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Focus and Scope

The African Journal of Tropical Medicine and Biomedical Research is a multidisciplinary and international journal published by the College of Health Sciences, Delta State University of Abraka, Nigeria. It provides a forum for Authors working in Africa to share their research findings on all aspects of Tropical Medicine and Biomedical Sciences and to disseminate innovative, relevant and useful information on tropical medicine and biomedical sciences throughout the continent. The journal will publish original research articles, reviews, editorials, commentaries, short reports, case reports and letters to the editor. Articles are welcome in all branches of medicine and dentistry including basic sciences (Anatomy, Biochemistry, Physiology, Pharmacology, Psychology, Nursing etc) and clinical sciences (Internal Medicine, Surgery, Obstetrics and Gynaecology, Dental surgery, Child Health, Laboratory Sciences, Radiology, Community Medicine, etc). Articles are also welcome from social science researchers that document the intermediating and background social factors influencing health in countries of Africa. Priority will be given to publication of articles that describe the application of the principles of primary health care in the prevention and treatment of diseases.

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Journal Contact

All correspondence, including manuscripts for publication (in triplicate) should be addressed to:

Professor P.S. Igbigbi
The Editor-in-Chief,
Department of Anatomy,
Faculty of Basic Medical Sciences,
College of Health Sciences,
Delta State University, Abraka,
Delta State, Nigeria.

Or:
Professor Lawrence Omo-Aghoja
Editor
Department of Obstetrics and Gynecology,
Faculty of Clinical Medicine,
Delta State University, Abraka, Nigeria.
Email: journalajtmbr@yahoo.com
Cc: all email to
eguono_2000@yahoo.com
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The title page should include the following information: 1. the title and sub-title; 2. the name(s) of the author(s); 3. the affiliation(s) of the author(s); 4. name and address of the corresponding author and 5. three to six key words for indexing and retrieval purposes.

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Table of Contents

Duration-Dependent Post-Trauma Sleep Deprivation Differentially Modulates PTSD-Like Anxiety and Oxidative Markers in Mice

[*1]Ben-Azu B, [1]Omogbiya AI, [1]Ayereoghene SM, [2]Usin SG, [2]Oyovwi MO

Abstract

Introduction: Post-traumatic stress disorder (PTSD) is characterized by intrusive memories and persistent hyperarousal, with sleep playing a critical role in traumatic memory consolidation. While normal sleep supports memory refinement, post-trauma sleep disruption may shift outcomes toward fear retention or extinction. This study examined the duration-specific effects of post-trauma sleep deprivation (SD) on PTSD-like behaviors and oxidative neurobiological alterations.

Materials and Methods: Male Swiss mice (n = 10 per group) were subjected to the single prolonged stress (SPS) protocol, restraint, forced swimming, and ether exposure followed by varied SD regimens: no SD, daily SD for 2, 4, or 8 hours over 7 days, or a single 24-hour deprivation. Anxiety-related behavior was assessed using the light–dark box test. Oxidative stress markers, including superoxide dismutase (SOD), glutathione-S-transferase (GST), and sulphite oxidase (SO), were quantified in the hippocampus and prefrontal cortex.

Results: Brief SD (2–4 h daily) mitigated SPS-induced anxiety-like responses, increased GST activity, and normalized SO hyperactivity, suggesting interference with aversive memory consolidation and enhanced antioxidant defense. In contrast, prolonged daily SD (8 h) intensified anxiety and depleted antioxidant capacity, whereas a single 24-hour SD produced partial behavioral recovery with variable oxidative outcomes.

Conclusion: Post-trauma SD exerts duration-dependent, biphasic effects on PTSD-relevant behaviors and redox homeostasis. Limited SD promotes adaptive modulation by disrupting traumatic memory stabilization and enhancing antioxidant resilience, whereas extended deprivation aggravates oxidative imbalance and anxiety-like symptomatology.

Keywords: Post-traumatic stress disorder, Single prolonged stress, Sleep deprivation, Anxiety-like behaviour, Oxidative stress, Traumatic memory processing

[1]*DELSU Joint Canada-Israel Neuroscience and Biopsychiatry Laboratory, Department of Pharmacology, Faculty of Allied Health Sciences, College of Health Sciences, Delta State University, Abraka, Delta State, Nigeria.*
[2]*Department of Human Physiology, Faculty of Basic Medical Sciences, Delta State University of Science and Technology, Ozoro, Delta State, Nigeria.*

***Corresponding author:** Email: pharmben4ever@yahoo.com; bben-azu@delsu.edu.ng; Tell: +2348030881152
ORCID: https://orcid.org/0000-0003-3569-3575

INTRODUCTION

Characterized by intrusive recollections, chronic hyperarousal, and the avoidance of trauma-linked stimuli, post-traumatic stress disorder (PTSD) is a severe psychiatric condition triggered by exposure to extreme stressors such as combat or violence[1,2]. While the global annual prevalence is approximately 3.9%, these rates are significantly higher in populations with frequent trauma exposure, including refugees and military

personnel[3]. Established evidence suggests that the development of PTSD is closely tied to the maladaptive processing of traumatic memories, a process regulated by the complex interplay between sleep and the timing of trauma[4,5].

The stabilization and refinement of neural memory traces are fundamentally dependent on sleep architecture. Both rapid eye movement (REM) and non-REM sleep stages are critical for the consolidation and modification of memories[6,7]. REM sleep, in particular, facilitates emotional regulation through coordinated activity between the hippocampus and the amygdala[8,9]. However, in the context of PTSD, REM sleep may play a dualistic role: it can either promote the extinction of fear or reinforce traumatic memories, leading to persistent flashbacks[10–12]. The influence of sleep on trauma processing is closely regulated by the hypothalamic–pituitary–adrenal (HPA) axis. Acute glucocorticoid surges may transiently enhance memory consolidation; however, chronic HPA dysregulation disrupts synaptic plasticity and impedes fear extinction through sustained amygdala excitation and prefrontal inhibition[13,14].

Circadian misalignment, such as sleep deprivation (SD), profoundly influences the encoding and consolidation of traumatic memories. Its impact depends on both duration and temporal proximity to the traumatic event[15,16]. Acute SD immediately following trauma may disrupt fear consolidation by altering synaptic plasticity in the amygdala, hippocampus, and prefrontal cortex[17,18]. Conversely, prolonged or repeated SD intensifies oxidative damage, leading to impaired neurochemical homeostasis, behavioural regulation and delayed fear extinction[19–21]. Despite extensive studies on PTSD models such as single prolonged stress (SPS), which is a multimodal triple-hit model which mimics pathobiological features of PTSD[17,22], the role of post-trauma SD duration in shaping behavioural and neurobiological outcomes in the SPS model remains unknown. Hence, this study explores how varying intervals of post-trauma SD affect PTSD-like behaviour and associated brain changes in mice subjected to SPS. We evaluated anxiety-like phenotypes and measured markers of oxidative stress, including superoxide dismutase (SOD), glutathione-S-transferase (GST), and the molybdenum enzyme sulphite oxidase within the prefrontal cortex and hippocampus. We hypothesized that brief SD would exert neuroprotective effects by disrupting traumatic memory consolidation, whereas extended SD would exacerbate symptoms via oxidative imbalance. These findings aim to refine the "Sleep to Remember or Forget" hypothesis and contribute to the development of non-pharmacological early interventions for PTSD.

MATERIALS AND METHODS

Animal Use and Care

A total of 70 adult male Swiss albino mice (6–8 weeks old, 20–35 g) were used, randomly assigned to seven groups (n = 10 each). Sample size was determined a priori using effect sizes from previous PTSD studies[23]. Animals were obtained from the Animal House of the Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria. Animals were housed in standard plastic cages within a temperature-controlled environment (22 ± 3 °C) under a 12-hour light/dark cycle. They were provided unrestricted access to a balanced rodent diet and clean water. Mice were acclimated for at least two weeks prior to the start of the experiments. All experimental procedures were conducted in accordance with the ethical guidelines of the Faculty of Basic Medical Sciences, Delta State University, and approved by its Research Ethics Committee (RBC/FBMS/DELSU/25/935). Effect sizes reported in comparable prior studies were used to

inform sample size determination. The sample size for this study was determined based on previously reported effect sizes from previous studies[23,24].

Chemicals and Reagents

Trichloroacetic acid (TCA), thiobarbituric acid (TBA), Tris buffer, and 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Sodium hydrogen phosphate and other analytical-grade reagents were supplied by LOBA Chemie (India). All reagents were freshly prepared using distilled water and maintained at pH 7.4 unless otherwise stated

Experimental Design: SPS-Induced PTSD Model

The single prolonged stress (SPS) procedure was conducted between 9:00 a.m. and 2:00 p.m. following established protocols with minor modifications to incorporate sleep deprivation (SD) conditions[23–26]. Each mouse underwent a sequence of three stressors: Restraint stress - immobilisation for 2 hours in a ventilated restrainer; Forced swimming - 20 minutes in a transparent cylinder (50 cm height, 24 cm diameter) filled two-thirds with water maintained at 24 °C; Ether exposure - brief inhalation until loss of consciousness. After swimming, mice were dried and given a 15-minute recovery period before ether exposure. Following the SPS procedure, animals were subjected to sleep deprivation.

Sleep Deprivation (SD) Modelling and Animal Grouping

After completing the SPS procedure, the mice were randomly divided into seven groups of ten animals each. The first group served as the control and received no treatment. The second group was exposed only to the SPS procedure. The third group was used as a sleep deprivation control and experienced eight hours of sleep deprivation daily without SPS exposure. The remaining four groups were subjected to both SPS and different durations of sleep deprivation. These durations included two, four, or eight hours per day and night for seven consecutive days, as well as one group that experienced a single 24-hour period of sleep deprivation immediately after SPS exposure. Sleep deprivation began immediately following SPS. It was carried out using a modified grid-over-water technique, in which mice were placed on a metal grid positioned one centimetre above water in a plastic cage. The grid bars were spaced two centimetres apart, preventing the animals from entering sustained sleep but allowing them to move, eat, and drink freely. This setup effectively maintained wakefulness throughout the scheduled deprivation periods. At the end of the experimental phase, all animals underwent behavioural assessments designed to measure PTSD-like symptoms, including anxiety-related behaviours, exploratory activity, social interaction, and cognitive performance.

Behavioural Tests

Assessment of Anxiety-Like Behaviour

Anxiety-like behaviour was evaluated on the sixth day of the experiment using the light–dark box (LDB) tests. The LDB apparatus measured 21 × 42 × 25 cm and contained a light compartment (two-thirds of the box) and a dark compartment (one-third), separated by a small opening (3 × 5 cm). Each mouse was placed in the light compartment at the start of the test, and the number of transitions and time spent in each compartment were recorded for five minutes. After each trial, the apparatus was cleaned with 70% ethanol to remove residual odours and prevent scent-based bias.

Tissue Collection and Biochemical Analyses

Twenty-four hours after the final behavioural test

(day 8), mice were deeply anaesthetised with ketamine hydrochloride (100 mg/kg, intraperitoneally) and euthanised. Blood samples were collected via cardiac puncture into sterile 2 mL vials for corticosterone analysis. The brain was immediately removed and placed on an ice-cooled tray (4 °C). The prefrontal cortex and hippocampus, which are key regions implicated in PTSD due to their involvement in fear regulation, emotional control, and memory processing, were carefully dissected[27,28]. Brain tissues were homogenised in 1 mL of 0.1 M phosphate buffer (pH 7.4) and centrifuged under the same conditions. The resulting supernatants were collected into 1.5 mL vials and stored for biochemical analyses.

Assay for Oxidative Markers

Brain oxidative markers, including superoxide dismutase (SOD) and glutathione-S-transferase (GST). The activity of SOD was expressed as units per mg protein, with one unit defined as the amount of enzyme required to inhibit the rate of epinephrine autoxidation by 50%. The activity was expressed in Unit (U)/mg[29]. GPx activity was measured by mixing brain homogenate with phosphate buffer (0.1 M, pH 7.4), EDTA, sodium azide, glutathione reductase, GSH, NADPH, and H_2O_2. The rate of NADPH oxidation was monitored spectrophotometrically at 340 nm, and GST activity was expressed as nmol NADPH oxidized/min/mg protein[29].

Determination of Molybdenum Enzyme Activities

The activity of molybdenum-dependent enzyme, namely sulphite oxidase, was measured in the hippocampal and prefrontal cortex homogenates using spectrophotometric methods[29]. These enzymes are important indicators of oxidative metabolism and cellular stress. Sulphite oxidase activity was quantified by measuring the oxidation of sodium sulphite to sulphate, with absorbance read at 600 nm after forming a barium sulphate precipitate using barium chloride. The enzyme assays were carried out in 0.1 M phosphate buffer (pH 7.4) at 37 °C. Protein concentrations were determined using the Lowry method, and all measurements were performed in triplicate to ensure reliability and reproducibility.

Statistical Analysis

Data were analyzed using one-way or two-way ANOVA as appropriate, followed by Bonferroni's post hoc tests. Factors for two-way ANOVA included treatment (SPS/SD) and SD duration. Data normality was verified using the Shapiro–Wilk test, and outliers were defined as values >2 SD from the group mean. Results are presented as mean ± SEM, with significance set at $p < 0.05$.

RESULTS

Effect of Sleep Deprivation in Modulating Anxiety-Like Behaviours in a Duration-Dependent Manner in SPS-induced PTSD

Latency to enter the dark zone (Fig. 1a), a measure of avoidance behaviour, was significantly reduced by SPS ($p < 0.01$) compared to the saline control. However, SPS mice that underwent SD for 2 h ($p < 0.0001$), 4 h ($p < 0.01$), and 8 h ($p < 0.05$) had increased latency to dark compared to SPS, indicating amelioration of anxiety-like behaviour. Similarly, in the light-dark box (LDB) (Fig. 1b), SPS reduced time in the light compartment ($p < 0.0001$) but increased dark zone duration. The SPS with SD intervention for 2 h displayed an intensified avoidance behaviour ($p < 0.0001$), while those with 24 h of SD intervention after SPS had reversed ($p < 0.01$), suggesting that 24 h of SD immediately after traumatic events may reduce anxiety-related behaviour.

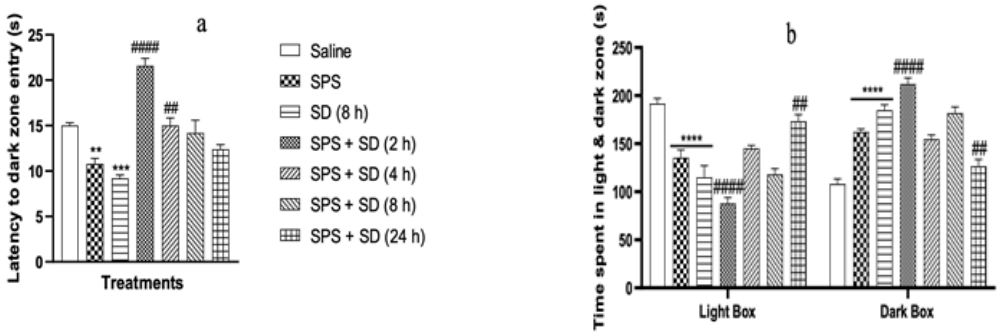

Fig. 1: Sleep Deprivation Modulates Anxiety-Like Behaviours in a Duration-Dependent Manner: (a) Latency to dark in light & dark box (LDB), (b) Time spent in light and dark zone. Bar are expressed as mean ± SEM (n = 10), ****p < 0.0001 vs Saline; ##p < 0.01, p < 0.001, ####p < 0.0001 vs SPS; where SPS = Single Prolong Stress, SD = Sleep Deprivation.

Effects of Sleep Deprivation on Anti-oxidative Levels in the Prefrontal Cortex and Hippocampus of Mice Exposed to SPS-induced PTSD

Fig. 2a shows that SPS significantly reduced GST activity in both the prefrontal cortex and hippocampus ($p < 0.0001$), denoting impaired phase II detoxification. SD (8 h) alone produced similar reductions ($p < 0.0001$) relative to the saline group. Notably, short-term SD (2–24 h) in SPS mice restored GST activity in the prefrontal cortex ($p < 0.001 – 0.0001$), suggesting compensatory antioxidant activation, except SPS + SD (8 h), which further suppressed GST ($p < 0.0001$). Regarding SOD activity, SPS decreased SOD activity in the prefrontal cortex and hippocampus ($p < 0.05$, $p < 0.0001$; Fig. 2b), whereas SD (8 h) reduced SOD activity only in the hippocampus ($p < 0.05$). Combined SPS + SD (8 h, 24 h) further lowered SOD activity ($p < 0.05$, $p < 0.001$), reflecting aggravated oxidative stress.

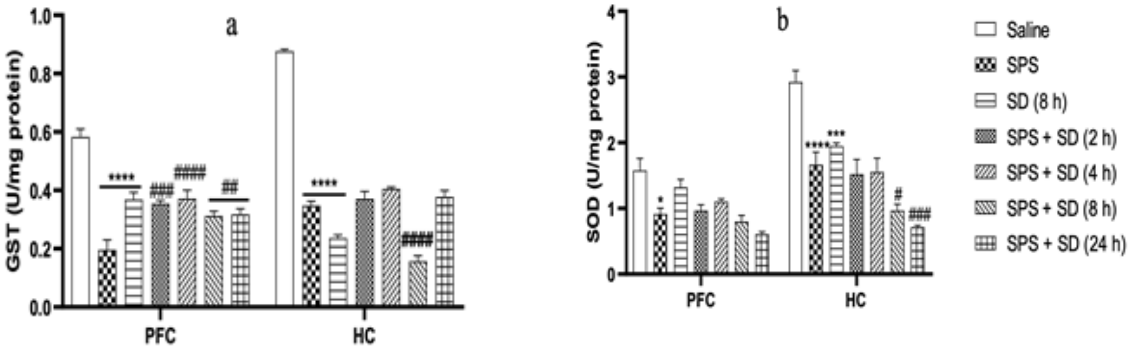

Fig. 2: Effects of Sleep Deprivation on Anti-oxidative Levels in the Prefrontal Cortex and Hippocampus of Mice Exposed to SPS-induced PTSD: (a) Glutathione-S-transferase (GST) and (b) Superoxide dismutase (SOD). Bar are expressed as mean ± SEM (n = 10), ****p < 0.0001 vs Saline; #p < 0.05, ##p < 0.01, ###p < 0.001, ####p < 0.0001 vs SPS; where SPS = Single Prolong Stress, SD = Sleep Deprivation.

Effects of Sleep Deprivation on Molybdenum Enzyme Activities in the Prefrontal Cortex and Hippocampus of SPS-induced PTSD Mice.

The effects of SPS and durations depended SD on molybdenum enzyme activity, sulphite oxidase in the prefrontal cortex and hippocampus are shown in Fig. 8c, SPS caused a significant rise in sulphite oxidase activity ($p < 0.001$) in the prefrontal cortex, while SD alone (8 h) produced a modest increase ($p < 0.05$). Short-term SD (2 h, 4 h) significantly reduced sulphite oxidase relative to the SPS ($p < 0.01$, $p < 0.001$), suggesting partial restoration of redox balance. Short-term SD (24 h) further elevated SO ($p < 0.05$), indicating enhanced oxidative enzyme expression and ROS generation (Fig. 3).

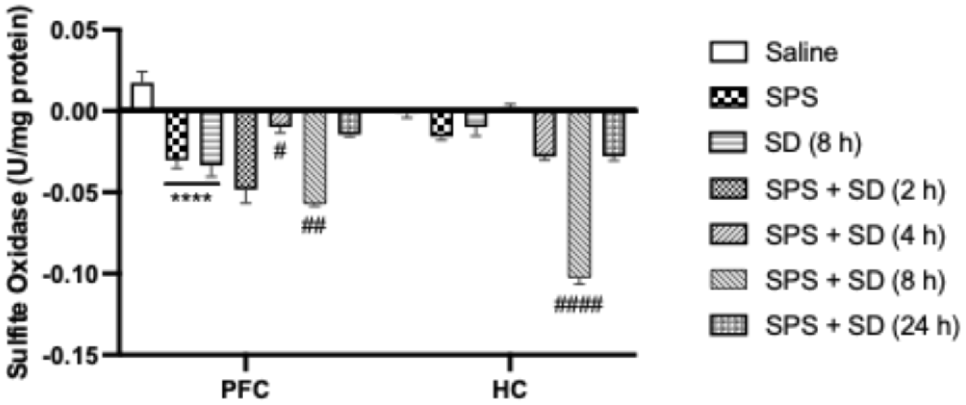

Fig. 3: Effects of Sleep Deprivation on Sulphite Oxidase in the Prefrontal Cortex and Hippocampus of SPS-induced PTSD Mice. Bars are expressed as mean ± SEM (n = 10), ****$p < 0.0001$ vs saline; #$p < 0.05$, ##$p < 0.01$, ####$p < 0.0001$ vs SPS; where SPS = Single Prolonged Stress, SD = Sleep Deprivation.

Discussion

The present study investigated how varying durations of post-trauma SD modulate anxiety-like behaviour and oxidative balance in mice exposed to SPS, an established model of PTSD. Using the LDB test and oxidative biomarkers, GST, SOD, and sulphite oxidase, we demonstrate that SD exerts duration-dependent, bidirectional effects on behavioural and biochemical indices of stress adaptation.

Exposure to SPS alone produced the expected behavioural signature of heightened anxiety and avoidance, evidenced by reduced latency to enter the dark compartment and prolonged time spent therein. These findings align with prior studies reporting that SPS evokes persistent hyperarousal and impaired risk appraisal through dysregulation of the amygdala–prefrontal–hippocampal circuitry[30,31]. When SD was introduced after trauma, its effects varied with duration. Brief SD periods (2–4 h daily) mitigated anxiety-like behaviours, increasing latency to dark entry and reducing avoidance tendencies. Conversely, extended wakefulness (8 h per day) worsened anxiety indices, while a single 24 h SD episode immediately after SPS partially normalized behaviour. This pattern suggests that both the timing and length of sleep disruption critically shape post-traumatic behavioural outcomes.

These behavioural patterns can be interpreted through the framework of sleep-dependent memory processing. Short, acute SD soon after

trauma may transiently interrupt consolidation of aversive memories, thereby dampening conditioned fear responses[17,18]. In contrast, chronic or poorly timed deprivation disrupts emotional regulation by exacerbating stress hormone release and impairing prefrontal inhibition of amygdala reactivity[32]. The partial anxiolytic effect observed with a single 24 h SD period may reflect adaptive recalibration of limbic circuits or compensatory neurotransmitter modulation that supports emotional recovery following acute stress exposure.

Oxidative stress parameters further support this biphasic interpretation. SPS markedly suppressed GST and SOD activities in the prefrontal cortex and hippocampus, consistent with depleted antioxidant capacity and elevated redox strain. Notably, short-term SD restored GST levels, suggesting activation of compensatory antioxidant mechanisms. In contrast, prolonged or repeated SD accentuated SOD depletion, indicating oxidative exhaustion. These findings suggest that brief SD may induce a preconditioning effect that strengthens redox resilience, whereas extended deprivation amplifies oxidative injury. Changes in sulphite oxidase (SO) activity reinforce this duality: reduced SO following short SD implies redox stabilization, while increased SO after prolonged SD or SPS reflects escalated reactive oxygen species (ROS) generation. Since SO is a key molybdenum-dependent enzyme involved in oxidative metabolism, its upregulation under stress likely represents both a marker and driver of cellular oxidative load[29,33]

Collectively, these results indicate that the influence of post-trauma SD on PTSD-like outcomes is duration-dependent and mechanistically linked to redox homeostasis. Brief, controlled SD may disrupt maladaptive fear consolidation and enhance antioxidant defence, whereas sustained wakefulness intensifies oxidative dysfunction and anxiety-like behaviour. These findings refine the "Sleep to Remember or Forget" framework by emphasizing the temporal window during which sleep manipulation can shift neural and biochemical recovery trajectories after trauma. Future work employing polysomnography and region-specific molecular assays will be valuable in delineating the precise neurochemical pathways through which SD duration governs adaptive versus pathological outcomes.

In conclusion, this study demonstrates that the behavioural and biochemical consequences of post-trauma sleep deprivation are distinctly duration-dependent in mice subjected to single prolonged stress. Short-term deprivation (2–4 h) after trauma alleviated anxiety-like behaviours and partially restored antioxidant enzyme activities, suggesting adaptive modulation of fear consolidation and redox balance. In contrast, extended or repeated deprivation exacerbated oxidative stress and behavioural disturbances, reflecting metabolic exhaustion and impaired emotional regulation. Alterations in glutathione-S-transferase, superoxide dismutase, and sulphite oxidase activities indicate that oxidative mechanisms are central to these effects. Together, the findings highlight that controlled timing and duration of sleep loss can differentially influence post-traumatic adaptation, offering new insight into the potential of sleep-based interventions as adjunct strategies for preventing or mitigating PTSD-like outcomes.

Compliance with Ethical Standards

All experiments received approval and were conducted in accordance with the guidelines of the Faculty of Basic Medical Sciences, Delta State University, Animals Ethics Committee (REC/FBMS/DELSU/23/187) and the National Institutes of Health Guide for the Care

and Use of Laboratory Animals (Publication number: 85-23, revised 1985).

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Declaration of competing interest
Authors declare that they have no conflict of interest

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