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Cognitive, Sensory, and Motor Impairments Associated with Aluminium, Manganese, Mercury and Lead Exposures in the Onset of Neurodegeneration

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Abstract

Neurobehavioral investigations are essential for assessing the risk of heavy metal toxicity. This review provides a general overview of the cognitive and motor consequences associated with Al, Mn, Hg, and Pb exposure during early life as well as during adult stage in the onset of neurodegenerative diseases. This review showed that heavy metal exposure in early life results in more impacts due to the vulnerability of the blood brain barrier. The effects of Al, Mn, Hg, and Pb includes defects in habituation, decreased in rearing activity; intense defecation, motor impairments, decreased spatial memory and performance; declines in reference, recognition and working memory. It also causes an increase in the number of errors, an increase in the time it takes to find the platform, an increase in swimming distance, and a decrease in step-through latency and many others. Hence, heavy metals are acknowledged inducers of behavioural toxicity and serve as sensitive endpoints of chemically produced neurotoxicity.

Keywords: *Neurodegenerative disease, behavioural alterations, neurotoxicity, heavy metals*

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Introduction

Risk evaluation for neurotoxic chemicals in recent times have frequently use the developing field of behavioural toxicology due to the high sensitivity of behaviour to neurotoxic agents and the integration of numerous underlying processes and neurofunctions, such as motor, sensory, attention, and motivational functions in behavioural functions. The study of behavioural mechanisms of neurotoxicity can provide useful information to assess safe exposure levels and prevent the emergence of early deleterious effects on the nervous system: behavioural testing can be utilized effectively in environmental and occupational decision-making; to assess risk or make predictions regarding human toxicity (Lucchini *et al*., 2000). The most reliable animal-based indicators are animal behaviour and health, with researchers and advisors rating best in the case of animal behaviour; indicators at the farm level, such as good housing and feeding, are also crucial for welfare enhancement (Averós *et al*., 2013).

Neurobehavioral studies are crucial for risk assessment, since behaviour can be seen as the culmination of sensory, motor, and cognitive processes taking place in the neural system and might possibly serve as sensitive endpoints of chemically caused neurotoxicity. Numerous etiopathologic factors that contribute to the onset and progression of neurodegeneration in neurodegenerative disorders have made it difficult to truly understand the disease subcellular manifestations and to create viable treatments (Bedse *et al*., 2015). Rodent models are frequently used in toxicology studies to acquire mechanistic understanding of heavy metal exposure and chronic diseases. These experiments simulate exposures using invasive procedures like oral gavage or by repeatedly injecting some doses of heavy metal salts into the water supply (Freeman *et al*., 2020). Since heavy metals are constantly transformed by human activity rather than being created or destroyed expose to heavy metals is inevitable, they can provoke a countless variety of effects. According to Sayre *et al*. (2000), several metals have been linked to neurodegenerative illnesses, but none are likely the sole culprits, aluminium in the event of dialysis dementia is one exception to this rule. Significantly elevated brain Mn levels has been linked to behavioural abnormalities (Calabresi *et al*., 2001).

Mn exposure has been linked to increased motor activity in rats, although these effects are frequently short-lived (Kern *et al*., 2010; Vacher *et al*., 2006).

According to Banks *et al.* (1997) lead affects some behaviours more than others, animal findings are consistent with lead-induced attention deficits in children, and basic learning is less influenced by lead than more difficult activities. Lead acetate considerably decreased the rat's forelimb grip strength, the number of rearing, and the number of lines they crossed (Owoeye & Onwuka, 2016). In most of the animal studies, the researchers first tested the exposed animals for their locomotory activity and their reactivity to object novelty in an open field, then for spatial memory. This review provides an adequate background of the behavioural alterations associated with Pb, Mn, Al and Hg exposure using different behavioural maze test.

Materials and Methods

Searches for relevant research articles were conducted independently in several online database, including Google Scholar, PubMed, and Scopus, using terms like "effect of Pb on animal behaviour," "effect of Al in behavioural alteration," "Mn and its behavioural effects," "Hg and behavioural toxicity," "effect of heavy metal toxicity in animals," etc. By assessing and evaluating each article's title and abstract, the full texts of all collected papers were filtered for just those that explored the behavioural toxicity of Pb, Al, Mn, and Hg or any two of the metals in rats. Duplicate publications found after searching multiple databases, reviews, and articles on behavioural toxicity in fish and monkeys were among the articles that were excluded.

Results and Discussion

Effect of Lead Exposure in Neurobehavioural Alteration

Despite the establishment of public health policies meant to eliminate Pb. It is a prevalent environmental pollutant still present in the environment. Pb interacts with cells, enzymes, and tissues because of its chemical properties as a divalent ion, contributing to pathological and behavioural changes (Hernández-Coro *et al*., 2021). Lead toxicity is particularly dangerous to developing brains. There is substantial proof that Pb exposure has serious negative consequences on cognitive function in both adults and children, including behavioural problems and intellectual and learning difficulties (Glass *et al*., 2009). Exposure to Pb during development impairs the cognitive and behavioural traits that linger even into adulthood (Ramirez Ortega *et al*., 2020). Pb exposure affects behaviour, particularly aggression, anxiety, and depression, as well as learning deficits and changes in locomotor activity. Its presence has also been related to aberrant neurotransmitter release and other metabolic changes that are associated with these diseases (Hernández-Coro *et al*., 2021). According to Ramírez Ortega *et al*. (2021) exposure to Pb alters movement, causes aggression, impairs the ability to coordinate movements and respond appropriately, hinders the ability to solve problems and learn new information, and damages memory and learning abilities.

Ramirez Ortega *et al*. (2020) investigated the immediate effects of lead treatment during lactation period (23 PND) on mice locomotor activity and discovered that the total distance travelled as well as the ambulatory time considerably decreased in the mice of Pb^{2+} group compared to control group. However, no differences between the control group and Pb^{2+} group were discovered when the long-term effect (60 PND) was assessed. Prenatal, preweaning, and post weaning Pb exposure in animal models results in neurobehavioral impairments that last even in adulthood. The buried food locating test was used to assess the learning and memory of mice (60 PND) treated with Pb^{2+} during the breastfeeding period. In the training phase the Pb^{2+} group of mice displayed the same pattern of learning as the control group, where they figured out how to get to the target. These findings imply that Pb^{2+} had no impact on the acquisition stage. The distance travelled and the time needed to approach the target, however, were higher in the Pb^{2+} group than in the control group when long-term memory was examined 24 hours after acquisition, suggesting memory consolidation impairment in the Pb^{2+} group (Ramirez Ortega *et al*., 2020).

The Morris water maze (MWM) is a rodent spatial learning test that involves moving from starting points along the edge of an open swimming arena to a submerged escape platform using distal cues. Repeated trials are used to evaluate spatial learning, and preference for the platform region in the absence of the platform serves as a measure of reference memory (Vorhees & Williams, 2006). Another well-known test of spatial memory in rodents is the radial arm maze (RAM), which requires rodent to explore a grid of visually identical arms that are positioned all around the start point. The rat must keep track of which arms it has visited while being baited with a reward at each one returning to a previously visited arm is logged as an error, and one may determine how the rat is using different signals based on the pattern of navigation and errors (Shelton *et al*., 2013). In a laboratory experiment, lead injection into the hippocampus caused a severe impairment in the Morris water maze (MWM). According to Jett *et al*. (1996) lead can both interact pharmacologically with brain regions specific to cognitive processes and impair the development of the hippocampus. Both male and female rats exposed to lead on a regular basis have similar learning disabilities. Mansouri *et al*. (2013) noted that deficits in spatial learning and memory were seen in both sexes. The memory impairment caused by lead exposure in the spatial task was greater in male than female rats, but considering the values of Pb determined, it is possible that these differences may be caused by the higher Pb concentrations found in male rat brains as compared to female rat brains.

One of the tests that is most frequently used to evaluate anxiety-like behaviour is the elevated plus maze (EPM) test. The test is based on rodent innate fear of elevated and open spaces as well as on their spontaneous natural curiosity about new environments. The device comprises of open and closed arms that are crossed perpendicularly in the middle, as well as a central space. All the arms are open to the mice, and they can move freely between them. Indicators of open space-induced anxiety in mice include the frequency of entrances and the amount of time spent in the open arms (Komada *et al*., 2008). In an elevated plus-maze (EPM) test and dark-light box test, Benammi *et al*. (2014) findings demonstrated a clear anxiogenic effect of acute exposure to Pb in adult rats which was attributed to impairment of serotonin levels within the dorsal raphe nucleus (DRN). They also found a substantial 40.7 percent reduction in the amount of time spent in the open arms in intoxicated rats compared to controls; the dark-light box test showed a significant reduction in the time spent in the dark box in the Pb exposed rats

Another reliable indicator of neurological function is provided by motor testing; Rota rod is one of the most popular tests used to evaluate rat neurological motor impairments, it evaluates how long a mouse can balance on a moving rod (Brooks & Dunnett, 2009). The rota rod performance test is particularly helpful for evaluating the impact of experimental treatments or following traumatic brain injury; a specific animal's stability, coordination, physical condition, and motor planning are gauged by how long it remains on the rotating rod (Mouzon *et al*., 2012). The rota rod task has a built-in sensitivity for identifying cerebellar impairment. However, the cerebral cortex, hippocampus, and basal ganglia also have significant effects on how well the task is performed (Scholz *et al*., 2015). Some few findings have been obtained from research utilizing rota rod with varying rotation speeds and higher Pb exposures (Ma *et al*., 1999; Moreira *et al*., 2001). In a 2012 study, it was found that while lead-induced hyperactivity does manifest after shorter exposure intervals, motor coordination impairment in male rats exposed to lead during maturity is only evident after long-term (six months) exposure (Mansouri *et al*., 2012). In 2013, Mansouri *et al*. found a significant treatment, gender, and treatment-gender interaction effect in male and female rats exposed to 50ppm of Pb. The fall latency of male Pb-exposed rats was considerably decreased (237±10s) as compared to control rats (315±16s), however there was no significant difference between the fall latency of female Pb-exposed rats (234±14s) and equivalent controls (244±9s). These findings likely imply that lead exposure may have an impact on striatal and cerebellar neural circuits important in controlling motor activity and motor coordination, respectively, with the former being more delicate and thus more susceptible to lead-induced changes in brain function (Mansouri *et al*., 2013). Sprowles *et al*. (2018) reported that Pb exposed rats had impaired spatial learning and memory

Some studies looked at two metals to evaluate the neurobehavioural interaction and synergetic effects of the metals. According to El-Moneum Goma & Tohamy, (2016) rats given 2g/l of Pb and 3.5g/l of Al had significantly longer feeding time than other rats, with the greatest increases occurring in the 2g/l Pb exposed rats. Additionally, 2g/l Pb rats showed a substantial increase in drinking frequency compared to other groups. However, compared to other treated groups and the control, laying time fell significantly in the low Al exposure group and high lead exposure group. El-Moneum Goma & Tohamy, (2016) also compared mobility activities in treatment groups and the control, mobility activities considerably increased in the low lead (1g/l) exposure group. In contrast to other treatment groups, the 2g/l Pb group experienced considerably higher cage and overall exploration frequencies. Additionally, none of the treatment effects on standing time, licking, scratching, and frequency of trough probing were statistically significant (El-Moneum Goma & Tohamy, 2016), Sprowles *et al*. (2018) reported that Pb-Mn rat groups had decreased anxiety, reduced acoustic startle, contextual freezing, initial hypoactivity deficit in egocentric learning in Cincinnati Water Maze (CWM) and deficit in latent inhibition in MWM. Table 1 summaries the study on the effect of lead in behavioural alteration using different behavioural task.

Table 1: Effect of lead in different behavioural tests

S/N	Test	Exposure duration	Exposure route	Dose	Animal/Sex	Effects	References
1.	OFT	23 PND	Oral: drinking water	500 ppm	Female mice	• Decreased total distance travelled and ambulatory time • memory impairment for food location in single pellet reaching task	(Ramirez Ortega *et al*., 2020)
2.	OFT	6 months	Oral: drinking water	50 ppm	Male and female rats	• Hyperactivity in male rats, significant increased ambulatory time, rearing and grooming activities in males • No significant difference in the ambulatory time, rearing and grooming activities in the females when compared to the male and the control • No significant difference in sniffing activity in all the groups	(Mansouri *et al*., 2013)
3.	MWM	6 months	Oral: drinking water	50 ppm	Male and female rats	• Deficit in spatial learning and memory in both sexes	(Mansouri *et al*., 2013)
4.	Rota rod	6 months	Oral: drinking water	50 ppm	Male and female rats	• Impaired motor coordination • Male displayed significantly reduced fall latency • Female rats exposed to Pb did not significantly differ in their fall latency when compared with control.	(Mansouri *et al*., 2013)
5.	EPM	3 days	Intraperitoneal	25mg/kg b. w	Male rats	• Significant reduction of time spent in the open arm	(Benammi *et al*., 2014)
6.	Dark-light Box test	3 days	Intraperitoneal	25mg/kg b. w	Male rats	• Significant reduction of time spent in the dark arm	(Benammi *et al*., 2014)
7.	Multiple behavioural patterns	5 weeks	Oral: drinking water	1g/l and 2g/l	Adult rats	• Feeding time, frequencies of cage, drinking and total exploration increased more in rats administered with 2g/l than 1g/l and the control • Lying time decreased in rats administered with 2g/l dose	(El-Moneum Goma & Tohamy, 2016)
8.	EPM	4 weeks	Oral gavage	10mg/kg	Male and female rats	• Spent less time in the open arm • Less head dips	(Sprowles *et al*., 2018)
9.	CWM	4 weeks	Oral gavage	10mg/kg	Male and female rats	• Made fewer errors • Time to reach the platform not significant among the groups	(Sprowles *et al*., 2018)
10.	MWM	4 weeks	Oral gavage	10mg/kg	Male and female rats	• Impaired learning and memory deficits • reduced MWM acquisition primarily in males	(Sprowles *et al*., 2018)
11.	CWM	4 weeks	Oral gavage	Pb=10mg/kg Mn=100mg/kg	Male and female rats	• Impaired egocentric learning, • deficit in latent inhibition conditioning	(Sprowles *et al*., 2018)
12.	OFT	4 weeks	Oral gavage	Pb=10mg/kg Mn=100mg/kg	Male and female rats	• decreased anxiety • hypoactivity • reduced acoustic startle	(Sprowles *et al*., 2018)

Effect of Manganese Exposure in Neurobehavioural Alteration

As an essential metal element, Mn is typically found as inorganic soluble compounds in food, water, and airborne particles. Examples include the fungicide Maneb Mn ethylene-1,2-bisdithiocarbamate and the gasoline adjuvant methylcyclopentadienyl Mn tricarbonyl (Bolté *et al*., 2004; Wasserman *et al*., 2006) While environmental exposure to Mn is caused by ingestion and inhalation, occupational Mn exposures are frequently obtained through the respiratory tract, digestive tract, and skin interactions (Kwakye *et al*., 2015). Excessive manganese (Mn) in the brain promotes a variety of abnormal behaviours, including memory deficits, decreased motor skills and psychotic behaviour resembling Parkinson's disease. Manganese has been linked to Parkinson's disease, perhaps because of its ability to trigger the creation of reactive oxygen species, which harm neurons (Carpenter & Carpenter, 2001). In the absence of significant motor abnormalities and learning deficits, Mn intoxication causes a Disinhibitory Behavioral Syndrome, an evidence of early clinical phase of Manganism (Calabresi *et al*., 2001).

According to Rommelfanger *et al*. findings, neurotransmitter depletion in the rat brain may be the cause of behavioural abnormalities following Mn poisoning (Rommelfanger *et al*., 2007). Excessive accumulation of Mn damages the transport system, which causes ataxia in the basal ganglia; research findings showed that after exposure to Mn, locomotor activity and rotating rod endurance decreased. The rota rod test has also been used to demonstrate that Mn causes motor impairment (Cordova *et al*., 2013a; Delaville *et al*., 2012; Sanchez-Betancourt *et al*., 2012) Ordoñez-Librado *et al*. (2010) proposed that the motor alterations caused by the inhalation of Mn are related to nigrostriatal dopaminergic function. The results showed that mice developed obvious deficits in motor performance manifested as akinesia, postural instability, and action tremor (Ordoñez-Librado *et al*., 2010). Animals exposed to excessive Mn exhibited cataleptic behaviour, which serves as another indicator of dopaminergic neuron impairment, according to the findings, rats motor and non-motor functions are altered by a considerable decrease in neurotransmitter levels (Bouabid *et al*., 2014; Olanow, 2004).

According to Niu *et al*. (2004) occupational Mn exposure causes changes in the neuroendocrine, humoural, and neurobehavioral systems in addition to behavioural abnormalities. According to (Peixoto *et al*., 2007) the youngest stage of postnatal life (1–5 days old) appeared to be more vulnerable, this suggests that, at least in part, the absence of permeability selection may be responsible for a potential impairment in the function of cerebral structures. Dinamene *et al*. (2013) demonstrated that Mn caused long-lasting functional effects, even after brain Mn levels returned to normal. It also demonstrated that even after brain Mn levels reduced, the recovery from Mn-induced neurotoxicity was not fully complete.

Mice showed clear motor function abnormalities after inhaling Mn mixture for five months, manifesting as akinesia, postural instability, and action tremor (Ordoñez-Librado *et al*., 2008).
In rats, short-term oral administration to relatively low doses of manganese reduce locomotor activity without increasing orofacial dyskinesia as evaluated by vacuous chewing movements and tongue protrusion (Ávila *et al*., 2008). The object recognition test, which evaluates largely spatial short-term memory dependent on the prefrontal cortex and hippocampus is important given that the prefrontal cortex and hippocampus are susceptible to Mn (Pamplona *et al*., 2009). According to Peres *et al*. (2015) investigation for possible short-term memory deficits, animals exposed to the highest dose (20 mg/kg Mn) were unable to recognize the presence of a familiar object when the second object was replaced by a new one. This suggests that early exposure to Mn causes cognitive impairment that lasts into adulthood.

The Passive Avoidance Test (PAT) measures the step through latency, which is the length of time required for rats to enter a dark compartment that is thought to be punitive and related with an unpleasant stimulus (Liaquat *et al*., 2019). Avoidance test (AAT) of animals that inhaled Mn for 14 weeks induced significant effect on step-down latency in the inhibitory avoidance test, as demonstrated by (Schmitz *et al*., 2014). Step-down latencies dramatically increased during tests in control animals, showing both short (1.5 h) and long-term memories (24 h) were preserved. Comparing rats treated with a dose of (25 mg/kg Mn) administered intraperitoneally once a day for two weeks to the control group, the passive avoidance test (PAT) revealed a substantial effect in memory impairment. (Chopra *et al*., 2021).

Repetitive turning, which has been linked to stereotypy connected to dopaminergic dysfunction, like obsessive compulsive disorders, was also noticed in Mn-exposed rats (de Haas *et al*., 2011). Fordahl *et al*. (2012) used 24-hour video surveillance to track Mn-induced changes in activity while doing behavioural analysis throughout the fourth, fifth, and sixth weeks of Mn-exposure. The Mn-exposed group total activity, as defined by total distance walked, was significantly higher after six weeks of exposure, and enhanced locomotion was highly linked with higher levels of globus pallidus (GP), striatal, and plasma Mn. According to Scheer *et al*. (2003) changes in these exploratory activities go against normal nocturnal behaviour and raise the possibility that Mn exposure may mess with the circadian clock. Dinamene *et al*. (2013) found a substantial reduction in ambulation 1, 10 and 30 days after the final Mn dose; the rearing of Mn-exposed rats was also revealed to have decreased significantly across all time points in comparison with the control group. However, in the study by Schmitz *et al*. (2014) Mn-treated mice showed no changes in locomotor activity. It emphasized that the work differs from the other studies in terms of treatment duration, animal age and strain, route of Mn delivery, and animal strain. When compared to doses used in other studies, the dose employed in the study of Schmitz *et al*. (2014) is lower

Behavioural responses such locomotor activity, hyperactivity, and inquisitive behaviours are measured using the open field test (OFT). In neuroscience, locomotor activity, or total distance walked, is frequently employed as an indicator of the presence of neurotoxic impacts of sedative, poisonous, or stimulating effects of substances. Movement is the most fundamental and frequently seen outcome of OFT, but it can also be modified by a variety of factors, including motor output, exploratory drive, emotional acuity, illness, freezing or other fear-related behaviours, relative time in the circadian cycle, and many more (Stanford, 2007). The rearing response, which requires less motor work to execute, demonstrates a better animal ability for habituation (Peixoto *et al*., 2007). Rearing refers to the lifting of the forelimbs onto the glass cylinder walls and enables analysis of motor coordination through untrained, instinctive exploration (Freeman *et al*., 2020). All physical activity that is not considered to be formal exercise falls under the category of ambulatory activity. Lower ambulatory activity in animals with impaired motor muscle function is often correlated with decreased horizontal and vertical activity, total distance travelled, and movement time (Johnson *et al*., 2018). It is common practice to evaluate the behaviour of young mice using negative geotaxis, an automatic, dependable, stimulus-bound orienting and movement directionally against gravitational cues. It is also useful for evaluating neonatal rat postures and motor responses to quite strong angles of inclination (Motz & Alberts, 2005). In the absence of considerable striatal neuronal loss and gliosis, Calabresi *et al*. (2001) reported the appearance of a complex behavioural condition in rats exposed to $MnCl_2$ (20 mg/ml of water) in place of their drinking water for 10 weeks. In fact, it was discovered that rats exposed to Mn were substantially more active than control animals and did not exhibit habituation in the bare open area. Rats exposed to Mn displayed a progressive increase in interactions with novel objects across sessions, and treated animals had more boluses throughout the whole experiment. A hyperactive behaviour is highly suggested by this pattern of behavioural changes that includes increased activity, habituation flaws, decreased neophobia, and intense defecation. according to Chopra *et al*. (2021) the total locomotory activity of the Mn-treated rats with a dose of (25 mg/kg body weight) delivered i.p. once daily for two weeks was significantly lower than that of the control group after day seven. According to Johnson *et al*. (2018) Mn significantly reduced locomotory activity when compared to the control group on multiple metrics, including total distance travelled, ambulatory activity, and stereotypic activity counts. Animals administered with 20 mg/kg of Mn for 5 days in the open field test demonstrated a reduction in travel distance when compared to controls, there was a decrease in

grooming frequency and speed. The rearing frequency was unaffected by Mn treatment alone (Cordova *et al*., 2012).

Morris water maze test reported by Li *et al*. (2017) revealed that Male Sprague-Dawley rats were given intraperitoneal injections of $MnCl_2$ five days a week for a period of 12 weeks, at a dose of 6.55 mg/kg Mn body weight; Mn exposure significantly reduced spatial learning and memory ability; in the spatial navigation test for evaluating learning abilities, Mn-treated rats displayed learning impairments that were characterized by an increased escape latency and swimming distance, in comparison to those of the control group; On the other hand, in the spatial probe trial for evaluating memory, the number of platform crosses by the Mn-treated rats was lower than those of the control group. Additionally, there was no difference in swimming speed across the groups, proving that the Mn-induced deficits were not caused by any potential muscle adverse effects of the Mn injections.

Ordoñez-Librado *et al*. (2008) demonstrated a significant consequence of the Mn-exposed group in single-pellet reaching task. Prior to inhaling Mn, the ability of all animals to recover pellets was compared, but after exposure to Mn, there was a clear decline in both accuracy and the number of successful retrievals. The results of the qualitative assessment included postural shifts, impairments in limb extension (resulting in many reduced reaches), aim, and supination-pronation of the paw during grabbing and releasing the pellet into the mouth. Another behavioural aspect assessed is the ability of the animals to maintain balance and be strong which is assessed by the beam-walking test, whereas their capacity for performing exact and refined movements is assessed by the single-pellet task (Whishaw, 2000). The single-pellet task evaluates both the capacity to collect pellets in the broad sense as well as reaching accuracy, which is more perceptive of minor deficits and compensatory reaching techniques that may not be picked up by other motor tests (Biernaskie *et al*., 2004). Mn exposed mice behaved unusually when recovering the pellet. Schmitz *et al*. (2014) using single-pellet and beam-walking tests on 2-month-old Swiss mice to analyse Mn behavioural modification; treated mice showed small motor deficits in the single-pellet test but not in the beam-walking test, the result indicated that there were subtle motor deficits. As a result, the data suggest that prolonged Mn exposure may have an impact on one's capacity for precise movement, much like early-stage idiopathic Parkinson disease (IPD).

After two, four, six, and eight Mn inhalations, Ordoñez-Librado *et al*. (2008) reported that the time it took Mn-exposed mice to cross the beam significantly decreased, indicating hyperactivity. In comparison to control mice, these mice then had a significantly longer time to traverse the beam and a significantly potentiated freeze behaviour. Animals were also seen to have weak hind limbs, delayed motor initiative (akinesia), unsteady posture, and action tremor. Chopra *et al*. (2021) revealed that on day 7, the open arm entries in the Mn-treated group in the elevated plus maze test were significantly lower than those in the control group.

The motor impairment seen in the rota rod test suggests that the striatum of rats exposed to Mn (10 and 20 mg/kg) on PND14 may have developed improperly because of Mn build-up. Rota rod test results showed that rats exposed to Mn performed noticeably worse than controls, indicating impaired motor coordination and balance (Peres *et al*., 2015). Additionally, Mn dramatically reduced rota-rod activity, which indicated impaired motor coordination in the juvenile rats. Rats treated with 5 mg Mn/kg and controls were able to complete the learning task, however animals given 10 or 20 mg Mn/kg displayed decreased total latency for slipping off the rota rod in comparison to controls. According to Johnson *et al*. (2018) mice exposed to Mn (30 mg/kg) intranasally continuously for 21 days had considerably shorter retention durations on the bar than the control group. Mn treated with a dose of (25 mg/kg body weight) delivered i.p. had a shorter retention duration on the revolving rod than the control group (Chopra *et al*., 2021). Male Mn mice spent less time on the rota rod than control mice, according to Freeman *et al*. (2020) the time spent on the rota rod by females after manganese exposure was not considerably reduced like that of the male. Daily intraperitoneal (i.p.) exposure of developing rats to Mn for 20 days revealed that there was no difference in overall performance on the rota rod test between controls and rats given 5 or 10 mg Mn/kg for the same period. However, when compared to controls, animals given 20 mg Mn/kg demonstrated a substantial reduction in the overall latency for falling off the rota rod (Cordova *et al*., 2013b)

When comparing the Mn-treated group to the control group, Chopra *et al*. (2021) found a substantial rise in the catalepsy bar test that indicated muscle rigidity as of day 7 in the Mn-treated group. In both male and female Mn mice, Freeman *et al*. (2020) noted a decline in rearing behaviour. Males were much more affected than females by the duration of exposure in terms of rearing behaviour. Males in the cylinder test displayed less rearing behaviour than exposed females.
Ye & Kim (2015) used the Barnes maze to determine whether intranasal Mn and/or Hfe (High iron or Fe) deficit affects spatial memory ability. Neither Mn exposure nor Hfe deficiency showed altered learning capacity during the training sessions for the first four days. On day 5, however, Mn-infused mice spent less time close to the target hole, indicating a reduced spatial memory, whereas both Hfe+/+ and Hfe-/- mice demonstrated a similar level of spatial memory performance. The fact that overall activity, as measured by total distance travelled, remained constant across all treatment groups suggests that the decreased memory function brought on by Mn exposure was not attributable to a lack of motor or exploratory activity. These findings show that Hfe deficit has no effect on spatial memory, which is significantly impacted by intranasal manganese.

Olfactory signals are necessary for social memory, which can be aided by a variety of cognitive-enhancing pharmaceuticals (Perio *et al*., 1989). Parkinson disease and other neurodegenerative diseases have been linked to early symptoms of impaired olfactory function (Doty, 2008). Sen *et al*. (2011) reported that the olfactory bulb is a region susceptible to Mn accumulation. In contrast, a study by Peres *et al*. (2015) found no differences between Mn-treated rats and controls in their preference for a familiar compartment during an olfactory discriminating test. In rats given the highest doses of Mn, social recognition abilities were impaired even though olfactory discrimination appeared to be unaffected, the diminished social recognition cannot be attributed to olfactory impairment since olfactory dysfunction cannot explain the diminished social recognition. However, the results of the social recognition test support the cognitive impairment caused on by Mn.

Ye & Kim, (2015) investigated mice exposed to 5 mg of $MnCl_2$ daily for 22 days on the ability to recognize novel objects to determine whether Mn exposure affects recognition memory. After receiving intranasal Mn, Hfe+/+ mice spent considerably less time with novel objects, showing that Mn exposure in the presence of Hfe impairs short-term (0.5 hr) memory. Significant interaction between Hfe deficiency and Mn exposure may be seen in the fact that Hfe-/- mice did not exhibit the memory loss caused by Mn exposure. Furthermore, Mn-infused Hfe+/+ mice had a significantly lower 0.5-h recognition index than Hfe-/- mice. However, there was no difference in a long-term recognition memory, which is defined as memory that occurs 24 hours after the original identification, regardless of Mn exposure or Hfe deficiency. This shows that olfactory Mn decreases short-term memory recognition memory, which is recovered by Hfe deficit. Additionally, short- and long-term memory were also hampered by Mn inhalation for 14 weeks. However, no more noteworthy distinctions between the groups were seen since mice in the object location test showed similar performance across all groups (Schmitz *et al*., 2014). Table 2 summaries the study on the effect of Mn in behavioural alteration using different behavioural task.

Effect of Aluminium Exposure in Neurobehavioural Alteration

One of the main heavy metals that contributes to the onset and progression of neurodegenerative diseases is aluminium (Al), which has a direct impact on the multiple metabolic cascades in the nervous system (Chen *et al*., 2021). Due to its strong connection to Alzheimer's disease (AD), aluminium-induced neurotoxicity is receiving great attention. In addition to being able to traverse the blood-brain barrier, aluminium also makes the BBB more permeable (Flaten, 2001).

Table 2: Effect of manganese in different behavioural tests

S/N	Test	Exposure duration	Exposure route	Dose	Animal/Sex	Effects	References
1.	OFT (using Clever system home case scan with video surveillance)	6 weeks	Oral: drinking water	100 mg/kg	Rats	• Significant decreased in rearing activity during the dark cycle • Significant increase in total distance travelled • Significant increase in repetitive turning during light cycle	(Fordahl *et al*., 2012)
2.	Beam walk test	4 weeks	Inhalation using ultranebulizer	Mixture of 40mM of $MnCl_2$ and 20mM of $Mn(AOc)_3$	Swiss mice	• No significant difference among all the groups	(Schmitz *et al*., 2014)
3.	Step down inhibitory avoidance task	4 weeks	Inhalation using ultranebulizer	Mixture of 40mM of $MnCl_2$ and 20mM of $Mn(AOc)_3$	Swiss mice	• Significant effect on step down latency • Impaired short and long term memory	(Schmitz *et al*., 2014)
4.	OFT using object location and single pellet task	4 weeks	Inhalation using ultranebulizer	Mixture of 40mM of $MnCl_2$ and 20mM of $Mn(AOc)_3$	Swiss mice	• Successful reaches with no significant difference among all the groups	(Schmitz *et al*., 2014)
5.	OFT	1, 10, 30 or 70 days	Intraperitoneal (ip) injections	alternate days with 8 doses of $MnCl_2$ (25 mg/Kg)	Male wistar rats	• significant decrease in ambulation at 1, 10 and 30 days after the last Mn dose • significant decrease in rearing	(Dinamene *et al*., 2013)
6.	OFT	10 weeks	Drinking water	20mg/ml	Male wistar rats	• Significantly increased activity • Defects in habituation • reduced neophobia, and • intense defecation	(Calabresi *et al*., 2001)
7.	RAM	10 weeks	Drinking water	20mg/ml	Male wistar rats	• treated animals did not differ in the total time spent to run the maze • constant high running speed • learning procedures and spatial memory abilities were not impaired	(Calabresi *et al*., 2001)
8.	OFT	two weeks	Intraperitoneal (ip) once daily	25 mg/kg body weight	Male wistar rats	• significant decrease in the total locomotor activity of Mn treated group	(Chopra *et al*., 2021)
9.	Rota rod	two weeks	Intraperitoneal (ip) once daily	25 mg/kg body weight	Male wistar rats	• Decreased retention time	(Chopra *et al*., 2021)
10.	EPM	two weeks	Intraperitoneal (ip) once daily	25 mg/kg body weight	Male wistar rats	• Significant decrease in the open arm entries	(Chopra *et al*., 2021)
11.	OFT	3 weeks	Via intranasal instillation in the left nostril	2µl of $MnCl_2$ (30 mg/kg)	Male mice	• Significant decrease in the locomotory activities measured by total distance travelled, ambulatory and stereotypic activities	(Johnson *et al*., 2018)
12.	Rota Rod	3 weeks	Via intranasal instillation in the left nostril	2µl of $MnCl_2$ (30 mg/kg)	Male mice	• Significantly reduced retention time • Impaired motor coordination	(Johnson *et al*., 2018)
13.	Rota rod	20 days	Intraperitoneal	5, 10 and 20 mg/kg	Male and female rats	• No significant differences between the control and rats exposed to 5 or 10 mg/kg of Mn • Significant decrease in the overall latency for fall of rats exposed to 20mg/kg of Mn	(Cordova *et al*., 2013b)
14.	OFT	5 days 20 days	Intraperitoneal	5, 10 and 20 mg/kg	Male and female rats	• decreased distance and speed travelled in rats exposed to 20 mg/kg of Mn • No significant differences between the control and rats exposed to 5 or 10 mg/kg of Mn	(Cordova *et al*., 2012, 2013a)
15.	MWM	12 weeks	Intraperitoneal injections of $MnCl_2$ five days	6.55 mg/kg	Male rats	• increased escape latency and swimming distance	(Li *et al*., 2017)

						• in the spatial probe trial for assessing memory, the number of platform crosses of the Mn-treated group was decreased	
16.	Single pellet task	5 months	mixture of 0.04 M manganese chloride ($MnCl_2$) and manganese acetate (Mn(OAc)3)	1 h twice a week for 5 months	Male mice	• Mn resulted in postural shifts and impairment in limb extension (resulting in many shortened reaches), aim, and supination-pronation of the paw during grasping and release of the pellet into the mouth • Mice also failed to supinate the paw completely and place the snout into the slot to retrieve the pellet with the tongue.	(Ordoñez-Librado *et al*., 2008)
17.	Beam walking test	5 months	Inhalation of mixture of 0.04 M manganese chloride ($MnCl_2$) and manganese acetate ($Mn(OAc)_3$) in acrylic chamber	1 h twice a week for 5 months	Male mice	• Mn-exposed mice showed a significant decrease in the duration to cross the beam after 2, 4, 6 & 8 Mn inhalations suggesting hyperactivity. • Significant increase in the time to cross the beam and a significant potentiation of freeze behaviour • Exhibit hind limb weakness, delayed motor initiative (akinesia), postural instability and action tremor	(Ordoñez-Librado *et al*., 2008)
18.	Rota rod	5 days	Intraperitoneally	5, 10 and 20 mg/kg	Male Wistar rat	• Significantly worse performance on the rota rod with a reduced latency to fall • Induced motor impairments	(Peres *et al*., 2015)
19.	Olfactory discrimination	5 days	Intraperitoneally	5, 10 and 20 mg/kg	Male Wistar rat	• Normal olfactory discrimination ability • The number of crossings from one compartment to the other was similar between the groups	(Peres *et al*., 2015)
20.	OFT: Locomotory activities, recognition task	5 days	Intraperitoneally	5, 10 and 20 mg/kg	Male Wistar rat	• Absence of gross locomotor activity deficits. • Rats exposed to the highest Mn dose (20 mg/kg) failed to recognize when a familiar object was replaced by a new one • disruption in the social recognition ability of adult rats exposed to highest doses of Mn	(Peres *et al*., 2015)
21.	Barnes maze	daily for 3 weeks	Intranasally instilled	5 mg/kg	mice	• Mn exposed mice showed reduced spatial memory and performance • total distance travelled not significant among groups	(Ye & Kim, 2015)
	Novel Object recognition task	daily for 3 weeks	Intranasally instilled	5 mg/kg	***Hfe***$^{-/-}$ and ***Hfe***$^{+/+}$ mice	• Impairs a short-term recognition memory in wild-type mice, but not in $Hfe^{-/-}$ mice • Significantly reduced time spent with a novel object in Mn instilled $Hfe^{+/+}$ mice	(Ye & Kim, 2015)

Acute $AlCl_3$ administration caused observable behavioural impairments; in a study using the Morris water maze, the radial arm maze, and passive avoidance, aluminium exposure was linked to substantial decreases in spontaneous locomotory and exploratory activity as well as significant deficits in learning and memory (Abdel-Aal *et al*., 2011).Animals exposed to Al also showed a longer period of immobility, it was discovered that there was a considerable reduction in muscular and mobility activities. As a result, excessive levels of Al influence not only the memory but also the motor functions, which results in a reduction in motor activity (Bhalla *et al*., 2010). Liaquat *et al*. (2019) reported that rats given $AlCl_3$ injections showed cognitive deficits and neuropsychiatric abnormalities that could be attributed to the neuropathological alterations. Yellamma *et al*. (2010) reported hypokinesia in rat exposed to sub-lethal Al injections for 25 days in OFT. In female mice exposed to Al_2O_3 NPs, behavioural assessments revealed decreased spontaneous movement, exploratory activities, and increased depressive-like behaviour; environmental ultrafine particles were linked to symptoms of depression (Zhang *et al*., 2015). Rats given oral $AlCl_3$ (100 mg/kg) daily for 15 days displayed degenerative alterations marked by considerable weight loss, decreased working and exploratory memory, frontal-dependent motor impairments, cognitive decline, memory failure and anxiety (Olajide *et al*., 2017). Mice exposed to Al showed decreased grip strength and motor activity (Hu *et al*., 2005).

In behavioural test batteries, tests like the forced swim and tail suspension are used. The depressive-like behaviour of mice and rats has been evaluated using these procedures for decades (Castagné *et al*., 2010). The tail suspension test involves hanging a mouse or rat by fastening its tail to a box or rod using tape or another adhesive material (Can *et al*., 2011). When the suspended animal remains motionless for a certain amount of time, depressive-like behaviour is estimated based on the observed behaviour. The forced swim test is conducted using a clear cylindrical piece of equipment. The cylinder is filled with water until the mouse or rat's legs cannot touch the bottom of the cylinder, and the animal is then submerged in the water to observe its behaviour (Yankelevitch-Yahav *et al*., 2015). The amount of time an animal spends immobile is used once more to estimate depression-like behaviour. Additionally, a behavioural alteration affecting rodent protective aversion to open spaces was reported by an increase in time spent in the central region along with concurrent decreases in both walked distance and time spent in peripheral areas (Crépeaux *et al*., 2017).

In forced swimming Test (FST) $AlCl_3$ injection caused the rats depression to worsen in terms of increased immobility time which is a depression-like symptoms seen in FST (Liaquat *et al*., 2019). Zhang *et al*. (2015) reported that male mice showed no discernible differences between the control and treatment groups. When compared to female controls, female mice exposed to Al_2O_3 NP had a longer period of immobility during the 5-minute FST.
In an active avoidance test, the number of times the animals fled in a series of ten trials was used by Nehru *et al*. (2006) to evaluate cognitive behaviour, animals treated with 100mg/kg aluminium for 6 weeks were discovered to have escaped 5.4 trials, as opposed to typical control animals, who had only escaped 1.8 of the provided set of trials.

In an open field test conducted by Sethi *et al*. (2009) male Wistar rats given Al through drinking water at a dose of 50 mg/kg/day for 6 months in both young (4 months) and old (18 months) groups demonstrated a significant effect of toxicity and a non-significant effect of age on the defecation index of the various groups in a defecation index, While the rearing activity showed a significant relationship between age and toxicity in the Al group as compared to the control, the observed ambulatory activity showed no significant interaction.

Allagui *et al*. (2014) reported pronounce Al toxicity in aging rats and young rats according to their findings, the total distance travelled by old rats and old Al-treated rats was less than that of their younger counterparts in the results of the open field test used to measure the motor activities of rats. In addition, the immobility period was significantly prolonged in old animals and was even more pronounced in old Al-treated rats. In contrast, the total number of rearing movements (vertical movements) was decreased. These findings demonstrated that Al exposure caused a noticeable reduction in motor function in old rats. In the open field test, aluminium reduced the spontaneous locomotive capacity and inquisitive activity in animals. Aluminium did not significantly affect the measures used to assess anxiety (the delay to commence movement and the quantity of faecal balls) (Abdel-Aal *et al*., 2011).

Another study according to Zhang *et al*. (2015) reported that Al_2O_3 nanoparticles treated female mice in the OFT showed reduced central zone duration and increased peripheral zone duration, which indicated less exploratory behaviour and spontaneous locomotion in comparison to female controls. The Y-maze test, which is frequently used to assess short-term memory, requires that movements and various visual stimuli be immediately associated sequentially. In the context of associated pathology, it might also aid in assessing the cognitive state associated with hallucinations or delusions in animal models. This test evaluates a mouse's capacity to connect a given clue, the location, which is briefly explored during training with the desired object (the water, in a test session after 24 h). Understanding the causal linkages between linked events and accurately matching prior beliefs with novel observations depend on latent learning, an association learning (Managó *et al*., 2016). Rats exposed to $AlCl_3$ was reported to have entered the central square or tarried the central square (exhibiting anxiety and poor motor function), making them redundant in the open field; entry frequency and duration of the exposed rats in the central square were significantly lower than those of the control group (Olajide *et al*., 2017). $AlCl_3$ injection dramatically reduced rats' exploratory behaviour in the OFT as reported by Liaquat *et al*. (2019) with a reduction in the number of squares the rats crossed, which occurred as a depressive reaction to an unknown environment. (Chen *et al*., 2021) reported that $AlCl_3$-provoked AD animals showed decreased ambulation, reduced rearing, increased grooming, and more faecal pellets when compared to control animals.

In MWM, where experimental rats were exposed to long-term Al toxicity administered through drinking water at a dose of 50 mg/kg/day for 6 months in both young (4 months) and old (18 months) male Wistar rats, Sethi *et al*. (2009) discovered that both young and old experimental animals confirmed a significant effect of Al-toxicity compared to control on latency to acquire hidden platform. The outcomes demonstrated a significant interaction between treatment (control vs. Al treated) and trial days. Kumar *et al*. (2011) findings revealed that chronic administration of aluminium chloride significantly impaired cognitive function and resulted in progressive deterioration of spatial memory as determined by Morris water maze task paradigms, aluminium-treated rats dramatically increased the acquisition latency to reach the visual platform, indicating memory impairments; the study reported that the mean acquisition latency (on day 20) and retention latencies (1 and 2 Retention Latency on day 21 and 42, respectively) to escape onto the hidden platform were shown to be considerably longer after aluminium treatment compared to the control group. Rats injected with $AlCl_3$ had altered cognitive functions, test rats in MWM displayed a substantial increase in escape latency and took longer to reach the submerged platform than control rats (Liaquat *et al*., 2019).

Abdel-Aal *et al*. (2011) reported that aluminium exposure was linked to decrease spatial memory and accuracy in both acquisition and probe trials (significantly longer time to complete the task and greater mean distance travelled) significant increase in the time required to reach target quadrant and decrease in time spent in target quadrant. Aluminium-induced impairment in Morris water maze did not seem to be due to motor impairment as the swimming speed was not altered by aluminium (Abdel-Aal *et al*., 2011). According to Abdel-Zaher *et al*. (2017), rats given 100 mg/kg/day of aluminium chloride intravenously for 90 prior to the test and during the experimental procedures had longer escape latencies to reach the platform and slower swimming speeds over the course of the six-day trials in comparison with control. When compared to the control group, during the Probe trial animals treated with 100 mg/kg/day of

aluminium chloride, administered intraperitoneally for 90 days, took longer to reach the hidden platform, and spent less time in the target quadrant. The results of the MWM test in the Chen *et al*. study showed that the memory and learning processes in the $AlCl_3$-provoked AD mice were noticeably impaired. The higher escape delay of the AD animals showed that learning ability was severely impacted. Rat escape latency and memory were successfully increased and repressed by the $AlCl_3$ challenge, as seen by the decrease in time spent in the target quadrant (Chen *et al*., 2021). Olajide *et al*. (2017) also reported that rats exposed to 100mg/kg $AlCl_3$ daily for 15days had a significantly high escape latency than control.

Abdel-Aal *et al*. (2011) linked aluminium exposure to a deterioration in reference and working memory in RAM test with significant increase in the mean number of errors and significant lengthening of the time needed to complete the task in a radial arm test. Abdel-Aal *et al*. (2011) critically stressed that cognitive dysfunction, rather than a drop in appetite, was primarily responsible for the animals poor performance in the radial arm maze test. The average number of working memory errors and reference memory errors determined for the old, treated rats demonstrated that older rats and old rats exposed to aluminium had more errors in both categories than young rats (Allagui *et al*., 2014).

Rats performance in inhibitory avoidance is evaluated using PAT. Short-term memory was discovered to be considerably affected following Al exposure and a decrease in retention trial time which indicates that the rats did not learn the task. Rats treated with $AlCl_3$ showed significantly reduced step through latency and impairment in memory retrieval during PAT evaluation (Liaquat *et al*., 2019). Older rats treated with $AlCl_3$ for 4 months also showed noticeably longer time spent in closed arms (Allagui *et al*., 2014). The findings suggested that anxious behaviour increased with aging because the old rats spent more time in closed arms after seven pre-training days than the young ones.

The elevated plus maze serves as a model for anxiety assessment in rodents. Bhalla *et al*. (2010) claimed that Al impairs rodent cognitive behaviour and raises their stress levels and suggested that animals exposed to Al have higher anxiety levels. Al-treated animals had more entries in the open arm when compared to normal control rats. Additionally, Al treated animals spent more time in open arm than in close arm. Because animals spent longer time in the open arm and made more entries into it. Olajide *et al*. (2017) reported that rats given 100mg/kg $AlCl_3$ daily for 15 days displayed considerably higher levels of anxiety compared to control. Table 3 summaries the study on the effect of aluminium in behavioural alteration using different behavioural task

Effect of Mercury Exposure in Neurobehavioural Alteration

Mercury in all its forms has harmful effects on the body, affecting tissues and organs. The chemical form, mercury concentration, exposure time, and exposure route all affect how severe the damage is (Clarkson & Magos, 2006). Cross-fostering tests confirm that mercury has direct harmful consequences on behaviour. In the offspring of dams treated with 50 ppm of Hg in drinking water, the rooting reflex, the formation of the vibrissae placement response, the righting reflex, the grip strength, and the negative geotaxis behaviour were all delayed; the delay was more pronounced in the group treated with 100 ppm of hg in drinking water; At maturity, a decline in anxiety in maturity was discovered (Chehimi *et al*., 2012). According to Chehimi *et al*. (2012) $HgCl_2$ disrupted maternal behaviours; lactation and pup licking were reduced, retrieval latencies were increased, and mothers spent more time eating and drinking away from the nest.

Mohammad Abu-Taweel & Al-Fifi, (2021) found that $HgCl_2$ exposure during pregnancy significantly increased depression in the mice offspring in FST. In $HgCl_2$ -induced disruptions, FST elements exhibited depressive behaviour via increased immobility increased; significantly decreased swimming and climbing Within 2, 4, and 6 minutes of the test when compared with the control

The results of the open-field test demonstrated by Mohammad Abu-Taweel & Al-Fifi, (2021) showed that the perinatal effects of $HgCl_2$ had a considerable impact on the locomotor behaviour of mouse offspring. When compared to the control, there was a substantial increase in the period of immobility and a significant decrease in the number of squares crossed, wall rear, animal speed (square/sec), and locomotion duration. In an open field test carried out by Peixoto *et al*. (2007) habituation did not develop in rats treated in the first phase, and the frequency of crossing responses was decreased in rats exposed to mercury in the final phase. In summary, the first postnatal phase (1st phase) showed behavioural abnormalities than the other phases studied, suggesting that this phase was more vulnerable to mercury exposure than the other phases under study. Peixoto *et al*. (2007) also demonstrated the toxicity of mercury ($HgCl_2$ 5 mg/kg/day for 5 days) applied at specific developmental stages (1-5, 8-12, or 17-21 days old, 1st, 2nd, and 3rd phases, respectively) showed that the rats during the first or second period of development presented similar numbers of crossing; when considering the ambulation number as indicative of exploratory behaviour showed that the two earlier phases of exposure appear to be more affected than the 3rd phase. Considering this parameter as a motor activity, it is easy to see that the latter group displayed a damage of motor activity. According to Peixoto *et al*. (2007) Hg-exposed rats during the first period showed a lack of apparatus habituation and a longer exit latency from the initial area. The assignment in this instance was carried out 25–26 days after the treatment; the data demonstrated a genuine impairment of exploratory behaviour when considering the levels of Hg at 31 days of birth and the immaturity of cerebral tissue (early age).

Mohammad Abu-Taweel & Al-Fifi, (2021) in an EPM reported that mice offspring exposed to $HgCl_2$ during pregnancy showed abnormalities in anxiety behaviour, when compared to control groups, $HgCl_2$ treated animals were shown to spend more time in the closed arm and less time in the open arm. According to the findings, the number of entries into the closed arm considerably increased but reduced in the open arm when compared to the control. Multiple metrics in the elevated plus maze showed the effects of Hg exposure in rodents. Pups prenatally exposed to 50 and 100 ppm of Hg in the open arms spent significantly longer time in the maze. Additionally, the pups exposed to $HgCl_2$ showed a marked increase in the ratio of latencies on open arms; when compared to the control group, only the lower dose (50 ppm) of metal increased the frequency of open arms entrances. Between the $HgCl_2$ treated and control groups, there was no appreciable change in the number of entries in the closed arm of the EPM. Finally, there was no difference between the $HgCl_2$-treated group and the control group on a variety of head scans and head dips toward open arms (Chehimi *et al*., 2012).

In the negative geotaxis task, Oliveira *et al*. (2016) found that exposure to either of the two doses (10 or 50 µg Hg^{2+}/mL) for 41 days (gestational/lactational exposure) had no effect on the emergence of the negative geotaxis response in pups. It was postulated that the absence of behavioural changes might be associated with a reduction in mercury build up in the brain. Franciscato *et al*. (2009) discovered that the increased Hg burden in the cerebrum and cerebellum is likely related to the motor function damage brought on by inorganic mercury.

In rim escape task performance, Peixoto *et al*. (2007) revealed that when the Hg treatment was administered during the first or second stage of development, the rats that had been exposed to the Hg had poorer results and animals showed an increase in the percentage of access to refuge. The performance of the Hg treated group was impacted when the treatment was administered during the third period (17–21 day), which coincided with the task period (17–20 day). The metal-exposed rats displayed a disordered profile for this score across the sessions; this behavioural activity is correlated with muscular growth and strength. Table 4 summaries the study on the effect of mercury in behavioural alteration using different behavioural task

Table 3: Effect of aluminium in different behavioural tests

S/N	Test	Exposure duration	Exposure route	Dose	Animal/Sex	Effects	References
1.	Multiple behavioural pattern	5 weeks	Oral: drinking water	2g/l and 3.5g/l	Adult rats	• Increased feeding time, frequencies of cage, drinking and total exploration in rats administered with 3.5g/l than 2g/l and the control • Lying time decreased in rats administered with 2g/l Al dose	(El-Moneum Goma & Tohamy, 2016)
2.	OFT	60 days	Intraperitoneally	100mg/kg	Male Wistar albino rats	• Crossings were significantly reduced in the Al exposed rats • The number of rearings was significantly decreased in Al exposed rats • All group did not show any significant difference in latency to initiate movement • Significant reductions in spontaneous locomotory and exploratory activities	(Abdel-Aal *et al*., 2011)
3.	RAM	60 days	Intraperitoneally	100mg/kg	Male Wistar albino rats	• decline in reference and working memory • significant increases in the number of errors • significant increase in the meantime required to end the task	(Abdel-Aal *et al*., 2011)
4.	MWM	60 days	Intraperitoneally	100mg/kg	Male Wistar albino rats	• significant increase in the time latency to find the platform relative • swimming distances were significantly increased • swimming distance was not affected by aluminium • significant increase in the time required to reach hidden platform area relative to control • significant reduction in time spent in target quadrant	(Abdel-Aal *et al*., 2011)
5.	PAT	60 days	Intraperitoneally	100mg/kg	Male Wistar albino rats	• Significant decrease in step-through latency	(Abdel-Aal *et al*., 2011)
6.	Rota rod	60 days	Intraperitoneally	100mg/kg	Male Wistar albino rats	• No significant differences among groups in the time latency to fall	(Abdel-Aal *et al*., 2011)
7.	PAT	2 months	Orally	100 mg/kg b.wt./day	Female Sprague–Dawley rat	• Significant decrease in the retention time was observed in Al treated animals when compared to normal control	(Bhalla *et al*., 2010)
8.	AAT	2 months	Orally	100 mg/kg b.wt./day	Female Sprague–Dawley rat	• Significant increase (in the number of escaped trials was observed in Al exposed animals	(Bhalla *et al*., 2010)
9.	EPM	2 months	Orally	100 mg/kg b.wt./day	Female Sprague–Dawley rat	• The number of entries in the open arm was increased in Al treated rats • Al treated animals spent more time in open arm rather than in close arm	(Bhalla *et al*., 2010)
10.	OFT: locomotory, NOR, FST, light dark transition (LDT)	7 days	Intraperitoneally	150 mg/kg	Male wistar rats	• Test rats displayed depression in open novel space • showed low locomotor and exploratory activity • significant reduced number of squares crossed by test rats as compared to control rats • marked impairment in recognition memory was observed in $AlCl_3$ injected rats as indicated by significantly decreased discrimination index in test rats • Test rats spent more time on sniffing familiar object rather than novel object that indicates impaired recognition memory	(Liaquat *et al*., 2019)

						• $AlCl_3$ injected rats indicated significant increase in immobility time in FST Test rats exhibited anxiogenic behaviour indicated by significant reduction in time spent in LDT test	
11.	MWM	7 days	Intraperitoneally	150 mg/kg	Male wistar rats	• Increase in escape latency of test rats • Marked impairment in working memory was observed following acute Al intoxication	(Liaquat *et al*., 2019)
12.	PAT	7 days	Intraperitoneally	150 mg/kg	Male wistar rats	• Significant increase in step through latency of $AlCl_3$ injected rats	(Liaquat *et al*., 2019)
13.	OFT	28 days	Inhalation	Mean concentrations of Al_2O_3 NPs were 0.5 mg/m^3	male and female ICR mice	• Al_2O_3 NPs treated female mice exhibited less duration in the central zone and enhanced duration in peripheral zone which implied less exploring behaviour and spontaneous locomotion after 14 & 28 days • Male mice did not show significant differences between control and treatment in OFT	(Zhang *et al*., 2015)
14.	FST	28 days	Inhalation	Mean concentrations of Al_2O_3 NPs were 0.5 mg/m^3	male and female ICR mice	• Female mice exposed to Al_2O_3 NPs had higher immobility time during the 5 min FST than female control after 14 & 28 days • Male mice did not show significant differences between control and treatment in FST	(Zhang *et al*., 2015)
15.	Y-Maze	15 days	Orally	100 mg/kg	Male rats	• Marked reduction of correct spontaneous alternating behaviour in rats of the $AlCl_3$ group compared • $AlCl_3$ impaired working and cognitive memory in rats	(Olajide *et al*., 2017)
16.	MWM	15 days	Orally	100 mg/kg	Male rats	• The escape latency was significantly highest in the $AlCl_3$ treated rats	(Olajide *et al*., 2017)
17.	EPM	15 days	Orally	100 mg/kg	Male rats	• Significantly increased anxiety levels	(Olajide *et al*., 2017)
18.	OFT	15 days	Orally	100 mg/kg	Male rats	• Al treated rats were redundant in the open field as they merely made entry to the central square or tarry within the square (showing anxiety and poor motor functions) • Significantly lower entry frequency and duration of rats in the central square in the Al exposed rats	(Olajide *et al*., 2017)
19.	MWM	6 weeks	Orally	100 mg/kg	Male rats	• Significantly delayed acquisition latency to reach the visual platform • Delay mean acquisition latency (on day 20) and retention latencies • Significant cognitive impairment	(Kumar *et al*., 2011)
20	Elevated 0 maze	180 days (4-day interval between injection)	Im injection	200, 400 and 800 µg Al/kg	Female CD1 mice	• No significant difference between groups	(Crépeaux *et al*., 2017)
21.	Novel recognition task, Wire-mesh hang test, Accelerating rota rod, hot plate test and Tail suspension test	180 days (4-day interval between injection)	Im injection	200, 400 and 800 µg Al/kg	female CD1 mice	• No significant difference between groups	(Crépeaux *et al*., 2017)
22.	Grip strength test	180 days (4-day interval between injection)	Im injection	200, 400 and 800 µg Al/kg	female CD1 mice	• Animals injected with Alhydrogel® at 200 µg Al/kg tended to have less strength compared to controls	(Crépeaux *et al*., 2017)

23.	OFT	180 days (4-day interval between injection)	Im injection	200, 400 and 800 µg Al/kg	female CD1 mice	• Animals injected with 200µg Al/kg showed decreased locomotor activity levels assessed by lower total distance crossed in the open field	(Crépeaux *et al*., 2017)
24.	AAT	6 weeks	Orally	100 mg/kg	female rats	• Animals treated with aluminium escaped 5.4 trials as compared to normal control animals, who escaped 1.8 trials	(Nehru *et al*., 2006)
25.	PAT	6 weeks	Orally	100 mg/kg	female rats	• Impairment in short-term memory	(Nehru *et al*., 2006)
26.	MWM	6 months	Drinking water	50 mg/kg/day	male wistar rat	• Significant effect of treatment on latency to reach the hidden platform in Al-treated	(Sethi *et al*., 2009)
27.	OFT	6 months	Drinking water	50 mg/kg/day	male wistar rat	• High ambulation • Elevated anxiety • Increased defaecation index	(Sethi *et al*., 2009)
28.	EPM	4 months	Oral gavage	50 mg/kg BW/day	male wistar rat	• The old rats spent more time in closed arms than the young ones • The time spent in closed arms was also noted to be considerably higher in old rats	(Allagui *et al*., 2014)
29.	RAM	4 months	Oral gavage	50 mg/kg BW/day	male wistar rat	• The mean number estimated for the working and reference memory errors for the old, treated rats indicated a higher number of working memory errors and reference memory errors in the aged rats and old Al-exposed rats as compared to the young rats	(Allagui *et al*., 2014)
30.	OFT	4 months	Oral gavage	50 mg/kg BW/day	male wistar rat	• The total distance travelled by old Al-treated rats was shorter than the one travelled by their young counterparts. • The total number of rearing movements (vertical movements) was reduced more markedly in old Al-treated rats	(Allagui *et al*., 2014)
31.	OFT	25 days	Orally	175 mg/kg	Sprague Dawley rats	• Diminished ambulation frequency, rearing frequency and • Improved grooming frequency • Increased faecal pellets	(Chen *et al*., 2021)
32.	MWM	25 days	Orally	175 mg/kg	Sprague Dawley rats	• Increased escape latency • Reduction in the time spent in the target quadrant • Memory and learning deficits	(Chen *et al*., 2021)
33.	MWM	90 days	Intraperitoneally	100mg/kg	male Albino Wistar rats	• Increased escape latency to reach the platform • Decreased swimming speed in acquisition trials • Increased time to reach the hidden platform • Reduced time spent in the target quadrant	(Abdel-Zaher *et al*., 2017)
34.	RAM	90 days	Intraperitoneally	100mg/kg	male Albino Wistar rats	• Increased the reference and working memory errors • Increased time required to end the task	(Abdel-Zaher *et al*., 2017)
35.	PAT	90 days	Intraperitoneally	100mg/kg	male Albino Wistar rats	• Decreased the step-through latency	(Abdel-Zaher *et al*., 2017)

Table 4: Effect of mercury in different behavioural tests

Test	Exposure duration	Exposure route	Dose	Animal/Sex	Effects	References
Light-dark experiment (Depression test)	day one of pregnancy until post-natal day 15 (PD 15)	N/A	10 ppm of $HgCl_2$	Mice offspring	• Significantly increased Stretch attend posture, grooming and dark chamber duration • Significantly Decreased latency to enter the dark chamber, transitions (number of light and dark entries), • Significantly decreased number of squares crossed) • Significantly decreased wall rear, rear and light chamber duration	(Mohammad Abu-Taweel & Al-Fifi, 2021)
EPM	day one of pregnancy until post-natal day 15 (PD 15)	N/A	10 ppm of $HgCl_2$	Mice offspring	• $HgCl_2$ treated animals spent more time into the closed arm and less time into open arm • The number of entries into the closed arm was increased significantly whereas in open arm it was decreased	(Mohammad Abu-Taweel & Al-Fifi, 2021)
FST and Tail suspension test (Depression test)	day one of pregnancy until post-natal day 15 (PD 15)	N/A	10 ppm of $HgCl_2$	Mice offspring	• increase depression in offspring significant • increased Immobility and immobility duration • significant reduction in the frequency of Swimming and climbing • significant reduction in swimming and climbing reduction	(Mohammad Abu-Taweel & Al-Fifi, 2021)
OFT	day one of pregnancy until post-natal day 15 (PND 15)	N/A	10 ppm of $HgCl_2$	Mice offspring	• Number of squares crossed, wall rear, rear, animal speed (square/sec) and locomotion duration were decreased • Number of wash cleaning and immobility duration were increased significantly	(Mohammad Abu-Taweel & Al-Fifi, 2021)
Sensorimotor development tests: rooting reflex, vibrissae placing response, righting reflex, negative geotaxis, suspension test and rotating grid	Gestation period	Drinking water	50 ppm (Hg50) and 100 ppm	Pups	• Rooting reflex was abolished on PND 1-4 in Hg50 and Hg100 pups • In rooting reflex prenatally treated pups responses were low when their facial regions were stimulated on PND 5 • The number of Hg50 and Hg100 pups eliciting vibrissae placing response was less • Slowness of righting reflex increased according to the amount of $HgCl_2$ administered to females during the whole period of pregnancy • Significant decrease of time of righting reflex of offspring exposed to $HgCl_2$ • Negative geotaxis reflex was significantly delayed in pups exposed to $HgCl_2$ prenatally • Decrease in angles of the fall of rat particularly for Hg100 in rotating grid • The rats prenatally treated with Hg50 or Hg100 fell sooner than control group in the suspension test • The eyes of pups were opened one or two days later than control group	(Chehimi *et al*., 2012)
EPM	Gestation period	Drinking water	50 ppm (Hg50) and 100 ppm	Pups	• The number of open arms entries was increased only with the lower dose of metal • The ratio of latencies on open arms was significantly increased for the pups exposed to $HgCl_2$	(Chehimi *et al*., 2012)

					• There was no significant difference on the number of entries in closed arm between the $HgCl_2$ treated (Hg50 and Hg100) and control groups • There was no difference between $HgCl_2$-treated and control on numerous head scan towards open arms and head dips.	
Rim escape task	5 days	Injection	3.7 mg/kg)	pups	• The improvement of rim escape task performance was damaged in rats exposed to Hg. • All animals presented an increase in the percentage of access to refuge, • The Hg exposed rats presented lower scores. • The metal exposed rats showed a disorganized profile for this score.	(Peixoto *et al*., 2007)
Spontaneous alternation task (T-maze)	5 days	Injection	3.7 mg/kg)	pups	• The parameters registered in the spontaneous alternation task were not altered • Slight increase in the latency to alternate the maze arm in animals of the 3rd interval of exposure.	(Peixoto *et al*., 2007)
OFT	5 days	Injection	3.7 mg/kg)	pups	• Demonstrated that the rats during the first or second period of development presented similar numbers of crossing in the two earlier phases of exposure appear to be more intensely affected than the 3rd phase. • The rearing response, however, shows a better habituation capacity of animals • Hg-exposed rats during the first period presented absence of habituation to apparatus and larger exit latency of the initial area than the control rats	(Peixoto *et al*., 2007)
Beaker test and Negative geotaxis task	41 days (gestational/lactational exposure	Drinking water	0, 10 and 50µg	pups	• No significant alteration among the groups	(Oliveira *et al*., 2016)

Discussion

The studies reviewed showed that lead-induced behavioural alterations manifested in either acute, sub-acute and chronic exposures, young, exposed rats exhibited cognitive and behavioural traits that linger into adulthood, the studies reviewed showed that aggression, anxiety, depression, learning deficit with significant motor coordination impairment are behavioural indicators of rats exposed to lead which manifest in the onset and progression of neurodegenerative disorders.

Excessive Mn in the brain promotes a variety of abnormal behaviours, including memory deficits, decreased motor skills and psychotic behaviour resembling Parkinson's disease. Manganese has been linked to Parkinson's disease, perhaps because of its ability to trigger the creation of reactive oxygen species, which harm neurons. The reviewed studies revealed that Mn intoxication causes a Disinhibitory Behavioural Syndrome an evidence of early clinical phase of Manganism, while prolonged Mn exposure may have an impact on the capacity for precise movement, much like early-stage idiopathic Parkinson disease (IPD). Mn have been implicated in neurotransmitter depletion in the rat brain which causes behavioural abnormalities such as cataleptic behaviour, which serves as another indicator of dopaminergic neuron impairment, Repetitive turning has been linked to stereotypy connected to dopaminergic dysfunction, like obsessive compulsive disorders according to the findings, rats motor and non-motor functions are altered by a considerable decrease in neurotransmitter levels. Excessive accumulation of Mn damages the transport system, which causes ataxia in the basal ganglia. From the reviewed studies Mn obvious motor impairment indicators include weak hind limbs, decreased endurance, delayed motor initiative (akinesia), unsteady posture, and action tremor. postural shifts, impairments in limb extension (resulting in many reduced reaches), and supination-pronation of the paw during grabbing and releasing the pellet into the mouth.

Al has a strong connection to Alzheimer's disease. As a result, excessive levels of Al influence not only the memory but also the motor functions, which results in a reduction in motor activity. This review showed that Al toxicity causes motor and cognitive deficits and neuropsychiatric abnormalities that could be attributed to the neuropathological alterations through indicators such as increased depressive-like behaviour; elevated anxiety, hypokinesia, decreased ambulation, reduced rearing, higher immobility, increased defaecation index, increased grooming, increased acquisition latency to reach visual platform, increase in escape latency , Increased the reference and working memory errors. The findings from several studies suggested that anxious and depressive behaviour increased with aging because the old rats spent more time in closed arms after several pre-training days than the young ones.

The outcome of Hg-induced behavioural alterations can also be verified by several factors, including motor output, exploratory drive, emotional acuity, freezing or other fear-related behaviours, relative time in the circadian cycle, and many more. Cross-fostering tests confirmed that mercury has direct harmful consequences on behaviour. Studies associated Hg toxicity with disrupted maternal behaviours; lactation and pup licking with significant reductions, increased retrieval latency, and mothers spent more time eating and drinking away from the nest, others behavioural alteration include depressive behaviour via increased immobility increased; significantly decreased swimming and climbing, delayed rooting reflex, delayed formation of the vibrissae placement response, decreased righting reflex, reduced grip strength, and the negative geotaxis behaviour, these behavioural alteration can lead to progression in neurodegenerative diseases.

Conclusion

Motor, sensory, and cognitive functions are impaired by exposure to Pb, Al, Mn, or Hg, exposure to heavy metals increase the permeability and vulnerability of the blood brain barrier resulting in bioaccumulation in the brain, which in turn causes detrimental behavioural effects in animal models of neurotoxicity and the onset of neurodegeneration. Young animals are more sensitive, and the absence of permeability selection is probably to be blamed for a potential and increased sensitivity for behavioural change in young animals. It can be concluded that heavy metals exposure affects animal welfare at various stages, beginning with behavioural changes and can progressively degenerate the neuronal system, this review documented these levels and types of change to detect how an animal behaviour is changing in response to these environmental pollutants, which will undoubtedly have an impact on human health. Additionally, it suggested a comparison of short and long window of time between exposure and behavioural tests; behavioural alterations to the heavy metal mixture to know if there will be a synergetic or negative effect of exposure to more than one metals in combination, but more research is needed to understand the biomarkers responsible for behavioural alterations.

Declarations

Competing Interest

The authors declare no competing interest.

Authors' Contributions

Chinyere S. Dike: Original draft; writing, review and editing
Mfoniso A. Antia: Review and editing
Bolaji B. Babatunde: Conceptualization and supervision
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Francis D. Sikoki: Conceptualization and supervision

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