**LASU Journal of Medical Sciences**
*Official Publication of the Faculty of Basic Medical Sciences and Faculty of Basic Clinical Sciences*
*Lagos State University College of Medicine, Ikeja*
*www.lasucom.edu.org.*
*E-mail: lasujms@lasucom.edu.ng*

**Research Article**

# Influence of Light-Dark Alteration on Performance of Mice in Some Memory and Learning Paradigms

**Umar Abdullahi H[1], Hussaini Aisha M[1], Isa Ahmed-Sherif[1], Yusuf Adamu M[1], Musa Lilian A[1], Suleiman Ibrahim[1], Imam Maryam I[1], Yusha'u Yusuf[1], Ishaku Aisha A[2]**

[1]Department of Human Physiology, Ahmadu Bello University, Zaria, Nigeria. [2]Department of Human Physiology, University of Maiduguri, Nigeria

[*]***Author for Correspondence:***
E-mail: ahumar09@gmail.com.

**Keywords:**
light; dark; memory; learning

## ABSTRACT

**Objective:** The study of neurobehavioral development focuses on the mechanisms through which the experience of an individual influences the ontogeny of the brain circuit that ultimately controls complex functions, such as social engagement, mood, emotional regulation and control, as well as memory and learning. The aim of this work is to investigate the effect of light-dark exposure on performance of mice in various neurobehavioral models.

**Methods:** Fifteen apparently healthy litter mice were used for the study. The animals were divided into three groups (n = 5), and bred in permanent light (PL), permanent dark (PD) and normal day/night (control) conditions till maturity. The adult animals were subjected to the Morris water maze (MWM), elevated plus maze (EPM) and Barnes maze (BM) experiment models for learning and memory.

**Results:** The result of MWM test showed that mean latency to locate escape platform was significantly higher in PD group in days one and two when compared to PL and control groups. There was no significant difference in latency to enter closed arm during the retention phase of EPM experiment. In the BM test, mean latency to enter the escape box was significantly lower in PD group when compared to both PL and control groups.

**Conclusion:** In conclusion, this study has demonstrated that breeding mice in permanent light or permanent dark conditions affect their neurobehavioral development and cognitive ability.

## INTRODUCTION

Circadian rhythms, which are basic biological phenomena that exist throughout phylogeny, are influenced by zeitgebers (time-givers) and regulate various physiological events, including the cell cycle, sleep-wake cycle, body temperature, metabolism, feeding, etc.[1] Operation of the circadian clock, which is an internal regulator in cells of organisms, and its biological connection with memory formation is less understood and remain a subject of intense investigation.

The circadian rhythm coordinates physiological and behavioural activities with daily environmental variations. Thus, misalignment of the circadian clock with environmental cues alters the timing of the sleep-wake cycle, which eventually leads to a number of circadian rhythm sleep disorders.[2]

It is clear that humans and other living creatures are subject to biological clock in a number of physiological conditions, especially sleep-wake cycle and behaviour.[3] Light is considered a universally constant and powerful stimulus that modulates many types of behaviour. Biological rhythms are regular fluctuations in any living process and are modulated by environmental light-dark cycle. Change in the duration of light-dark cycle has been shown to have possible effect on the visual system, as well as other brain structures. The circadian system modulates many behavioural and physiological processes.[4] There is evidence that this circadian variation may be a general feature of the performance of animals in learning and memory. Many physiological processes which exhibit circadian variations, such as hormone secretions, could be the basis of these changes.[5] Melatonin has been shown to act as a modulator of particular cognitive functions. Light exposure during the post-natal period of mice cause structural and neurochemical changes in the suprachiasmatic nucleus of the hypothalamus, which may in turn modify animal behaviour.[6]

A growing body of research examine the correlation of a disrupted circadian rhythm with cardiovascular events,[7] obesity,[8] and neurological problems like depression and bipolar disorder.[9] Because of the observed relevance of the circadian rhythm to physiological functions, researchers studying chronobiology (the branch of biology concerned with cyclical physiological phenomena) were awarded the 2017 Nobel Prize in physiology or medicine. It was jointly awarded to Jeffrey C. Hall, Michael Rosbash and Michael W. Young for their discoveries of molecular mechanisms controlling the circadian rhythm.

The Circadian rhythms is known to regulate the biological processes of living organisms, and is linked to the patterns of brain activity, hormone production, cell regeneration, etc. Circadian rhythms are endogenously driven[10] and organisms are able to maintain their

behavioural and physiological rhythms even under constant environmental conditions. In mammals, the master circadian centreis located in the suprachiasmatic nucleus (SCN) of the hypothalamus, where the circadian machinery is self-sustained and maintained by a cellular feedback loop.[11]

During the circadian feedback loop, the circadian proteins, including the Circadian Locomotor Output Cycles Kaput(CLOCK) and Brain and Muscle ARNT-Like 1 (BMAL1),heterodimerize and bind to the Period (PER) and Cryptochrome (CRY) genes promoter regions, thereby activating them. Once translated, PER and CRY proteins build up in the cytoplasm of the cell over the course of the day, and eventually form hetero- and homodimers that inhibit CLOCK:BMAL1-mediated transcription. The timing of nuclear entry is balanced by regulatory kinases that phosphorylate the PER and CRY proteins, leading to their degradation.[12]

The hippocampus is well-known for its role in memory consolidation and learning and for its ability of neurogenesis,[13] as such, any factor that influences neurogenesis in the hippocampus may also affect subsequent development of memory. Light is one of the factors that exert significant effects on the structure and functions of the hippocampus.[14] As neurogenesis form the neurobiological basis of memory formation and learning, growing evidence suggests that various factors such as stressors, immobilization stress, exercise, social isolation, hormones, oxidative stress, metabolic disorders, and the light-dark cycle could affect neurogenesis.[15]

Circadian and sleep parameters have been shown to influence cognitive function, and disruption of the circadian rhythms may lead to poorer cognition, as decline in normal circadian function can lead to cognitive impairment.[16] In mammals, the circadian rhythm is modulated by the clock genes, and the circadian clock regulates memory process over the daily sleep-wake cycle.[17] Light exerts a significant effect on an organism's physiology and behaviour, including entrainment of circadian rhythms, regulation of sleep, pupillary constriction, regulation of hormones as well as modulation of cognitive processes. These non-visual responses do not involve the image-forming pathways but depend upon detection of changes in environmental irradiance (brightness).[18]

Studies show that any alteration in the light-dark cycle, such as those experienced by people working in the night shift, is associated with cardiovascular diseases, obesity, cancer, depression, mood disorders, metabolic diseases, and cognitive behaviour dysfunction.[19]Studies have reported learning and memory impairment following an alteration in light intensity and exposure time. Regarding the role of the hippocampus, it appears that memory and learning deficiencies could be the result of a deficiency in hippocampal neurogenesis. Fujioka *et al*.[20] reported that exposure to constant light significantly decreased proliferation in the dorsal ganglion layer of hippocampus. They also demonstrated that exposure to constant light impaired spatial learning task performance. Each day, we are exposed to both light and dark environments at varying degrees and durations which can have either positive or negative effects on our ability to learn and recall information by its effect on the neurogenesis of the hippocampal neurons,[21,22] which are essential structures for learning and memory in the brain.[23] Hence, there is need to determine the effects of alteration in the light-dark cycle on memory and learning, so as to determine the perfect condition required to achieve a better and improved learning and memory ability and also to fight against the increasing rate of memory disorders. This work was designed to determine the influence of light and dark exposure on performance of mice in animal model of cognition. Our experimental design was based on the hypothesis that alteration in the light-dark cycle will modulate learning and memory behaviours.

Memory and learning were assessed using the Morris water maze (MWM), elevated plus maze (EPM), and Barnes maze (BM) models. Spatial learning and memory in laboratory animals can be assessed using navigational ability in mazes, most popular of which are the water and dry-land (Barnes) mazes. Improved performances of the animals over trials reflect learning and memory. The BM, made of a circular platform top with several holes equally spaced around the perimeter edge is considered less stressful than the water maze.[24] The surface is exposed to a bright light, which serve as the aversive stimulus, and the holes lead to an open drop to the floor, except a single hole that leads to an escape box, a dark box in which the animal can hide. A rodent is naturally motivated to avoid open spaces and bright lights, and therefore attempts to find the escape box. The MWM is a test of spatial learning for rodents that relies on distal cues to navigate around the perimeter of an open swimming arena to locate a submerged escape platform. It has proven to be a robust and reliable test that is strongly correlated with hippocampal synaptic plasticity and NMDA receptor function.[25] Developed by Richard Morris in 1984, the MWM has become one of the "gold standards" of behavioural neuroscience.[26] The EPMis also a validated model for behavioural assay in rodents and it is used to assess anti-anxiety effects and working memory.[27]

## MATERIALS AND METHODS

The study was carried out in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Research Council.[28] A total of eight (8) apparently healthy female Swiss mice were obtained from the animal house of the Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria. They were artificially brought into oestrous (heat) by administration of oral suspension of 100 µg ethinyl oestradiol, followed by 1 mg progesterone (subcutaneously) 48 hours and 6 hours prior to pairing respectively.[29] The animals were mated overnight with healthy male counterparts at a ratio of 2:1. Vaginal smear was observed microscopically and pregnancy was confirmed by presence of spermatozoa in the smear. After confirmation of pregnancy, the pregnant mice were housed in plastic cages in a well-ventilated animal house in the Department of Human physiology, Ahmadu Bello University, Zaria with natural day light cycle until parturition. After normal vaginal delivery, three (3) dams and their litters (5 litters per dam) were selected and randomly placed and bred in one of permanent light (PL), permanent dark (PD) and normal light dark (control) conditions. Twenty-eight (28) days post-partum, the dams were removed while and the litters were left in the same condition for another four weeks before commencement of the experimental procedure. The animals were fed on standard commercial rat chow with water

ad libitum throughout the experimental period.

**Light dark alteration**

Permanent light condition was established by keeping the animals in a 50 $ft^2$ room that was kept constantly illuminated with a fluorescent light bulb (85 watts/274 lux). Permanent dark condition was achieved by keeping the animals in a 50 $ft^2$ room, with all sources of light covered using a black curtain. Animals in the control group were kept under natural day light condition. All conditions were maintained throughout the period of the study.

**Experimental protocols**

**Morris water maze**

In this study, the MWM test was carried out as described by Snow *et al*.[30] and Barnhart et al.[31], with slight modifications. It consisted of a circular swimming pool of 100cm in diameter and 30cm deep, with an escape platform submerged about 5mm below the water surface in the centre of the designated target quadrant. In the acquisition phase, made up of 4 trials/day (commencing each trial from a different quadrant) for 3 consecutive days, the Mice were placed gently at the edge of the pool and allowed to find the hidden platform within 60 seconds. Upon locating the platform, the animals were allowed to remain on the platform for 20 s, following which they were returned to their home cage. Escape latency (time to locate platform) was recorded in seconds. If the animal failed to locate the platform after 60 seconds, it was gently guided to the platform and allowed to remain on it for 20 seconds. Twenty-four hours after the last acquisition trial, a probe trial was carried out by removing the escape platform and allowing the animal to explore the pool and search for the missing platform for 60 seconds. The time taken by the animal to locate the escape platform (in seconds) was recorded.

**Figure 1:** Rat in a circular pool during the Morris Water Maze test

**Elevated plus maze (EPM)**

The EPM apparatus, which was fabricated using wooden material and painted black, consists of two open arms without walls and two closed arms with 15.25 cm high walls. Each arm is 30 cm long and 5 cm wide, and is elevated 40 cm above the floor.[27] On the first day (acquisition), the animals were placed individually at the edge of one of the open arms, facing outward, and then allowed to explore the apparatus for a maximum period of 90 seconds. The time taken for the animal to locate and enter into the closed arm (with the hind-limbs inside the closed arm) was recorded and the animal was allowed to explore for further 20 seconds. Any animal that fail to enter the closed arm after 90 seconds is guided to it and allowed to explore for 20 seconds. After 24 hours, the procedure was repeated (retention) and time taken for the animal to enter the closed arm (in seconds) was also recorded.

**Figure 2:** Elevated Plus Maze test performed during the experiment

**Barnes maze**

The circular Barnes maze used in this study was made of an elevated white disc with 40 evenly spaced holes cut in the perimeter,[32] with an escape box mounted underneath one of the holes and visual cues pasted on the wall. The escape box was maintained on the same location throughout the trial period, and the maze was cleaned with 70% ethanol after each trial.[33] The mice were placed in the middle of the maze with light switched on, and allowed to navigate and locate the escape box. Once the mouse is inside the box, the light was turned off and the animal allowed to stay in the box for 30 seconds, after which it is removed and returned to its home cage until the next trial. During the training session, each anima received four trials per day for two days, with an inter-trial interval of 15 minutes. If the animal fail to locate the escape box after five minutes, it is guided gently and allowed to stay inside for 30 seconds. On the third day (probe trial), the escape box was removed and the latency to reaching to previous escape tunnel location were recorded (in seconds).

**Figure 3:** Barnes Maze apparatus used during the study

**Statistical analysis**

Data obtained from the behavioural assay were presented as mean ± standard error of mean (SEM). Mean differences between the groups were analysed by one-way ANOVA, followed by Tukey's post hoc test. Analysis was carried out using SPSS version 23 software for windows (SPSS Inc, Chicago). Statistical significance was set at $p < 0.05$.

**RESULTS**

Result of the MWM test shows that the mean latency to locate the escape platform was significantly higher in the PD group in day one and day two when compared to the PL group ($p = 0.000$), as well as to the control ($p= 0.003$). On day three however, the latency did not statistically vary between all the groups ($p = 0.090$) (Figure 1). On the other hand, within group analysis shows that animals in the PL group have higher latency to locate the escape platform on day one, but the latency reduced significantly on day two and day three (Figure 4). Animals in the PD and control groups, however, showed insignificant difference on days one and two, but the latency was significantly reduced on day three (Figure 4).

Result of the EPM test showed that mean latency to enter the closed arm during the acquisition phase was highest in the PL group, followed by the PD, and least in the control, and the differences were statistically significant (Figure 5). During the retention phase however, the mean latency was least in the in the PL group, followed by the PD group and highest in the control group, though the differences were not statistically significant. The PL group showed significantly higher mean latency to enter the closed arm during the acquisition phase than the retention phase, while the control group showed significantly lower mean latency during acquisition than retention. Difference between acquisition and retention latencies was however not statistically significant in the PD group, although the retention time was lower than the acquisition time (Figure 5).

In the Barnes maze test, the mean latency to enter the escape box in day three was significantly lower in the PD group as compared to the PL and control, while differences in days one and two were not statistically significant, although the PD group had the least latencies. Within group differences between days also showed no statistically significant differences in the PL and control groups, but the PD group showed significantly higher latency in day one when compared to days two and three (Figure 6).

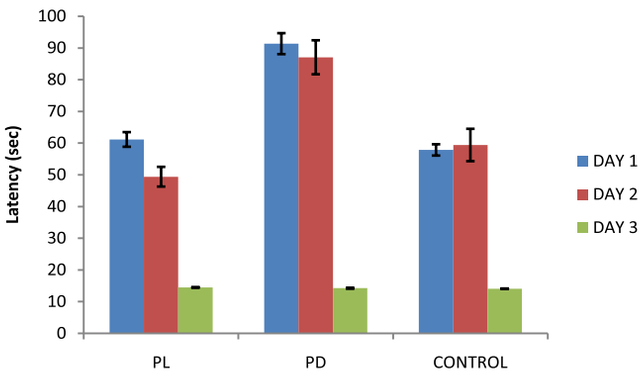


**Figure 4:** Effect of light-dark exposure on latency of mice to locate escape platform in Morris Water Maze experiment
a,b = statistically significant differences between groups: *,#,† = statistically significant intra-group differences between days one, two and three.
PL, Permanent light group; PD, Permanent dark group

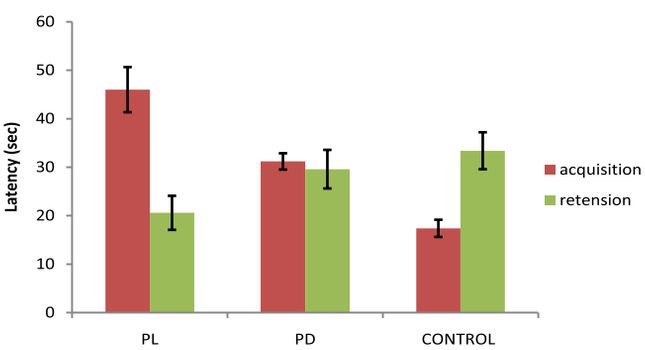


**Figure 5:** Effect of light-dark exposure on latency of mice to enter closed arm during the acquisition (day 1) and retention (day 2) phases of Elevated Plus Maze memory task
a,b,c = statistically significant differences between groups. *# = statistically significant difference between acquisition and retention within the same group. PL; Permanent light group, PD; Permanent dark group

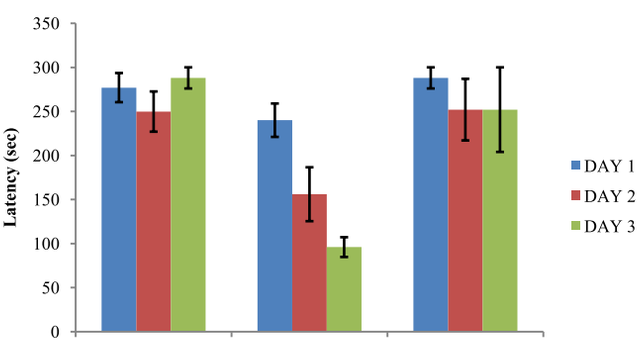


**Figure 6:** Effect of light-dark exposure on latency of mice to locate escape box in Barnes maze experiment.
a = statistically significant difference between the groups: *statistically significant intra-group differences between days one, two and three. PL; Permanent light group, PD; Permanent dark group

**DISCUSSION**

Mice lacking rods and cones can still make use of light-dark cycles to entrain their circadian rhythms, indicating that there is presumably some photoreceptor in the inner layer of the retina that serves the circadian system.[34]The endogenous circadian system is an important player that can modulate animal's physiology and behaviour, and light exerts widespread effects on the physiology and behaviour of all mammals. For example, light exposure has been shown to depress locomotor activity in rats.[35]

Measures of performance on learning and memory in this study were determined by latency (time from start to goal) in seconds. Learning and/or memory is indicated by reduced latency to reach desired goal. This study has demonstrated that exposure to permanent light or dark condition influences the behaviour of male Swiss mice in the memory paradigms used. Many types of behaviour in nocturnal rodents show circadian variations, with higher activity during the dark period and lower activity during the light period.[36]In this study, mice bred in PD condition spent longer time to locate the escape platform on days 1 and 2 of the MWM test when compared to control and those bred in PL condition, indicating that mice bred in PL condition showed significantly improved memory in MWM task than those bred in PD condition. In addition, PL mice were able to locate the escape platform on days two and three much faster than they did on day one, a behaviour not observed with the PD mice. This suggests memory improvement in mice bred under PL condition in the MWM.

In the EPM test, the mean latency to enter the closed arm during the acquisition phase was highest in the PL group, followed by the PD, and least in the control, and the differences were statistically significant. During the retention phase however, the mean latency was least in the in the PL group, followed by the PD group and highest in the control group, although the differences were not statistically significant. The PL group showed significantly higher mean latency to enter the closed arm during the acquisition phase than the retention phase, while the control group showed significantly lower mean latency during acquisition than retention. Difference between acquisition and retention latencies was however not statistically significant in the PD group, although the retention time was lower than the acquisition time.

In the Barnes maze test, the mean latency to enter the escape box on day three was significantly lower in the PD group when compared to the PL and control, while differences on days one and two were not statistically significant, though the PD group had the least latencies. Within group analysis between days also showed no statistically significant differences between the PL and control groups, but the PD group showed significantly higher latency on day one as compared to days two and three. The result of our study is in agreement with a previous work by Warthen *et al*., [37] which showed that light modulates responses to previously acquired conditioned-fear stimulus through the rods and/or cones. A study by Chaudhury and Colwell[38] also demonstrated that the ability to learn the fear-conditioning task is modulated by the circadian system. Circadian induced memory alteration has also been reported by Ruby *et al*.,[39] although Richetto *et al*.[40] that innate anxiety and spatial working memory are not affected by the daylight phase. Reduced visual acuity was reported in another study to significantly worsen performance of rats in the hidden platform version of the MWM test.[41] Light, as a pervasive stimulus, exerts numerous effects on physiology and behaviour, and also modulates higher-order cognitive functions such as anxiety, mood, and alertness/awakeness. The retina projects directly to brain regions involved in emotional responses, including the amygdala, bed nucleus of the stria terminalis and periaqueductal gray, and their activity is modulated by light.[42] A study by Song et al.[17] showed that aged mice had impaired spacial memory when compared to young mice. Adaptation to changes in the ambient light level, including light modulation of neuroendocrine function and temporal alignment of physiology and behaviour to the day-night cycle by the circadian clock, is of crucial importance to life. These non-image-forming (NIF) responses can function independent of rod and cone photoreceptors but depend on ocular light reception.[43] Behavioural changes in response to light has been shown to be influenced by the melanopsin retinal ganglion cells (intrinsically photosensitive retinal ganglion cells [ipRGC]) present in the inner retina. Photic activation of ipRGC, which contain the photo-responsive pigment melanopsin, send light information to SCN via the retinohypothalamic tract (RHT), which relays the information to other hypothalamic and limbic structures that are involved in memory processing, such as the hippocampus and amygdala.[6]

While rods/cones of the outer retina are known to mediate image-forming vision in the mammalian retina, photoreceptive melanopsin-expressing retinal ganglion cells of the inner retina sub serve most non-image-forming responses to light.[44] Mice lacking the melanopsin gene were reported to have impaired suppression of locomotion in the presence of bright light.[45] The light associated improved spatial memory observed in this study may be mediated via a melatonin related mechanism, as pineal melatonin suppression, as well as mood and cognition have been shown to be regulated by light.[18] Peak melanopsin sensitivity was reported to correlate with the photosensitivity of several NIF responses of animals or humans under natural conditions of prolonged light exposure when rods and cones have adapted, thus suggesting a role for melanopsin inNIF responses.[43] Mouse with poor visual ability were reported to perform poorly in the MWM spatial memory task, a performance believed to be not due to impairment in learning and memory, as visual ability significantly correlate negatively with measure of learning and memory. Impairment in Visio-spatial memory may be attributed to non-cognitive factors, such as poor swimming or visual ability.[46] Learning deficit in mice with retinal degeneration was associated with impairment in hippocampal long-term potentiation (LTP).[47]

A study by Song *et al*., [17] showed that isoflurane impaired early cognitive functions and disturbed circadian rhythm of young mice, effects which were prolonged and harder to reverse in aged mice. Albino mice are characterized by mutation in the tyrosine 3-monooxygenase(tyrosinase) enzyme, which synthesises melanin from tyrosine in the skin and eyes, resulting in deficiency of melanin in the retinal pigment epithelium (RPE), which give rise to a pink Eye

colour in albino mice. The albino mouse is also more sensitive to light, more susceptible to light-induced retinal damage and show impaired visual function. Melanin in the RPE also influences the developing neural retina, resulting in reduced rod photoreceptor numbers, thinner nuclear layers and reduced cell density in the retinal ganglion cell layer of albino mice. Furthermore, during development, the routing of fibres in the optic tract is affected, leading to defects in their optic chiasm.[18]

Circadian modulation of learning and memory may be through hormonal signalling, as melatonin administration has been shown to inhibit long term potentiation (LTP) in the hippocampus. The supra-chiasmatic nucleus (SCN)is also anatomically connected with the hippocampus, and it in turn mediates hippocampal activation. Many widely-used behavioural tests of learning and memory, such as the Morris water maze and Barnes maze, are visuo-spatial tests of cognitive function. Animals with impaired visual acuity may perform poorly on these tasks, not because of cognitive impairment but because of poor vision. Mice lacking rods and cones have been shown to be able to use light as a cue for making a voluntary and arbitrary response.[34] The circadian gene, period (per) has been suggested to regulate memory independently of its role in the generation of circadian rhythms, over expression of which enhances LTP.[6]

Fragile X protein has been shown to regulate circadian rhythms and memory in flies.[48,49]Cognitive testing during the light phase has been reported to induce pronounced behavioural inhibition as well as a cognitive disruption in mice,[50] a behaviour not improved even by environmental enrichment as animals bred in enriched environment showed reduced locomotor and exploratory activities in the light phase.[51]Processes that could contribute to circadian induced memory alteration include gene transcription and translation, epigenetic mechanisms, neurotransmitter release, neuronal activity and hormone secretion, each of which may have different effects on various phases of memory.

## CONCLUSION

This study has demonstrated that breeding experimental mice under different conditions of light/dark cycle affect their neurobehavioral outcome and cognitive ability. It is therefore recommended that researchers using mice for memory and learning experiments should put into cognisance their light/dark cycle.

### Conflict of Interest

The authors declare no conflicting interest

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