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Environmentally enriched housing conditions reduce the depression-inducing potential of chronic unpredictable among Sprague-Dawley rats

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Abstract

Background: Depression remains a leading cause of global disability, with current treatments unable to meet the needs of all patients. Environmental enrichment (EE), a non-pharmacological intervention involving enhanced physical, sensory, cognitive, and social stimulation, has demonstrated potential as an alternative therapy. However, most preclinical models of depressi
on, including the widely used chronic unpredictable mild stress (CUMS) paradigm, are conducted under standard housing conditions that may not reflect the actual, complex human environment.

Objective: This study evaluated the capacity of CUMS to induce depression-like behaviours in rats housed under extended EE conditions.

Methods: Twelve Sprague Dawley rats were randomly assigned to either an EE group, where they were housed under enriched housing conditions or an EE+CUMS group, where they were subject to CUMS while under enriched housing conditions. At the end of the four-week experimental period, weights were recorded alongside behavioural assessments, including the sucrose preference test (SPT), open field test (OFT), forced swim test (FST), and novel object recognition task (NORT).

Results: Findings revealed that EE+CUMS rats exhibited a cross-section of the classical signs of stress-induced depression. This included an absence of weight gain ($p = 0.82$), which was present in controls ($p = 0.0002$) and poor novel object recognition in comparison to controls ($p = 0.017$). Between the two groups, there were no significant differences in sucrose preference, FST or OFT performance. Furthermore, in the OFT, locomotor activity was comparable, and both groups equally preferred peripheral over central zones.

Conclusion: Although the CUMS model impaired weight gain and memory, the classical signs of depression, such as anhedonia, anxiety and helplessness, were absent. This could be due to stress resilience conferred by enriched housing or insufficient stress from the CUMS protocol. Further studies are required to assess the underlying neurobiological mechanisms and design a CUMS protocol capable of inducing depression under enriched housing conditions. This will contribute towards enhancing the translational relevance of preclinical studies for human depression research and treatment development.

Keywords: Environmental enrichment, chronic unpredictable mild stress (CUMS), stress resilience, anhedonia, depression

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INTRODUCTION

Depression is a multifaceted mental health disorder characterised by persistent low mood, anhedonia, and feelings of hopelessness [1,2]. Affecting over 322 million people worldwide, depression is a leading contributor to global disability and disease burden [3-5]. Although it can occur across all demographics, certain groups, including women, individuals with chronic illnesses, and those who have experienced traumatic life events, are at higher risk [4]. The pathophysiology of depression is complex and involves multiple interacting

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systems, including alterations in neurotransmitter levels, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, neuroinflammation, oxidative stress, and gut-brain interactions [6-7]. Despite advances in understanding these mechanisms, current pharmacological treatments remain inadequate for many individuals, with approximately one-third of patients failing to respond to available antidepressants [8]. This highlights the urgent need for novel therapeutic strategies and a deeper understanding of the biological and environmental factors that contribute to depression onset and persistence [9]. One novel therapy being explored is environmental enrichment (EE), which refers to the enhancement of daily living conditions through the addition of sensory, cognitive, physical, and social stimuli [10]. In animal models, EE has been shown to promote neuroplasticity, reduce neuroinflammation, improve cognitive function, and alleviate symptoms of mood disorders [11-13]. As a non-pharmacological intervention, EE modulates brain function through multisensory and social engagement, thereby creating a more resilient neurobiological state [13,14]. Emerging evidence suggests that EE can buffer the effects of chronic stress and prevent the development of depression-like behaviours in animal models of depression, such as chronic unpredictable mild stress (CUMS) [15,16].

CUMS and similar models continue to play a critical role in research, enhancing our understanding of the disease mechanisms and evaluating potential treatments [9,17]. However, much of the current understanding of CUMS-induced depression is based on studies conducted under standard housing conditions, which can be considered to be deprived [18], as these housing conditions lack the complexity and stimulation found in EE environments and the average human experience. There is thus a firm and tenable argument that EE represents a more natural housing condition for depression studies as opposed to the deprived conditions that are recognised as standard housing conditions [19,20]. Therefore, to enhance the translational potential of findings from preclinical studies, it is necessary to explore the use of EE as the housing condition for depression and associated intervention studies.

In this study, we investigate the capacity of a standardised CUMS protocol to induce depression-like symptoms in animals housed under environmental enrichment conditions. We discuss the implications of these findings on the refinement of animal models of depression to enhance clinical translation.

MATERIALS AND METHODS

Experimental animals

Twelve (12) Sprague-Dawley rats, aged 6 to 8 weeks at the beginning of the study, were obtained from the Noguchi Memorial Institute for Medical Research for use. In this study, animals were divided into two groups and housed in environmentally enriched conditions, which included unrestricted access to toys, tunnels, and running wheels within a large cage measuring 60 cm × 60 cm × 30 cm (Figure 1A). The location of the items in the enclosure was moved around every 3 days to enhance novelty. The laboratory conditions adhered to a 12-hour light/dark cycle, with an ambient temperature maintained between 22-24ºC and 60% humidity. Softwood shavings were utilised as bedding in both groups. Throughout the experiment, water and standard commercial rat chow (Agricare, Kumasi) were provided *ad libitum*, except during periods when restrictions were necessary for the sucrose preference test or as a stressor. One of these groups was randomly assigned to CUMS alongside EE (EE+CUMS), and the other served as a control (EE), remaining in EE housing (Figure 1B). All animals were handled in accordance with the Guide for the Care and Use of Laboratory Animals, and protocols were approved by the College of Health Sciences Ethical and Protocol Review Committee, University of Ghana **(**CHS-Et/M.8.P5.10/2023-2024**).**

Establishment of chronic unpredictable mild stress in the rat

Chronic Unpredictable Mild Stress (CUMS) is an established behavioural model for studying depression and related behavioural impairments, including anxiety and anhedonia. In the CUMS model, rats are subjected to a prolonged period of randomised mild stressors, including cage tilt, damp bedding, light/dark cycle disruption, and food and water deprivation. To maintain unpredictability, we have previously used one or two stressors applied at random each day to study CUMS induced depression (Table 1) [21]. The main benefit of the model is its capacity to produce neurobiological abnormalities such as dysregulation of the monoaminergic system, dysfunction of the HPA axis, neuroinflammation, and structural alterations in the brain, as well as depressive-like symptoms including anhedonia, behavioural despair, cognitive decline, and anxiety [21,22].

Sucrose preference test (SPT)

Sucrose preference tests were conducted according to Willner et al., with a few adjustments [23]. Rats were acclimated to sucrose for 2 days before being deprived of food and water for 24 hours on the day of testing. On the testing day, rats were single-housed with free access to two bottles containing 100 mL of either water or sucrose solution (1% w/v). After two hours, the volumes of sucrose solution and water consumed were recorded, and the sucrose preference ratio was calculated as follows:

$$Sucrose\ Preference = \frac{sucrose\ intake}{sucrose\ intake\ +\ water\ intake}$$

Sucrose preference tests were performed at the start and end of the four-week experimental period.

Open field test (OFT)

As described by Shukkoor et al., an open-field test was used to assess locomotor and exploratory behaviour [24]. A 50 cm × 30 cm x 30 cm box with 25 equal square sections

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divided by lines on the box's floor served as the open field equipment. The top of the cage was left open so that a video camera could record the animal's movements. For 6 minutes, each rat was placed in the middle of the field and given unrestricted access to the entire field. To eliminate olfactory cues, 70% ethanol was used to clean the enclosure after the rats were taken out of the field. During the open field test, rat activity was captured with a video camera (50 MP, Tecno Spark20, Tecno Mobile) for later analysis.

Forced swim test (FST)

The Forced Swim Test (FST) was employed to assess depressive-like behaviour, specifically behavioural despair, in accordance with the protocol described [25]. At the end of the four-week experimental period, each rat was individually placed in a transparent plastic container (dimensions: 40 cm height × 24 cm width; total volume: 1,000 mL) filled with water to a depth of 30 cm. The water temperature was maintained at 23 ± 2°C. Each test session lasted six minutes and was recorded using a 50 MP camera

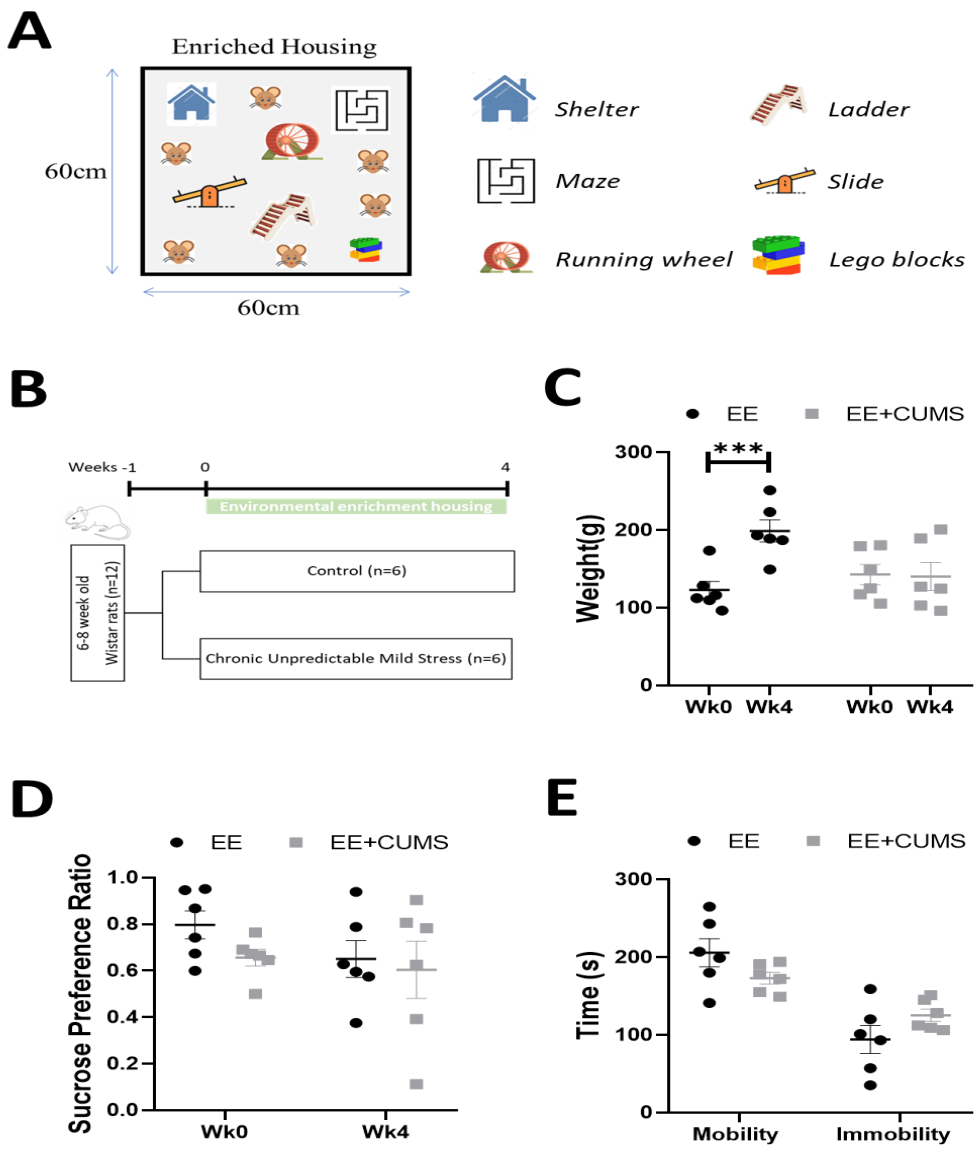

Figure 1. CUMS in EE impairs weight gain without inducing anhedonia or helplessness

Schematic representation of (A) enriched housing condition and (B) experimental protocol (C) Animal weights before (left) and after (right) experimental period of four weeks for both the stressed (EE+CUMS) and no stress (EE) groups. Paired T-test, ***p < 0.001 (D) Sucrose Preference Ratios before (Wk0) and after four weeks (Wk4) with no significant difference between the groups. (E) Mobility and immobility time as recorded in the forced swim test at the end of Week 4 with no significant difference between the two groups. Data represented as mean ± SEM.

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(Tecno Spark20) for subsequent offline analysis of the last 5 minutes. Following the test, the animals were gently dried with a towel and returned to their home cages to dry completely under ambient conditions. Behavioural parameters analysed included immobility time, defined as the duration during which the animal remained floating passively with its head above water and without making escape-directed movements.

Novel object recognition test (NORT)

The Novel Object Recognition Task (NORT) was used to assess recognition memory based on the animal's natural tendency to explore novel objects over familiar ones. The test was conducted in a metallic arena (50 cm × 30 cm × 30 cm) over three consecutive days.

On Day 1, animals were acclimatised to the experimental room for one hour, followed by a 20-minute habituation period in the empty arena. On Day 2, after a one-hour acclimatisation period, two identical objects were placed in the centre of the arena at pre-marked locations, and each rat was allowed to explore the objects for 10 minutes. The session was recorded using a 50 MP camera (Tecno Spark20) for later analysis. On Day 3, following another one-hour acclimatisation period, the animals were exposed to one familiar object and one novel object, placed in the same positions as the objects on the previous day. They were allowed to explore the objects for five minutes. Exploration was defined as sniffing or touching the object with the nose or forepaws while facing it directly.

The primary outcome measure was the discrimination index (DI), calculated using the formula:

$$Discrimination\ Index\ (DI) = \frac{T_{novel} - T_{familiar}}{T_{novel} + T_{familiar}}$$

where T_{novel} is the time spent exploring the novel object and $T_{familiar}$ is the time spent exploring the familiar object. A positive DI indicates a preference for the novel object and reflects intact recognition memory.

Data analysis

Results are expressed as the mean ± standard error of the mean (SEM). All behavioural tests were carried out during the light cycle by a researcher blind to the experimental group. Statistical tests and graphing were performed in GraphPad Prism version 8 (GraphPad Software, Inc., La Jolla, CA, USA). Paired T-Tests were used to compare changes in weight before and after the 4-week experimental period. Unpaired T-Tests or Mann-Whitney U Tests were used to compare values between the two groups after 4 weeks. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

To investigate the resilience-building capacity of EE, the animal experiment schedule was arranged as shown in Fig. 1B. The effect of either EE alone (EE) or CUMS under EE conditions (EE+CUMS) was assessed by weighing rats at the beginning (week 0) and the end (week 4) of the experiment. It was observed that there was a significant weight gain in the EE group (from 122.8±10.9 g to 199±14.3 g; Paired T-test, $p = 0.0002$), which was absent in the EE+CUMS group (from 142.8 ± 13.6 g to 140.2±18.1 g; Paired T-test, $p = 0.82$) (Figure 1C). There was no significant difference in the sucrose preference between the two groups at either the start (Wk0: Mann-Whitney U, $p = 0.13$) or end (Wk4: Mann-Whitney U, $p > 0.99$) of the experimental period (Figure 1D). Furthermore, in the forced swim test, both groups spent equal amounts of time immobile (Unpaired T-Test, $p = 0.14$; Figure 1E). Anxiety and locomotor activity were assessed using the open-field test. Here, three separate parameters were measured: total distance travelled, time spent at the periphery, and time spent in central zones. In the open field test, both EE and EE+CUMS showed overall active movement, although more time was spent in the peripheral zones than in the central zones (Figure 2A). Between the two groups, there was no significant difference in the total distanced travelled

Table 1. Chronic unpredictable mild stress protocol used to study stress induced depression

Day	Stressor			
	Week 1	Week 2	Week 3	Week 4
Monday	Overnight illumination and Bed wetting	No bedding and Overnight illumination	No bedding and Cage Tilting	Food Deprivation
Tuesday	No bedding and Food Deprivation	Food Deprivation and Cage tilting	No bedding and Food Deprivation	No bedding and Cage Tilting
Wednesday	Cage tilting and Water Deprivation	Overnight illumination and Empty botles	Water Deprivation and Overnight illumination	Overnight illumination and Empty Bottles
Thursday	No bedding and Overnight illumination	No bedding and Cage Tilting	No bedding and Cage Tilting	No bedding and Overnight illumination
Friday	Cage tilting and Bed wetting	Overnight illumination and Food Deprivation	Cage Tilting and Overnight illumination	Water Deprivation and Overnight illumination
Saturday	Food Deprivation	Cage Tilting and No bedding	Water Deprivation and Food Deprivation	No bedding and Cage Tilting
SUNDAY	Overnight illumination and Cage Tilting	Overnight illumination and Bed wetting	No bedding and Overnight illumination	Food and Water Deprivation

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(Unpaired T-Test, p = 0.61), time spent in the peripheral zones (Unpaired T-Test, p = 0.68) nor time spent in the central zones (Unpaired T-Test, p = 0.68) (Fig. 2B). For the NORT, although there was no significant difference in the raw times spent investigating either object (Fig 3A and B), a significant difference in the discrimination ratio indicates that animals in the EE group had a preference for the novel object (Fig 3C. Mann-Whitney U Test, p = 0.017).

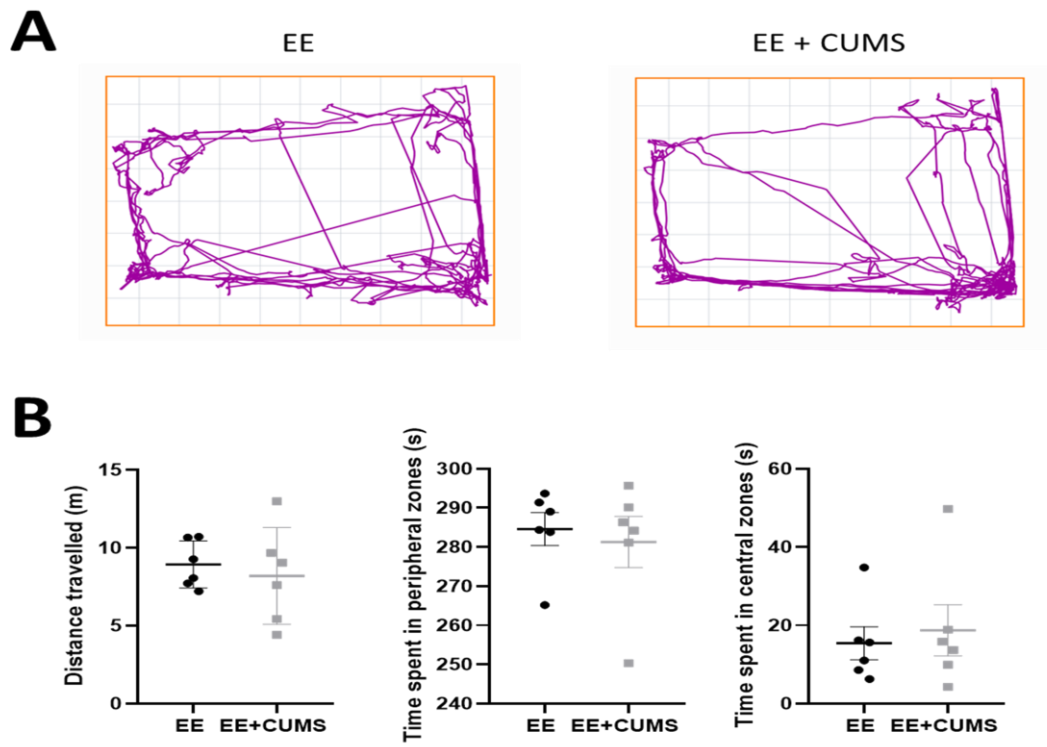

Figure 2. CUMS in EE fails to heighten anxiety like behaviour in the open field test: (A) Sample tracking plots from the open field test of an individual animal in the enrichment group (EE; left) and the stressed plus enrichment group (EE+CUMS; right) at the end of week 4. Parameters analysed in the open field test include (B: left) distance travelled, (B: middle) time spent in the periphery, and (B: right) time spent in the center. There was no significant difference between the two groups in all three parameters. Data represented as mean ± SEM

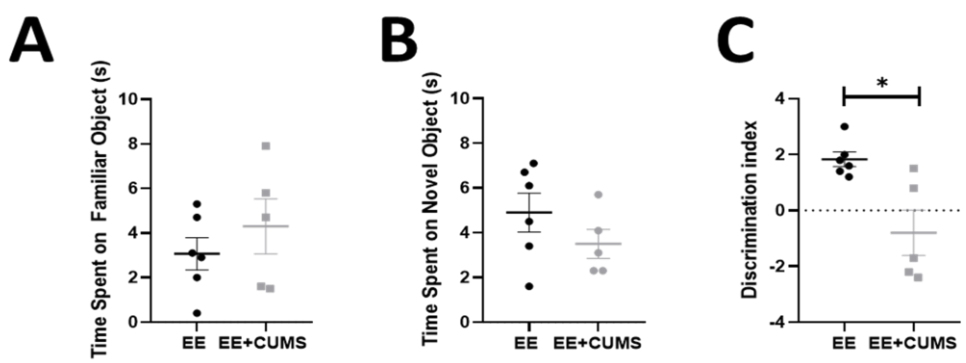

Figure 3. CUM in EE impairs novel object recognition. Parameters of the novel object recognition test analysed for both groups were the (A) time spent investigating the familiar object, (B) time spent investigating the novel *object* and (C) the discrimination ratio. There was no significant difference between the two groups (EE: no stress and EE+CUMS: stress) for the first two parameters (A and B) but lower discrimination ratio in the stressed group. Mann Whitney U test. *P<0.05. Data represented as mean ± SEM.

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DISCUSSION

In this study, we investigated the ability to induce depression- and anxiety-like behaviours using the CUMS models in rats housed under environmental enrichment conditions. We report that under enriched housing conditions, CUMS impaired weight gain and novel object recognition. However, it failed to induce core depressive-like behaviours such as anhedonia, helplessness, and anxiety. These results indicate that the full behavioural expression of stress-induced depression could not be achieved in our current study using an established CUMS model.

Animal studies of depression utilising the CUMS model typically report weight loss or absence of weight gain [26,27], and we have previously shown the same [21]. In this study, the EE+CUMS group did not show significant changes in body weight, although the EE group gained weight over the same time period, suggesting that CUMS specifically impaired weight gain. This impairment in weight gain is also typically observed in studies involving CUMS under standard housing conditions. Previous reports have shown that stress-induced metabolic changes are responsible for the weight changes observed after CUMS [20,28,29]. However, EE is known to have a buffering or protective effect against these same mechanisms, including an enhancement of glucose metabolism [16,20]. Our findings suggest that the buffering effect of EE was insufficient to fully protect against stress-induced weight loss. Therefore, this specific protection conferred by EE may be overcome by the existing CUMS protocol.

The novel object recognition test assesses the ability to discriminate between novel and familiar objects (discrimination index), and this is a component of memory that may be impaired alongside depression [30-32]. In the current investigation, the discrimination index of the enriched group (EE) was considerably greater than that of the enriched and stressed group (EE+CUMS), suggesting a CUMS-induced impairment within associated structures. Specifically, activity in the prefrontal cortex and hippocampal regions has been linked to the novel object recognition test [31]. Available evidence suggests that a reduction in the discrimination index may be due to multiple factors, including neuronal atrophy and synaptic loss in the medial prefrontal cortex and hippocampus [33-35]. Although other studies have reported that EE promotes neurogenesis and neuronal cell survival in these regions [36], it appears that the CUMS-induced deficits outweighed the expected EE benefits. Alternatively, the appearance of CUMS-induced deficits surpassing the expected EE benefits could be a consequence of the experimental protocol employed here. This is because the effects of both CUMS and EE are time-dependent; therefore, the duration of the study and the data collection time points, as well as the age of the animals, which are still within a developmental period, could influence the conclusions drawn. A study specifically designed to investigate the time-dependent relationship between CUMS and EE will be required to provide further understanding of this phenomenon. Aside from weight loss and memory impairments, anhedonia remains a classic hallmark symptom of depression. No anhedonia was observed in the EE+CUMS group, as sucrose preference remained stable across time. This aligns with the hypothesis that enriched environments may counteract the neurobiological underpinnings of CUMS induced anhedonia, such as dopaminergic dysfunction and neural hypoactivity in reward pathways [37]. Alternatively, the intensity of the CUMS may have been insufficient to induce anhedonia, as depressive-like behaviours can be induced in animals and depend on multiple factors, including the depression-induction model of choice and the timing of stress induction [38]. Without a larger sample size, a positive control group (standard housing + CUMS) and further neurobiological measures, we are unable to categorically conclude that CUMS failed to induce anhedonia due to the buffering effect of EE. Similarly, there were no significant differences in immobility time in the FST between the EE and EE+CUMS groups. This supports previous suggestions that environmental enrichment attenuates the behavioural impact of chronic stress [14,39]. However, it also further highlights the limitation of the CUMS protocol in EE-housed rats as used in this study and its inability to induce despair-like behaviour, which is another classic hallmark of stress-induced depression.

In the past decade, environmental enrichment has been well-documented to enhance neuroplasticity, increase neurogenesis, and improve cognitive and emotional outcomes in animal models [11-13,36]. Several studies have shown that EE influences behaviour through mechanisms that include reduced neuroinflammation, improved HPA axis regulation, and enhanced synaptic plasticity [36,40,41]. By providing multisensory, cognitive, and social stimulation, EE fosters an adaptive neurobiological environment that counters the deleterious effects of stress. It has been proposed that the observed benefits may be due in part to the fact that standard housing conditions represent a deprived environment [16,18,20]. Therefore, environmental enrichment models may represent a more natural state of living. According to recent studies, environmental cues such as sensory and motor stimulation, increased opportunities for exercise, and social interaction have a significant impact on immune inflammation and brain plasticity, which, in turn, shape animal behaviour [11,42]. This suggests that, regardless of the mechanism being studied, the animals' housing conditions (standard or enriched) may influence results, with implications for the potential clinical translation of findings from animal studies.

The study we report here is largely based on behavioural data, which is prone to multiple confounding factors and variability. Considering the absence of molecular and electrophysiological markers of stress-induced depression, our findings warrant further investigations into the role of

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housing conditions when studying depression in preclinical models. Environmental enrichment must be considered a critical variable in modelling depression in animals, as it can significantly impact findings and affect the translational potential of preclinical studies. Based on our results, follow-up studies using a modified CUMS protocol to highlight the benefits of EE are required. Such studies will have to include molecular, behavioural, imaging and electrophysiological data to fully determine the appropriateness of CUMS as a model for studying depression induced under enriched housing conditions.

Conclusion

This study evaluated the ability of the chronic unpredictable mild stress (CUMS) paradigm to induce depression-like behaviours in rats housed under environmentally enriched (EE) conditions. While CUMS impaired weight gain and recognition memory, it did not elicit hallmark features of depression such as anhedonia, helplessness, or heightened anxiety. These findings suggest that enriched housing may confer resilience against some behavioural manifestations of stress, or alternatively, that the CUMS protocol employed was insufficient to overcome the buffering effects of EE. Importantly, the results highlight the need to reconsider housing conditions as a key variable in preclinical models of depression to improve their translational relevance for human mental health research and treatment development.

DECLARATIONS

Ethical consideration

This study was approved by the College of Health Sciences Ethical and Protocol Review Committee, University of Ghana (CHS-Et/M.11 – P 4.2/2023-2024).

Consent to publish

All authors agreed on the content of the final paper.

Funding

None

Competing Interest

The authors declare no conflict of interest

Author contribution

TAT was responsible for Conceptualisation, Methodology, Resources, Data collection, Analysis, Writing, Review and Supervision. AB was responsible for data collection, Analysis, writing, and Review. ED was responsible for Data collection, analysis, and Review. CA and AL were responsible for Data collection. KKEK was responsible for Methodology, Resources, Review and Supervision.

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Availability of data

Data is available upon request to the corresponding author

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