Research Article

Sleep Recovery Improves Cognitive Function and Reduces Oxidative Stress and Beta-Amyloid Expression in the Hippocampus of Total Sleep-Deprived Adult Male Wistar Rats

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Abstract

Aim: Lack of sleep has been linked in studies to increased beta-amyloid levels, oxidative stress, and memory impairments. Furthermore, sleep is known to help clear toxins that accumulate in the brain.This study investigated the restorative potentials of recovery sleep on total sleep deprivation-induced memory impairment, oxidative stress, stress response and changes in beta amyloid plaques in the hippocampus of adult male Wistar rats. **Materials and Methods:** Twenty-four male Wistar rats weighing between 150 and 200 g were divided into four groups. Group I remained in their home cages, while Groups II, III, and IV underwent sleep deprivation for 5 days. Groups III and IV then had recovery periods of 7 and 21 days, respectively. Spatial learning and memory was measured using the Novel Object Recognition test. The rats were euthanized with ketamine, oxidative stress was analyzed using hippocampal tissue homogenate and beta-amyloid plaques in the CA1 and CA3 regions using Congo red stain. **Results:** Comparing the sleep-deprived group to the sleep-recovered group, the discrimination ratio increased significantly ($p < 0.0001$). Sleep recovery also decreased levels of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and malonaldehyde (MDA) and corticosterone ($p < 0.01$). Additionally, extracellular amyloid-beta expression in the CA1 and CA3 regions of the sleep recovery groups was significantly reduced ($p < 0.0001$ and $p < 0.01$). **Conclusion:** Recovery sleep was found to improve memory and decrease beta amyloid expression and oxidative stress in the CA1 and CA3 areas of the hippocampus.

Keywords: Sleep deprivation, sleep recovery, memory deficit, oxidative stress, beta amyloid

Introduction

These days, sleep deprivation (SD) is common among a substantial portion of the population, which is frequently brought on by things like drinking alcohol and caffeine, working shifts, being around a lot of light and noise, stress, anxiety, and a number of illnesses. [1] SD may also result from sleep disorders such as obstructive sleep apnea and insomnia. [1] Memory and mood are two cognitive functions that are adversely affected by SD. [2-3] Research has demonstrated that sleep deprivation either completely or partially impairs memory acquisition in rats [4-5], reduces working memory capacity and interferes with learning and memory. [6]

Evidence suggests that sleep is essential for memory and learning, with SD impairing hippocampus-dependent processes and sleep enhancing them. [7-8] Loss of sleep is a stressor that triggers the sympathetic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis. [9] According to Aliahmat et al. [10], SD raises oxidative stress, which results in higher levels of malondialdehyde and lower antioxidant enzyme activities. Sleep may help reduce oxidative stress by facilitating the removal of reactive species that have accumulated during wakefulness. [11] Sleep disturbances can change the body's ability to repair itself, which can impact behavior and disease susceptibility. [12]

Alzheimer's disease is caused by the buildup of beta-amyloid, a waste product that is present between neurons and affects communication and brain function. [13] Studies have shown that poor sleep is associated with elevated beta-amyloid levels [14-15], and human imaging studies have linked poor sleep to elevated amyloid burden. [16-17] Since elevated amyloid burden can also affect sleep, this relationship is bidirectional. [18] Impaired brain function is correlated with elevated amyloid levels. [19] Thus, this study investigated the restorative potentials of recovery sleep on total sleep deprivation-induced memory impairment, oxidative stress, stress response and changes in beta amyloid plaques in the hippocampus.

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Materials and Methods

Ethical approval was obtained from the Ahmadu Bello University Ethics Committee on Animal Use and Care by the institution's established policies and procedures, with permission number ABUCAUC/2024/034.

Experimental Animals Procurement and Maintenance

Twenty-four (24) apparently healthy male Wistar rats (150 g – 220 g) were used for this study. The rats were obtained from the Animal House Facility, Department of Human Anatomy, Faculty of Basic Medical Sciences, Ahmadu Bello University (ABU), Zaria, Nigeria. The rats were housed in clean plastic cages with soft wood shavings as bedding. The rats were allowed access to a standard rat pellet diet (rat chow-vital feed) and clean drinking water *ad libitum* in the Neuroscience Laboratory, Department of Human Anatomy, Faculty of Basic Medical Sciences, (ABU), Zaria. The rats were maintained in this condition for two weeks to acclimatize before the commencement of the experiment.

Chemicals and Assay Kits

75 mg/kg ketamine hydrochloride (Randlab, Australia), 10 % formal saline, xylene, alcohol and phosphate buffered solution (PBS), Rat superioxide dismutase (SOD), catalase (CAT), reduced gluthathione (GSH) malondialdehyde (MDA), and corticosterone (CORT) assay kits (Bio diagonistic Co, Cairo Egypt).

Experimental design

A total of twenty-four male Wistar rats were divided into four groups (I-IV), each consisting of six rats. The rats in Group I (Control), remained in their home cages for the duration of the experiment. For five days, rats in groups II, III, and IV were sleep-deprived for twenty-four hours every day. [20-21] Groups III and IV rats, on the other hand, were allowed a 7-day and 21-day sleep recovery period in their home cages, respectively.

Induction of Rapid Eye Movement (REM) Sleep Deprivation (SD)

Rapid Eye Movement (REM) Sleep Deprivation (REM-SD) was induced using the Modified Multiple Platform (MMP) method, as described by Machado et al. [22] The 120 x 46.5 x 44.5 cm sleep deprivation tank was constructed from plastic material with ten circular platforms adhered to the bottom. These platforms are 6.5 cm tall and 8 cm in diameter, with 13 and 10 cm between them horizontally and vertically, respectively. To prevent the rats from getting out, wire mesh is used to enclose the tank. The tank was filled with water up to 1 cm from the top of the platform.

For five consecutive days rats from the same group were kept in the sleep deprivation tank for twenty-four hours each. The rats could jump from one platform to another to move about the tank. As a result of the REM sleep-related loss of muscle tone, the rats wake up whenever they come into contact with the water. A feeding trough was hung around the wall of the sleep deprivation tank, and water bottles were set up on top of the enclosed wire mesh to provide the rats with unfettered access to water and standard rat chow.

Every day after the Wistar rats were taken out of the tank, the water was replaced, and they were put back in right away. [88] Following five days of complete sleep deprivation, the Wistar rats in groups III and IV were put back in their home cages for seven and twenty-one days, respectively, to recuperate. Prior to being deprived of sleep, the rats were habituated to the modified multiple platforms for two days (one hour per day). The modified multiple platform was selected for this study because they do not hinder social isolation or mobility.

Novel Object Recognition (NOR) Test for Short Term Memory

The Novel Object Recognition test (NOR) was used to assess short term memory in the rats. The apparatus consists of a wooden square chamber (40 cm length x 40 cm breadth x 40 cm width) with high walls. This test measures the ability of rats to recognize a novel object in an otherwise familiar environment. It is based on rodents' natural tendency for exploring novel things, without the need for reinforcers. This is a common test to assess short-term memory. [23] In the novel object recognition test, rat's interest in a novel object versus a familiar one is measured and compared. The time spent by the rat exploring each object is calculated. If the exploration of the novel and the familiar object is equal, this can be interpreted as a memory deficit. The novel object index (NOI), which is the time spent exploring the novel object divided by the time spent exploring the two objects, was used to evaluate recognition memory formation. [24]

Parameters that were assessed include the duration (in seconds) spent exploring the familiar object (TF), the time (in seconds) spent exploring the novel object (TN), and the total time (in seconds) spent exploring both objects (TF + TN). The percentage of the discrimination index (DI) was determined by using the equation below:

$$DI\ (\%) = \frac{TN}{(TN+TF)} \times 100\ \%$$

Animal Euthanization

After 5 days of total sleep deprivation for groups II, III, and IV, followed by 7 days of recovery for group III and 21 days for group IV, the rats were anesthetized with 75 mg/kg of ketamine. The rats were humanely euthanized and blood sample was collected via cardiac puncture and the serum obtained was used to estimate corticosterone level. The brains were removed and, the hippocampus dissected out from one half of the cerebral hemisphere and immediately homogenized in 0.1 molar 7.4 pH phosphate buffered saline (PBS). The homogenate was centrifuged 3000 rpm/minute and supernatant obtained was used for biochemical analysis. The remaining half of the brains were harvested and fixed in 10 % formal saline for 48 hours for proper fixation. The fixed brain samples were taken to the Histological Unit of the Department of Human Anatomy, ABU, Zaria for histological processing.

Assessment of Hippocampal Lipid Peroxidation (MDA) Activity Levels

Lipid peroxidation was determined as thiobarbituric acid reactive substance according to Ohkawa *et al.* [25] with modification by Atawodi *et al.* [26] using 15 % trichloroacetic

acid (TCA) and 0.67 % of thiobarbituric acid (TBA). Lipid peroxidation generates peroxide intermediate which upon cleavage releases malondialdehyde, a product that reacts with thiobarbituric acid to give a colored complex product that absorbs light at 353 nm and can hence be measured. The 2 ml of 15 % trichloroacetic acid was measured in a test tube. Then 2 ml of thiobarbituric acid and 100 µl of tissue homogenate was added. The mixture was incubated at 80 ºC for 30 minutes in a water bath and allowed to cool for some time, after which it was centrifuged at 3000 rpm for 10 minutes. A clear supernatant was collected and the absorbance was determined at 535 nm in a spectrophotometer.

Assessment of Hippocampal Catalase (CAT) Activity Levels

Catalase (CAT) activity was measured using the method of Abebi [27] Firstly 10 µl of supernatant was added to a test tube containing 2.80 ml of 50 mM potassium phosphate buffer (pH 7.0). The reaction was initiated by adding 0.1 ml of freshly prepared 30 mM of hydrogen peroxide (H_20_2) and the decomposition rate of hydrogen peroxide (H_20_2) was measured at 240 nm for 5 minutes on a spectrophotometer. Molar extinction coefficient € of 0.041 mM^{-1} cm^{-1} was used to calculate the activity.

Assessment of Hippocampal Superoxide Dismutase (SOD) Activity Levels

Superoxide dismutase activity was determined by the method reported by Fridovich [28]. About 0.1 ml of microsome was diluted in 0.9 ml of distilled water to make a 1:10 dilution of microsome. An aliquant mixture of 0.20 ml of the diluted microsome was added to 2.5 ml of 0.05 M carbonate buffer. The reaction was initiated with the addition of 0.3 ml of 0.3 mM adrenaline and 0.20 ml of distilled water. Absorbance was measured every 30 seconds up to 150 seconds at 480 nm.

Assessment of Hippocampal Glutathione Peroxidase Activity Levels

Glutathione peroxidase concentration was performed with the method described by Ellman [29] based on the development of a yellow colour when DTNB (5, 5'-Dithio-Bis (2-Nitrobenzoic Acid) is added to the compound containing sulfhydryl groups in bried. 0.8 mL of tissue homogenate was added to 0.2 ml of 0.25 % sulphosalylic acid and the tubes was centrifuged at 2500 rpm for 15 minutes. The supernatant (0.5 ml) was mixed with 0.025 ml of 0.01 M DTNB and 1 ml TBS (pH 7.4). Finally, absorbance at 412 nm was recorded. Total glutathione peroxidase content was expressed as nmol/mg.

Assessment of Hippocampal Corticosterone Activity Levels

The collected blood sample was centrifuged at 3,000 rpm, for 15 min. The obtained blood serum was aliquoted and stored at -20˚C. The determination of corticosterone level was performed using the ELISA kit, the mean value of absorbance of the standards against concentration. The values of the samples were interpolated on the standard curve to obtain the corresponding values of the concentrations expressed in ng/ml.

Assessment of Beta Amyloid Plaques Using Congo red stain

Processed tissue were sectioned at a thickness of 8 µm using a microtome. The sections were then mounted onto glass slides and allowed to dry. The tissue sections were then stained with a saturated aqueous solution of Congo red for 30 minutes, followed by washing in 80 % ethanol with 0.2 % NaOH, to remove excess stain. The stained sections were then dehydrated in ascending concentrations of ethanol, cleared in xylene, and cover-slipped using a mounting medium. After staining, Aβ deposits appear as bright red, apple-green birefringent structures under the microscope. The birefringence of Congo red-stained Aβ deposits is due to the alignment of the beta-pleated sheet structure of Aβ fibrils with the polarized light. [30] Quantification of beta-amyloid plaques was performed using ImageJ software from the captured photomicrographs.

Data Analysis

All data obtained were analyzed using graph pad prism (version 9.5.1) and the results expressed as mean ± SEM (standard error of mean). The differences between the groups were analyzed using analysis of variance (ANOVA) followed by Turkey *post hoc* test. Values of $P<0.05$ were considered statistically significant and the results obtained were presented in graphs.

Results

Effect of Total Sleep Deprivation and Sleep Recovery on Novel Object Recognition (NOR) Test Discrimination Ratio

The effect of total sleep deprivation and sleep recovery on the discriminatory power of the Novel Object Recognition (NOR) test is shown in Figures 1A and 1B.

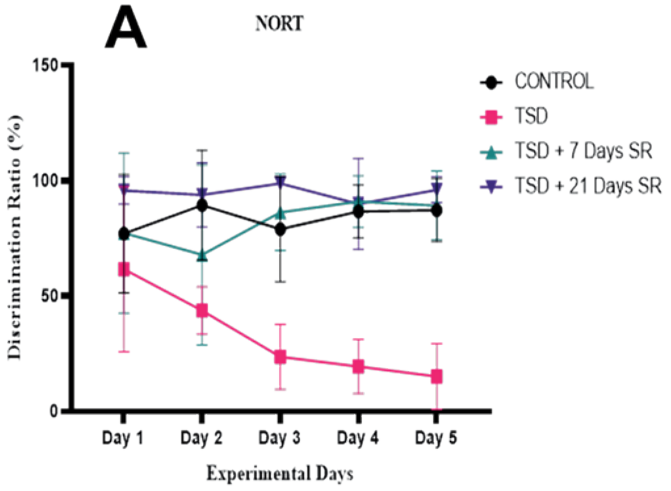

Figure 1A: Effect of total sleep deprivation and sleep recovery on short-term memory using Object Recognition test. (A)

The result revealed a significant decrease ($p < 0.05$) in the discrimination ratio of the sleep-deprived group (5 days total sleep deprivation) when compared to the control group (not subjected to sleep deprivation) and sleep recovery groups (7 days sleep recovery and 21 days sleep recovery) throughout the five days of the experiment **(Figure 1A).**

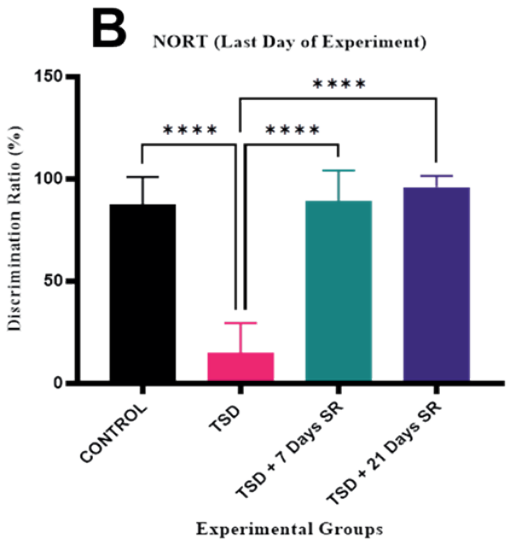

Figure 1B: Discrimination ratio (%) across five days of sleep deprivation and last five days of sleep recovery. n = 6, mean ± SEM, Two-way (Mixed effect) ANOVA, Tukey post hoc test, *0.05 statistically different. (B) Discrimination ratio (%) on the last day of sleep deprivation and sleep recovery. n = 6, mean ± SEM, One-way ANOVA, Tukey's post hoc test, ****0.0001 statistically different. TSD = Total Sleep Deprivation; SR = Sleep Recovery; CONTROL = Not Subjected to Sleep Deprivation.

There was a significant decrease ($p < 0.001$) in the discrimination ratio in the sleep-deprived group (5 days total sleep deprivation) with mean value of 15.15 ± 6.384 % when compared to the control group (not subjected to sleep deprivation) with mean value 87.2 ± 6.096 % in the last day of the experiment. However, there was a significant increase ($p < 0.05$) in the discrimination ratio in the sleep recovery groups (7 days sleep recovery and 21 days sleep recovery) with mean values of 89.135 ± 6.654 and 95.962 ± 2.476 % respectively when compared to the sleep-deprived group (5 days total sleep deprivation) with mean value of 15.15 ± 6.384 % in the last day of the experiment **(Figure 1B).**

Effect of Total Sleep Deprivation and Sleep Recovery on Serum Corticosterone Levels

The effect of total sleep deprivation and sleep recovery on serum corticosterone levels in adult male Wistar rats is shown in Figure 2.

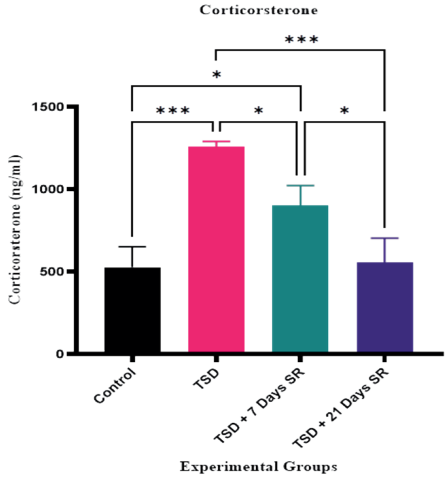

Figure 2: Effect of total sleep deprivation and sleep recovery on serum corticosterone levels in adult male wistar rats. n = 6, mean ± SEM, One-way ANOVA, *Tukey's post hoc* test, *0.01 ***0.0001 statistically different. TSD = Total Sleep Deprivation; SR = Sleep Recovery; CONTROL = Not Subjected to Sleep Deprivation.

The result of corticosterone revealed a significant increase ($p<0.0001$) in the corticosterone levels in the sleep-deprived group (5 days total sleep deprivation) with mean value 1258.13 ± 19.04 ng/ml when compared to the control group (not subjected to sleep deprivation) with mean value 527.687 ± 72.37 ng/ml. Whereas, a significant decrease ($p<0.05$) in corticosterone level was observed in the sleep recovery groups (7 days sleep recovery and 21 days sleep recovery) with mean values 903.137 ± 69.83 ng/ml and 557.17 ± 85.05 ng/ml respectively when compared to the sleep-deprived group (5 days total sleep deprivation) with mean value 1258.13 ± 19.04 ng/ml **(Figure 2).**

Effect of Total Sleep Deprivation and Sleep Recovery on Hippocampal Malondialdehyde (MDA) Levels

The effects of total sleep deprivation and sleep recovery on oxidative stress biomarkers: (A) Malondialdehyde (MDA) and (B) Catalase (CAT). (C) Superoxide dismutase (SOD) (D) Glutathione (GSH) is shown in Figures 3A, 3B, 3C and 3D.

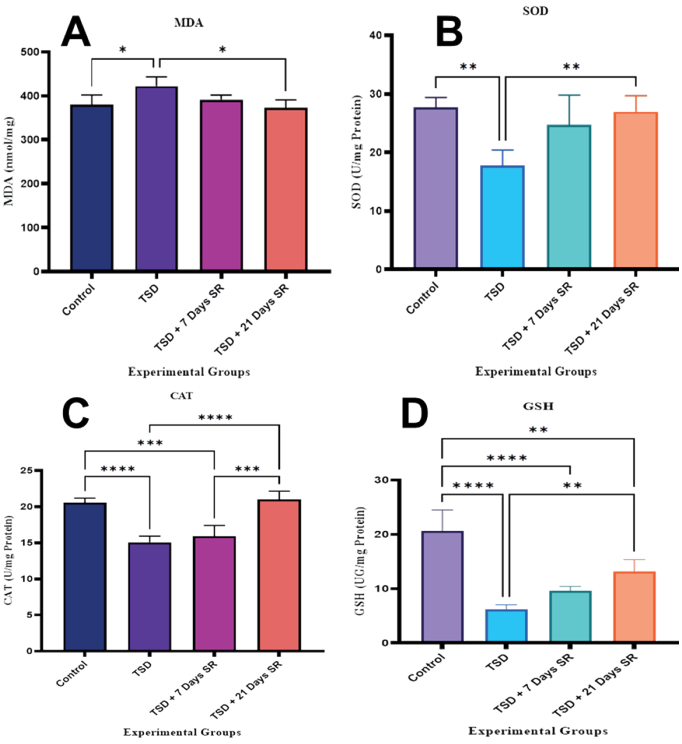

Figure 3: Effect of total sleep deprivation and sleep recovery on oxidative stress biomarkers. (A) Malonaldehyde (MDA) (B) Catalase (CAT). (C) Superoxide dismutase (SOD) (D) Glutathione (GSH). n = 6, mean ± SEM, One-way ANOVA, *Tukey's post hoc* test, **0.001, **0.05, ***0.001, ****0.0001 statistically different. TSD = Total Sleep Deprivation; SR = Sleep Recovery; CONTROL = Not Subjected to Sleep Deprivation.

Hippocampal MDA levels significantly increased ($p < 0.05$) in the sleep-deprived group (5 days total sleep deprivation) with mean value 422.5 ± 10.67 nmol/mg when compared to the control group (not subjected to sleep deprivation) with mean value 380.175 ± 10.91 nmol/mg. However, a significant decrease ($p < 0.05$) in MDA level was observed in the 21 days sleep recovery group with mean value 373.525 ± 8.756 nmol/mg when compared to the sleep-deprived group (5 days total sleep deprivation) with mean value 422.5 ± 10.67 nmol/mg **(Figure 3A).**

Effect of Total Sleep Deprivation and Sleep Recovery on Hippocampal superoxide Dismutase (SOD) Activity Levels

Hippocampal SOD activity levels significantly decreased ($p<0.05$) in the sleep-deprived group (5 days total sleep deprivation) with mean value 17.80 ± 1.316 U/mg when compared to the control group (not subjected to sleep deprivation) with mean value 27.70 ± 0.852 U/mg. Meanwhile, there was a significant increase ($p<0.05$) in the SOD activity levels in the 21 days sleep recovery group with a mean value 26.97 ± 1.371 U/mg when compared to the sleep-deprived group (5 days total sleep deprivation) with mean value 17.80 ± 1.316 U/mg **(Figure 3B).**

Effect of Total Sleep Deprivation and Sleep Recovery on Hippocampal Catalase (CAT) Activity Levels

Hippocampal CAT activity levels significantly decreased ($p<0.05$) in the sleep-deprived group (5 days total sleep deprivation) with mean value 15.05 ± 0.4349 U/mg when compared to the control group (not subjected to sleep deprivation) with mean value 20.57 ± 0.3038 U/mg. However, a significant increase ($p<0.05$) in CAT activity level was observed in the 21 days sleep recovery group with mean value 20.98 ± 0.5760 U/mg when compared to the sleep-deprived group (5 days total sleep deprivation) with a mean value 15.05 ± 0.4349 U/mg **(Figure 3C).**

Effect of Total Sleep Deprivation and Sleep Recovery on Hippocampal Reduced Glutathione (GSH) Activity Levels

Hippocampal GSH activity levels significantly decreased ($p<0.05$) in the sleep-deprived group (5 days total sleep deprivation) with mean value 6.23 ± 0.3923 U/mg when compared to the control group (not subjected to sleep deprivation) with mean value 20.65 ± 1.924 U/mg. However, a significant increase ($p<0.05$) in GSH activity level was observed in the 21 days sleep recovery group with mean value 13.13 ± 1.120 U/mg when compared to the sleep-deprived group (5 days total sleep deprivation) with a mean value 6.23 ± 0.3923 U/mg **(Figure 3D).**

Estimation of β – amyloid Expression in the CA1 and CA3 Regions of the Hippocampus

Microscopic images of the hippocampal section (CA1 and CA3) are shown in Figures 4A and 4B.

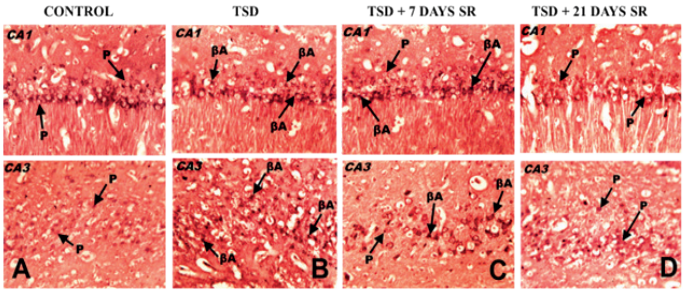

Figure 4: Photomicrograph of hippocampal (CA1 and CA3) section. (A) Control group with normal appearance of pyramidal cells (B) Group II (total sleep deprivation-only) with marked expression of amyloid-beta plaques (C) Group III (total sleep deprivation + 7 days of sleep recovery) with Moderate expression of amyloid-beta plaques (D) group IV (total sleep deprivation-only + 21 days of sleep recovery) with moderate expression of amyloid-beta plaques. Congo Red Stain (X250). Pyramidal cell (P); Cornu Ammonis (CA); Beta Amyloid (βA).

The effect of total sleep deprivation and sleep recovery on the mean grey matter volume of amyloid-beta plaques in the CA1 and CA3 regions is shown in Figure 5.

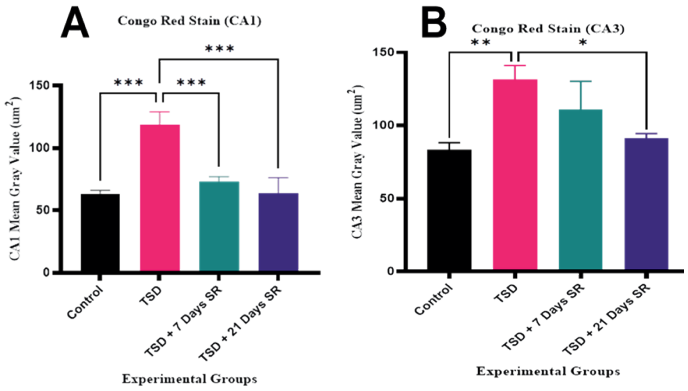

Figure 5: Effect of total sleep deprivation and sleep recovery on CA1 & CA3 mean gray area of amyloid-beta plaques. n = 6, mean ± SEM, One-way ANOVA, *Tukey's post hoc* test, ***0.0001 statistically different. TSD = Total Sleep Deprivation; SR = Sleep Recovery; CONTROL = Not Subjected to Sleep Deprivation.

The hippocampal CA1 and CA3 regions of the rats in the control group (not subjected to sleep deprivation) with decreased expression of amyloid-beta plagues**.** In contrast, a significant increase ($p<0.05$) in the expression of amyloid-beta plagues was observed in the CA1 and A3 regions of the hippocampus of the sleep-deprived group (5 days total sleep deprivation) was observed when compared to the control group (not subjected to sleep deprivation). Interestingly, a significant decrease ($p<0.05$) in the expression of extracellular amyloid-beta was observed in the CA1 and CA3 regions of the hippocampus of the recovery groups (7 days sleep recovery and 21 days sleep recovery) **(Figure 4A & B).**

Discussion

Lack of sleep has a major effect on memory, especially on the hippocampus, a part of the brain that is essential for memory and learning. [31-32] By utilizing rodents' innate propensity to investigate new objects, the novel object recognition (NOR) test evaluates short-term memory and makes assumptions about memory based on the amount of time spent investigating various objects. [33] Rodents that spend more time exploring the novel object demonstrate intact recognition memory and learning ability. [34]

In this study, Wistar rats that were sleep deprived showed a significantly lower discrimination ratio than the control group, suggesting that their recognition memory was compromised. Disrupted hippocampal synaptic plasticity, which is essential for memory consolidation, could be the cause of this deficit. [31,35] Lack of sleep is known to decrease dendritic spine density and long-term potentiation (LTP), both of which are essential for encoding and forming new memories. [31,36] Reduced object recognition memory can result from increased oxidative stress and inflammation brought on by sleep deprivation, which can harm neurons and interfere with synaptic function. [31,36] This is corroborated by Palchykova et al. [37], who revealed that mice who were sleep deprived following an acquisition phase were unable to discriminate between new and familiar objects, most likely as a result of compromised hippocampus synaptic plasticity. They concluded that sleep is important for memory consolidation.

According to a different study, sleep deprivation hampered attentional processing, which is essential for learning new information when performing the NOR task. Particularly, a 12-hour sleep deprivation prior to the task decreased preference for novel objects and attention to sample objects. [38] Similarly, a 12-hour REM sleep deprivation hampered memory consolidation, retrieval, and reconsolidation during the NOR task. [39] Moreover, rats that were sleep deprived spent more time with familiar objects and had trouble identifying new ones. [40]

But in the current study, the discrimination ratio in Wistar rats was significantly higher after 7 and 21 days of sleep recovery when compared to the sleep-deprived group. The role of recovery sleep in memory consolidation is well established, and it is enhanced by hippocampus replay while you sleep. [41-42] Sleep is the primary time for memory consolidation, which stabilizes recently learned memories. [41]. For various aspects of memory processing, both rapid eye movement (REM) and slow-wave sleep (SWS) are essential. [43] The brain strengthens synaptic connections during SWS by replaying neuronal activity linked to previously encoded information. [44] Emotional and procedural memory processing is facilitated by REM sleep. [41] Furthermore, sleep controls key genes involved in memory processing and synaptic plasticity, including immediate early genes and transcription factors that regulate neuronal activity and long-term synaptic modifications. Among these are activity-regulated cytoskeleton-associated protein (Arc), c-Fos, and brain-derived neurotrophic factor (BDNF), which are critical for synaptic strengthening, neuronal signaling, and memory consolidation. [45] This study supports others that demonstrate how recovery sleep improves memory impairments brought on by sleep deprivation in the NOR test. In contrast to the performance deficits seen in mice that were sleep deprived, Palchykova et al. [37] showed that delayed sleep facilitated memory consolidation. Rats' performance on a serial NOR task further demonstrated that sleep deprivation hampered short-term recall, but that performance improved after recovery sleep. [40]

Researchers are now paying a lot of attention to oxidative stress because of its role in cellular damage. Oxidative damage to proteins, fats, nucleic acids, and carbohydrates is caused by an imbalance between free radicals and antioxidants.[46] Due to the overproduction of reactive oxygen species (ROS) and the biological systems' incapacity to detoxify them, this imbalance can damage proteins, lipids, and DNA, which can lead to a number of pathophysiological conditions.[47] By compromising neuronal function and neurotransmission, oxidative stress is associated with neurodegenerative diseases like Parkinson's and Alzheimer's.[48] Remarkably, the hippocampus and frontal lobe are predominantly susceptible, impacting memory and learning. [48-49] Lack of sleep makes ROS buildup worse, which increases the risk of neurodegenerative diseases and cognitive decline. [50] Research indicates that sleep deprivation decreases antioxidant defenses in key brain regions and increases oxidative stress markers. [51-52]

In this study, rats that were sleep deprived showed significantly higher levels of hippocampal malondialdehyde (MDA), which suggests increased oxidative stress and lipid peroxidation. One of the main sources of ROS in the brain, mitochondrial function, is known to be hampered by sleep deprivation. [53] Lack of sleep causes mitochondria to become less effective, which raises the production of ROS. [54] Oxidative damage results from antioxidant systems being overloaded.[55] Additionally, lack of sleep causes neuroinflammation, which intensifies oxidative stress by activating glial cells and releasing pro-inflammatory cytokines.[56] Furthermore, sleep deprivation decreases antioxidant enzyme activity and raises oxidative stress by disrupting the NRF2/HO-1 signaling pathway, which is essential for antioxidant defense.[11]

The association between increased MDA levels and sleep deprivation is supported by multiple studies. For instance, Chen et al.[12] reported elevated plasma MDA levels following a single night of sleep deprivation, while Coluk et al.[57] discovered that oxidative stress was induced in both REM and control sleep deprivation models. Nonetheless, the 21-day sleep recovery group showed notable drops in MDA levels, indicating that recovery sleep helps to lower lipid peroxidation and restore redox balance. Through the restoration of mitochondrial function and the reduction of neuroinflammation, recovery sleep restores antioxidant defenses that have been depleted during wakefulness and stress. [11-12]

Cellular protection against oxidative stress depends on SOD, a strong antioxidant[58] Superoxide radicals are catalyzed to change into less dangerous molecules.[59] In addition, glutathione and catalase are essential for reducing oxidative damage. [60] Sleep-deprived rats in the current study showed significantly lower levels of SOD, CAT, and glutathione, suggesting weakened antioxidant defenses. According to Davinelli et al.[11], this impairment might result from a disruption in NRF2 signaling, which lowers the production of these vital enzymes.

It's interesting to note that the 21-day recovery period improved the brain's capacity to fight oxidative stress by considerably raising hippocampus SOD, CAT, and glutathione levels in comparison to controls. In animal models, recovery sleep improves oxidative stress markers, normalizes antioxidant enzyme activities, and restores important antioxidants.[12] For example, Mathangi et al.[61] showed that changes in glutathione levels and lipid peroxidation were reversed by restorative sleep after REM deprivation.

In response to stress, the hypothalamic-pituitary-adrenal (HPA) axis causes the adrenal cortex to release the glucocorticoid steroid hormone corticosterone.[62] Psychological and physical stressors cause the hypothalamus to release corticotropin-releasing hormone (CRH). The adrenal cortex produces corticosterone in response to this hormone's stimulation of the pituitary gland's secretion of adrenocorticotropic hormone (ACTH).[62] Energy, immune responses, and stress responses are all significantly influenced by corticosterone.[63] Even though it aids the body's reaction to short-term stress, long-term stress and persistently elevated corticosterone levels can overwhelm physiological systems, resulting in fatigue, hypertension, inflammation, and a weakened immune system.[64]

Lack of sleep has a direct impact on corticosterone levels by interfering with the HPA axis's regular operation and changing corticosterone secretion.[65] The stress response brought on by sleep deprivation is frequently linked to elevated corticosterone, whereas decreased corticosterone may suggest a change in the HPA axis state.[66] These modifications may have an impact on the body's stress response and sleep architecture, which may have metabolic and cognitive repercussions.[67] In the current

study, the sleep-deprived group's plasma corticosterone levels were significantly higher than those of the control group, suggesting that the HPA axis was activated and that the stress response was heightened. This activation implies that sleep deprivation interferes with regular physiological functions, causing the hypothalamus to release CRH, which in turn stimulates the secretion of ACTH and, ultimately, increases the production of corticosterone.[65] Loss of sleep may also interfere with the HPA axis's feedback systems. Sleep deprivation may disrupt the negative feedback mechanism that normally controls corticosterone's release, resulting in prolonged corticosterone secretion.[65] The findings of this study are consistent with earlier studies that found that experimental rodents with sleep deprivation had higher corticosterone levels.[65,68] Gao et al.[68] found that both REM fragmentation and REM deprivation resulted in higher corticosterone levels than baseline, indicating that continuous sleep disruption raises stress markers in a comparable way. In addition, Tartar et al.[69] discovered that rats with sleep disturbances had higher plasma corticosterone levels than controls.

However, a meta-analysis and systematic review of 24 studies revealed no discernible difference in total cortisol levels between participants who had normal sleep and those who had experienced acute sleep deprivation.[70] Even lower cortisol levels after sleep deprivation were reported in some studies. For example, Thompson et al.[66] discovered that young, healthy adults' morning cortisol levels dropped when they experienced acute sleep deprivation. Remarkably, when compared to the sleep-deprived group, corticosterone levels were significantly reduced after 7 and 21 days of sleep recovery. This decrease could be explained by recovery sleep's capacity to reset the baseline activity of the HPA axis, reestablishing regular feedback systems and lowering total corticosterone secretion. [71]

Slow-wave sleep (SWS), which has been demonstrated to suppress HPA axis activity and may help lower cortisol levels, is frequently increased during recovery sleep.[72] Due primarily to increased SWS during recovery, Vgontzas et al.[73] showed that sleep deprivation significantly decreased cortisol secretion the next day. In line with the current investigation, Voderholzer et al.[74] found that following a night of sleep deprivation, cortisol secretion returned to baseline levels during recovery sleep. Likewise, Meerlo et al.[75] discovered that corticosterone and ACTH levels rose during sleep deprivation but dropped back to normal after four hours of rest.

The membrane protein known as amyloid beta precursor protein (APP) is mostly present in neuronal synapses and is involved in both neural plasticity and synapse formation.[76] Amyloid-beta (Aβ) peptides, particularly the Aβ42 isoform, are produced from APP and aggregate to form amyloid plaques, a defining feature of Alzheimer's disease (AD). When these plaques build up, they interfere with neuronal signaling, which causes malfunction and cell death.[77] Notably, it has been demonstrated that lack of sleep raises Aβ levels in the brain, especially in areas linked to AD, because it hinders Aβ clearance and increases deposition, increasing the risk of neurodegeneration.[78]

In this study, we measured the amount of β-amyloid in the hippocampal CA1 and CA3 regions. The findings showed that lack of sleep increased β-amyloid buildup. This increased accumulation could be explained by a number of mechanisms. The disruption of the glymphatic system, which removes Aβ and other metabolic waste from the brain while you sleep, is one important mechanism.[79] Cerebrospinal fluid, which effectively flushes out toxins from the brain during deep sleep, is hampered by sleep deprivation, leading to an accumulation of Aβ.[80] Additionally, while neuronal firing decreases during slow-wave sleep, allowing Aβ clearance, increased neuronal activity during wakefulness encourages Aβ production.[81] Additionally, studies have shown that lack of sleep disrupt the balance between the production and clearance of Aβ, which increases the deposition of Aβ plaques.[82]

Several studies have reported that sleep deprivation increases the accumulation of Aβ, which is consistent with our findings. Using positron emission tomography (PET), Shokri-Kojori et al.[83] demonstrated that a single night of sleep deprivation significantly increased the Aβ burden in healthy adults' thalamus and hippocampal regions, which are particularly vulnerable in the early stages of Alzheimer's disease. Similarly, another study discovered that higher levels of Aβ in cerebrospinal fluid (CSF) and increased Aβ deposition were linked to shorter sleep duration and poorer quality of sleep.[84] While chronic sleep deprivation was associated with increased Aβ plaque formation in transgenic mice, Kang et al.[14] showed that acute sleep deprivation increased interstitial fluid Aβ levels.[78]

It's interesting to note that the recovery groups showed a notable decrease in Aβ expression in the hippocampal CA1 and CA3 regions. The removal of β-amyloid (Aβ) from the brain, especially in the hippocampus, depends heavily on sleep. The elimination of waste products, including Aβ, from the extracellular space is aided by the increased activity of the lymphatic system during sleep. [79]

Similar to the current study, a number of other studies have documented decreases in amyloid-beta (Aβ) levels while you sleep, highlighting the significance of sleep for Aβ clearance. Xie et al.[85] , for example, showed that Aβ is eliminated from the rodent brain much more quickly during slow-wave sleep (SWS) than during wakefulness, indicating that sleep improves the glymphatic system's capacity to eliminate Aβ. According to Ooms et al.[86], healthy middle-aged men who had one night of undisturbed sleep had a 6% drop in cerebrospinal fluid (CSF) Aβ42 levels, which was not seen following sleep restriction.

Furthermore, in a mouse model of Alzheimer's disease, Kang et al.[14] demonstrated that Aβ levels in the interstitial fluid rose during wakefulness and fell during sleep, demonstrating a clear connection between Aβ dynamics and the sleep-wake cycle. [87]

Conclusion

The study showed that sleep recovery enhanced cognitive function and reduced oxidative stress and beta-amyloid plaques expression in the hippocampus of total sleep-deprived adult male Wistar rats.

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Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

This experiment was authorized in compliance with ethical standards by the Ahmadu Bello University Ethics Committee on Animal Use and Care, with permission number ABUCAUC/2024/034.

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Conflict of interest

There is no conflict of interest to declare.

Author contributions subject and rate

- Ekpo Ubong Udeme (40%): Design the research, data collection and analyses and wrote the whole manuscript
- Umana Uduak Emmanuel (20%): Organized the research and supervised the article write-up.
- Abubakar Addamu Sadeeq (20%): Contributed with comments on research design and supervised the article write-up.
- Sohnap James Sambo (20%): Contributed with comments on manuscript organization write-up, supervised the article write up.

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