Journal of Advanced Zoology
ISSN: 0253-7214
Volume 45 Issue 2 Year 2024 Page 672-682

Object Recognition And Morris Water Maze To Detect Cognitive Impairment From Neurodegenerative Diseases In Rats.

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Abstract:

Cognitive dysfunction refers to a variety of learning disabilities that affect problem solving, language, attention, memory, and decision making. Cognitive impairment occurs in a variety of neurological diseases, including Alzheimer's disease, frontotemporal dementia, focal dementia, and Parkinson's disease. Cognitive impairment is a condition in which people have difficulty remembering, learning, reasoning, and making decisions about new things that affect their daily lives. A cognitive disorder refers to a disorder of one or more cognitive functions, and depending on the severity of the disorder, it can be classified into mild mental disorders and dementia. Treatments for learning disabilities include physical activity, cognitive training and exercise, and proper sleep and relaxation techniques can be beneficial for mental health. The Mediterranean diet may help people with mental disorders. The Morris water maze (MWM) is a comprehensive learning test for rats that relies on long distances from a starting point along the perimeter of an open swimming area to find an underwater discharge platform, and the MWM is one of the most widely used paradigms. Assess hippocampus-based learning and memory. The MWM test has become one of the most widely used research tools in various areas of behavioral neuroscience. This review details the Morris water maze model, risk factors, current treatments, and animal studies in psychological disorders.

Keywords: Neurodegenerative disorders, Dementia, Morris water maze, cognitive impairment, Alzheimer's disease.

INTRODUCTION:

Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS) are irreversible neurological diseases that cause severe disability and death. For most people, there is no known genetic cause for this neurological disorder, but the discovery of mutated genes and genetic changes that alter risk has led to the spread of the disease [1]. These genetic clues contribute to the pathophysiology of neurodegenerative diseases and the biochemical identification of proteins such as amyloid β (Aβ), alpha-synuclein, tau, and TDP-43 that define the pathological hallmarks of these diseases. It provides important insights into an opportunity to create animal models of this disease. Genetic variants in a human

disease are not necessarily a complete phenocopy of that disease, but are often generative in nature, adding internal validity to genetics-based models of neurodegenerative diseases. Indeed, genetic models of these diseases have provided insight into the molecular and temporal mechanisms of human disease variation and helped identify candidates for disease-modifying therapies [1,2].

COGNITIVE DYSFUNCTIONS:

The term "cognitive dysfunction" refers to a variety of mental disorders that affect learning, memory, attention, problem solving, and decision making. Both a person's ability to function normally and quality of life can be affected by mental disorders. This can happen for many reasons, including aging, mental health problems, brain damage, and neurological disorders. For affected individuals, cognitive impairment can have a significant impact on daily functioning and quality of life [3].
Cognitive impairment occurs in a variety of neurodegenerative diseases, including Alzheimer's disease (AD), frontotemporal dementia (FTD), Lewy body dementia, and Parkinson's disease (PD). Generally, intellectual disability can be classified into several cognitive systems, including general intelligence, executive function, memory, attention, psychomotor speed, visuospatial function, and language. All these areas can be identified by relevant scales or tests. General intelligence is measured by the Wechsler Adult Intelligence Scale (WAIS) and the Mini-Mental State Examination (MMSE), and executive functioning includes several domains such as verbal communication, inhibitory control, and planning. In addition, memory domains are more complex and include long-term and short-term memory. Episodic memory is part of long-term memory, while working memory, verbal memory, and visuospatial memory are referred to as short-term memory [3,4].

COGNITIVE IMPAIRMENTS:

Cognitive impairment can result from loss of performance in many mental abilities, such as concentration, recall, reasoning, learning, and decision-making [5]. Learning disabilities combined with medical conditions such as type 2 diabetes mellitus (T2DM) can be serious. As a result, patients may miss appointments and neglect treatment. According to the medical literature, patients with T2 diabetes often experience cognitive impairment with age. In addition, age-related structural and physiological deterioration of the brain appears to be accelerated in older individuals with type 2 diabetes mellitus [6]. Consequently, if these patients do not receive timely and planned treatment, their cognitive decline will accelerate. In addition to the prevalence of diabetes, with the increase of the elderly population, cognitive disorders will also increase. In addition, cognitive impairment was a predictor of neurocognitive impairment. Therefore, it is appropriate to identify risk factors in these people so that interventions can be started earlier and before the development of complete neurocognitive impairment. Early diagnosis undoubtedly helps to reduce the human and socio-economic responsibility in the medical field and thus reduce the burden on caregivers [7].

Table 1: Diagnosis, causes, and treatment of current psychiatric disorders from neurological disorders

Diagnosis	• Depends on subjective scoring • Objective assessment is expensive
Causes	• Excitation/inhibition imbalance • Anatomical hyper plasticity • Immune dysfunction • Dysfunction Gut-brain axis • Retina changes • Hormonal imbalance • Oxidative stress • Genetically factors
Treatments	• Early intervention • Immune therapy • Drugs and supplements • Electrophysiology • Sensory processing training • Physical activity • Behavioral therapy

Types of Cognitive impairments:
The National Institute on Aging and the Alzheimer's Association has published an instrument that includes six different stages of Alzheimer's disease (AD) [8]. The first stage of the disease is characterized by the absence of subjective or objective evidence of cognitive impairment (CI) or behavioral disorder. The second transition stage includes people with subjective memory complaints (SMC), subtle objective disorders, or mild behavioral symptoms. These two stages are called "Pre-Income Stage" and the third stage is called "Mild Cognitive Impairment" (MCI). Finally, stages 4 to 6 represent the different clinical courses of mild, moderate and severe dementia [8,9].

Mild cognitive impairment (MCI) is a syndrome defined as a decline in cognitive function that is greater than expected for a person's age and level of education, but does not significantly interfere with activities of daily living. It is characterized by cognitive impairment (CI), measured objectively using validated neuropsychological tests [9]. Patients with CI are at increased risk of developing AD or other types of dementia compared to the general population [10].

Dementia is a progressive neurological disease that can begin up to 20 years before diagnosis. CI is highlighted as a precursor to a pathology characterized by a decline in cognitive function when the patient does not meet the diagnostic criteria for dementia. Therefore, early detection of CI is essential at this pre-clinical stage, when more benefit is expected from disease-modifying treatments or slower disease progression [11].

Mental memory impairment (SMC) is defined as the subjective perception of reduced cognitive ability compared to previous levels of functioning in individuals with normal cognitive abilities. Evidence suggests that SMC may represent the first preclinical manifestation of AD [12]. Currently, awareness of Alzheimer's disease is increasing and more people are expressing concern about cognitive decline [9]. In addition, people who are individually at risk of dementia may be more sensitive to some symptoms of memory loss [13]. In this regard, it has been suggested that people who express concern about perceived cognitive decline are at increased risk of developing cognitive decline or dementia [9].

Pathophysiology
A common pathology of cognitive impairment is damage to nervous tissue. This involves damage to the gray matter, which includes the axon sheaths connecting the cortex and thalamus, basal ganglia, and gray matter. Damage in some areas causes some defects. For example, damage to the parietal lobe can lead to impaired attention and visual-spatial functioning. Damage to the frontal lobe system can cause deficits in planning and abstract understanding, and damage to the temporal lobe can cause language and memory deficits [14,15].

Causes of this damage include metabolic disorders and neurotoxicity due to heavy metals and other toxins (such as toluene and infections) or ischemic insults such as stroke, hemorrhage, head injury, cancer, and surgery. Damage can also be caused by neurodegenerative processes such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and Huntington's disease. The disease directly damages nerve tissue through immune interactions with abnormal proteins [14-16].

Risk factors
Cognitive impairment refers to impairment of one or more cognitive functions and is classified into mild cognitive impairment (MCI) and dementia based on its severity. Compared to healthy adults, MCI patients, who show subjective cognitive decline with objective cognitive impairment and learning and memory deficits, have a 16% annual increased risk of dyspnea [17].

People over the age of 90 typically experience loss of sensation, difficulty providing accurate and reliable information, higher levels of anxiety, and higher rates of dementia. Most of them are usually women. Factors associated with the risk of cognitive impairment in young adults are no longer predictable, suggesting that comorbidities are more predictive than single diseases [18]. Because most people over 90 years of age now have early stages of cognitive impairment (MCI), studies are often cross-sectional and can only estimate the risk of dementia or Alzheimer's disease (AD). Furthermore, potential interventions at this age may have long-term benefits. The aim of this study was to determine the risk and protective factors for developing MCI in mentally healthy individuals aged 85–89 years enrolled in the Mayo Study on Aging (MCSA) [19].

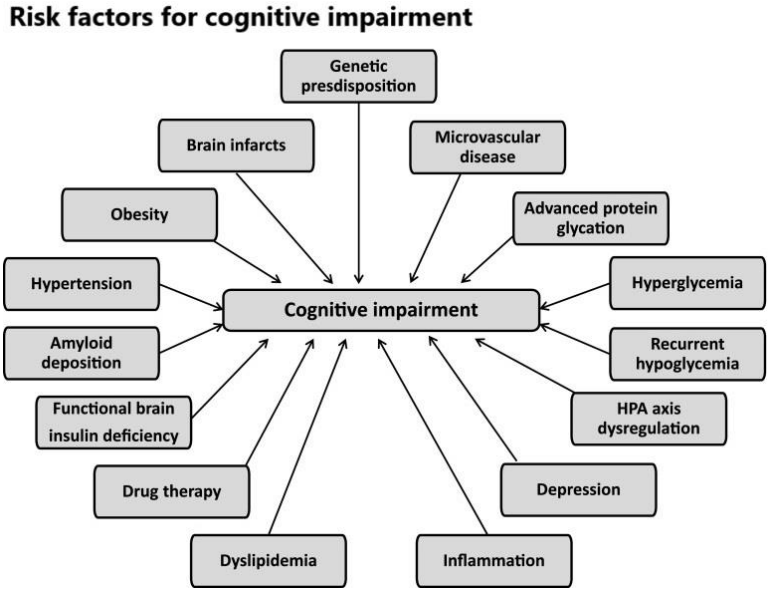

Figure 1: Risk factors for cognitive impairments

TREATMENTS ON COGNITIVE IMPAIRMENTS:

If testing suggests another cause for cognitive impairment (eg, hypothyroidism, OSA) it should be treated. We should pay attention to blood vessels that contribute to cognitive decline, such as high blood pressure, diabetes, and smoking. Medications that cause cognitive impairment, especially anticholinergic medications, should be reduced or discontinued if possible [20]. Normal pressure hydrocephalus (NPH) is treated with ventriculoperitoneal shunt surgery. Physical activity, cognitive exercise, and proper sleep and relaxation techniques support cognitive health. A Mediterranean diet may help people with cognitive impairment. Occupational therapy focuses on teaching patients various strategies to reduce the impact of cognitive impairment on daily life (Table 1) [20].

Pharmacotherapy:

As of 2020, there are no approved treatments for neurological diseases, but many treatments are being studied in clinical trials. Available treatments are symptomatic.

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors such as donepezil, galantamine and rivastigmine are indicated for use in AD dementia and may be effective in vascular dementia and DLB [21]. Acetylcholinesterase inhibitors may worsen FTD behavior and there is insufficient evidence in MCI [20, 22]. Acetylcholinesterase inhibitor therapy aims to improve memory by blocking the breakdown of the neurotransmitter acetylcholine, which is released by cholinergic neurons in the basal ganglia known to affect Alzheimer's disease, and by improving or stabilizing attention [23].

Memantine

Memantine, an N-methyl-d-aspartate (NMDA) receptor antagonist, is thought to act by blocking the effects of excess glutamate and by regulating NMDA receptor expression [24]. Memantine is indicated for use in moderate to severe Alzheimer's disease, and there is evidence to support off-label use in mild to moderate dementia [25]. Memantine has been shown to produce modest improvements in thinking, daily life, behavior, and mood. Memantine is generally well tolerated, but the most common side effect is dizziness. As with acetylcholinesterase inhibitors, patients and families should be advised that the benefits of memantine are small [26].

Environmental, Psychological, and Behavioral Interventions

Various lifestyle interventions that can improve quality of life and slow functional decline are important in the management of learning disabilities. When diagnosed with dementia, doctors should counsel patients and families about a safe, organized, social, and productive day. All patients with SKD, MCI and dementia should be physically, mentally and socially active. Activities that somehow combine physical, mental and social activities are important. For example, join a book club (intellectual and social stimulation) or take a dance class

(stimulation of all three). Unfortunately, the COVID-19 pandemic has made many lifestyles unsafe for the elderly due to the risk of mass infection. Custodians should strive to facilitate a safe yet stimulating experience. As an example, we can refer to home sports programs and social experiences based on video conferencing [27].

Exercise

Exercise programs for people with dementia have been shown to improve or stabilize functional and cognitive status. In patients with MCI or AD, the best evidence-based regimen is 3–45 minutes of moderate-intensity aerobic exercise three or four times a week [28]. Mind-body exercises (eg, yoga, tai chi) have been shown to improve cognitive function in MCI [29].

Cognitive stimulation

Studies have shown that cognitive stimulation activities such as computer work, video games, and virtual reality programs have specific benefits against MCI and dementia [30]. It makes sense to refer patients to accessible and affordable wellness/mental health programs. Clinicians should strive to incorporate cognitive stimulation activities into daily life. The activity chosen depends on the patient's abilities and interests. Mindfulness can help MCI patients build mental reserves, improve social engagement, and better understand their diagnosis [31]. Speech therapy can help people with language difficulties.

Social engagement

Lack of social interaction (e.g., loneliness) is associated with dementia risk, and community cultural participation (e.g. museum visits, theater attendance) may be a protective factor for dementia risk [32]. Social influence is more effective when people outside the patient's inner circle are involved. Some caregivers try to provide round-the-clock support, but interaction with others in the form of home visits, senior day programs, or home visits can help. This is for the benefit of the patient and the caregiver. . An old friend takes the patient out for lunch once a week [33].

Sleep

Behavioral interventions for sleep disorders include sleep health counseling, light therapy, and referral to cognitive behavioral therapy for insomnia [34]. Sleep disorders can be aggravated by excessive sleep and inactivity during the day. Having a more active day, such as getting out of the house during the day, can improve sleep [35].

Nutrition

The Mediterranean diet is associated with a reduced risk of progression from MCI to dementia. Patients with dementia are at risk of malnutrition, and nutritional status can affect functional status [36]. Nurses should prepare daily meals and snacks for patients at risk of malnutrition. (Many people eat when they are being served, even if they say they are not hungry.) You can get additional nutrition from nutritional supplements like shakes. Patients should avoid moderate or heavy alcohol consumption [37].

Different type of animal model used in cognitive impairments:

Pharmacological models are the most commonly used models of cognitive deficits. This is key to determining how the neurotransmitter receptor system is selected to be involved in various aspects of cognitive function, including learning, memory, and attention. Pharmacological models are more likely to use cognitive-enhancing drugs to treat cognitive disorders such as Alzheimer's disease and aging-related syndromes, attention-deficit/hyperactivity disorder (ADHD), Parkinson's disease, and schizophrenia. Acetylcholine testing is the best transporter system based on cognitive function [38]. Both muscarinic and nicotinic cholinergic receptors have been shown to be strongly involved. The glutamate system, especially those using NMDA (N-methyl-D-aspartate) receptors, is also heavily involved in learning. Addiction can also lead to cognitive impairment syndromes [39].

Mice are increasingly valuable for elucidating the molecular basis of cognitive function. In addition, genetically engineered mice are increasingly used to create models for the development of new drugs. For these applications, it is important to develop several reliable, valid, and rapid tests to measure cognitive performance in mice. Using transgenic mice for complications caused by age-related amyloid deposition is a promising platform for developing new treatments for Alzheimer's disease and other age-related mental disorders. Pharmacological models suggest that acetylcholine plays an important neural role in cognitive function. Cholinergic receptor knockout mice have been used to determine the role of various aspects of the cholinergic system in cognitive function [39].

Open maze, elevated plus maze, and elevated plus zero maze are widely used behavioral tests to assess cognitive deficits in laboratory animals [40].

MORRIS WATER MAZE (MWM):

Although many water mazes have been built, one known as "water maze" was created by Richard Morris [41,42]. This maze was developed as a method to assess spatial or spatial learning and is referred to here as the Morris Water Maze (MWM). Morris described the original method in 1984 and later added details and methods for assessing learning and memory type [43]. Several features contribute to MWM's popularity. These include the lack of previous training, high reliability across various experimental configurations and procedures, the use of species (rats, mice, humans (in virtual mazes)), and hippocampal-based spatial navigation and context memory. . The main focus of the work is the role (genetic, medicinal, nutritional, toxicological, scientific) in various secondary experimental therapeutic effects and differential immunity. damage). The latter is a feature common to all water heaters, and MWM takes advantage of this strength. For example, hippocampal and septohippocampal lesions in rats are believed to cause hyperactivity, but such animals show MWM deficits [44]. On the other hand, medications that cause hypoactivity can be separated from learning deficits in MWM. For example, in addition, if the test animal is immobile during the test, the measurements recorded during the test do not affect swimming speed and separate learning and performance [45].

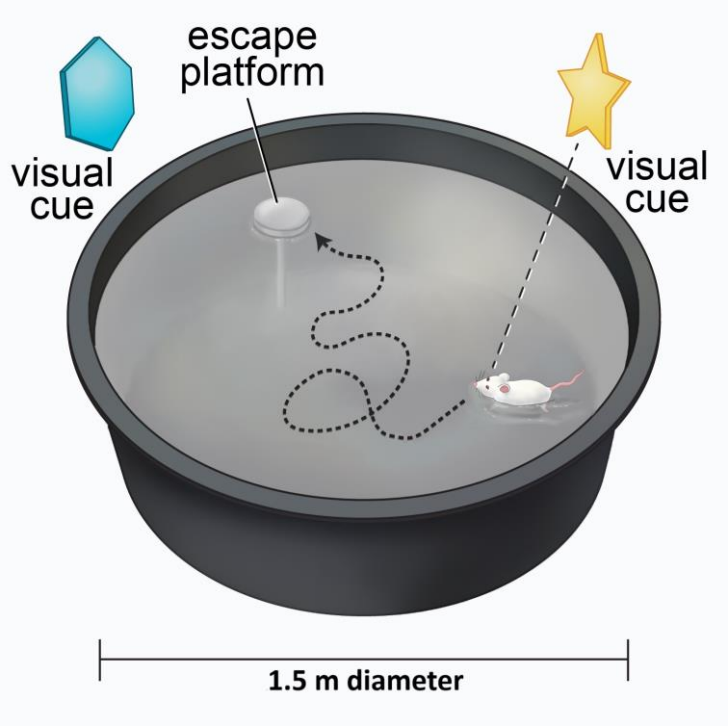

Figure 2: Apparatus of Morris Water Maze

The use of the MWM in the assessment of learning and memory, as well as the relationship between both MWM function and neurotransmitter system and drug effects, have been investigated [46,47]. MWM performance is associated with long-term potentiation (LTP) and NMDA receptor function [48], making it an important technique in the study of hippocampal circuits. In addition, it has been shown to involve the entorhinal and perirhinal cortices as well as the prefrontal cortex, cingulate cortex, neostriatum and, to a lesser extent, the cerebellum [46].

METHODS FOR MWM:

Apparatus setting up [49,50]

- The maze is made of a circular polypropylene pool with a diameter of 110 cm and a depth of 20 cm.
- A 1.5 m diameter and 45 cm deep MWM is filled with water to a depth of 26.5 cm at room temperature (Figure 2).
- To provide camouflage for the white flow platform, 500ml of toxic white liquid enhancement paint was added to make the water transparent.

- I filled the basin up to a height of about 5 cm with water and mixed 100 ml of white liquid tempera paint with 25 ml of water.
- Pour diluted paint concentration into the pool. The platform was then reinserted into the pool until it was submerged in 1 cm of white water.
- The water is left overnight until it reaches room temperature (22±1 ℃).
- The swimming pool is divided into four quadrants. Ace; "North-West", "North-East", "South-West", "South-East". The boundary of the quadrant is measured at the edge of the pond with a tape measure and marked north, south, east, and west.
- A plexiglass cylinder (diameter 13.75 x 9 cm) is used as an escape platform for the maze. The cylinder is filled with water and weighed in the tank.
- The platform has a moving red and yellow stripe (diameter 3 cm* 9 cm) and a colored flag is placed in the middle.
- The water level in the pool is set at 0.5 cm from the top of the screen and the drain platform is visible (or) made 0.5 cm above the white cylinder (if the top is not torn). made Invisible created.

Test conditions [51].

- The water temperature is adjusted according to the age of the mouse. 29 ° C (± 0.5) from 16 years to 20 days; 29°C (±0.5) from 16 years to 20 days. 27 ° C (± 0.5) for PND 20-27 and 25 ° C (± 0.5) for adult mice.
- Immediately after the behavioral test, the mice were given a habituation period of 10-15 minutes (adaptation to the white light).
- Mice were placed on the platform for 1 min before performing three swimming trials.
- During each training session, the rat is removed from the platform and released 12-18 inches from the platform.
- The rat then swam to the platform as instructed by the experimenter.
- 12 trials with a rest period of 30 seconds. Two sets of six runs—four runs from each of the four starting positions—with a 30–45-min rest period in a small heated cage in a separate room (separate test period).
- During testing, the rat is placed in water in one of the four initial positions facing the wall and must use the distal marker to move to the platform.
- All starting locations are away from the platform and immediately adjacent to the wall in the middle of the quad that does not include the platform.

Pre-training for the water maze: [52-54]

- For water maze training, the platform must be in the middle of the pool and 1 inch above the water so the animal knows it is there. The water temperature should be between 1°C and 26°C.
- Each animal was tested three times in a row. First, put the animal on the platform for 20 seconds.
- The water maze has four starting locations: north, south, east, and west. Bring the animals to one of these locations. Hold the animal by hand and slowly lower it into the water tail-first. Do not submerge your pet with his head.
- Allow the animal to swim or explore the platform for 60 seconds. First, the animal can swim to the edge of the pool to get out. Eventually the animal learns to find and climb the platform.
- When the rodent reaches the platform, stop the timer and record the time. If the platform is not found in 60 seconds, record the duration of this test for 1 minute. If the animal can not reach the platform, do not lift it. Teach the animal to swim to the platform. So gently guide the animal to the platform by hand. Allow the animal to sit on the platform for 15 seconds. If it falls or jumps, cover it gently. This teaches the animal to stay on the platform to escape to the pool.
- Repeat the same steps for the other two tests, starting from a different direction for each test.
- After the animal has completed all three trials, dry the towel. Repeat 3 experiments in order for all animals. Make sure all directions are the same and record the time.
- Now that the animal is trained, it is ready to do the water maze test.

One of the most frequently modified learning tests from the MWM is the Spanning Learning and Memory Test for Close Associations [55]. In this modified version of the MWM, animals learn to associate a distance point with an escape platform. They learn the same skills as in the training phase of the remote spatial version of the MWM [56]. Although research in breadth has often focused on distal problems, research has shown that the use of proximal beacons is equally important for search strategies, joint/conceptual capabilities, and provides

reliable indicators for problem assessment. can provide. . memory However, it should be noted that the importance of local (beacon) and global (significant) cues can vary depending on the species, the magnitude of the stimulus, and individual experience [58]. The main advantage of the MWM proximal signal version is that it does not require a long training time. Although this is not a problem in the laboratory (MWM tests are routinely performed and so far only used), it hinders the use of the method in field studies. Keeping wild animals for several days in field research is rarely possible and can be dangerous. Therefore, the intention to test the cognitive ability of free-ranging animals is rejected [59].

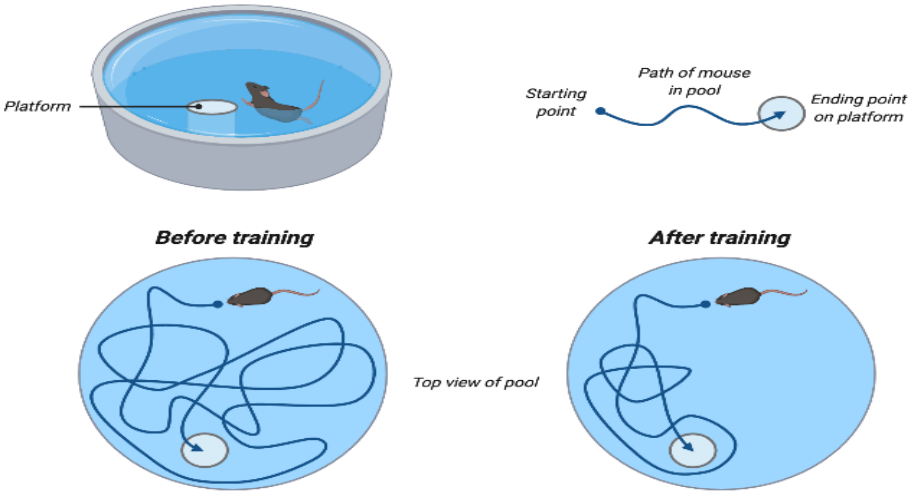

Figure 3: Morris Water Maze test.

Advantages of Morris Water Maze test: [60-62]

- Researchers can test animals' cognitive mapping abilities by measuring their spatial learning abilities using the Morris water maze.
- Versatility: Applies to a wide range of species and is commonly used in rodents, allowing experiment designers flexibility.
- Minimal stress: Compared to other behavioral tests, non-aggressive behavior reduces stress in animals and increases ethical considerations.
- Objective measurement: Objective data can be analyzed using measurable parameters such as swim path and escape latency.
- Neuroscience Applications: Frequently used in neuroscience research to study effects of drug therapy, genetic modification, memory, and hippocampal function.
- Assessment of long-term memory: Suitable for assessment of long-term spatial memory, which is important for understanding cognitive function.
- Consistency: Validity of results across studies is enhanced by reproducible results.
- Real-world relevance: By simulating real-world spatial challenges, the pilot design achieves environmental validation.

Disadvantages: [63,64]

- The Morris water maze test may not represent all aspects of spatial learning and memory well.
- Performance can also be affected by other variables such as stress levels, motivation and sensory abilities.
- It is important to consider these limitations when interpreting the results..

CONCLUSION:

Learning disability is not a disease, but a manifestation of the human condition. It means you have problems with things like memory and attention. It can be difficult to communicate and understand. They also have trouble recognizing people, places, and things, and can become overwhelmed in new places or situations. Treatment depends on the cause of the learning disability. We need to pay attention to blood vessels that contribute to cognitive decline, such as high blood pressure, diabetes, and smoking. Medications that cause cognitive impairment, especially anticholinergics, should be reduced or eliminated as much as possible.

In animal studies, MWM has become one of the most widely used concepts for assessing hippocampal-based learning and memory. The MWM test has become one of the most widely used research tools in various branches of behavioral neuroscience. This test has so many advantages and is used in so many different applications that it is sometimes cited as one of the best tests for extensive learning and memory in laboratory mice. The relative simplicity of the MWM task is one of the reasons for its continued success, as well as the inability to distinguish between spatial (hidden platform) and non-spatial (visible platform) task conditions and task switching. Different methods for investigating working memory, reference memory, and problem-solving strategies.

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