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Modulatory Role of N-acetylcysteine on Memory and Motor Function Deficits in a Rodent Model of Restraint Stress

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ABSTRACT

Stress is a condition that disrupts physiological and psychological states of the body, impairing normal brain functioning. Prolonged and sustained exposure to restraint stress can induce memory and motor function deficits. N-acetylcysteine (NAC) is a glutathione precursor that maximises a cell's protective capabilities against stress-induced oxidative damage. This study investigated the role of NAC on memory and motor function deficits induced by restraint stress in Wistar rats. Twenty-four Wistar rats of both sexes were randomly assigned to control, restraint stress only and NAC (500 mg/kg) + restraint stress, with 8 animals per group. All treatments lasted for three weeks. Neurobehavioural evaluation was conducted using the elevated plus maze and beam walk test to assess memory and motor coordination, respectively. All analyses were done using two-way analysis of variance followed by Tukey's and least significant difference *post hoc* tests. The results showed a significant decrease ($p < 0.05$) in closed arm latency between the control, restraint stress only and restraint stress + NAC groups, with lower latency in female rats compared to the males in the control group. A significant increase was also observed in goal box latency in the restraint stress-only group when compared to the restraint stress + NAC group. Additionally, female rats showed significantly ($p < 0.05$) lower frequency in foot slips compared to the males. In conclusion, sub-chronic restraint stress induced memory and motor coordination deficits in Wistar rats, which were ameliorated by NAC administration. We also observed that female rats demonstrated enhanced short-term memory and motor coordination functions compared to the males.

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Keywords

Memory and learning, Motor coordination, N-acetyl cysteine, Restraint stress

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INTRODUCTION

Stress is defined as a condition that disrupts physiological and psychological homeostasis, and it is known to affect the function and morphology of the hippocampus and other brain structures, such as the cerebral cortex, cerebellum, and basal ganglia, which consequently affect short-term memory and motor functions. The exact underlying cellular mechanism that mediates the detrimental effect of stress remains poorly understood. However, restraint stress is known to largely reduce the ex-

pression of several growth factors and neurotropic factors, such as brain-derived neurotropic factor (Castel *et al.,* 2009). Stressors may affect the short-term and long-term memory abilities differently depending on the source, duration, strength, and the timing of the stress (Dhabhar, 2018). It also has varying effects on the prefrontal cortex, amygdala and hippocampus, based on the age and sex of individuals (Canto-de-Souza *et al*., 2025).

Short-term stress can cause physiological changes that improve the body's behaviour and help it overcome challenges. On the other hand, when stress becomes chronic, the physiological changes that enhance behaviour are harmful to the body. In order for the body to adjust to the chronic stress scenario, it initiates processes that result in the activation of the hypothalamus-pituitary-adrenal axis, which produces the release of cortisol in reaction to the stress and the activation of the autonomic nervous system on a short-term basis (Beck *et al*., 2023).

Overexposure to prolonged stress has been shown to cause brain damage, particularly to the hippocampus. When the hypothalamus recognises a threat, it activates the pituitary gland via neural signalling, which subsequently triggers the adrenal glands to secrete cortisol, the primary stress hormone (Fowler et *al*., 2021). When the amount of cortisol in the body reaches a specific level, the hippocampus activates the hypothalamus to turn off the mechanism that causes cortisol secretion. This resulted in cortisol overwhelming the brain due to its ability to cross the blood-brain barrier, leading to the hyperactivation of the hypothalamo-hypophyseal-pituitary pathway, thereby causing severe damage to the hippocampus and the amygdala, consequently leading to anxiety, depression and cognitive decline (Biltz, 2025). Therefore, the loss of the modulatory activity of the hypothalamic-pituitary-adrenal axis due to chronic exposure to environmental stressors associated with motor and cognitive deficits could lead to neurological and neurodegenerative diseases such as ataxia, Parkinson's disease, Alzheimer's disease and motor neuron disease.

Restraint stress, whether acute or chronic, has been demonstrated to induce cognitive deficit and impair motor coordination through multiple physiological signalling pathways, including activation of the hypothalamic-pituitary-adrenal axis and the consequent release of stress hormones such as corticosterone, which in turn disrupt insulin signalling in rats (Metz *et al*., 2005; Woo *et al*., 2018). Restraint stress also impairs motor skills and cognitive performance through activation of neural pathways associated with oxidative stress, apoptosis and downregulation of brain-derived growth factor (BDNF), acetylcholine, dopamine and insulin signalling. These alterations distort central nervous functioning and contribute to motor and memory impairment by disturbing the balance of neurotransmitters such as dopamine and acetylcholine (Woo *et al*., 2018; Idrissi *et al*., 2023; Martins *et al*., 2024). Therefore, therapeutic interventions aimed at ameliorating motor and cognitive deficits induced by stress may play a pivotal role in enhancing memory and motor skills, while also serving as promising therapeutic strategies against neurological conditions.

N-acetylcysteine (NAC) is an acetylated cysteine residue used in the treatment of various medical conditions, including cystic fibrosis and chronic obstructive pulmonary disease, due to its mucolytic and antioxidant properties (Mokra *et al.,* 2023). It is also an established antidote for paracetamol overdose because it promotes glutathione synthesis, which aids in counteracting toxicity (Prescott, 2024). Studies have also highlighted the neuroprotective potential of NAC due to its antioxidant capacity, enhancement of neurotransmitter synthesis such as dopamine and serotonin, modulation of neuroinflammation, promotion of neurogenesis and synaptic plasticity and restoration of cellular redox balance in a variety of neurological diseases (Ikram *et al*., 2024). NAC is naturally found in plants of the Allium species, especially onions, and it is widely used as a mucolytic agent, making it beneficial in respiratory conditions associated with increased mucus production and viscosity (Boskabady *et al*., 2022; Tieu *et al*., 2023).

The connection between memory loss, motor function deficits, and stress remains unclear, and the aetiology of most motor and cognitive disorders related to stress is still not fully understood. In both animals and humans, physical restraint stress has been proposed as a significant factor in cognitive and motor impairment (Woo *et al*., 2018; Idrissi *et al*., 2023; Martins *et al*., 2024). However, there is still a wide gap in knowledge regarding the sex-dependent influences of physical restraint stress on motor and cognitive functions and the modulatory role of NAC in young adult Wistar rats. Therefore, there is a need for research focused on developing effective therapeutic interventions to ameliorate stress-induced motor and cognitive impairment. Thus, this study investigated the modulatory role of NAC on motor coordination and short-term memory in a mice model of restraint stress.

MATERIALS AND METHODS

Drugs preparations and Administration

NAC (500 mg/kg, A7250-100G, Sigma Aldrich, USA) was dissolved in normal saline and administered orally (positive control). Normal saline was administered orally to the negative control groups (Lai *et al*., 2023).

Animals and Management

A total of twenty-four (12 male and 12 female) Wistar rats, with an average weight of 65 g, were obtained from the Animal House Facility of the Department of Human Physiology, Faculty of Basic and Allied Medical Sciences, Gombe State University, Nigeria, and used for this study. Rats of both sexes were housed separately. Animals had free access to standard commercially available feed and water. All experimental protocols were carried out in accordance with Gombe State University's research policies, ethics, and regulations governing the care and use of experimental animals. Ethical clearance was obtained from the Faculty of Basic and Allied Medical Sciences Research and Ethical Committee with an approval number: GSU/COMS/FBAMS/R&EC/24/P022. The experiments were conducted in a quiet laboratory

from 9:00 h to 16:00 h, with a light-dark cycle of about 12:12 h.

Experimental Design

The mice were allowed to acclimatise for two weeks before the commencement of the experiment. Following acclimation, they were randomly divided into three groups, each consisting of eight animals (4 males and 4 females per group), and randomly assigned to the following groups:

Group 1: Control group (n=8): Male and female rats received 0.2 mL/kg normal saline orally and were not subjected to restraint stress.

Group 2: Restraint group (n=8): Male and female rats received 0.2 mL/kg normal saline orally and were subjected to restraint stress only for 3 h daily.

Group 3: (n=8) Male and female rats received NAC (500 mg/kg dissolved in normal saline) orally and were subjected to restraint stress 30 min later for a period of 3 h daily for 21 days.

All drug administration and exposure to restraint stress lasted for three weeks simultaneously, after which neurobehavioural studies were carried out for memory evaluation on the 22nd and 23rd days and beam walking test on the 24th day. The behavioural studies were done in a quiet neurobehavioural room with a red lighting.

Induction of Restraint Stress

Restraint stress was induced by placing the animals in a mesh wire restrainer for three hours daily over 21 days, as previously described (Moazzam *et al*., 2013). The restrainer (18 × 8 × 8 cm) was constructed from Plexiglas.

Elevated Plus Maze Test

The elevated plus maze is primarily designed to evaluate anxiety-related behaviours in rodents. However, with some modifications, it can be used to assess short-term memory. Short-term memory was assessed using a modified elevated plus maze paradigm designed to evaluate aversive (avoidance) spatial reference memory, following the procedure of Itoh *et al*. (1990). The maze was composed of wood; it consisted of two open arms (29 × 5 cm) and two enclosed ones (29 × 5 × 15 cm) extending from the central platform. The maze was supported 15 cm high above the floor. This test is based on the rodent's natural aversion to open, elevated spaces and their preference for enclosed ones. Prolonged transfer latency in the retention phase is interpreted as a deficit in spatial memory.

The test was conducted in two phases. In the acquisition phase, each rat was placed at the distal end of an open arm, facing away from its centre. The transfer latency (TL), defined as the time taken to move from the open arm to either enclosed arm, was recorded with a maximum cutoff of 90 s. Upon entry, the rat was allowed to explore the maze for 30 s. Twenty-four hours later, the second phase (retention test) was performed, and the TL was recorded again with a maximum cut-off time of 90 s. An increase in transfer latency during the retention test is interpreted as a deficit in memory. All behaviour testing was conducted in a dimly lit, semi-soundproof room. The maze was thoroughly cleaned with 70% ethyl alcohol and dried between each trial to eliminate olfactory cues.

Beam Walk Test

The beam walk test was used to test for motor coordination as described by Stanley *et al*. (2005). Briefly, the beam walk apparatus consists of a beam, ruler, goal box, and an elevated wooden stand. The beam was made of wood, 8 mm in diameter, 80 cm long, and elevated 30 cm above the bench by a wooden support. Rats were allowed to walk from a start platform along a ruler (80 cm long and 2.5 cm wide) elevated 100 cm above the bench by a wooden support to the goal box. A ruler was used to train the rat, and once the rat was able to cross and reach the goal box, they were moved immediately to the test beam. The rats were placed on the test beam at one end and allowed to walk to the goal box. Rats that fell from the beam were returned to the position they fell from, with a maximum time of 60 s allowed on the beam. The measurements that were taken were time (latency) on the beam (this is the total time the rat spent crossing the beam) and the number of foot slips (when one or both hind limbs slipped from the beam). After each trial, the maze was wiped with cotton wool dipped in 70% ethyl alcohol and allowed to dry to remove any olfactory cues.

Statistical Analysis

Data are expressed as mean ± SEM. Statistical analyses were conducted using SPSS version 20. One-way analysis of variance (ANOVA) was used to compare group means, while two-way ANOVA evaluated the effects of treatment and sex on the variables. For multiple comparisons, Tukey's and least significant difference post-hoc tests were applied, with statistical significance set at $p \leq 0.005$.

RESULTS

Effect of NAC on Short-Term Memory in the Elevated Plus Maze (EPM)

A one-way ANOVA showed a significant effect of treatment on closed-arm entry latency [$F(2, 18) = 25.211$, $p = 0.001$]. The post-hoc analysis revealed that NAC (500 mg/kg) significantly ($p < 0.05$) reduced latency (18.5 ± 5.94 s) in the restraint-stressed rats when compared to the control (36.88 ± 5.94 s) and restraint-stress (76.88 ± 5.94 s) groups, respectively (Table 1).

A two-way ANOVA further showed a significant main effect of treatment × sex interaction [$F(1, 18) = 9.817$, $p = 0.006$]. Males in the control group (55.5 ± 8.41 s) had a significantly higher latency than females in the control group (18.25 ± 8.41 s; $p = 0.006$). No significant differences were observed between males and females in the restraint stress (males: 70 ± 8.41 s, females: 83.75 ± 8.41 s; $p = 0.263$) or the restraint stress + NAC groups (males: 16.5 ± 8.41 s, females: 20.5 ± 8.41 s; $p = 0.740$), respectively (Fig. 1).

Table 1: Effect of NAC on closed arm latency in rats subjected to restraint stress in the elevated plus maze

Group	Latency (s)
Control	36.875 ± 5.94*
Restraint Stress	76.875 ± 5.94*
Restraint Stress + NAC (500 mg/kg)	18.5 ± 5.94

* Indicates significance ($p < 0.05$) when compared to the restraint stress + NAC (500 mg/kg) group; NAC = N-acetylcysteine.

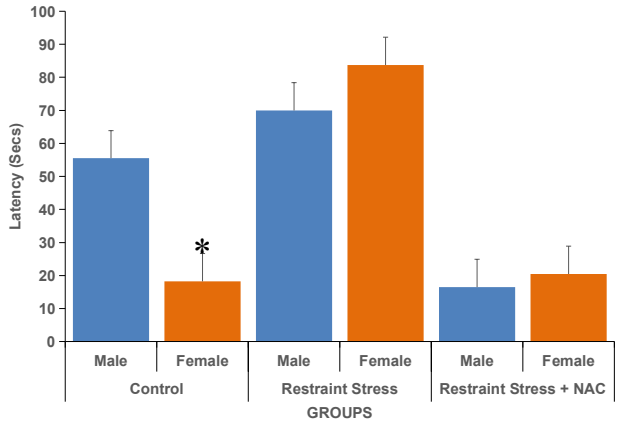

Fig. 1: Effect of NAC on latency in male and female rats exposed to restraint stress in the elevated plus maze test. * Indicates significance at $P < 0.05$ compared to the male control group. NAC: N-acetylcysteine

Effects of NAC on Foot Slips and Latency in the Beam Walk Test

Table 2 shows the effect of NAC on foot slips and latency of rats subjected to restraint stress in the beam walking test. The results revealed that NAC treatment significantly [$F (2, 18) = 3.479$, $p = 0.05$] reduced latency to cross the beam in the restraint stress + NAC (500 mg/kg) (49.25 ± 9.78 s) when compared to rats subjected to restraint stress only (84.875 ± 9.78 s). Although, there was no significant change when compared to the control group. Additionally, there was no significant change in the number of foot slips for the three treatments ($F (2, 18) = 1.083$, $p = 0.36$).

The sex-dependent effect of NAC on rats exposed to restraint stress in the beam walking test is shown in Figures 2 and 3. There was no significant interaction between treatment and sex [$F (1, 18) = 0.178$, $p = 0.678$] in beam walk latency in the control, in males (78 ± 13.831 s) compared to females (69.75 ± 13.83 s), the restraint stress group [$F (1, 18) = 0.275$, $p = 0.607$] in males (79.75 ± 13.83 s) compared to the females (69.75 ± 13.83 s), and the restraint stress + NAC group [$F (1, 18) = 1.323$, $p = 0.265$] in male (60.5 ± 13.83 s) compared to female (38 ± 13.8 s) rats, respectively (Fig. 2).

In contrast, there was a significant interaction [$F (1, 18) = 5.491$, $p = 0.031$] of Treatment × Sex observed in foot slip frequency in the control group between the male (3.5 ± 0.98 s) and the female rats (0.25 ± 0.981 s), with males being significantly higher. There was no statistically significant difference [$F (1, 18) = 0.032$, $p = 0.859$] in the restraint stress groups in male rats (3.13 ± 0.981 s) compared to the females (3.25 ± 0.981 s) and in the restraint stress + NAC groups [$F (1, 18) = 5.491$, $p = 0.031$], in the male rats (3 ± 0.981 s) when compared to the females (3.25 ± 0.981 s) (Fig. 3).

Table 2: Effects of NAC on latency and foot slips in the beam walking test

Groups	Latency (s)	Foot slips
Control	73.875 ± 9.78	1.875 ± 0.69
Restraint Stress	84.875 ± 9.78*	3.125 ± 0.69
Restraint Stress + NAC (500 mg/kg)	49.25 ± 9.78	3.120 ± 0.68

* Indicates significance ($p < 0.05$) when compared to the restraint stress + NAC (500 mg/kg) group; NAC = N-acetylcysteine

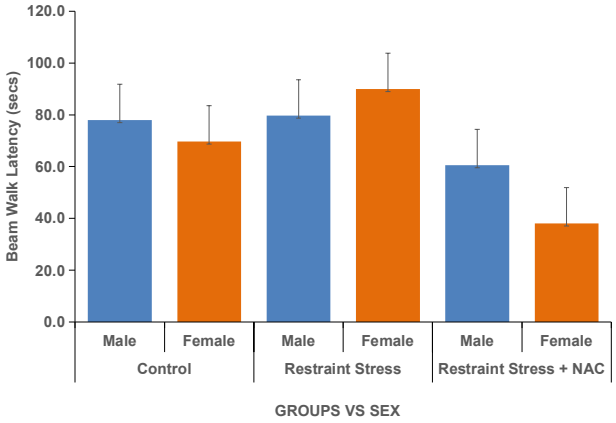

Fig. 2: Effects of NAC on latency in male and female rats in the beam walk test. NAC = N-Acetylcysteine

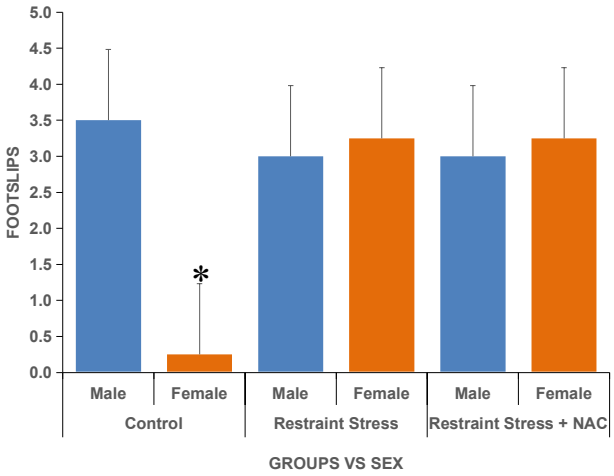

Fig. 3: Effects of N-acetylcysteine on foot slips in male and female rats in the beam walk test. * Indicates significance at $P < 0.05$ compared to the male control group. NAC = N-Acetylcysteine

DISCUSSION

This study evaluated the effects of NAC on short-term memory and motor coordination using the elevated plus maze and beam walking test in a rodent model of restraint stress. The results of our study revealed significant improvement in motor co-ordination and memory deficits induced by restraint stress after sub-acute NAC administration. Restraint stress has been reported to negatively affect motor and cognitive functions through activation of neural pathways involving oxidative stress, apoptosis and down-regulation of BDNF, acetylcholine, dopamine, acetylcholine, and insulin signalling, thus affecting the central nervous function, leading to motor and memory impairments (Woo *et al*., 2018; Idrissi *et al*., 2023; Martins *et al*., 2024). The study's findings indicated that restraint stress caused impairments in short-term memory, as demonstrated by an increased latency to enter the closed arms in the EPM test. This effect was ameliorated by NAC treatment, which significantly reduced closed-arm latency lower than both the restraint stress and the control groups. These findings suggest that NAC can positively improve short-term memory, particularly under stressful situations. This agrees with previous studies that reported significant improvement in both short-term and long-term memory following NAC administration in stress-induced sleep deprivation (Ontawong *et al*., 2025; Rosyidah *et al*., 2025).

Further analysis showed significant differences in closed-arm latency between male and female rats in the control group, with female rats having lower latency, demonstrating better memory performance compared to males. However, no significant difference was observed between male and female rats in the restraint and restraint stress + NAC groups. Several mechanisms have been proposed for NAC's beneficial effects in cognitive function, including suppression of inflammatory markers, reduction of acetylcholinesterase activity and cortisol levels, attenuation of endoplasmic reticulum stress signalling, modulation of oxidative stress responses, and enhancement of BDNF levels in the brain (Bakirhan *et al*., 2025; Ontawong *et al*., 2025; Rosyidah *et al*., 2025; Yonatan *et al*., 2025). While most existing studies were primarily focused on the effects of NAC in pathological conditions and other stress conditions such as chronic unpredictable mild stress and prenatal stress (Bernhardt *et al*., 2018; Fernandes *et al*., 2019), our research focused on the potential neuroprotective benefits of NAC in young adult Wistar rats subjected to physical restraint stress. Our findings demonstrate that sub-chronic exposure to restraint stress induced short-term memory impairments, which were ameliorated by NAC administration.

The results of the motor coordination from our study showed a significant increase in the goal box latency in the restraint stress group, indicating that restraint stress caused a motor coordination deficit. NAC treatment significantly decreased the latency to cross the beam, reflecting enhanced motor performance and coordination. This finding corroborates previous findings that NAC attenuates sensorimotor impairments (motor coordination, strength, and limb placing reflex) by decreasing short-term expression of inducible nitric oxide synthase and modulation of dopaminergic transmission in neonatal hypoxic-ischaemic brain injury and Parkinson's disease models in rats (Kesidou *et al*., 2022; Caridade-Silva *et al*., 2023). Although a biochemical assessment of antioxidant status was not performed in this study, we suggested that the observed improvement in both memory and motor coordination may be attributed to the antioxidant properties of NAC. This is likely mediated through replenishing glutathione levels, which may counteract restraint stress-induced oxidative damage and help preserve neuronal function (Fan *et al*., 2020).

In spite of the fact that there was no significant change in foot slips in all the groups, the beam walk test showed a significant decrease in the number of foot slips in female rats compared to the male rats in the control group, indicating an enhanced motor coordination in female rats in the current study. This suggests that female rats exhibited less motor impairment and better performance, consistent with previous memory outcomes in the current studies. This enhanced performance may be attributed to oestrogen, which is known to promote synaptic plasticity and neurotransmitter function, thereby improving motor and memory functions (Bajwa *et al*., 2025; Carpenter *et al*., 2025; Xie *et al*., 2025).

Conclusion

The study demonstrated that sub-chronic restraint stress caused deficits in memory and motor coordination in Wistar rats, which were mitigated by NAC ment. These findings align with other research showing that NAC can improve motor skills and cognitive function by reducing various animal models, including those related to stress exposure. Therefore, NAC shows promise as a therapeutic agent to counteract the adverse neurobehavioural effects of restraint stress.

DECLARATION

Acknowledgement

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Grants and Financial Support

Not Applicable.

Conflict of Interest

None declared.

Ethical Approval

Ethical clearance was obtained from the Faculty of Basic and Allied Medical Sciences Research and Ethical Committee with approval number GSU/COMS/FBAMS/R&EC/24/P022.

Authors' Contribution

MSM and ARO – Conceptualisation, design and execution of the research. EBE, JI, BA, JGA, ZYA and HAH - participated in the execution of the research and manu-

script preparations. ASI – participated in the design of the research, data analysis and interpretations. AHU and ASI - participated in the draft of the article and the final review of its content

Consent to Participate and Publish Data
Not Applicable.

The Use of Generative Artificial Intelligence
The authors used a generative artificial intelligence tool solely to rephrase passages to enhance the clarity and fluency of the manuscript, which was reviewed and edited appropriately. The scientific content, analysis, and conclusions remain entirely the authors' own.

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