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# Hippocampal overexpression of IL-1β and TNF-α associated with Zinc loss secondary to psychological stress is mitigated in probiotic-treated rats

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## Abstract

**Background:** Psychological stress (PS) disrupts the gut microbiome, accelerates cognitive decline, and causes a predisposition to certain neurodegenerative diseases. This study was designed to test the hypothesis that the administration of probiotics has beneficial effects on the neurohistology and neurochemistry of the hippocampus following exposure to psychological stress (PS).
**Methods:** Thirty-five adult male Wistar rats weighing 180±5g were randomly assigned to seven groups (n=5) comprising the control, acute PS, acute probiotic treatment (probio), acute PS+probio, chronic PS, chronic probio, and chronic PS+probio groups. Acute stress and chronic PS or probio treatment lasted seven and 14 days, respectively. Each animal in the probio groups was fed 10×106 colony-forming units of lactobacillus acidophilus every other day. In contrast, the PS groups were exposed to predator stress for one hour between 7-10 am daily. The treatments lasted for 14 days. Following euthanasia, blood and hippocampal samples were collected for histology, and ELISA-based assays of interleukin-1β (1IL-1β), Tumor Necrosis Factor-α (TNF-α), dopamine, serotonin, malondialdehyde (MDA), catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH).
**Results:** Data analysis reveals that acute and chronic psychological stress significantly depresses hippocampal serotonin and dopamine levels, induces the overexpression of IL-1β and TNF-α, and causes increased lipid peroxidation and impaired antioxidant parameters. The probiotics groups exhibited statistically better results on all parameters assessed, including bringing hippocampal IL-1β and TNF-α levels toward normal. No obvious histoarchitectural damages were observed in any group.
**Conclusion:** Overall, this study suggests that the gut microbiome might play a significant role in hippocampal function as supplementing it mitigates stress-induced perturbations of hippocampal neurochemistry and redox status.

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## Highlights

**What is the current knowledge?** The negative impact of PS on the hippocampus, like on every other biological organ system, is a matter of scientific consensus. It is also known that gut microbiota significantly influences brain neurochemistry and function.

**What is new in this study**? This study demonstrates that the negative effect of PS is partly mediated via hippocampal overexpression of IL-1β and TNF-α and Zn loss. More importantly, this study shows that supplementing gut microbiota downregulates stress-induced elevated IL-1β and TNF-α and increases hippocampal Zn concentration. Consequently, it improves hippocampal redox status, suggesting probiotics' potential usefulness in stress management.

## Introduction

Psychological stress (PS) refers to the sensation of being under emotional strain and tension, whereas stressors are typically perturbations in the system or environment that threaten to disrupt the organisms' optimal functioning (1).

Predator-induced PS has been shown to affect the hippocampus, a brain structure deeply embedded in the temporal lobe of each cerebral cortex, regulating motivation, emotions, learning, and memory (2). Predator-induced PS increases glucocorticoid receptors in the hippocampus, decreases mineralocorticoid receptors, and induces detrimental changes to the hippocampal structure and functions, such as learning and memory (3).

Gut microbiomes comprising the collective genomes of micro-organisms in the gastrointestinal tract (GIT) can exert numerous effects on the intestinal neuroimmune system and influence various host functions (4). The impact of gut microbiota on the gut-brain axis has been further supported by studies on manipulating gut microbiota through probiotics and or antibiotics (5).

The concentration of secretory IgA (SIgA) in the gut is increased by probiotic strains such as Lactobacillus casei and Bifidobacterium, and Bifidobacterium particularly induces the immune cells to secrete IL-1 and IL-6 (6).

Subjection to stress reduces the abundance of lactobacillus species (7). Weaning stress reduces the abundance of Lactobacillus in the stomach, jejunum, and ileum while increasing the abundance of the pathogenic streptococcus seen in piglets' stomachs (8). A study that assessed the impact of PS on students during examination revealed that stress indeed reduces the number of Lactobacillus in humans (9). Infant monkeys showed reduced bifidobacteria and lactobacilli when subjected to prenatal stress by acoustic startle (10).

However, whether probiotics with these bacteria can mitigate stress-induced inflammatory responses is unknown. It is clear how much PS disrupts the gut microbiome; therefore, the present study hypothesized that the administration of probiotics should benefit either or both the neurohistology and neurochemistry of the hippocampus. Accordingly, this study aims to further elaborate on the hippocampal neurochemistry during PS and evaluate if supplementing gut microbiota affects stress-induced hippocampal changes.

## Methods

This research was conducted in strict compliance with the internationally accepted practices of laboratory animal use and care and approved by the Institution Research Ethics Committee (CMUL/ACUREC/01/15/1083) of the College of Medicine, University of Lagos, Idi-Araba, Lagos, Nigeria. Thirty-five sexually matured male Sprague-Dawley rats weighing 180±5g were obtained and maintained in the departmental Animal Holdings. The probiotic was obtained from CVS Pharmacy Ltd (Nigeria).

### Experimental design, drug administration, and stress induction

Following acclimatization, animals were randomized into seven groups of five rats, including the control, acute PS, chronic PS, acute PS+probiotic treatment (probio), chronic PS+probio, acute probio, and chronic probio groups. Animals

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in acute groups were euthanized after seven days of stress exposure and treatment with probiotics, while the chronic groups were euthanized on day 14.

One capsule containing 200 million colony-forming units of probiotics was dissolved in 1ml of distilled water and was administered orally daily to the probiotics-receiving groups. The rats in the stress groups were exposed to predator stress for one hour, between 7-10 am, as described by Figueiredo et al. (11).

### Sample collection

Following euthanasia by cervical dislocation, blood samples were collected via cardiac puncture into plain sample bottles for corticosterone measurement. The right hippocampus was recovered, formalin-fixed, and processed for H&E and Nissl staining. The left hippocampus was homogenized in ice-cold 0.1M PBS, centrifuged at 3000 rpm for 15 minutes, and used for biochemical assays.

### Measurement of corticosterone, serotonin, dopamine, IL-1β, TNF-α, MDA, SOD, CAT, and GSH

Biochemical assays of corticosterone, serotonin, dopamine, IL-1β, TNF-α, and zinc were done with commercially available ELISA kits (Biovision, San Francisco, USA) and done strictly according to manufacturer instructions. The MDA level was measured as described by Mihara and Uchiyama (12). The activity level of SOD was determined by the method described by Sun and Zigman (13). The catalase (CAT) activity was determined as reported by Aebi (14), and Glutathione (GSH) level was determined as described by Ellman (15).

### Statistical analysis

One-way ANOVA was performed with Bonferroni's multiple comparison post-test with GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, California). The statistical significance was set at $P<0.05$; data are reported with the mean's plus or minus standard error (±SEM).

## Results

### Effect of probiotics on serum corticosterone and Hippocampal dopamine and serotonin following exposure to PS

Significant elevation of corticosterone was observed in acute PS and acute PS+probio compared with any other group (Figure 1a). Dopamine is a neurotransmitter that mediates pleasure in the brain (Figure 1b). Exposure to acute and chronic predator stress significantly lowers dopamine levels in acute and chronic PS compared to control and other groups. Increased administration of probiotics showed no significant difference in dopamine levels in acute PS+probio and chronic PS+probio. Serotonin levels decreased significantly in rats exposed to acute and chronic predator stress compared with the control group (Figure 1c). Dopamine and serotine levels significantly increased in chronic PS treated with probiotics compared to the untreated groups.

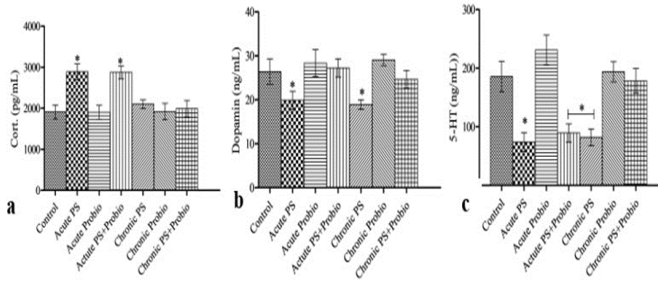


**Figure 1. Hippocampal dopamine and serotonin levels following exposure to PS and treatment with Probiotics. * in Figure 1a is significantly (P<0.030) higher compared to other groups, while it is significantly lower compared to other groups in 1b and 1c.**

### Hippocampal Redox status improved with probiotic supplementation following stressed-induced attenuation

A significant rise in MDA levels was observed in chronic PS compared to the control. MDA levels were significantly lower in acute probio, chronic probio, and chronic PS+probio (Figure 2a). Exposure to acute PS with or without probiotic treatment caused a significant rise in SOD activity compared with the control or any other group. At the same time, chronic PS significantly attenuated SOD activity compared to any other group (Figure 2b). CAT activity significantly decreased in chronic PS compared with any other group, while acute PS with or without probiotic treatment increased CAT activity (Figure 2c). The concentration of GSH significantly decreased in acute PS regardless of treatment with probiotics (Figure 2d). However, GSH significantly increased in the chronic PS+probio group.

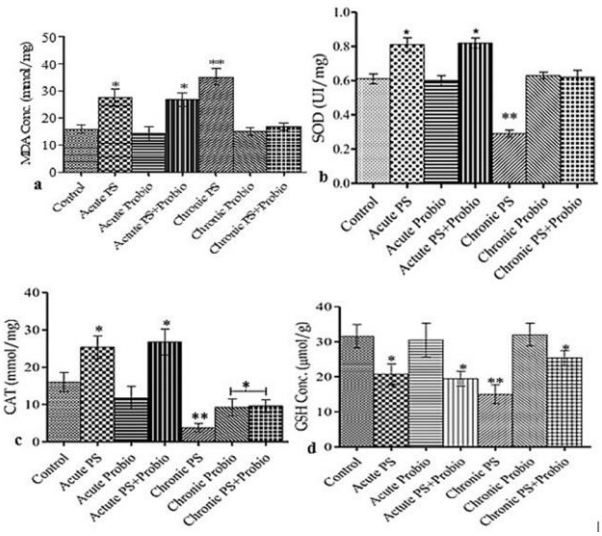


**Figure 2. Hippocampal redox status following stress and treatment with probiotics. * is a significant (P<0.011) difference in comparison to the control group, and ** is the significant (P<0.021) level of difference in comparison with the acute PS, chronic probio, and chronic PS+probio groups.**

### Probiotics prevent significant Hippocampal zinc loss during exposure to PS

Serum zinc levels (Figure 3a), regardless of treatment with probio, were significantly decreased in rats exposed to acute or chronic predator stress compared with the control. Treatment with probiotics allowed hippocampal zinc levels to remain significantly higher during stress compared to the stressed animals without probiotic treatment. Hippocampal zinc levels (3b) decreased significantly following acute and chronic stress but significantly increased in the chronic stress group treated with probiotics.

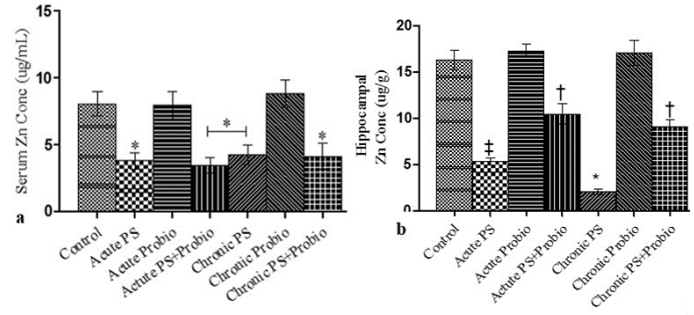


**Figure 3. Effects of probiotics on serum and hippocampal zinc levels. In Figures 3a and 3b, * shows significantly lower zinc levels compared with other groups, while ** in Figure 3b is significantly (P<0.007) lower compared with ***, significantly (P<0.009) lower compared with control and chronic probio groups.**

### Probiotics mitigate PS-induced overexpression of TNF-α and IL-1β

Exposure to PS caused significant ($P<0.05$) elevation in TNF-α and IL-1β expression compared with the control (Figures 4a and b). Treatment with probiotics maintained hippocampal TNF-α and IL-1β expression during stress. However, during chronic exposure to PS, TNF-α remained significantly ($P<0.05$) higher compared with the control but was nonetheless significantly ($P<0.05$) lower compared with chronic exposure to PS without probiotics.

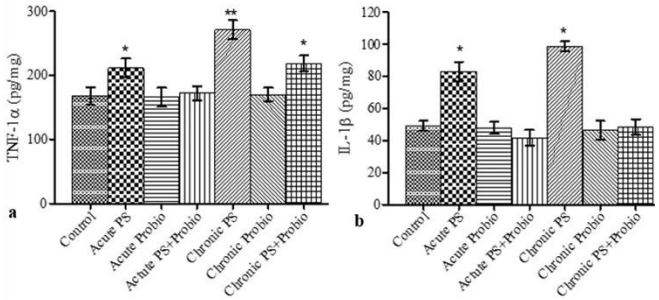


**Figure 4. Hippocampal TNF-α and IL-1β after exposure to stress and probiotic treatment. In Figures 4a and 4b, * indicates significantly (P<0.014) higher levels of the parameters compared to other groups except for the chronic group (** in Figure 4a), which is significantly (P<0.011) higher than *.**

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**Effect of probiotics on Hippocampal Histoarchitecture following stress exposure**

The histological appearance of H&E and Nissl stained hippocampus did not reveal definitive or marked microstructural changes across groups (Figure 5). The basic outlines are preserved, making the hilus, molecular layer (M), granular cell layer, granular zone, cornu ammonis (CA) 1, 2, 3, and subiculum (s) identifiable with no apparent structure distortions.

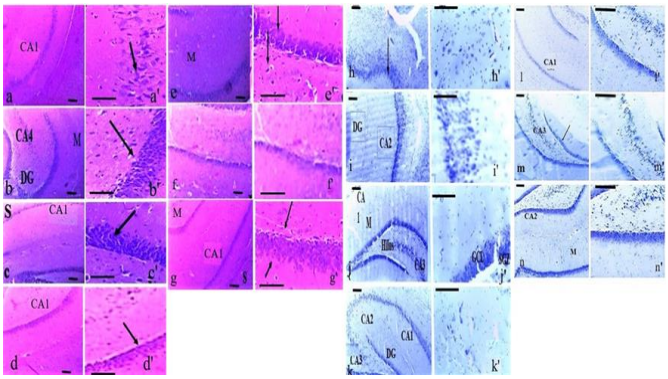

**Figure 5. Photomicrograph of the hippocampus in control; (a & a') arrow pointing to normal pyramidal layer; acute predator stress (b & b') acute probio. (c & c') while plate acute PS+probio (d & d') chronic probiotics (e & e'); chronic PS+probio (f & f) in h & h' – n-n,' Nissl staining of hippocampal regions are demonstrated. In all, arrows pointing to the pyramidal cell layer, M= molecular layer, GCL= Granular cell layer, SGZ=, and subgranular zone, CA1-4= cornu ammonis 1-4, S= Subiculum, DG= dentate gyrus. Scale bar= 50µ.**

## Discussion

In the present study, acute and chronic PS caused a significant decrease in dopamine levels compared with any other group. These findings are in line with previous studies showing that exposure to PS is associated with dampened striatal dopaminergic function and increased vulnerability to mental illnesses (16) and that long-lasting changes in dopamine function occur after single stress exposures, including altered responsivity to future stimulation (17); a mechanism similar to that of drug abuse, an initial escalation and then a relapse (18). Exposure to mild stressors potentiates dopaminergic activity, while severe chronic stressors are associated with attenuating dopaminergic function (17). Besides, data analysis in the current study reveals no significant difference between dopamine levels in the acute probiotics, chronic probiotics, and the control, suggesting that psychologically stress-induced dopamine loss was significantly ameliorated by probiotics supplementation.

Moreover, the current study reveals a significant decrease in serotonin in rats exposed to acute PS and chronic PS, suggesting altered hippocampal functions as serotonin is one of the critical modulators of emotional states and cognitive processing. Meanwhile, the significantly decreased serotonin levels seen in the acute PS+probio group were significantly upregulated in the chronic PS+probio, suggesting that the duration of exposure to predator stress plays a role in the ameliorative role of probiotics. Predator stress decreases serotonin levels in the hippocampus (19); alterations in serotonin levels show increased anxiety-related behaviors and altered stress susceptibility, and predator exposure/psychosocial stress may alter serotonin levels in the rat hippocampus (20)

In this study, MDA significantly increased in chronic PS compared with other groups suggesting an increased level of free radicals leading to oxidative cell damage with an indication that the duration of exposure has a role in PS. PS is linked with the stimulation of MDA production due to triggering oxidative free radical formations. Overwhelming psychological stimuli activate neuronal oxidative phosphorylation at the mitochondrial site leading to an imbalance between pro-oxidant and antioxidant levels, causing profound lipid peroxidation (21). MDA levels in acute PS and acute PS+probio showed no significant difference, drawing more attention to how long it takes for probiotics to exert their protective effect. High MDA serum level is associated with oxidative damage that induces cognitive impairment (21).

Superoxide is a highly reactive oxygen species continuously generated in vivo. It can cause toxicity, but it is being tamed by the antioxidant enzyme – superoxide dismutase, which plays a crucial role in scavenging oxygen. The current study observed a significant increase in SOD levels in acute PS and acute PS+probio, suggesting that increased activities of this antioxidant enzyme may act as the rats' first line of defense, especially in stress conditions. This increase may be attributed to the antioxidant potential of probiotics (acute PS+probio) or modulations of physiological antioxidant defense mechanisms as the first line of defense in the acute PS group.

Meanwhile, a decrease in SOD level in chronic PS can be attributed to an overwhelming superoxide generation in a longer duration of stress exposure. The difference in SOD activities across the group can also be attributed to changes in the relative abundance of cell types in the rats, as previous studies on rats suggest SOD activity is 10-fold higher in glial cells than in neurons. Increased oxidative stress, as seen in chronic PS, decreases these antioxidant defense mechanisms due to the endogenous production of free radicals (22). Catalase is another antioxidant that mitigates oxidative stress by breaking down cellular hydrogen peroxide to produce water and oxygen (22). Groups administered probiotics showed a marked increase in catalase activity, mediating the detoxification of hydrogen peroxide. PS increases oxidative stress, as shown by the decreased level of catalase in chronic PS; this can be attributed to an imbalance in the pro-oxidants and antioxidants. Reduced catalase activity has been associated with the pathogenesis of neurodegenerative disorders (22).

Decreased level of glutathione in chronic PS suggests increased oxidative stress. GSH involves many cellular processes, including cell differentiation, proliferation, and apoptosis. Glutathione depletion promotes cell death when mitochondrial function is inhibited (23). Increased GSH levels boost antioxidant capacity and resistance to PS-induced oxidative stress, as seen in groups administered probiotics. GSH plays a role in neuronal survival, exerts neuroprotective effects, and prevents and reverses cellular damage (23).

Zinc is abundant in the hippocampus and mossy fibers, as seen in the control group and chronic probio; zinc has antioxidant functions through the catalysis of copper/zinc-superoxide dismutase. Zinc plays a crucial role in modulating spatial learning and memory (24). Zinc deficiency induces degeneration, cognitive decline disorders, and decreased learning and memory. Decreased zinc levels in groups administered probiotics raise doubts about the efficacy of probiotics in restoring hippocampal zinc levels. While gut microbiome augmentation may demonstrate potency in improving specific molecules that play essential roles in hippocampal neurochemistry and function, the overall improvement in outcome may require a combination of probiotics with micronutrients such as zinc.

Although previously considered an immune-privileged site, the central nervous system is now established to be where cytokines such as TNFα, IL-1β, and other interleukin are tonically expressed and function. TNF-α promotes apoptosis through its receptor, TNFRI (25). In the current study, PS caused a significant overexpression of TNFα and IL-1β, suggesting stress can activate inflammatory response in the hippocampus.

When environmental demands disrupt the usual balance, stress is the additional expense that an organism or organ must incur to maintain homeostasis. The neuroendocrine and immune systems form an integral part of the stress response. IL-1β is a pro-inflammatory cytokine whose expression is seen outside the boundaries of the immune system in organs such as the GIT and the brain. In the brain, IL-1β is expressed by both neuronal and glial cells. It is expressed in hypothalamic-pituitary-adrenal (HPA) axis stress reactivity (26). Indicatively, electrical stimulation of the afferent vagus nerve significantly increases the expression of IL-1β mRNA in the hippocampus. Besides, a significant increase in hippocampal IL-1β protein is observed following the stimulation (26). The current study has a similar outcome: the stress groups significantly overexpress TNF-α and IL-1β.

The gut microbiota has been described as the brain peacekeeper based on different lines of evidence establishing gut microbiota's influence on the brain (27). Demonstratively, Lactobacillus enhances the secretion of TNF-α in dendritic cells, while Bifidobacterium stimulates the secretion of IL-1 and IL-6 (6). The current study reveals that TNF-α was significantly overexpressed following exposure to stress. The observed reversal of overexpressed TNF-α and IL-1β in the current study in groups treated with Lactobacillus and Bifidobacterium appear to contradict early reports. However, considering the different conditions under which previous studies and this study were conducted, this apparent contradiction is eliminated and suggests that this microbiota can regulate cytokine upward or downward depending on the need. In the current study, stress-induced elevated glucocorticoid levels resulted in the overexpression of IL-1β and TNF-α. It will enhance stress-induced oxidative stress since TNF-α has been linked to elevated production of free radicals to promote apoptosis (28). Augmenting gut microbiota with Lactobacillus and Bifidobacterium in elevated hippocampal TNF-α and IL-1β resulted in a downregulation of these pro-inflammatory proteins.

Mice deficient in both IL-1α and IL-1β show a very significant reduction in brain injury after the occlusion of the middle cerebral artery (29); therefore, the attenuation of IL-1β overexpression seen in the current study in the probiotic-treated-group suggests the neuroprotective ability of the gut microbiota under PS.

The H&E and Nissl staining showed the number of intact neurons in the hippocampal regions across the groups. The control group showed a typical arrangement of viable neurons and glial cells. No apparent histological alterations were seen in any group relative to the control.

## Conclusion

The present study concluded that acute and chronic PS significantly diminished hippocampal serotonin and dopamine levels while inducing the overexpression of IL-1β and TNF-α, causing increased lipid peroxidation and impaired antioxidant parameters. However, argumentation with probiotics significantly reversed these changes, suggesting that gut microbiota play an essential role in hippocampal neurochemistry and function, particularly during stress.

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## Ethical statement
The Health Research and Ethics Committee of the College of Medicine, University of Lagos, Idi-Araba, Lagos, Nigeria, approved this study.

## Conflict of interest
The authors have no conflict of interest to declare.

## Author contributions
LJM was responsible for the concept, design, and definition of intellectual content, literature search, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. He is also the guarantor of this work. OOM contributed to the design, definition of intellectual content, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. TWT contributed to literature search, data acquisition, data analysis, manuscript preparation, manuscript editing, and manuscript review. DUO contributed to literature search, data acquisition, data analysis, manuscript preparation, editing, and review. OEA contributed to literature search, data acquisition, data analysis, manuscript preparation, editing, and review. AGO contributed to literature search, data acquisition, data analysis, manuscript preparation, editing, and review. AAAO contributed to defining intellectual content, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review.

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