three groups: Control, REMSD, and CSD. **n** = 0.038 Control vs. CSD, BDNF: brain-derived neurotrophic factor; CSD: control sleep deprivation group; REMSD: rapid eye movement sleep deprivation group

Table 2 Evaluation of brain BNDF and oxidative stress marker measurements

Group	MDA (µmol/g)	GSH (µmol/g)	Ascorbic Acid (mg/g)	NOx (nmol/g)	BDNF (pg/mg)
Control	191.72 ± 14.88	5.22 ± 0.51	4.77 ± 0.55	164.40 ± 6.73	161.95 ± 40.99
REMSD	456.63 ± 51.03 [a]	3.05 ± 0.51 [c]	3.47 ± 0,0.60	92.48 ± 12.86 [g]	176.43 ± 43.25 [q]
CSD	502.64 ± 16.69 [b, r]	2.66 ± 0.42 [d, t]	1.41 ± 0,0.32 [e, f]	79.70 ± 5.17 [h, m]	280.76 ± 52.40 [n, v]

a*p* = 0.036 Control vs. REMSD; **b***p* = 0.031 Control vs. CSD; **r***p* = 0.070 REMSD vs. CSD; **c***p* = 0.026 Control vs. REMSD; **d***p* = 0.024 Control vs. CSD; **t***p* = 0.058 REMSD vs. CSD; **e***p* = 0.033 Control vs. CSD; **f***p* = 0.044 REMSD vs. CSD; **g***p* = 0.021 Control vs. REMSD; **h***p* = 0.015 Control vs. CSD; **m***p* = 0.011 REMSD vs. CSD; **n***p* = 0.038 Control vs. CSD; **v***p* = 0.056 REMSD vs. CSD; **q***p* = 0.065 Control vs. REMSD; Kruskal-Wallis test BDNF, brain-derived neurotrophic factor; CSD, control sleep deprivation; GSH, glutathione; MDA, malondialdehyde; NOx, nitrite/nitrate; REMSD, rapid eye movement sleep deprivation; SD, standard deviation

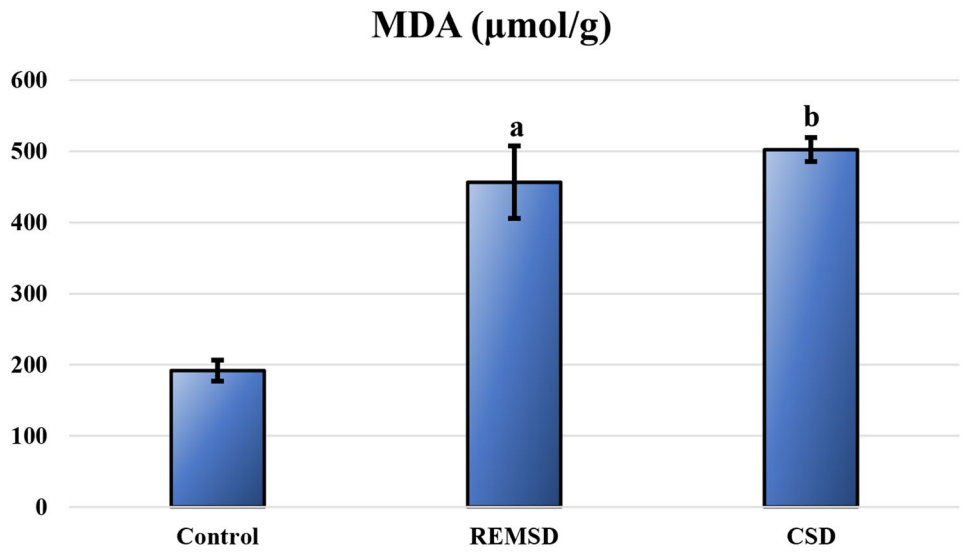

Fig. 2 Comparison of brain MDA levels in three groups: Control, REMSD, and CSD. **a** *p*= 0.036 Control vs. REMSD; **b** *p*=0.031 Control vs. CSD MDA, malondialdehyde; CSD, control sleep deprivation group; REMSD, rapid eye movement sleep deprivation group

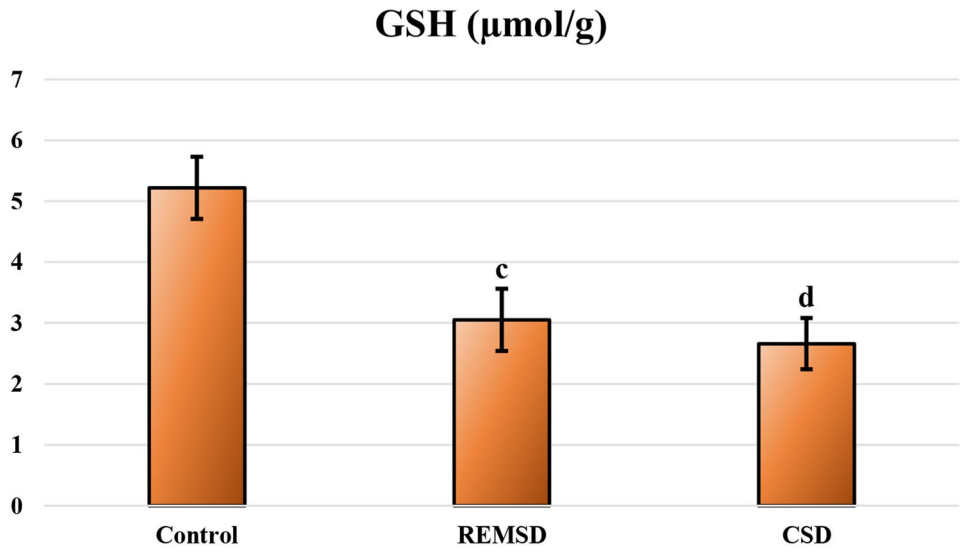

Fig. 3 Comparison of brain GSH levels in three groups: Control, REMSD, and CSD. **c** *p*= 0.026 Control vs. REMSD; **d** *p*=0.024 Control vs. CSD GSH, glutathione; CSD, control sleep deprivation group; REMSD, rapid eye movement sleep deprivation group

Discussion

The present study investigated the effects of REM sleep deprivation on oxidative stress and BDNF, a neuroprotection biomarker, in the brain tissue of male Wistar rats. Our findings suggest that both REM sleep deprivation and control sleep deprivation models induce oxidative stress in the brain, as evidenced by increased MDA levels and decreased GSH and NO levels. These findings support previous research demonstrating the detrimental

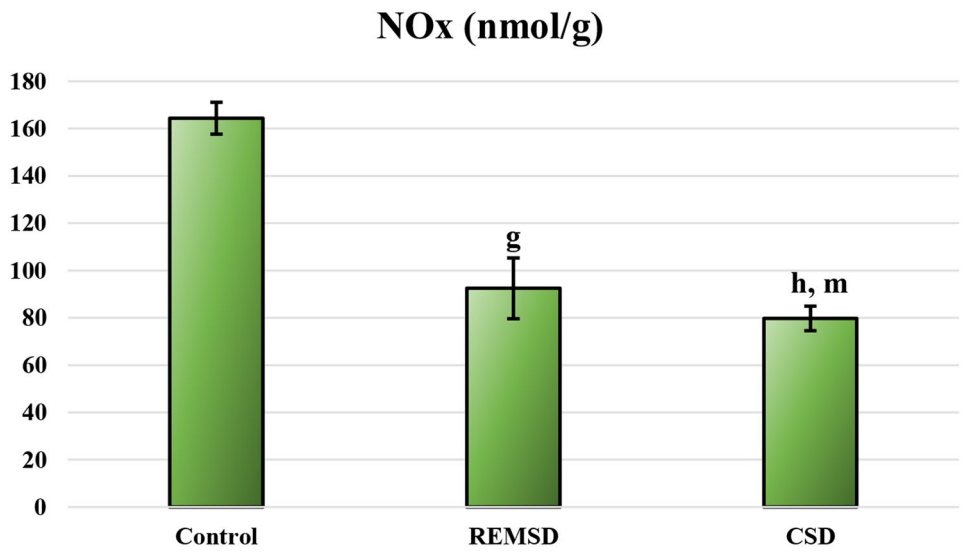

Fig. 4 Comparison of brain NOx levels in three groups: Control, REMSD, and CSD. **g***p*= 0.021 Control vs. REMSD; **h***p*=0.015 Control vs. CSD; **m***p*= 0.011 REMSD vs. CSD. NOx, nitrite/nitrate; CSD, control sleep deprivation group; REMSD, rapid eye movement sleep deprivation group

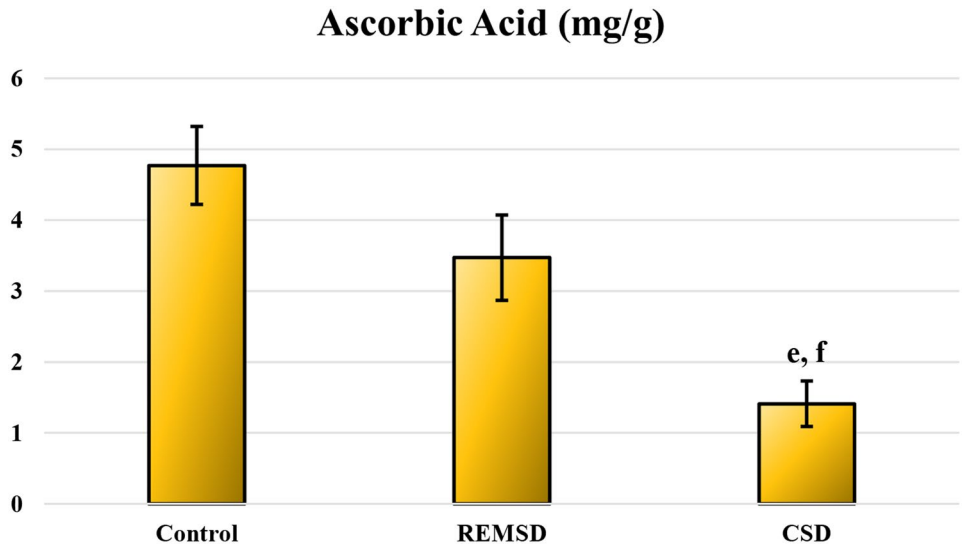

Fig. 5 Comparison of brain AA levels in three groups: Control, REMSD, and CSD. **e***p*= 0.033 Control vs. CSD; **f***p*=0.044 AA, Ascorbic Acid; CSD, control sleep deprivation group; REMSD, rapid eye movement sleep deprivation group

effects of sleep deprivation on brain oxidative balance. While both REM sleep deprivation and control sleep deprivation models induced oxidative stress, serum BDNF levels did not differ significantly between the groups. Brain tissue ascorbic acid (vitamin C) levels were significantly lower only in the control sleep deprivation group compared to controls. By contrast, brain tissue BDNF levels were statistically higher in the control sleep deprivation group compared to the control group but there were no statistically significant differences between the REM sleep deprivation group and the control and control sleep deprivation group.

During sleep, the brain is protected against free radicals by increased antioxidant activity and decreased production of reactive oxygen species [15]. Due to their structural diversity, antioxidants act as a first line of defense by neutralizing free radicals and preventing damage caused by reactive oxygen species (ROS) [16]. Previous studies have similarly demonstrated that sleep deprivation leads to an increase in MDA, which is in line with our findings [17]. Studies employing various sleep deprivation methods in different animal species, including rats, have consistently demonstrated a decrease in GSH and NO levels due to oxidative stress as a consequence of sleep deprivation [18]. The data in the current study demonstrate similar results.

BDNF is the most abundant neurotrophin in adult brain tissue. It controls the enhancement of long-term

memory potential by regulating neuronal plasticity [19]. The neurotrophic functions of BNDF are associated with a variety of physiological functions, particularly neuroplasticity, memory, and sleep [20]. The frontal cortex, olfactory bulb, and hippocampus are the regions in which BDNF is predominantly produced in the adult brain; it is transported retrogradely to the brain stem and basal ganglia [21].

Although BDNF is also produced in other cells, such as endothelium and peripheral blood mononuclear cells, cerebral cortical neurons are the main source of BDNF in the adult brain [19]. In addition, cortical BDNF is the main source of BDNF in plasma. BNDF, which is stored in high amounts in platelets, increases rapidly in the plasma during exercise and acute stress conditions [22].

The accumulation of BDNF in cortical GABAergic neurons during wakefulness plays an important role in physiological sleep regulation [23]. Cortical or intraventricular injection of BDNF increases slow-wave activity (SWA) and non-REM (NREM) sleep in rats [19, 20].

Depression decreases serum BDNF levels, and serum levels of BDNF increase with antidepressant therapy [24]. In addition, serum BDNF levels decrease when the duration of the NREM N3 sleep phase is reduced in sleep disorders [19, 25]. In various neurophysiological conditions, serum BDNF levels are almost always associated with mood and memory [26].

While the correlation between brain BDNF, especially in the cerebral cortex and hippocampus, and serum BDNF levels remains under investigation, the prevailing theory suggests their levels are similar. This is because cerebral cortical BDNF is considered the primary source of serum BDNF [27]. However, our results showed no difference in serum BDNF levels between the control group, REM sleep deprivation group, and control sleep deprivation group, whereas the brain BNDF level was significantly higher in the control sleep deprivation group. No significant difference was observed in brain BNDF levels in the REM sleep deprivation group compared to other groups.

The relationship between REM sleep deprivation and BDNF levels remains complex, with prior studies demonstrating diverse outcomes in both serum and brain tissue. For instance, Jiang et al. [28] observed elevated hippocampal BDNF following 48 h of REM sleep deprivation. However, Sei et al. [29] found no significant changes in hippocampal BDNF after 6 h of selective REM sleep deprivation. In addition to these findings, our study did not detect significant alterations in brain BDNF levels following REM sleep deprivation. In contrast to the results regarding REM sleep deprivation, our results indicating increased BNDF levels in the brain tissue in control sleep deprivation group, which are similar to those reported in previous studies, may be due to the deprivation of the NREM sleep component in total sleep deprivation [30, 31].

Fujihara et al. [31] reported a significant rise in hippocampal BDNF following non-selective sleep disruption for 3 and 6 h. Notably, their results showed a significant increase in the hippocampal BDNF level, but no change was observed in BDNF levels in the brain stem and cerebellum. The absence of a significant change in the brainstem, which contains the neural network responsible for the initiation and maintenance of the REM sleep period, suggests that an increase in BDNF gene expression after short-term sleep deprivation might not be directly linked to REM sleep alterations.

The increase in cortical BDNF level seen in short-term sleep deprivation is considered a homeostatic response to an increased sleep drive [19, 20]. Stress due to sleep deprivation disrupts the hypothalamic–pituitary–adrenal axis and thus the body's response to increased cortisol. This causes sleep disorders and makes the body vulnerable to stress [32].

Mahboubi et al. [33] employed a similar platform technique to induce REM sleep deprivation and reported no significant difference in BDNF levels between exercise and REM sleep deprivation groups of rats. However, their study observed a notable increase in BDNF levels in the post-exercise REM sleep deprivation group compared to either the exercise or the REM sleep deprivation group alone. This finding suggests a potential interaction between exercise and REM sleep deprivation in BDNF regulation, which warrants further investigation.

Studies investigating the effects of chronic sleep deprivation on BDNF levels have yielded conflicting results. These contrasting results highlight the complexity of how sleep deprivation impacts BDNF. Several factors, such as duration of sleep deprivation, allostasis, and sampling time, might contribute to these discrepancies.

Zielinski et al. [3] observed a region-specific response in rats. After 18 h of acute sleep deprivation, BDNF levels increased in all brain regions compared to controls. However, with chronic deprivation (3 and 5 days), BDNF expression increased in the basal forebrain but decreased in the cortex and hippocampus. However, Taishi et al. [34] reported an increase in cortical BDNF after 8 h of sleep deprivation, while hippocampal levels remained unchanged.

Wallingford et al. [35] observed a duration-dependent effect, with a greater BDNF increase in the frontal cortex, hippocampus, and basal forebrain after 27 h of sleep deprivation compared to 99 h. This suggests a potential ceiling effect or adaptation over time.

Huber et al. [36] showed an increase in the mRNA levels of BDNF in the cerebral cortex in rats after 6 weeks of sleep deprivation, and the increase in BDNF level was correlated with an increase with slow-wave (delta)

activity during sleep following sleep deprivation. In addition, while cortical BDNF injections increase SWA in NREM sleep, injections of antibodies that block BNDF function decrease this activity [20].

Our 21-day sleep deprivation study, in which we showed an increase in brain BDNF levels in control sleep deprivation, might have captured a different stage in this potential response timeline.

Deurveilher et al. [37] observed homeostatic changes in the form of a rebound increase in NREM and REM sleep stages and NREM electroencephalography (EEG) delta activity in intermittent sleep periods for 4 days in a 3/1 chronic sleep deprivation model. In their study, the increase in NREM delta activity seen in intermittent sleep periods for 4 days gradually decreased toward the end of the fourth day and disappeared after the end of sleep restriction. This has been interpreted as an allostatic response to chronic sleep deprivation. Previous studies [35, 37, 38] have shown an allostatic response to chronic sleep deprivation similar to that reported in the study by Deurveilher et al. [37]

BDNF reaches its highest level in the brain at midnight in rats while it is lowest in peripheral blood. BNDF fluctuates in reverse phases in the brain and blood [39]. This might explain why we observed increased brain BDNF without a corresponding change in blood BDNF levels.

We believe that the different results of BDNF levels after sleep deprivation in various studies may be because of differences in sleep restriction and sleep deprivation models.

Possible limitations of the study are the lack of EEG records, sex specificity, and brain region specificity. While this study found an overall increase in brain BDNF levels, it did not examine changes in specific regions.

Our results show a decrease in GSH and NO levels and an increase in MDA levels in the 21-day REM sleep deprivation and control sleep deprivation models, reflecting oxidative stress in the brain. Additionally, we report an increase in brain BDNF levels in control sleep deprivation model. Considering the role of BDNF in neural plasticity and its neuroprotective effects, we think that an increase in brain BNDF levels is a response to adaptation to chronic sleep deprivation.

Conclusion

In conclusion, the present study adds to the growing body of evidence on the complex relationship between sleep deprivation and BDNF levels. Our findings highlight the potential importance of distinguishing between REM sleep deprivation and total sleep deprivation when examining BDNF responses. To elucidate the lack of a statistically significant increase in brain tissue BDNF levels in the REM sleep deprivation group compared to the control sleep deprivation group and control group, future studies could employ a multiplatform sleep deprivation model, incorporating various cage configurations and disk sizes. By analyzing EEG recordings, these studies could assess whether the reduction in NREM 3 sleep phase contributes to this discrepancy. The question of whether BDNF changes are a direct result of insomnia or a response to the stress of sleep deprivation remains unanswered. Addressing this question will be vital for developing targeted interventions that modulate BDNF levels to improve sleep health in individuals with insomnia.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04127-2.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

YC, GY, and EGGP conceptualised and designed the study. YC, GY, SY and EGGP contributed to the collection and assembly of data. YC and EGGP wrote the first draft of the manuscript. All authors contributed to the data analysis, data interpretation, and writing—review and editing. All authors are accountable for all aspects of this work. All authors read and approved the final manuscript.

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Data availability

The data analysed in this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Giresun University Animal Research Local Ethics Committee (18.12.2018/17) and performed in accordance with the principles of The Declaration of Helsinki. We confirm that informed consent regarding use of animals in our study was obtained from the laboratory's authorized personnel.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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