Effect of Acute Phase Mild Stress Model of Depression on Cognitive Performance, Visuospatial Function and Appetite Behaviour in Wistar Rats.

Anaetochukwu Samuel, Olorunfemi O. Joyce
Department of Human Physiology, College of Health Sciences University of Port Harcourt, Port Harcourt, Choba, Rivers State, Nigeria.
olorunfemi.oluwadare@uniport.edu.ng. +2348035760596

Abstract - Cognitive deficits as a result of chronic stress if unchecked may accumulate and result into mental disorders such as clinical depression which will hamper the normal daily living of the patient. The effect of mild stress model of depression on cognitive performance, visuospatial function and appetite behaviour during acute phase in rats was investigated. 50 Wistar rats were randomly divided into 5 groups of similar weight as follows; Group I (served as the negative control, received no stressor); Group II (Positive Control, received 0.5ml of Cerebrex); Group III (received Electro stimulation induced Stress and Tail Pinch Stress); Group IV (received Reversed Light/Dark Cycle and Food and water deprivation stress); Group V (received Wet Cage bedding stress and Ice cold swimming stress).. The acute phase lasted for two weeks. Cognitive parameters were assessed using various cognitive tasks. Assessment of the effect of stress on spatial learning, memory retention, cognitomotor function, visuospatial function and appetite behaviour were evaluated. The results showed that mild stress model of depression adversely affected cognitive function by down-regulating prompt learning and long-term memory retention. The results also showed that mild stress model of depression affected the reward system by affecting appetite behaviour negatively. The study equally demonstrated that acute unpredictable mild stress significantly increased the time expended on a given task, thus impairing learning and long-term memory retention. It insignificantly disrupted cognito-motor functioning but interfered in visuospatial function by decreasing the exploration time spent on the novel objects.

Keywords: Learning, memory, Cognitive deficits, visuospatial function, appetite behaviour

Introduction

Depression has been referred to as a state of low mood and aversion to activity. It has been reported to affect the thought processes of a person, a person's motivation, how a person behaves, how a person feels, and sense of well-being. Some associated features may include sadness, loss of concentration, inability to think properly and a significant increase or decrease in a person's appetite and sleeping time. There has also been reports of people experiencing depression to have feelings of dejection, hopelessness, and sometimes, suicidal thoughts. The experience may be short term or long term (de Zwart *et al.,* 2018). Stress has been referred to as any influence of the internal environment and/or the surrounding environment on living beings that can alter or disrupt its homeostasis (Shahsavarani *et al.,* 2013). Stress could be as a result of either external factors with environmental source, or as a result of internal perceptions of the individual. In its latter form, it could produce symptoms such as anxiety, and/or other negative feelings and emotions such as pain, sadness, depression, etc., and could result in serious psychological disorders such as post-traumatic stress disorder (Tse *et al.,* 2010). It has been reported that stressful events/experiences elicit the development of depression in humans (Kendler *et. al.,* 1999; R. Kessler, 1997). Stressful experiences/events predispose individuals to a variety of mental disorders, including depression, which has been reported to be one of the most serious and recurring psychiatric disorders that has very tremendous socioeconomic and personal consequences. Being exposed to aversive experiences can induce profound behavioural changes in humans and rodents, including depressive-like symptoms, anxiety and cognitive deficits, which are paralleled by physiological abnormalities (Mizoguchi *et al.,* 2000; Quan *et al.,* 2011). However, reproducing perfectly the symptoms of depression in humans is difficult to develop in an animal model. Self-reflection, consideration and self-consciousness are lacking in many animals, and the hallmarks of depression such as depressed mood, low self-esteem and suicidal thoughts can be hardly accessed in non-humans. Nevertheless, depression, like other mental disorders, is made up of endophenotypes that could be reproduced independently and evaluated in animals (Hasler *et al.,* 2004).

Materials & Method

Fifty (50) wistar rats weighing 120 to 200g were used for the study. The rats were put in wooden cages that were very well ventilated and well-spaced at the animal house of the Department of Human Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Port Harcourt, Port Harcourt, Nigeria. The rats were kept at a temperature range of between 26 - 30^{o}C under a twelve-hour light and dark cycle for two weeks (14 days) for them to acclimatize before the experiment began. They were given feed (Top feeds, Growers mash – Product of Eastern Premier Feed Mills Limited), water and sucrose solution twice weekly

The rats were divided into five groups with each group having ten (10) rats. Group I served as Negative Control, Group II served as Positive Control, while Groups III, IV and V served as the stressed groups.

Group I served as the negative Control group and was housed in normal condition without any stressor.

Group II served as the positive Control group and received 0.5ml of an Antidepressant drug (Cerebrex).

Groups III received Electroconvulsant therapy induced Stress and Tail Pinch Stress.

Group IV received Reversed Light/Dark Cycle and Food and water deprivation stress.

Group V received Wet Cage bedding stress and Ice cold swimming stress.

Appetite Behavior Test (Sucrose Preference Test)

The sucrose preference test was slightly modified from the previous description (Casarotto & Andreatini, 2007). Each group was provided with 300grams of sucrose solution and 300grams of normal water individually for three hours, the weights of the sucrose solution and water consumed were recorded accordingly before and after the test to determine the amount of intake. Baseline for sucrose consumption was taken as 150grams, therefore, any consumption of the sucrose solution below 150grams was considered as a decrease below baseline. During the two weeks of acclimatization, the sucrose consumption test was performed twice weekly (Tuesdays and Fridays) to habituate the rats to sucrose drinking. The Sucrose Preference test after the rats have been stressed was also conducted twice weekly (Tuesdays and Fridays).

Assessment of Spatial Learning and Memory (Modified Barnes Maze Test)

This maze test was developed by Carol Barnes to assess Spatial Learning and Memory where rats escaped from the circular platform surface to a small dark recessed chamber located under one of the holes around the perimeter of the platform. This test has become very popular in assessing spatial memory in rodents, as it takes advantage of their superior abilities in finding and escaping through small holes (Barnes, 1979). There is a bearing underneath the circular platform which makes it possible for the platform to rotate as the experimental animal makes movement while trying to locate the recessed chamber, thus changing the hole which leads to the recessed chamber. Because of this modification, the task becomes more complex than the usual static hole as proposed by Carol Barnes initially. This modified Barnes Maze is useful in the evaluation of the effects of chemical substances on cognitive performance, as well as in the assessment of cognitive impairments in rodents without the use of force on the subjects to perform a task under unnatural conditions.

Acquisition Period

Each rat was placed in the center between the surrounding holes on the circular platform of the Maze. After ten seconds, if the rat does not find its way into the target hole, it was guided to the side of the hole which leads to the recessed chamber, after which the tail was pulled gently in the opposite direction of the tail to cause the rat to enter the hole. If this failed, the rat was placed directly into the escape box. In addition, once in the escape box, it was allowed to remain there for one minute. The process was repeated until acquisition was established and the rats returned to their cages afterwards.

Probe Trial

This was done to determine retrieval of the location of the target goal. The number of wrong holes that were explored and the latency to reach the target hole was measured as an index for Learning Memory.

Assessment of Spatial Learning and Memory (Navigational Maze Test)

The Navigational Maze Test is widely used in Behavioural Neuroscience to evaluate Spatial Learning and Memory, it has also been found useful in the evaluation of injury to cortical structures of the brain (D'Hooge *et al.,* 2001). The Maze is designed to have a route/tour puzzle in the form of a branching passage through which the animals were expected to locate the point of exit. After acquisition trial (equal session and time were given to all experimental groups) and the establishment of acquisition, the animals were evaluated at a 24-hours interval during the period of research on daily basis for proof or recall (stored memory) and learning. The time taken (significant difference) to find and reach the point of exit was used as the proof of facilitation or impairment of Spatial Learning and Memory.

Assessment of Memory Retention Using the Passive Avoidance Test

The Passive avoidance apparatus is used widely to evaluate the effect of test substances on learning and memory retention (both short and long term memories). It has also found great use in the study and evaluation of other forms of cognitive functions and performances (Quillfeldt, 2006). Classically, the task uses fear-aggravated behaviours (aversion) in the evaluation of learning and memory (short and long term memories) on laboratory rodents. The Passive Avoidance apparatus has two chambers: a lit chamber and a dark chamber, in between the two chambers is a gate. The animal is initially allowed to explore both chambers. During the passive avoidance test, the animal learns to avoid passively the area/chamber where it was shocked on the foot previously. The Passive Avoidance Paradigm requires the animal to act contrary to their innate behaviour of preferring a dark area and remain in the bright area.

Acquisition Phase

During this phase, the rat was placed in the lit chamber and when it moved innately into the dark chamber, it received a mild shock on the foot. Thus, the animal learns the negative effect associated with going into the dark chamber. The animal has to learn to associate certain properties of the chamber with the foot shock it received and avoid such a place when re-introduced another time.

Test Phase

The retention of memory was deduced in correlation with the latency of the animal to remain in the lit chamber and not move across the gate between both chambers; the greater the latency, the better the recollection (indexed as long term memory consolidation). A maximum duration of five minutes was given for the test rat to remain in the lit chamber as proof of avoidance before it was returned to its cage.

Assessment of Motor Activity Using the Rotarod Test

The Rotarod test is used in the evaluation of motor coordination and motor learning. It has also found great usefulness in the evaluation of intoxication, sedation, stamina or strength (Sundaram *et al.,* 2015; Pritchett and Mulder, 2003). The animals had equal training time and session to maintain balance and longer latency to fall from the rotating rod. Animals having similar average initial performance were chosen for the probe study. After the animals had gone through the various stressors, they were placed gently and carefully on the rotor with the body axis perpendicular to the rotor's long axis and the head directed opposite to the direction of the rotating rod (27 rpm), the time taken for each rat to fall off from the rod was recorded accordingly.

Assessment of Visuospatial Function (Object Recognition Test Using the Open Field Cage)

Access to novelty (e.g., an object or an environment) can elicit approach behaviors in rats. According to the modified methods of Berlyne, (1950), and Aggleton (1985). The test is carried out in two sessions in the same context, divided by an intersession interval (ISI). During the first session (familiarization session), the animal is free to explore two similar objects, and during the second session (test session), one of the objects is replaced by a novel, unfamiliar object or the novel unfamiliar object will be added to the familiar ones. As defined by its authors, this test is really a one-trial task, as it does not involve learning of rules. In addition, the test does not require rein forcers and is purely based on the innate preference of the rodent to explore the novel object rather than the familiar one. Thus, a rodent that remembers the familiar object will spend more time exploring the novel object (Ennaceur and Delacour, 1988). In the course of this work, during the familiarization session, two objects (a round object and a triangular object) were put in the cage for a period of five minutes and the animals were allowed to explore these objects. While in the test session, two new objects (a square shaped object and a cross object) were introduced into the cage together with the other objects used during the familiarization session. A total of five minutes was given for each test session and the time spent exploring each object was recorded accordingly.

Method of Data Analysis

Data were analyzed using SPSS statistical package version 22. Results were represented as Mean ± Standard Error of Mean (SEM). Differences in parameters between the groups were determined by one-way analysis of variance (One-way ANOVA), followed with LSD Post-Hoc test at p values ≤ 0.05 considered as significant.

RESULT PRESENTATION

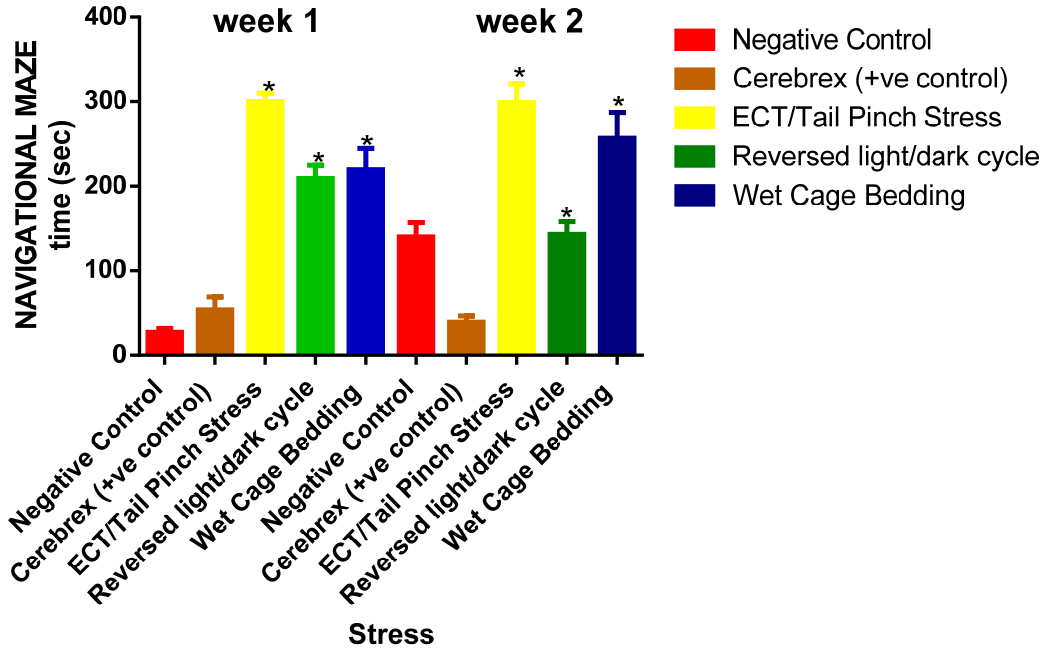

Fig.1. Effect of mild stress model of depression on learning and memory retention using Navigational Maze Test.

Values are expressed as Mean±SEM; n=5; *[Significant ($p \leq 0.05$) compared to Positive Control]

Key: Group 1 (Negative Control: No Stressor); **Group 2** (Positive Control: 0.5ml Cerebrex); **Group 3** (ECT/Tail Pinch Stress); **Group 4** (Reversed Light/Dark Cycle and Food and Water Deprivation Stress); **Group 5** (Wet Cage bedding stress and Ice cold swimming stress).

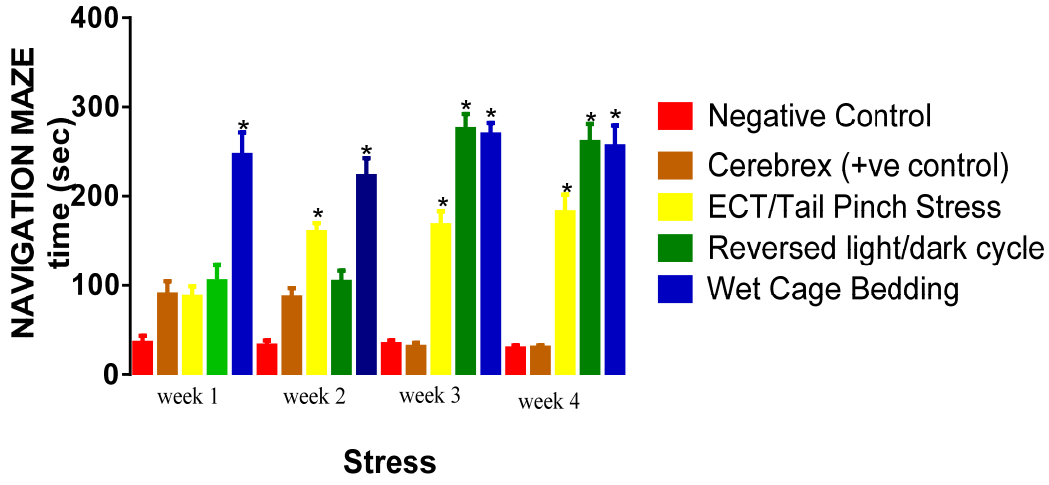

Fig. 2 Effect of mild stress model of depression on learning and memory retention using Navigational Maze Test(sub-acute)

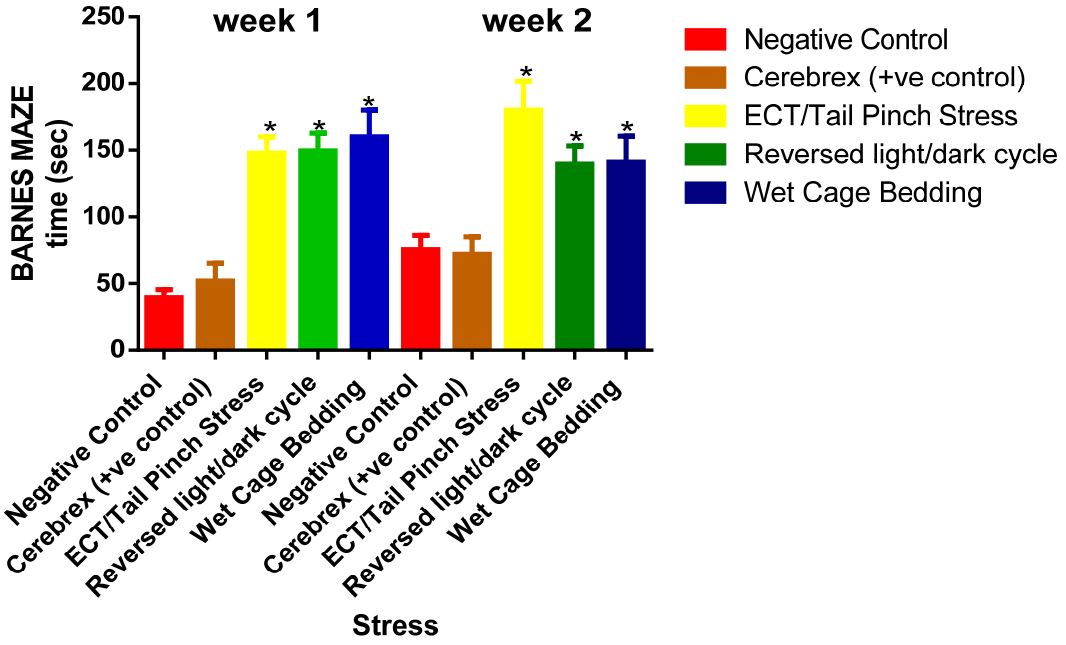

Fig. 3 Effect of mild stress model of depression on learning and memory retention using Barnes Maze Test.

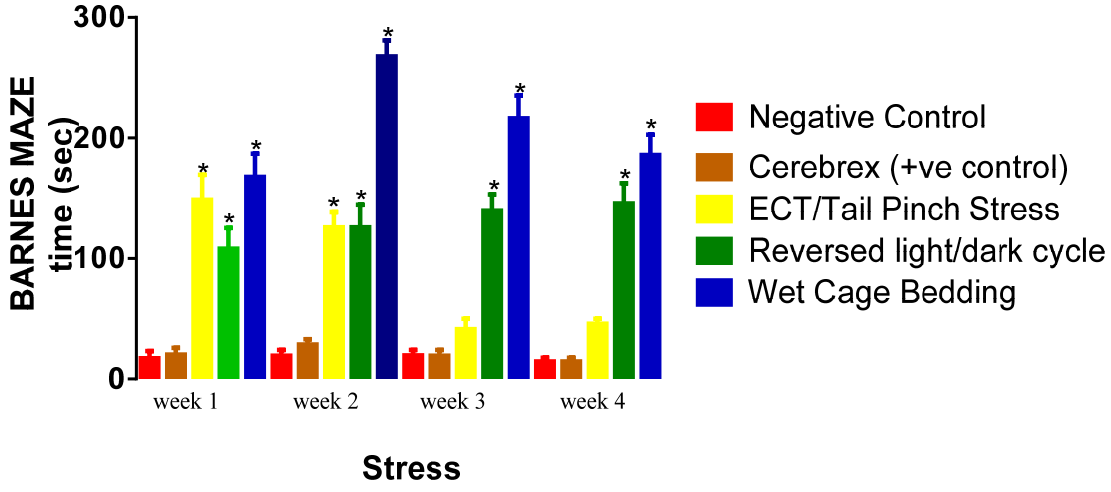

Fig. 4 Effect of mild stress model of depression on learning and memory retention using Barnes Maze Test(sub-acute)

Table 1 Effect of mild stress model of depression on learning and memory retention using Passive Avoidance Test (Acute Phase).

PASSIVE AVOIDANCE TEST		
GROUPS	WEEK 1	WEEK 2
GROUP 1 (Negative Control)	202.5±20.25	205.0±20.11
GROUP 2 (0.5ml Cerebrex)	230.6±23.14	162.1±21.23
GROUP 3 (ECT and Tail pinch Stress)	297.7±10.67	225.0±29.12
GROUP 4 (Reversed light/dark cycle and food and water deprivation stress)	168.4±11.07	195.9±26.30
GROUP 5 (Wet Cage bedding stress and Ice cold swimming stress)	281.7±15.62	266.0±24.27

Values are expressed as Mean±SEM; n=5; *[Significant ($p \leq 0.05$) compared to Positive Control]

Key: Group 1 (Negative Control: No Stressor); **Group 2** (Positive Control: 0.5ml Cerebrex); **Group 3** (ECT/Tail Pinch Stress); **Group 4** (Reversed Light/Dark Cycle and Food and Water Deprivation Stress); **Group 5** (Wet Cage bedding stress and Ice cold swimming stress).

Table 2 Effect of mild stress model of depression on learning and memory retention using Passive Avoidance Test(sub-acute)

PASSIVE AVOIDANCE TEST				
GROUPS	WEEK 1	WEEK 2	WEEK 3	WEEK 4
GROUP 1 (Negative Control)	275.2±17.64	229.3±15.51	259.9±14.27	230.8±16.98
GROUP 2 (0.5ml Cerebrex)	194.7±19.49	192.7±16.39	237.9±14.02	230.8±17.89
GROUP 3 (ECT and Tail pinch Stress)	139.4±19.11	113.6±7.91*	229.0±20.76	188.2±18.20
GROUP 4 (Reversed light/dark cycle and food and water deprivation stress)	116.7±21.22*	219.0±20.12	207.0±15.46	230.4±17.04
GROUP 5 (Wet Cage bedding stress and Ice cold swimming stress)	242.3±24.14	206.0±14.77	261.2±15.80	224.5±21.86

Values are expressed as Mean±SEM; n=5; *[Significant ($p \leq 0.05$) compared to Positive Control]

Key: Group 1 (Negative Control: No Stressor); **Group 2** (Positive Control: 0.5ml Cerebrex); **Group 3** (ECT/Tail Pinch Stress); **Group 4** (Reversed Light/Dark Cycle and Food and Water Deprivation Stress); **Group 5** (Wet Cage bedding stress and Ice cold swimming stress).

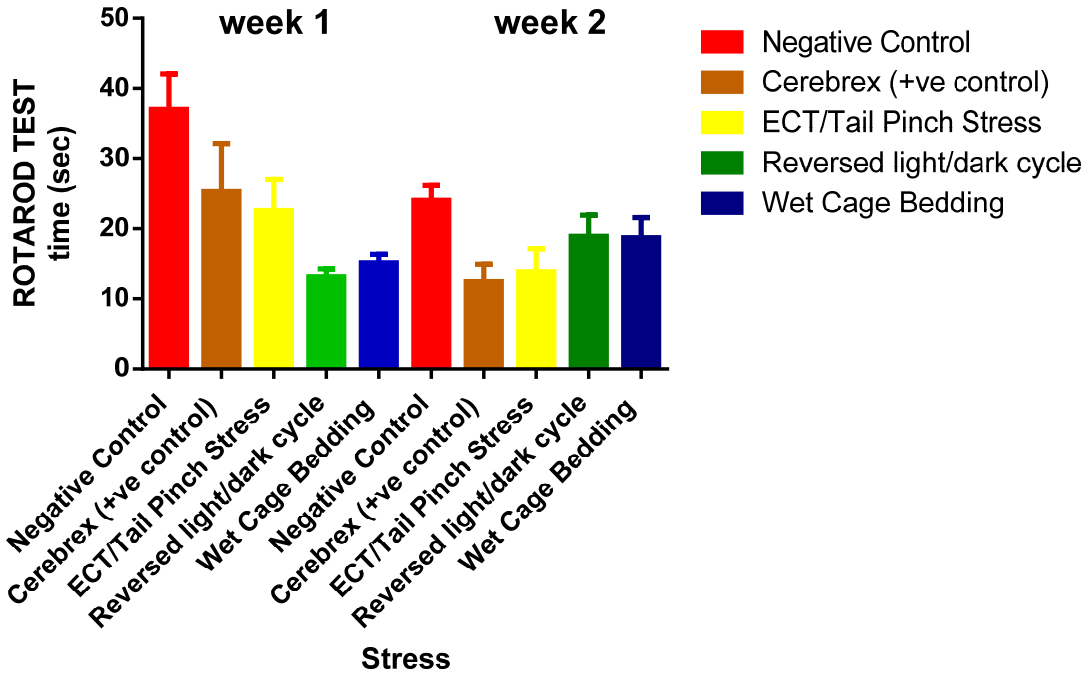

Fig. 5 Effect of mild stress model of depression on Motor Coordination using Rotarod Test (Acute Phase).

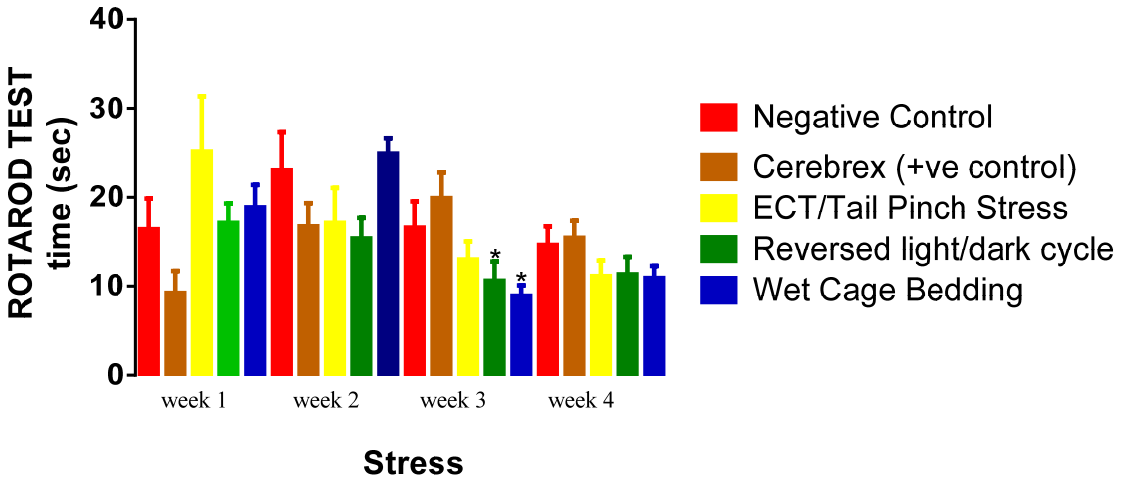

Fig. 6 Effect of mild stress model of depression on Motor Coordination using Rotarod Test (sub-acute).

Table 4.1.3 Effect of mild stress model of depression on Visuospatial Function using Novel Object Recognition Test (Acute Phase).

NOVEL OBJECT RECOGNITION TEST WEEK 1				
GROUPS	Round	Triangle	Square	Cross
GROUP 1 (Negative Control)	16.67±1.76	13.33±5.46	135.3±13.79	113.3±12.10
GROUP 2 (0.5ml Cerebrex)	30.67±5.81	29.67±4.53	140.0±15.21	77.67±9.12
GROUP 3 (ECT and Tail pinch Stress)	94.33±12.80*	37.33±6.57	91.67±10.87	31.67±5.76*
GROUP 4 (Reversed light/dark cycle and food and water deprivation stress)	126.0±16.05*	124.0±17.75*	86.7±19.60	41.7±18.33*
GROUP 5 (Wet Cage bedding stress and Ice cold swimming stress)	111.7±14.22*	60.67±10.76	186.0±20.21	35.33±12.43*

Values are expressed as Mean±SEM; n=5; *[Significant ($p \leq 0.05$) compared to Positive Control].

Table 4.1.4 Effect of mild stress model of depression on Visuospatial Function using Novel Object Recognition Test (sub-Acute Phase).

NOVEL OBJECT RECOGNITION TEST WEEK 2				
GROUPS	Round	Triangle	Square	Cross
GROUP 1 (Negative Control)	89.10±20.22	20.0±10.18	165.0±14.07	263.3±30.67
GROUP 2 (0.5ml Cerebrex)	118.3±12.84	13.33±1.67	77.00±12.12	175.0±18.84
GROUP 3 (ECT and Tail pinch Stress)	103.7±12.70	18.33±1.67	20.00±4.77*	6.67±1.00*
GROUP 4 (Reversed light/dark cycle and food and water deprivation stress)	113.7±14.18	58.33±10.14*	23.33±4.93*	10.67±5.81*
GROUP 5 (Wet Cage bedding stress and Ice cold swimming stress)	12.67±1.67*	30.00±5.77	83.33±10.44*	41.00±7.40

Values are expressed as Mean±SEM; n=5; *[Significant ($p \leq 0.05$) compared to Positive Control]

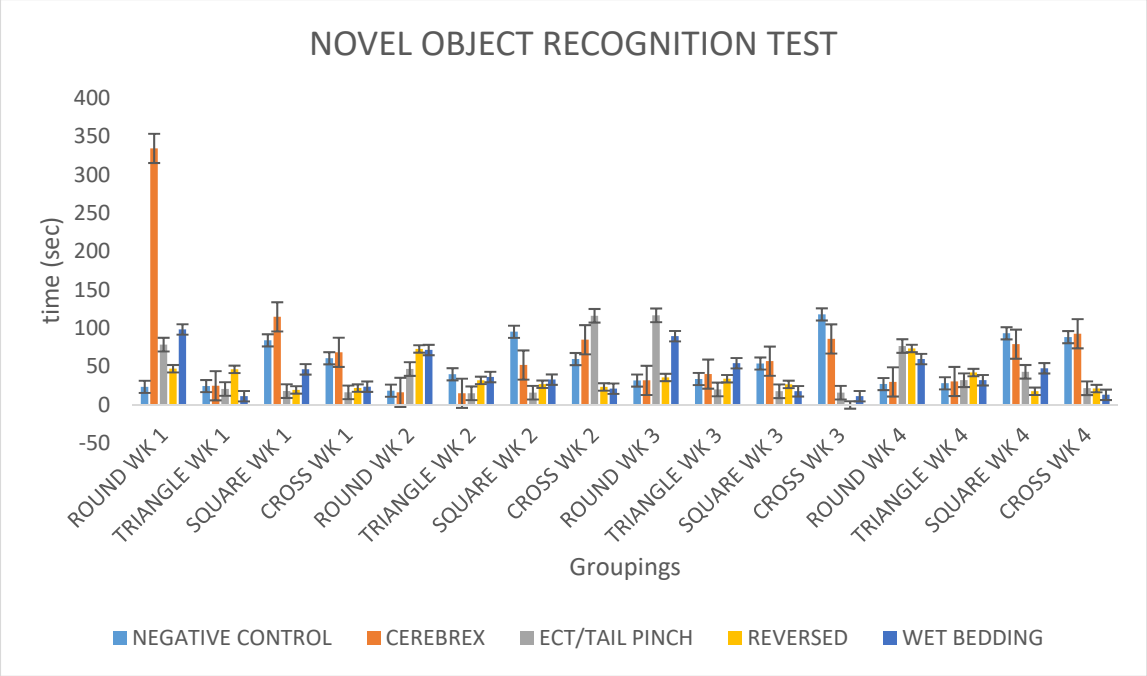

Fig. 4.1.7 Effect of mild stress model of depression on Visuospatial Function using Novel Object Recognition Test (sub-acute)

Discussion

This study was aimed at investigating the effect of mild stress model of depression on cognitive performance, visuospatial function and appetite behaviour in rats. An impaired capacity for new learning and inability to consolidate new information into long term memory denotes cognitive impairment and is suggestive of anterograde amnesia. The study demonstrated that chronic unpredictable mild stress negatively affected the ability of the rats to quickly recall the navigation route. Similar deficit/impairment to quickly locate the underneath chamber in the Modified Barnes maze test was also recorded, these deficits are reflected in the significantly ($p \leq 0.05$) increased time expended on the task, compared to the control groups.

In contrast, Electroconvulsant induced therapy (ECT) stress and Tail Pinch stress (Group 3 chronic subgroup) showed a reduction in the time taken to explore and locate the underneath chamber in the Barnes Maze test for weeks three and four of the chronic phase when compared to other stressed groups. This is indicative that the effect of stress on cognitive performance is dependent on the type of stressor as earlier reported by Duman, (2004), however, it also showed that spatial learning and long-term memory retention may also depend on the type of cognitive task as same stressed group showed a significant ($p \leq 0.05$) increase in the time taken to recall the navigation route in the Navigational Maze Test for same weeks three and four of the chronic phase.

Electroconvulsant induced therapy (ECT) stress and Tail Pinch stress significantly ($p<0.05$) decreased memory retention of foot shock received on the passive avoidance test only for week two of the chronic phase. While Reversed Light/Dark Cycle and Food and Water Deprivation Stress significantly ($p<0.05$) decreased memory retention of foot shock received on the passive avoidance test only for week one of the chronic phase. This suggests that the various stressors received by both subgroups affected learning (represented by the number of shocks received) and long-term retention of information under these conditions, when compared to the control groups. The present findings support and consolidate the hypothesis that relates cognitive impairments to stress and depression (Mizoguchi *et al.,* 2000; Quan *et al.,* 2011).

The results from the assessment of motor coordination effects using rotarod test showed that Reversed Light/Dark Cycle and Food and Water Deprivation Stress significantly ($p<0.05$) decreased the performance time spent on the rotor for only week three of the chronic phase, Wet Cage bedding stress and Ice cold swimming stress also significantly ($p<0.05$) decreased the performance time spent on the rotor for only week three of the chronic phase. The test for motor coordination showed also that the stressed groups for the acute phase were not affected significantly when compared to the control groups. This further suggests that the cognitomotor deficits observed may be associated with the cognitive areas involved in the performance of such task, and may not involve a deficit in the motor neuron activities.

The results from the assessment of visuospatial function using the novel object recognition test showed a significant decrease by all stressed groups in the acute phase and showed a non-significant decrease by all stressed groups in the chronic phase in the time spent exploring the novel objects when compared to the control groups. These results are in line with the results of Song *et. al* (2008) which showed that Chronic Mild Stress (CMS) exposure impaired cognitive performance and produced amnesia of acquired information in both object recognition test and object location test. Our findings also agree with the findings of Song *et. al* (2008) which indicated that Chronic Mild Stress (CMS) exposure-induced impairment of cognitive behaviours might be attributed to the stress-related alterations in the homeostasis of the brain (Song *et al.,* 2008). The cognitive impairment shown by Reversed Light/Dark Cycle and Food and Water Deprivation Stress also agrees with the results of Barnes *et. al* (2017) which indicated that a Long Photoperiod-induced depressive phenotype shows deficits in novel object recognition, and may have an altered cognitive response to total sleep deprivation (Barnes *et al.,* 2017).

The assessment of appetite behaviour using the Sucrose Preference test tries to model anhedonia (reduced ability to experience pleasure from natural rewards) which is a core symptom of depression. The results from the assessment of appetite behaviour using the Sucrose Preference test showed that appetite behaviour in the non-stressed control groups was unaffected. However, Reversed Light/Dark Cycle and Food and Water Deprivation Stress decreased the consumption of sucrose below baseline for weeks two, three and four of the chronic phase. Wet Cage bedding stress and Ice cold swimming stress also decreased sucrose consumption below baseline for weeks two, three and four of the chronic phase. Electroconvulsant induced therapy (ECT) stress and Tail Pinch stress showed a decrease in sucrose consumption below baseline only for week four of the chronic phase, this decrease is suggested to be due to the longer duration and increased intensity of the stressors. These results are in line with that of Jesper *et. al* (2011) which showed a decrease in sucrose consumption below baseline by the stressed groups compared to the control groups (Jesper *et. al.,* 2011). This study also agrees with previous researches that suggests a negative effect of stress on the reward system, and that the sensitivity to changes in activity/sleep due to the Chronic Mild Stress (CMS) procedure contributed to the decrease in consumption behaviour (Cabib and Puglisi-Allegra, 1996; Bachmanov *et al.,* 2001)

Conclusion

Findings from the present study showed that mild stress model of depression adversely affect cognitive function by hampering quick learning and long-term memory retention. The findings also showed that mild stress model of depression affected the reward system by affecting appetite behaviour negatively. The study demonstrated that chronic unpredictable mild stress significantly increased the time expended on a given task, thus impairing learning and long-term memory retention. It showed no adverse effect on cognitomotor functioning but affected visuospatial function by decreasing the exploration time spent on the novel objects.

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