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R E S E A R C H A R T I C L E

Effect of Induced Hypertension on Bilateral Activity, Task Performance and Spatial Memory in Albino Wistar Rat

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A B S T R A C T

The aim of this study is to evaluate the possible effect of induced hypertension on bilateral activity, task performance and spatial memory. Twenty albino wistar rats weighing between 100 and 230g were randomly divided into four (4) groups. The control group (group I) received only feed and water while the experimental group II were administered 6ml of dietary salt orally at 2ml each day for (3) days to induce hypertension and later treated with 1.6 ml methyldopa administered orally at 0.2ml for (8) days, group III were administered a total of 0.4ml atropine intraperitoneally to induce hypertension. Group IV were administered 0.4ml orally and 0.6ml amlodipine intraperitoneally to induce low blood pressure. The rats were released for task performance tests in inverted screen test, navigational maze, beam walk and hand grip. Spatial memory test was also carried out by recognition of novel objects in space as well as bilateral activity test. Results obtained from navigational maze test revealed that salt-induced hypertension significantly ($P<0.05$) enhanced navigation task performance in albino wistar rats. Results from inverted screen and hand grip test showed that induced-hypertension and low blood pressure significantly ($P<0.05$) impaired the motor functions in task performance of rats in inverted screen, beam walk and hand grip test. Results obtained from bilateral activity test indicated that the control group skewed equal attention to both clockwise and anti-clockwise direction. Thus induced hypertension and amlodipine-induced low blood pressure significantly ($P<0.05$) impaired the performance of rats in bilateral activity test. From the cognitive function (spatial memory) object recognition test, induced hypertension and amlodipine-induced low blood pressure significantly ($P<0.05$) enhanced spatial memory of rats in the cognition test.

Keywords: spatial memory, bilateral activity, methyldopa, amlodipine, navigational maze, beam walk and hand grip.

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1. Introduction

In the early part of the twentieth century, clinicians believed that essential hypertension was necessary for normal physiological function. More recent studies have clearly demonstrated the deleterious nature of chronic elevation of arterial pressure on many organ systems. Nearly 25 years ago, data from Wilke and Eisdorfer suggested that hypertension may lead to memory impairments (Wilkie *et al,* 1996), and many subsequent reports have supported this relationship in humans (Franceschi *et al,* 1978). It is estimated to affect 1 billion people worldwide and it is also associated with an increase of cardiovascular disease and all cause-mortality (Anderson; 2008). Spatial memory is a catchall phrase used to refer to memory for spatial information, such as the geographical layout of your hometown or the interior of a friend's house. It can be assessed by using a neuropsychological test which requires remembering the position of items or learning how to navigate through a maze. Research has suggested that long term memory in humans may be maintained by DNA methylation, (Miller *et al,* 2007).Rotational behavior (bilateral activity) has proved a popular technique for screening the behavioral effects of a wide variety of lesions, drugs, and other experimental manipulations on the brain of rodents. This test is widely carried out in experiments using animal models of Parkinson disease with unilateral lesions in the dopaminergic nigrostriatal system.

2. Materials and Methods

All experiments were performed in accordance with the national laws and the principles of laboratory animal care. This study did not require an approval by the competent authority because this study does not include any significant suffering or pain for the animals as the animal's weight and health were controlled each day.

Acclimatization:

The purchased nineteen albino wistar rats were acclimatized for a period of two weeks (14 days) as they were kept in a well-ventilated standard housing condition with proper bedding (saw dust). The animals were placed on standard animal's feed and water and the feeding and water troughs were thoroughly cleansed daily to ensure proper hygiene and healthy living condition. The animal's beddings were also changed regularly to ensure healthy environment for the animals.

Animals and Feeding Procedure:

Apparently, nineteen (19) healthy albino wistar rats of both sexes (male and female) weighing 100-230g were obtained from the department of pharmacology animal house, university of port Harcourt were used for the experiment which was carried out between June and July, 2016. The animals were kept in an animal cage as food and water was provided ad libitum. The animals also received their daily food ration (15-20 g/rat/day) after the test sessions. All experiments were performed in accordance with the national laws and the principles of laboratory animal care (NIH publication No. 86-23, revised 1985).

Induction of High Blood Pressure:

High blood pressure was induced using two different models, one (Group 2,salt-induced HBP group) by the oral administration for four days with (0.25g of salt+ 20ml of dist.H_2O) and 2ml administered per rat consecutively for three (3) days and 1ml of the salt solution was administered on the fourth (4) day; making a total of 7ml. This group was also treated with oral administration of methyldopa for eight (8) days at (0.2ml) making a total dose of 1.6ml. The second (Group 3, atropine-induced HBP group) was induced by the administration of atropine (0.2 ml, i.p) and blood pressure was monitored after five (5) and ten (10) minutes of administration respectively. On the second day also, another (0.2 ml) of atropine was administered intraperitoneally making a total dosage of 0.4 ml.

Group IV (antihypertensive group): Amlodipine was administered orally on the first day (2 tablets of amlodipine + 20 ml dist.H_2O) and 0.2 ml was administered each to five rats. Another 0.2ml was administered and blood pressure monitored but result indicated no significant effect. Administration was stopped on the second day and resumed on the third day but via intraperitoneal administration (2tablets +10 ml H_2O for injection). A dose of 0.2 ml was administered each and another 0.2 ml was later administered. On the fourth (4) day, 0.2 ml amlodipine was also administered intraperitoneally making a total dosage of 0.6ml (intraperitoneal) and a total dose of 0.4ml that was previously administered orally.

Determination of the effect of induced hypertension on bilateral activity, task performance adnd spatial memory in albino wistar rat.

Bilateral activity test was carried out manually by tying a paper tape on both fore and hind limbs i.e. right fore limb and right hind limb or left fore limb and left hind limb respectively and monitored for a duration of five (5) minutes each. In this study, each rat was exposed to this test for three trials. Spatial memory/explorative activity test was carried out by the introduction of novel objects of different shapes namely round, cylindrical, rectangular and squared objects. The ability of the rats to recognize mostly a particular shape was monitored for five (5) minutes each. Each rat carried out the explorative activity test for (3) three trials.Task performance test was carried out to examine the cognitive and motor functions of the rats. In this study, navigational maze test was used to assess cognition by placing each rat in an opaque maze of length 153.1 cm, the animal was monitored and the time it took to navigate through the box to the other end as noted using a stop watch. Each rat was exposed to this test for three times. Inverted screen, hand grip and beam walk tests were used to evaluate the motor functions of the rats. For inverted screen test, the rats were placed with both fore and hind limbs on inverted gauze and the duration of task performance was noted using a stop watch. The rats were exposed to this task three (3) times each.

The beam apparatus consists of 1 meter beams with a flat surface of 12 mm or 6 mm width) resting 50 cm above the table top on two poles. For beam walking test, each animal was placed on an elevated cylindrical beam of about 38cm in length and monitored .The time taken to perform task was noted using a stop watch. It was expected that the animal must have moved from one end of the beam to the other end in five (5) minutes each. This test was carried out three (3) times by each rat.

For hand grip test which is an easy way to objectively quantify the muscular strength of rodent (mouse and rat). In this study, the rat's forelimbs were placed on the grid while the other part of its body was suspended. Each rat was monitored and the time at which they lose grip was noted using a stop watch and since a normally coordinated rodent will show a low score if its muscular strength is low, results were analyzed accordingly. Each rat was exposed to the test for three (3) times.

Statistical Analysis:

The result obtained from the study was analyzed using SPSS .17.0 and presented as mean ± standard error. An anova was used to determine the significance difference among groups. An LSD post HOC analysis was used to compare the various group mean with the control. A p-value ≤ 0.05 was considered significant while p-values ≥ was considered non-significant.

3. Results and Discussion

This study evaluated the effect of induced hypertension on bilateral activity, task performance and spatial memory in albino wistar rats. Results obtained from the basal blood pressure of rats were normotensive as both systolic and diastolic values fell apparently within the normal range; high blood pressure was also induced and sustained by the administration of dietary salt and atropine via oral and intraperitoneal routes. Navigational Maze Study is mostly used to study spatial learning and memory in behavioral neuroscience. It can be a very accurate study of learning, memory and spatial working and can also assess damage to cortical regions of the brain (D'hooge and Deyn, 2001). But in this research, navigational maze is used to evaluate the cognitive function in task performance test.

Experimental data obtained from the behavioral test on cognition; navigational maze test demonstrated that salt-induced hypertension significantly (P<0.05) enhanced the navigational performance of the rats as seen in the Group II when compared to the control and the other groups as they took lesser time to navigate through the navigational maze box although the atropine-induced hypertension group took longer time than the amlodipine-induced hypotension Group III as well as the control in performing task. However, there was a significant continuous decline in the duration of task performance in Group II (salt-induced hypertension).Thus this showed that salt-induced hypertension significantly (P<0.05) enhanced navigational task performance in rats. Inverted screen test is a muscle strength test using all four limbs and it is used to evaluate the behavioral motor function in task performance (Kondziela, 1964). Results from the behavioral test for motor functions; the inverted screen test of the task performance showed that the control group performed better than the induced-hypertension groups and the amlodipine-induced hypotension group they took longer time in carrying out task. There was also a significant (P<0.05) continuous decline in the duration of inverted screen task performanceamong the induced hypertension group which indicated that the hypertensive rats declined in the task performance test as they carried out task within a shorter duration. This implied that induced-hypertension negatively affected the inverted screen test task performance in rats as well as amlodipine-induced low blood pressure.

Beam walk test is used to assess motor coordination and equilibrium with respect to hind limbs in neurobehavioral study (Goldstein and Davis, 1990). Walking on the beam task performance result showed that the control group performed significantly (P<0.05) better than the other test groups as they took the least time to walk from one end of the beam to the other and they also showed a continuous decline in the duration of beam walk on the three exposures when compared with other groups. This result showed that induced hypertension and amlodipine induced low blood pressure significantly (P<0.05) impaired walking on the beam task performance in rats.

Hand grip test is a noninvasive method of assessing limb strength in rodents (Luma*et al*, 2006). Experimental data obtained from hand grip task performance indicated that the control significantly (P<0.05) performed better than the induced hypertension and low blood pressure groups as the exhibited an increase in the duration of task performance in hand grip task performance whereas the induced hypertension and low blood pressure groups showed a significant decline in the duration of task performance in three consecutive trials. Thus the control performed task for a longer duration when compared with the other groups. This result indicated that salt-induced, atropine-induced hypertension and amlodipine-induced low blood pressure decreased task performance in hand grip test.

Bilateral activity test was used to assess the sensitivity of rats to a particular direction (Mukutenga, 2012). The results from the bilateral activity test which aimed at examining the attention of the rats which skewed to either clockwise or anti-clockwise directions among groups in comparison to the control. The results obtained indicated that the control group skewed equal attention to both clockwise and anti-clockwise directions. The group II (salt-induced hypertension + methyldopa) and group IV (amlodipine-induced low blood pressure) skewed more attention to anti-clockwise direction than the control and group III (atropine-induced hypertension group) as group III skewed the least attention to anti-clockwise direction.

However, group III (atropine-induced hypertension) skewed more attention to clockwise direction than the other groups including the control. It is also seen that group IV and

control skewed equal attention to clockwise direction while group II skewed the least attention to clockwise direction. Thus, induced hypertension and amlodipine induced low blood pressure significantly (P<0.05) impaired bilateral activity in rats. Spatial memory/explorative activity test measured the ability of rats to recognize a novel object in an otherwise familiar environment (John *et al*, 2010) and it is used to assess object memory as the time spent by the animal exploring each object was measured. Experimental data from the spatial memory /explorative activity test where the rats were examined on their abilities to recognize novel objects by shape, generally showed that the ability of the rats to recognize objects were apparently poor across the groups. This study is in line with a previous research that was done by Atunes, (2012).

However, results from the first exposure showed that group II recognized round and cylindrical objects better than the other groups but didn't recognize the squared object. Group III recognized the rectangular object better than the other groups whereas both group I and IV recognized the squared object better than the other groups. From the second exposure, it was seen that none of the groups recognized the round object while group I and III recognized the cylindrical object better than the other groups. Group II recognized the rectangular object most while group II and IV recognized the squared object better than the other groups.

Results from the third exposure indicated that all the groups performed poorly in recognition of round object whereas group III recognized the cylindrical object better than the other groups. The rectangular object was excellently recognized by most of the groups (II, IV and Control) when compared to other objects. Group IV recognized the squared object better than the other groups while both group II and III performed poorly in recognition of the squared object.

Duration of Study:

This research study lasted for a period of eight (8) weeks which comprises of two weeks of acclimatization and six (6) weeks of administration.

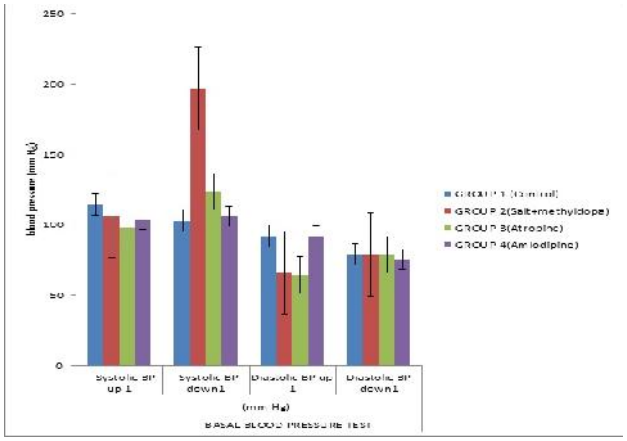

Fig 1: Bars showing results from basal blood pressure measurement across the four groups

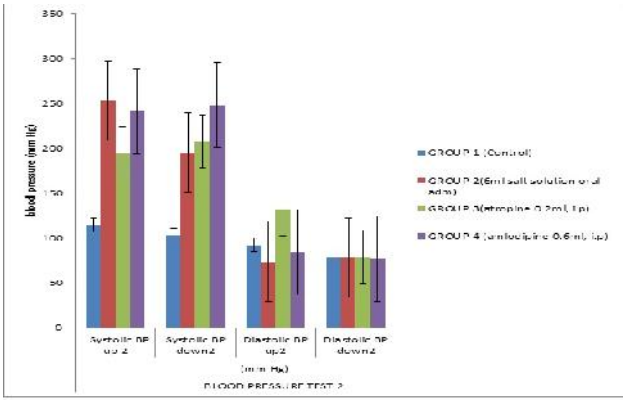

Fig 2: Bars showing results from blood pressure test 2 measurements across all groups

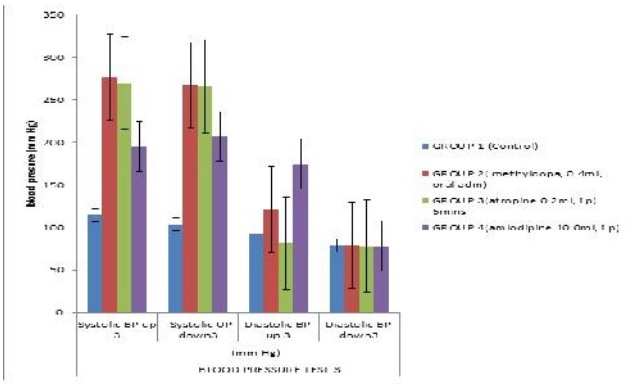

Fig 3: Bars showing results from blood pressure test 3 measurements across the test groups

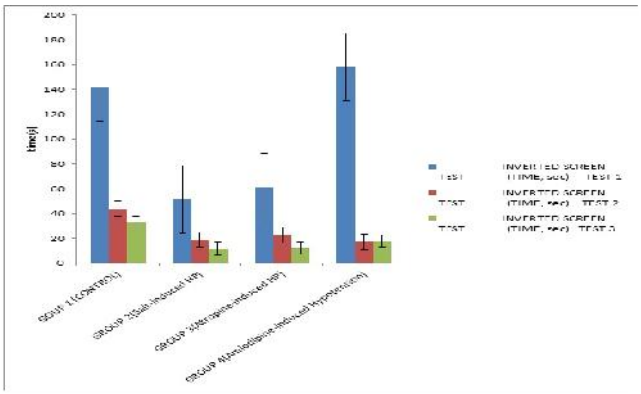

Fig 4: Bars showing results from inverted screen test across the test groups and the control

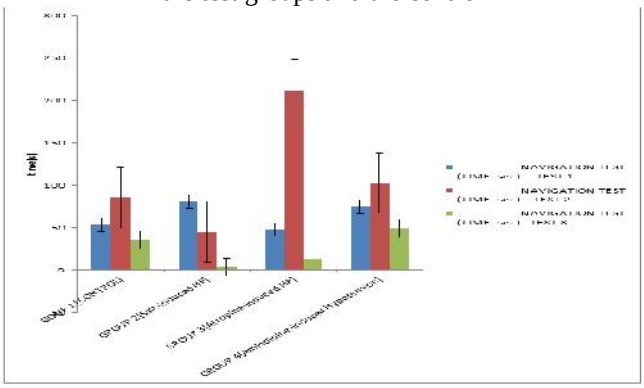

Fig 5: Bars showing results from navigational test across the test groups and the control

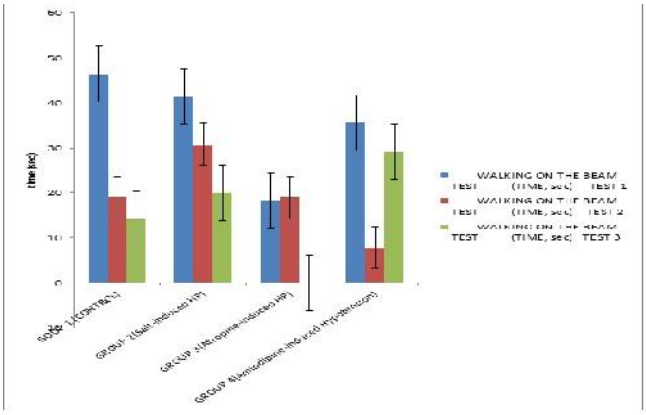

Fig 6: Bars showing results from beam walking test across the test groups and the control

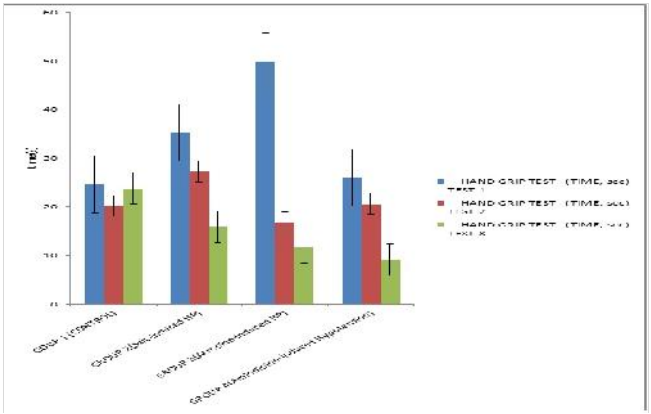

Fig 7: Bars showing results from handgrip test across the test groups and the control

Table 1: Showing bilateral activities test result

Groups	Bilateral Activities Test					
	Attention To The Left			Attention To The		Right
	Test 1	Test 2	Test 3	Test 1	Test 2	Test 3
Group 1(Control)	1	0.4	1	0.4	1	1
GROUP 2 (Salt-Induced HBP+Methyldop	1	1	1	0.2	0.4	0.2
GROUP 3(Atropine-Induced HBP)	1	0.3	0.2	1	1	1
GROUP 4(Amlodipine-Induced LBP)	1	1	1	1	1	0.4

KEY: 1=Attention to left or right is positive; 0≤1 = Attention to left or right is negative
Group 1= control group;Group2 = salt-induced High Blood Pressure + methyldopa
Group3 = atropine-induced High Blood Pressure; Group4 = amlodipine-induced Low Blood Pressure

Table 2: Showing spatial memory test result

Spatial Memeory Test(Explorative Activities) Recognition Of Objects By Shapes Test 1				
Groups	Round object	Cylindrical object	Rectangular Object	Squared object
Group 1(Control)	0	0.4	0.4	0.2
Group2(Salt-Induced HBP+Methyldopa)	0.2	1	0.2	0
Group3(Atropine-Induced HBP)	0	0.4	1	0
Group4(Amlodipine-Induced LBP)	0	0.4	0.4	0.2

KEY: 1= positive; 0≤1 = negative.
Group 1= control group; Group2 = salt-induced High Blood Pressure + methyldopa
Group3 = atropine-induced High Blood Pressure; Group4 = amlodipine-induced Low Blood Pressure

Table 3: Showing spatial memory test result

Spatial Memeory Test(Explorative Activities) Recognition Of Objects By Shapes Test 2				
Groups	Round object	Cylindrical object	Rectangular Object	Squared object
Group 1(Control)	0	1	0.2	0
Group2(Salt-induced HBP+methyldopa)	0	0.2	1	0.2
Group3(Atropine-induced HBP)	0	1	0.4	0
Group4(Amlodipine-induced LBP)	0	0.4	0.4	0.2

KEY: 1= positive; 0≤1 = negative.
Group 1= control group; Group2 = salt-induced High Blood Pressure + methyldopa
Group3 = atropine-induced High Blood Pressure;Group4 = amlodipine-induced Low Blood Pressure

Table 4: Showing spatial memory test result

Spatial Memeory Test(Explorative Activities) Recognition of Objects By Shapes Test 3				
Groups	Round object	Cylindrical object	Rectangular Object	Squared object

Group 1(Control)	0	0.2	1	0.2
Group2(Salt-induced HBP+methyldopa)	0	0	1	0
Group3(Atropine-induced HBP)	0	1	0.4	0
Group4(Amlodipine-induced LBP)	0	0.4	1	1

KEY: 1= positive; 0≤1 = negative.

Group 1= control group: Group2 = salt-induced High Blood Pressure + methyldopa

Group3 = atropine-induced High Blood Pressure:Group4 = amlodipine-induced Low Blood Pressure

4. Conclusion

This research studied the effects of induced-induced hypertension (salt-induced HBP+ methyldopa and atropine-induced HBP) and amlodipine induced low blood pressure on some cognitive (spatial memory), motor functions (task performance) in rats through explorative test (recognition of objects by shape, navigational maze test, hand grip test, beam walk and inverted screen test as well as bilateral activity. From the cognitive function and motor (task performance test), Salt-induced hypertension significantly ($P<0.05$) enhanced the navigational task performance in rats. This research when compared with a previous study that answered a research question "does hypertension alone lead to cognitive decline in spontaneously hypertensive rats?" carried out by Guttin in 2011 using Spontaneously Hypertensive Rats (SHR) animal model, a similar Wistar Kyoto Rats (WKR) and Sprague Dawley Rats whose results demonstrated that all the three strains showed the same level of impairment at the age of 20-months and suggested that the decline in the cognitive level seen in the learning impairment of the SHR group was not entirely by hypertension. Thus, it can be deduced from this research that 'hypertension' does not solely impair cognitive memory. Also in alliance with a result that supported the contention that hypertensive state does not directly contribute to the reduced expression of brain nicotinic acetyl receptor (Guttin *et al,*2011) that could play a role in the impaired ability in the performance of learning and memory related task.

Results also delineate a complex effect of induced high and low blood pressure on motor function tests for balance, strength and coordination as seen in the general impairment in the task performance of the rats in inverted screen, beam walk and hand grip test. Induced hypertension and low blood pressure test groups performed significantly ($P<0.05$) poor in all motor function task performance tests. This could be as a result of fatigue of the skeletal muscle cells (Myocytes) caused by the enhanced central sympathetic flow and increased peripheral resistance alongside other organ-system damage attributes of hypertension whereas the case of low blood pressure might be due to decreased blood flow to peripheral organs such as skeletal muscles resulting in shortage of oxygen and glucose supply in hypotensive state. Evaluations from the bilateral activity test showed that only the control group skewed equal attention to both clockwise and anti-clockwise directions when compared with other test groups thus induced hypertension and induced low blood pressure significantly ($P<0.05$) impaired bilateral activity in rats as well as motor coordination.

From the cognitive function (spatial memory) object recognition test, It can be deduced that all the other test groups performed significantly ($P<0.05$) better than the control group in the cognition test carried out by the recognition of novel objects of different shapes in rats thus induced hypertension and low blood pressure had no significant impairment effect on spatial memory and this is in line with the research carried out by Kadish (2001) which justified that chronic and severe hypertension does not impair spatial learning and memory in rats. This result is also in sharp contrast with some results from previous studies that showed that high blood pressure were correlated with inferior spatial learning performance as the two induced hypertension test groups performed better than the control group but rather mimics the study carried out by Nelson Ruiz-Opazo (2004) which demonstrated that Dahl S (salt-sensitive) rats did not demonstrate any significant impairment in object recognition and recommended that caution must be exercised when weighing the benefits of salt restriction in improving cardiovascular health especially in salt-sensitive hypertension against the potential undesirable effects of reduced cognitive function (Slooter *et al,*2009).

Conflict of Interest: We declare no conflict of interest.

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