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The Effects of Mkpuru Mmiri Consumption on Cognitive Performance and Brain Histology in an Animal Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Mkpuru mmiri, popularly known as ice or methamphetamine (METH) is one of the illegal substances that young people in Nigeria abuse most frequently. The purpose of the study is to determine how methamphetamine affects the cognitive-motor behavior of Wistar rats. In the study, twenty-five Wistar rats weighing between 117 and 138 grams were split into five groups: group A

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had only rat feed and water, group B - D received doses of METH ranging from 5 mg/kg to 20 mg/kg, and group E received a dose of 5 mg/kg of diazepam. Neurobehavioral tools such as the navigator maze test, elevated plus maze and beam walk were used to assess the rats' memory, anxiety-related behavior, balance, motor coordination, and working memory respectively. Two weeks after the injection, samples were taken and examined for oxidative stress markers (Malondialdehyde - MDA) and tissue antioxidant indicators (Superoxide dismutase - SOD, Glutathione - GSH, and Total Antioxidant Capacity - TAC). The data were analyzed using SPSS and post hoc LSD and the significance level was established at $p<0.05$. The results showed that the test groups' body weight was significantly lower than the control groups' ($p<0.05$). The test groups' relative brain weights increased significantly ($p<0.05$) when compared to the control group. The data also showed a significantly ($p<0.05$), level of antioxidant enzymes (SOD, GSH, and TAC levels) and a significantly ($p<0.05$) greater level of MDA when compared to the control group. When comparing the test groups' cognitive abilities to the controls, the experimental rats' cognitive powers significantly declined. The study's conclusion demonstrated that chronic consumption of methamphetamine may deteriorate cognitive function.

Keywords: Mkpuru mmiri; methamphetamine; crystal meth; cognito-motor activity.

1. INTRODUCTION

Substance abuse's effects on society are currently a hot topic and a significant public health problem [1]. Substance abuse has been connected to a significant reduction in cognitive capacities such as executive function, working memory, problem-solving, and attention deficit disorder. It is a major medical and public health concern that affects people all over the world [2,3]. According to Nwangwu et al. [4], drug abuse has become a serious health concern in Nigeria, as young people abuse even prescription medications. Similarly, results from the National Drug Use Survey were made public by the National Bureau of Statistics of Nigeria [5], revealing that 14.3 million Nigerians between the ages of 15 and 64 were drug users. Additionally, according to the National Bureau of Statistics (NBS) and the Center for Research and Information on Substance Abuse (CRISA), the poll found that three million Nigerians either use drugs or have diseases connected to substance abuse [5].

Methamphetamine use, or mkpuru mmiri in Igbo, is a trend that is currently prevalent. The teens' moniker for methamphetamine, "mkpuru mmiri," translates to "seed of water." Methamphetamine, also known as mkpuru mmiri, is administered by injection of the powder that has been dissolved in alcohol or water, smoking, snorting or sniffing, or eating the pill form.

This hallucinogenic crystal drug has the power to completely ruin a person's mental state. Regrettably, a large number of young users are negatively impacted. Their communities and families are now burdened by them [6].

It is against the law for young people to use methamphetamine or mkpuru mmiri. Excessive use increases the likelihood of major side effects such as accidents, unprotected sex, and interpersonal aggression [7,8].

Therefore, methamphetamine, also known as mkpuru mmiri, is a synthetic central nervous system stimulant that is illegal, extremely addictive, and utilized for a range of functions, including euphoria, greater sexual performance, increased alertness, productivity, vigilance, and coping [9].

As a result of The major negative health effects of using mkpuru mmiri also known as crystal meth or methamphetamine, such as widespread lack of sleep and physical activity, phobias, decreased appetite, rapid breathing, rapid and/or irregular heartbeat, elevated blood pressure, low body temperature, and health problems The most frequently cited factors contributing to the rise in methamphetamine usage in Igboland may be the drug's accessibility, affordability, desire for novel experiences, ignorance of its dangers, and hopes for enhanced erotic performance [6].

As a result, some young adults think that using mkpuru mmiri (methamphetamine) has more advantages than disadvantages. The drug's "high" begins and ends fast, and users frequently take multiple dosages in a "binge and crash" cycle. Methamphetamine users sometimes use the substance as a "run," skipping meals and rest periods in favor of taking hits every few hours for up to several days. Methamphetamine hurts the brain. It raises dopamine levels in the brain, which are naturally occurring chemicals. This affects motivation, how the body moves, and how rewarding behaviors are reinforced [6].

Fig. 1. Pictorial of crystal meth (Mkpuru Mmiri)

According to Mihalcikova et al. [10] methamphetamine is a potent psychostimulant that is highly addictive and has a sluggish metabolism. Methamphetamine has reportedly been more popular over the past few decades in other nations, where it is heavily abused. This global expansion of the substance is said to be caused by its comparatively low cost and ease of production when compared to other narcotics like cocaine (Marwick, 2000). In a similar vein, Mihalcikova et al. [10] contended that methamphetamine addiction has become one of the most prevalent drug abuses, posing major threats to human well-being.

In Sub-Saharan Africa, the medicine is not particularly new. For example, Nwangwu et al. [4] stated that methamphetamine misuse among male and female teenagers in Benin (2012), Ghana (2016), and Liberia (2017) was discovered by the Global School-based Student Health Survey (GSHS) undertaken in these countries Onyeaka et al., [11]. It was claimed that methamphetamine usage and its consequences on youth were found in other South African studies [12].

Though there aren't many of these studies, few conducted in Nigeria have revealed the prevalence of methamphetamine consumption in the nation [13]. In the National Drug Survey, the UNODC [14] reported that 0.1% of respondents, or 89,000 people, reported using methamphetamine, whereas the South East reported 0.06%, or 67,000 people, using the drug [4,8]. Subsequent research revealed that two of the twelve study participants had used methamphetamine at some point in their lives [4, 8]. A clinical study also linked methamphetamine use to acute urinary retention problems [4], and [8] discovered sexual risk behavior (unprotected vaginal or anal intercourse) among female study participants who use methamphetamine to increase their sexual pleasures.

The hippocampus plays a crucial role in the central nervous system, particularly in episodic memory and spatial navigation [15]. The amygdala is connected to the hippocampus, which is housed in the medial temporal lobe and governs how emotional memories are recalled and used. During these processes, it has a better functional relationship with the amygdala or anterior cingulate [16]. hippocampus is a complex structure with distinct subfields that may respond differently to various elements of cognitive function and the detrimental effects of aging.

It shares structural similarities with several different memory functions and more general cognitive abilities. Hippocampal neurogenesis occurs in two different brain regions: the olfactory bulb, which is involved in olfactory perception, and the hippocampus, which is mainly involved in memory consolidation [17]. Multipotent undifferentiated neural stem cells located in the subgranular zone of the dentate gyrus [18] generate neural progenitor cells in the hippocampus.

These cells proliferate, migrate into the granule cell layer, and ultimately differentiate into oligodendrocytes, astrocytes, or neurons. Kempermann [19] states that adult hippocampal neurogenesis in the dentate gyrus produces new excitatory granule cells, and the axons of these cells form the mossy fiber tract that connects the dentate gyrus to CA3. A study found that adult hippocampal neurogenesis, which is essential for memory and learning, is impacted by conditions

associated with anxiety, depression, or cognitive impairment [20].

Oxidative stress, which is caused by an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, can cause harm [21,22]. The antioxidant system uses both enzymatic and non-enzymatic mechanisms, such as superoxide dismutase, catalases, and peroxidases, to shield the organism from excessive ROS levels [23]. Mitochondria are a crucial location in brain cells where METH-induced ROS generation occurs [24]. Despite several studies on the effects of methamphetamine, there is a dearth of literature in this area concerning its effects on the functional morphology of the hippocampus in the Male Wistar rat model.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Wistar Rats (25 males, weighing 117–138g) were sold by The Animal House, Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus. The animals were kept in standard cages with a temperature of 27.2 °C. The animals have unrestricted access to water and are fed Grower feed, a normal laboratory diet. The animals were housed in cycles of 12 hours of light and darkness for two weeks before the methamphetamine administration.

2.2 Acute Toxicity of Methamphetamine

The median lethal dose (LD50) of methamphetamine was determined using the Lorkes technique [25], which is divided into two stages. This study was conducted in the Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus. In the end, 31.6 mg/kg was the result.

2.3 Experimental Animal Groupings

Group A served as control and received food and distilled water only

Group B received 5mg/kg of Methamphetamine

Group C received 10mg/kg of Methamphetamine

Group D received 20mg/kg of Methamphetamine

Group E received 5mg/kg of Diazepam

The administration lasted for 2-weeks through oral gavage. All experimental protocols were observed under strict supervision following the administration of the drugs.

2.4 Neurobehavioural Test

2.4.1 Navigator maze test

This maze is used to assess the memory and effectiveness of the male Wistar rat. After a total of five minutes, several of the rats managed to make it through the maze. Owing to medication and quick recollections, some rats moved more slowly than others.

2.4.2 Elevated plus maze

The Elevated Plus Maze (EPM) test is used to quantify anxiety-related behavior in mice models of CNS disorders. The EPM device consists of an elevated "+"-shaped maze, two oppositely positioned closed arms, two oppositely positioned open arms, and a center region. The rats move freely through the maze, while a video camera positioned above it records their movements. A video tracking system then analyzes the subjects' movements. The preference for open arms over closed arms is calculated (in the form of a percentage of entries or a percentage of time spent in the open arms).

2.4.3 Beam walk

A variation of the Male Wister Rat called the Beam-Walk is used to assess balance, motor coordination, and working memory. Male rats were handled and trained to complete neurological, balance, and motor coordination tests before ingesting the Crystal Meth. Rats can be frequently tested using the Beam-Walk method.

2.4.4 Collection of samples

The animals in the different groups were euthanized with chloroform in a sealed container 24 hours following the last dosage of Ativan and methamphetamine. The brain was removed, weighed, and preserved in a 10% formalin-saline solution.

2.4.5 Histological procedure

After being preserved in 10% formaldehyde, the tissues (brain) were rehydrated in four [5]

concentrations of isopropyl alcohol for an hour each. After being cleansed with xylene, they were submerged in melted paraffin wax to eliminate the isopropyl alcohol. Using a Leica RM 212 Rt. Rotary Microtome, samples were cut into 5-micrometer micro sections to be stained with hematoxylin and eosin (H&E) to display the overall structure of the tissue. The tissue slices were analyzed and interpreted by a histopathologist using a Leica DM 750 binocular microscope equipped with photomicrographic capabilities (Ahmed, 2016).

2.4.6 Statistical analysis of results

The data from the study were analyzed using Statistical Packages for Social Sciences (SPSS), version 25. The brain weight data were examined using ANOVA and post hoc LSD. The data were considered significant at $p<0.05$.

3. RESULTS AND DISCUSSION

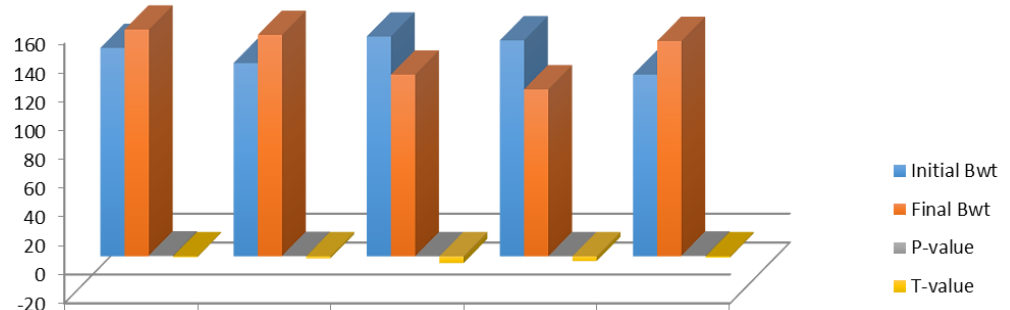
Addiction to drugs or other substances is widely recognized to have deleterious effects on brain function, frequently resulting in loss of function and physiological changes in different brain regions [26]. Methamphetamine, one of the most addictive drugs in the world, negatively impacts cognitive function [27]. The hypothalamic axis, which regulates energy homeostasis, may have altered as a result of METH's effects on body weight. Saito et al. [28] found a significant decrease in feed intake and body weight following methamphetamine use, which is in contrast to the study's findings. The results of this investigation are comparable with those of Krasnova et al. [29], who also observed a significant decrease in body weight following METH consumption.

Furthermore, the results of Manning and van den Buuse [30] showed a significant decrease in body weight following METH. A related study by Michael et al. showed that experimental rats' body weight significantly decreased after being exposed to toluene [31].

According to the study, the experimental groups' relative brain weight rose significantly ($p>0.05$) more than the control groups'. The oxidative stress that leads to neurological problems may be what's causing the alterations in the brain. In contrast to the present study, Grace et al. [32] discovered no appreciable alteration in brain weight following METH usage.

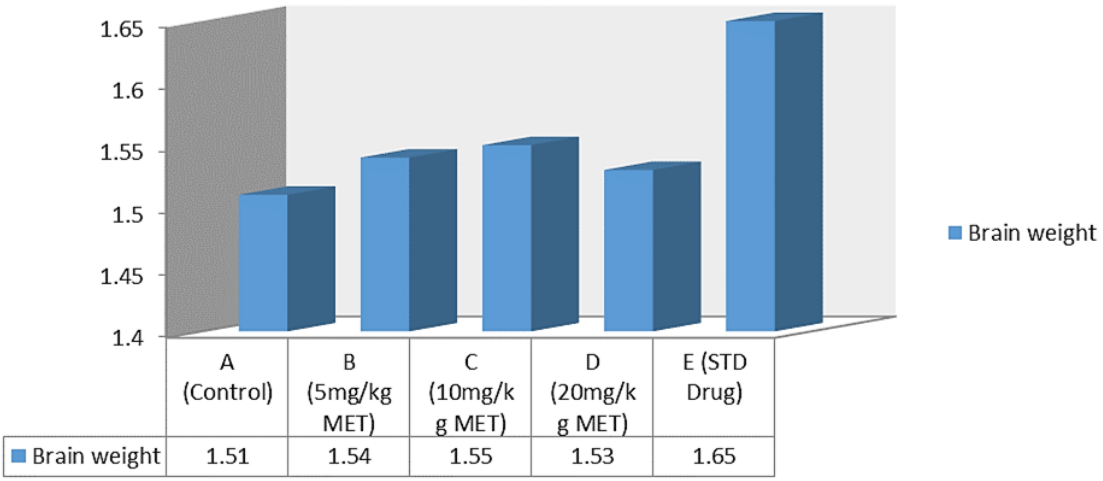
The study found that group A and C's animals' cognitive function significantly declined when exposed to METH.

The decline might be caused by the redox response of hippocampal neuronal cells. The results of this study contradict the findings of Wen et al. [33] who reported a significant increase in locomotive activity following METH treatment, as well as the findings of Pilhatsch et al. [34], who showed a significant decrease in working memory, attention, and cognitive control following METH treatment. Furthermore, this study supports the findings of Mizoguchi and Yamada [35] who reported a decline in cognitive function following METH use.



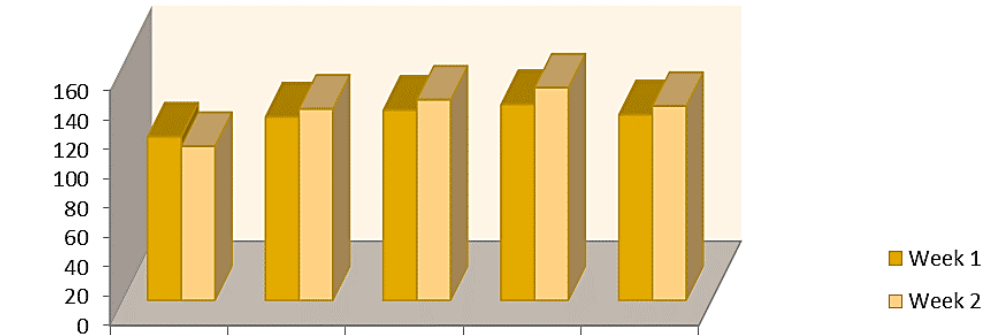
	A (Control)	B (5mg/kg MET)	C (10mg/kg MET)	D (20mg/kg MET)	E (STD Drug)
Initial Bwt	144.5	134	152.4	149.75	126
Final Bwt	157.25	153.5	126	115.75	149.33
P-value	0.571	0.248	0.009	0.046	0.468
T-value	-0.635	-1.429	-4.737	-3.3	-0.889

Fig. 2. Values of methamphetamine on body weight



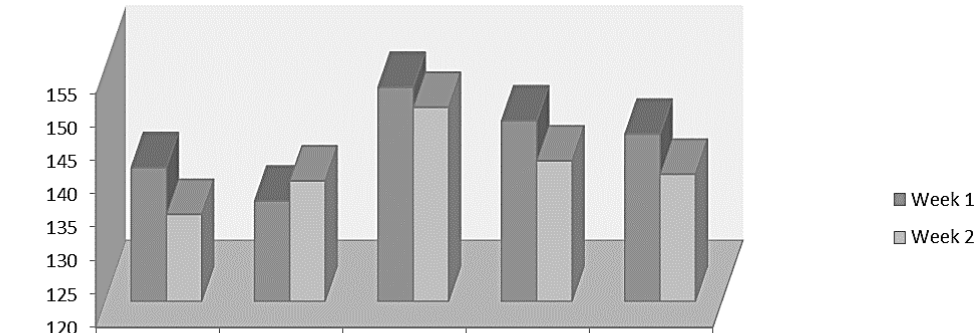
	A (Control)	B (5mg/kg MET)	C (10mg/kg MET)	D (20mg/kg MET)	E (STD Drug)
Brain weight	1.51	1.54	1.55	1.53	1.65

Fig. 3. Values of methamphetamine on brain weight



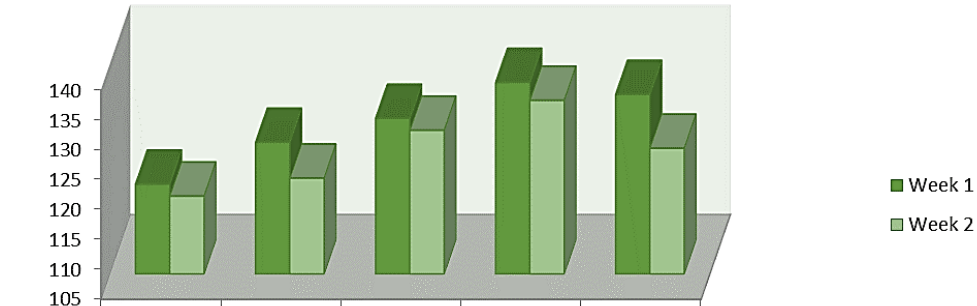
	A (Control)	B (5mg/kg MET)	C (10mg/kg MET)	D (20mg/kg MET)	E (STD Drug)
Week 1	111.23	124.77	129.33	133.23	126.21
Week 2	104.7	130	136.22	144.53	132.03

Fig. 4. Values of navigator maze test of study animals



	A (Control)	B (5mg/kg MET)	C (10mg/kg MET)	D (20mg/kg MET)	E (STD Drug)
Week 1	140	135	152	147	145
Week 2	133	138	149	141	139

Fig. 5. Values of elevated plus maze test of study animals



	A (Control)	B (5mg/kg MET)	C (10mg/kg MET)	D (20mg/kg MET)	E (STD Drug)
Week 1	120	127	131	137	135
Week 2	118	121	129	134	126

Fig. 6. Values of beam walk of study animals

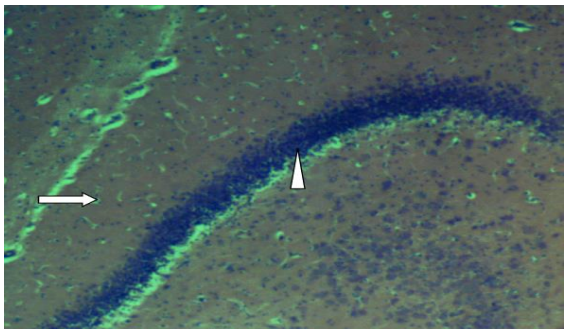


Plate A. Control, H&E x 400

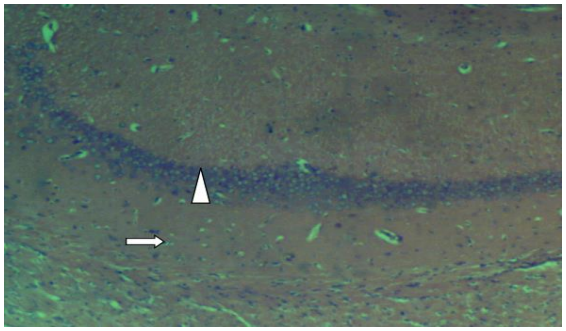


Plate B. H&E x 400

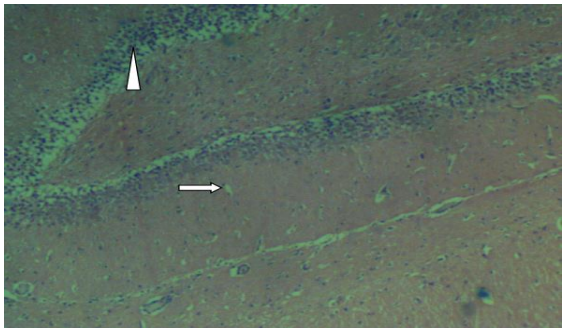


Plate C. H&E x 400

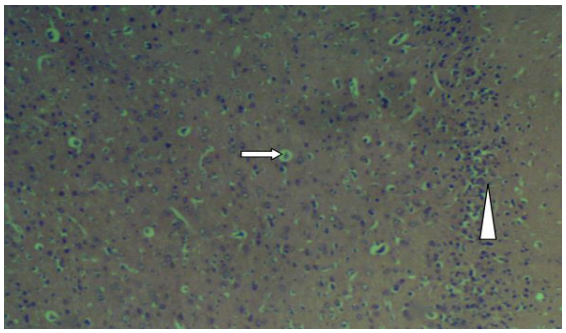


Plate D. H&E x 400

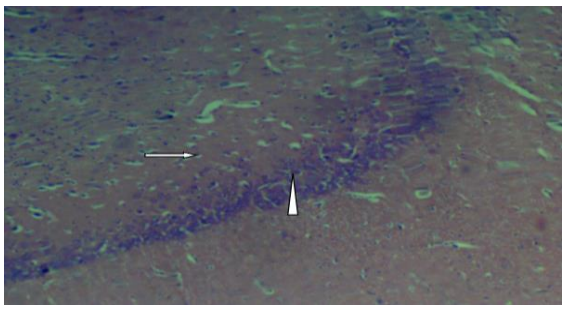


Plate E. H&E x 400

Plate 1A-E. Histological Examination

According to the current investigation, METH may have produced a sizable amount of reactive oxygen species (ROS). This was supported by the significant drop in superoxide dismutase (SOD) enzyme activity that was seen in the test groups relative to the control group.

This outcome is in line with the findings of Yalcin et al. [36] who discovered that antipsychotic drugs, both traditional and nontraditional, reduced SOD levels in patients with schizophrenia. The current study also showed a substantial increase in MDA in the treatment groups as compared to the control groups. METH-induced increases in polyunsaturated fatty acid (PUFA) peroxidation may be the reason for the notable rise in MDA levels. This observation aligns with the findings of Ahmed et al. [23], who demonstrated that patients on conventional antipsychotic drugs exhibited significantly higher levels of MDA. The findings of this study are consistent with those of Aguilar [21] who found that individuals with schizophrenia had greater plasma MDA levels than did control people.

The current research has also shown significant changes in the histology of the hippocampal tissues. Plate A (Control) has a hippocampal morphology that is consistent with a normal histology. Larger, histologically undamaged granular neurons of the endplate and densely packed granular neurons of the dentate fascicle are seen in this section (arrowhead). There are no signs of impairments. The pyramidal stratum on Plates B through E displayed a noticeable reduction in cell number as well as clumped aggregation. This indicates continued cellular damage to the histoarchitecture of the hippocampal tissues. A relatively sparse cellular population with poorly defined cellular outlines and nuclei has been seen in the stratum radiata.

Significantly atrophied hippocampal neurons have been reported by Wen et al. [22], Ovie et al. [29], and Bagheri et al. [37], which corroborate the study's findings. The results of the investigation are further supported by the discovery of altered hippocampal morphology by Mandyam et al. [38] following the administration of METH to an animal. Zhu et al.'s [15] findings of diminished neuronal effects on the hippocampal neurons following METH injection are consistent with the results of the current study. METH damages dopamine nerve fibers by causing oxidative damage and apoptosis through many cascades of proteomics mechanisms.

Furthermore, in line with the study's conclusions, Park et al. [20] discovered a decrease in hippocampal neuronal cells following oxidative stress damage generated by METH. The results of this investigation are in line with the observation made by Ijomone et al. [39] of neuronal loss following methamphetamine injection in the hippocampal pyramidal layer.

4. CONCLUSION

The investigation's findings demonstrated that methamphetamine reduced body weight and Increased brain weight. The histological analysis and the cognito-motor impairments observed in this study show a substantial correlation. However, its consumption should be done so with caution as it jeopardizes the hippocampus's and other brain regions' neuronal activity, which could result in brain dysfunction and memory loss.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval was given by Chukwuemeka Odumegwu Ojukwu University's Uli campus's Faculty of Basic Medical Science. The National Institutes of Health's guidelines for the care and management of laboratory animals are followed when handling and treating rats [40].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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