Behavioral tests for evaluating the characteristics of brain diseases in rodent models: Optimal choices for improved outcomes (Review)

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Abstract. Behavioral assessment is the dominant approach for evaluating whether animal models of brain diseases can successfully mimic the clinical characteristics of diseases. At present, most research regarding brain diseases involves the use of rodent models. While studies have reported numerous methods of behavioral assessments in rodent models of brain diseases, each with different principles, procedures, and assessment criteria, only few reviews have focused on characterizing and differentiating these methods based on applications for which they are most appropriate. Therefore, in the present review, the representative behavioral tests in rodent models of brain diseases were compared and differentiated, aiming to provide convenience for researchers in selecting the optimal methods for their studies.

Contents

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1. Introduction

The term 'brain disease' encompasses various conditions, including brain injuries [e.g., stroke, white matter injury (WMI), and traumatic brain injury] (1), neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis) (2), and affective disorders (e.g., depression and anxiety) (3), with the associated lesions mainly localized in the cortex, hippocampus, corpus callosum, and nerve nuclei (4). Patients with brain injuries and neurodegenerative diseases typically exhibit movement disorders and cognitive impairment (5,6), whereas those with affective disorders typically exhibit working memory deficits and impaired emotional processing (7). These conditions severely affect the quality of life of patients; however, the pathogenetic mechanisms underlying numerous brain diseases remain to be fully elucidated, and effective strategies for clinical treatment of such diseases are often lacking. Therefore, investigation of the pathogenesis and treatment of human brain diseases is of considerable clinical value. However, due to ethical and methodological limitations of experimentation involving human participants, the dominant approach for studying the nature, prevention, and treatment of human brain diseases involves the use of animal models.

Human brain diseases are mainly modeled in mice and rats, and considerable advancements have been made based on the data derived using these models (8,9). Despite such advancements, various testing methods with different principles, operational procedures, and assessment criteria have been used in animal research, and a specific optimal approach has not been generally accepted, to date. Selecting the optimal methods for investigating specific diseases will help in improving outcomes in both research and clinical settings. The methods used to assess brain disease in animal models can be generally categorized into pathological observation, specific marker identification, and behavioral performance assessment (10). Typically, behavioral tests are used to determine whether movement, cognition, working memory, and emotion have been affected, and such tests appear to be the most effective approach for evaluating whether animal models mimic the clinical characteristics of specific diseases (10,11).

The aim of the present review was to evaluate behavioral assessment methods for investigating the effects of brain diseases and relevant treatment strategies in animal models. First, the typical behavioral tests used in rodent models of brain diseases, including the Morris water maze (MWM) test, novel object recognition test, balance beam walking test, rotarod test, open field test (OFT), elevated plus-maze (EPM) test, tail suspension test (TST), and forced swimming test (FST), were summarized and reviewed. Then, the advantages and limitations of each approach were compared and recommendations that can aid researchers in selecting the optimal methods for their investigations were provided.

The present study was designed as a narrative review. It was performed by searching for the key words in databases (PubMed and Web of science) including 'behavioral tests', 'brain diseases', 'rodent models', and 'behavioral assessments'. The studies searched were covered between 1947 and 2021. After reading the abstract, the studies that met with the scope of the present study were included and finally 104 studies were cited.

2. Principles, procedures, assessment, and application of different behavioral tests

MWM test. The MWM test was originally developed in 1982 by Morris *et al*, who sought to take advantage of the congenital abilities for spatial navigation and swimming in rodents. This test also relies on the innate drive of the animals to escape the water by locating and reaching the standing platform, which has been considered to reflect motivation for learning and memorization. Following its development, this test was immediately adopted as the standard method for investigating cognitive function based on the spatial memory and navigation abilities of the animal (12). Morris *et al* developed the test based on prior electrophysiological study showing that some cells in the hippocampus responded during the spatial learning and exploration phase, whereas other cells exhibited electrophysiological activity only when rodents entered a familiar environment (usually a specific and restricted area) (12). Moreover, damage to the hippocampus or decreases in the number of hippocampal synapses can lead to deficits in spatial learning and memory (12). Several recent studies have aimed to verify the theory that the hippocampus functions as a dynamic central hub for the hippocampal-cortical network, whose activation is considered to occur during episodic memory acquisition and retrieval in both humans and rodents (13,14). The capacity for episodic memory acquisition and retrieval of an animal is usually considered to reflect their ability to perceive spatial factors or cues, which are processed and consolidated afterward and are finally used to locate the standing platform in the MWM test (15). However, a previous study suggested that the spatial learning and navigation aspects of the MWM test performance do not solely rely on hippocampal activity but require significant involvement of cortical and subcortical regions (16). In addition, in another previous study it was reported that focal injuries to the medial thalamus impair the ability to adopt search strategies and swimming behavior without impacting spatial mapping and navigation performance (17). Furthermore, another study examined several novel variables and measures including a spatial learning index, which has greatly enhanced the ability to assess subtle differences in the MWM test performance (15). This index has considerably facilitated comparisons among groups and has aided correlation analyses with neurobiological markers or other behavioral measures (15). Moreover, one study demonstrated that the spatial learning index was sensitive enough to detect delicate behavioral alterations among aged individuals (15). Therefore, findings of studies using this spatial learning index have improved our understanding of age-related cognitive decline and cognitive function maintenance in aged individuals.

The equipment for the MWM test comprises three main elements: A large water tank (150 cm in diameter), an escape platform (15 cm in diameter), and a video monitor placed above the tank. The MWM test involves a navigation training stage, followed by a spatial exploration test to assess cognitive abilities (18). Adult animals are trained during the first 5-6 days. During training, the rodents are placed in the tank and allowed to search for the platform (typically 2 min for rats and 1 min for mice), and escape latency (i.e., the time required to find the platform) is recorded. The mean escape latency during the training stage is then used as a measure of the capacity of the animal to understand spatial information. After 5-6 days of training, animals undergo the spatial navigation test (18). First, the rodents are placed in the third quadrant and allowed to swim freely in the tank (without the platform) for 1 or 2 min, and the number of times they cross the position of the removed platform is recorded for further analysis (19) (Fig. 1).

In the MWM test, the average escape latency and the number of platform crossings are used to evaluate learning and memory ability (20). To improve the assessment, researchers have developed a novel parameter known as 'proximity', which is calculated as the frequency at which the rodent comes near the platform in 1 sec. This measure generates two additional variables, cumulative search error and average proximity, which are more sensitive in detecting group differences in behavior. In addition to their sensitivity, proximity measures require a small number of experimental animals and can increase the throughput of behavioral characterization facilities (21). Although proximity measures allow for improved quantification of navigation ability in the MWM task, other measures are still necessary. Accordingly, researchers have proposed the 'learning index' that can be used to associate spatial learning ability with other behavioral or neurobiological measures. The rodents are subjected to four trials, and the average proximity of the four probe trials is finally calculated as the learning index (22). In summary, the evaluation indices for the MWM test include the average escape latency (sec), number of platform crossings, cumulative search error, average proximity, and learning index (Fig. 1).

The MWM test is primarily designed to assess spatial learning and memory function, as these processes are considered to be similar in rodents and humans, particularly in terms of episodic memory ability. Therefore, the MWM test has been widely used and is well-recognized as a method for evaluating cognitive ability in experimental models of brain injuries such as WMI, stroke, and traumatic brain injury (23-25). Moreover, as the 'visuospatial navigation' aspect of rodent performance is also reflected in 'everyday cognitive' processes in humans, the MWM test can be used to study neurodegenerative diseases

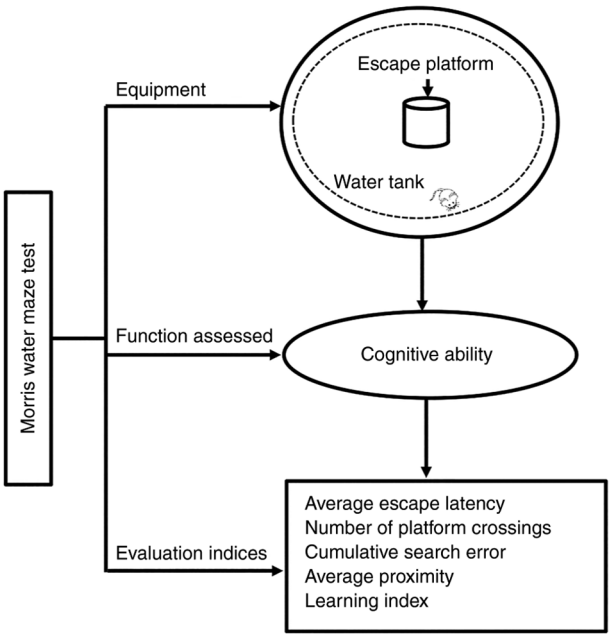

Figure 1. Illustration for Morris water maze test.

characterized by impaired cognition, such as Alzheimer's disease or Parkinson's disease (26,27). Additional studies have shown that reversal learning and other aspects of cognitive flexibility rely on the prefrontal cortex in both humans and rodents (21,28). Therefore, the MWM test has also been used to assess the therapeutic effects of potential treatments on cognitive deficits in experimental models, which can provide critical information for clinical studies (Table I; 23-52).

Novel object recognition test. The novel object recognition test is another behavioral assessment method that is primarily associated with cognitive ability. It was originally developed by examining the natural tendency of rodents to explore novel objects (53). This test is unique in that it does not follow strict rules: The rodents only need to be familiar with the arena prior to testing, and the procedure is flexible and easy to follow (54,55).

The novel object recognition test comprises three stages: Habituation, training, and testing. On the 1st day (habituation stage), rodents are placed in a plastic chamber (35 cm in length x35 cm in width x35 cm in height) for 10 min for familiarization with the arena. On the 2nd day (training stage), two objects are placed symmetrically along the central line of the arena, and the rodents are allowed to examine the objects for 3 min. The duration of exploration is recorded for each object as an index of exploratory behavior. On the 3rd day (testing stage), the rodents are returned to their home cages for 3 min, and one of the objects is relocated to another adjacent quadrant, following which the rodents are allowed to explore the objects again. The time spent exploring the novel object is recorded and recorded as the recognition index (56,57) (Fig. 2).

At present, there are two widely accepted indices used to assess exploratory behavior during the test session. One is the novel object preference ratio, which is calculated by dividing the exploration time for the novel object by the exploration time for the total objects. A value of >0.5 indicates preference for the novel object, whereas a value of <0.5 indicates preference for the familiar object. The exploration time for each object is also used as an index of exploratory activity, such that the duration for which the nose is within 1 cm of the object in the novel location is recorded as the recognition index (58,59). Moreover, this test can be used to evaluate memory ability based on the time required to identify the novel objects (60) (Fig. 2).

Currently, this method is extensively used in studies investigating conditions associated with memory deficits, such as Alzheimer's disease, aging, traumatic brain injury, and schizophrenia, as it can help in evaluating the neurobiology of non-spatial memory in rodents (29,30) (Table I).

Balance beam walking test. It is widely accepted that rodents exhibit innate abilities for coordination and balance. Researchers have taken advantage of this characteristic to develop the balance beam walking test, which is used to assess motor balance and coordination ability in rodents with damage to the motor cortex (61,62). This test is advantageous in that it is easier to set up and is less expensive than the rotarod test (63).

The modified beam walking test equipment comprises a beam (80 cm in length, 0.5 cm in width, and 50 cm above the floor), with a lamp on one end and a box (non-transparent) on the other end and video-capturing equipment hanging above. First, for training, the beam equipment is placed in a dark and enclosed room, and the rodents are placed at the end of the beam containing the lamp. During the training phase, the rodents are allowed to walk 30, 50, and 70 cm for a maximum time of 60 sec. For each rodent, three trials per day are performed for 3 consecutive days. Then, during testing, the rodents are allowed to walk along the beam, similar to that in the training phase, and the following three metrics are used to evaluate performance: The frequency of hind limb slippage, the time spent on the beam, and the number of falls when walking the full distance (64,65) (Fig. 3).

The balance beam walking test performance is a useful measure of fine coordination and balance (31). The results are typically used to determine a beam walking performance index, which is calculated using the frequency of hind limb slippage, the time spent walking along the beam, the number of falls when walking the full distance of the beam, the distance traveled within the set time, the number of left and right turns, and the number of left and right paw slips (66,67) (Fig. 3).

Since its development and widespread acceptance, the balance beam walking test has been primarily used in studies of age-related motor deficits (32,33), central nervous system lesions (34), and genetic and pharmacological manipulations (68). The test has also been used to assess models of WMI (31), Huntington's disease (35), Parkinson's disease (36), anxiety (37), stroke (38), and multiple sclerosis (39) (Table I).

Rotarod test. The rotarod test represents another widely accepted and utilized method for evaluating motor coordination and balance in rodents, and both the balance beam walking test and the rotarod test share nearly identical principles (69). The rotarod test is unique, in that it is useful in evaluating endurance in rodents and is especially sensitive to cerebellar disorders (70). Researchers have primarily taken advantage of

Table I. Applicable conditions for behavioral tests in rodent models of brain diseases.

Authors, year	Behavioral tests	Applicable conditions	(Refs.)
Kim H *et al*, 2020	Morris water maze test	White matter injury	(23)
Tucker LB *et al*, 2018		Stroke	(24)
Zhong JY *et al*, 2017		Traumatic brain injury	(25)
Schneider CB *et al*, 2017		Alzheimer's disease	(26)
Deng-Bryant *et al*, 2016		Parkinson's disease	(27)
Zhang R *et al*, 2012	Novel object recognition test	Alzheimer's disease, aging, traumatic	(29,30)
Sadegzadeh F *et al*, 2020		brain injury, schizophrenia	
Chen W *et al*, 2019	Balance beam walking test	White matter injury	(31)
Uematsu A *et al*, 2018		Age-related motor deficits	(32,33)
Gyengesi E *et al*, 2019		Central nervous system lesions	
Mychasiuk R *et al*, 2014		Huntington's disease	(34)
El-Sahar AE *et al*, 2020		Parkinson's disease	(35)
Sun J *et al*, 2021		Anxiety	(36)
Marques-Carneiro JE *et al*, 2014		Stroke	(37)
Bohr A *et al*, 2020		Multiple sclerosis	(38)
Mitra NK *et al*, 2020			(39)
Dong W *et al*, 2020	Rotarod test	Amyotrophic lateral sclerosis	(40)
Hayashi T *et al*, 2017		Cerebellar ataxia	(41,42)
Main SL *et al*, 2017		Traumatic brain injury	
Park G *et al*, 2021		Stroke	(43)
Owfard M *et al*, 2021			(44)
Chkhartishvili E *et al*, 2011	Open field test	Depressive disorder	(45)
Lecorps B *et al*, 2016		Anxiety-like behavior	(46)
Su X *et al*, 2020		White matter injury	(47)
Shoi H *et al*, 2021	Elevated plus-maze test	Anxiety-like behavior	(48)
Ren C *et al*, 2021	Tail suspension test	Anxiety	(49)
Castagné V *et al*, 2011		Depression	(50)
Wang W *et al*, 2021		White matter injury	(51)
Ráez A *et al*, 2020	Forced swim test	Depression	(52)
		Anxiety	

the ability of this test to assess motor coordination to investigate the sedative properties of novel drugs and determine their clinical value (71). However, researchers have also begun to realize that the test is associated with certain shortcomings. First, drug efficacy can differ between animal experiments and clinical settings, with some drugs exhibiting high sensitivity in rodents but insufficient sensitivity in humans (72). For example, administration of benzodiazepines or bretazenil exerts nearly no effect on mouse rotarod performance, although it can lead to excessive sedation in humans (63). Second, since most young adult mice can maintain balance during the testing interval (60 sec) even at a high speed (e.g., 44 rpm), researchers have argued that the rotarod test should not be used to evaluate whether motor coordination or balance ability has improved (73).

The rotarod is an automated apparatus comprising a cylindrical rotating beam connected to a computer. Before the trial, the rotarod is switched on with a starting rate of 4 rpm, and the computer is checked to ensure that it is properly connected for data recording. During the trial (generally lasting for 5 min), rodents are allowed to walk on the rotating rod (4 rpm) so that they can learn the motor coordination skills required for the activity. The rotation speed is then slowly and incrementally increased up to 40 rpm. The trial comes to an end when the tested rodent touches the magnetized pressure sensor upon falling from the rod. Three trials are conducted for each rodent, and the best trial result of each rodent is recorded as the score for that day (69,70) (Fig. 4).

The rotarod test is the dominant method for evaluating balancing ability in rodents (70). The test includes two stages: A constant speed stage and an accelerating speed stage. The constant speed stage is used to estimate muscle strength, whereas the accelerating speed stage is used to assess coordination, endurance, and muscular power (74). The rotarod test not only measures the maximum rotation speed at which the animal can maintain balance for a given running duration (e.g., 30 sec) but also calculates the latency to fall from the rod at different speeds and distances traveled. These are recorded as indices of motor coordination and balance performance, respectively (70). However, the surface and diameter of the rod as well as the rodents' body weight and physiological (e.g., fatigue) and biochemical parameters

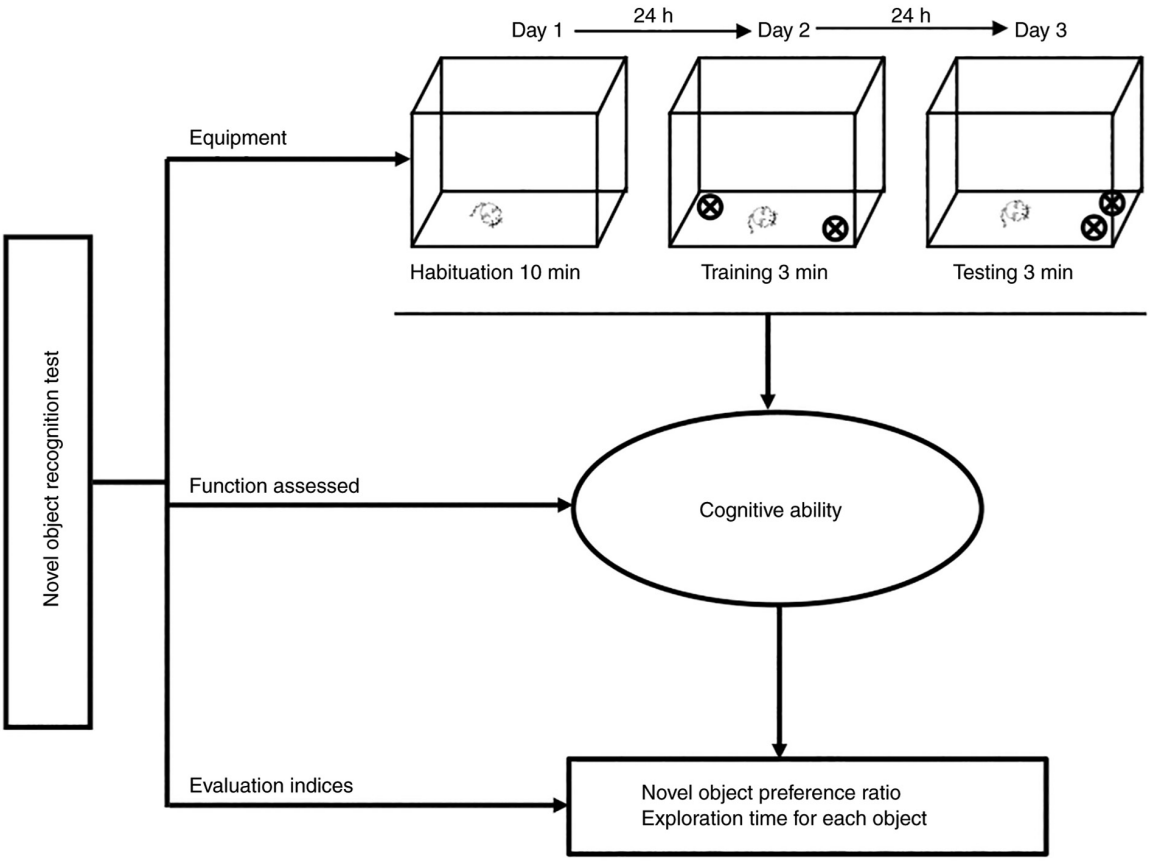

Figure 2. Illustration for novel object recognition test.

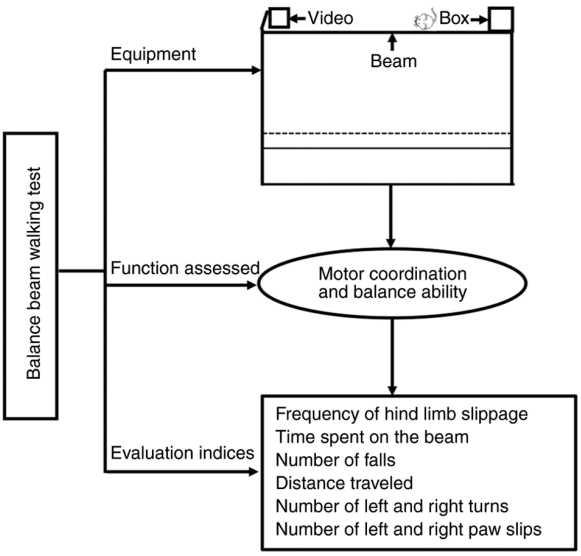

Figure 3. Illustration for balance beam walking test.

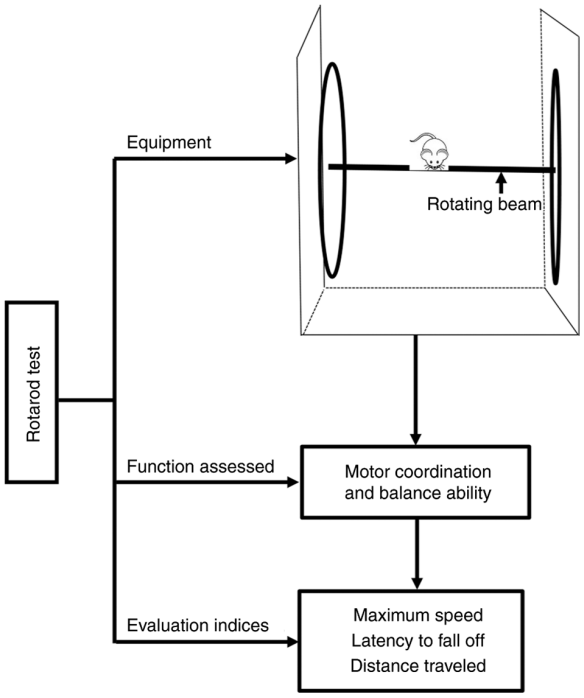

Figure 4. Illustration for rotarod test.

should be considered because they may influence the test results (69) (Fig. 4).

Given the extensive evidence accumulated thus far, researchers generally agree that the test can be used to assess sensorimotor abilities in several animal models, including those of amyotrophic lateral sclerosis (40), cerebellar ataxia disorders (41,42), traumatic brain injury (43), and stroke (44) (Table I).

OFT. While the balance beam walking test and rotarod test are widely used to evaluate motor coordination, the OFT is specifically used to assess overall locomotor function in

rodents. Although it was initially developed to assess 'timidity' in mice based on defecation (75,76), the test takes advantage of the ability of the rodent to perceive new surroundings. The test may seem contradictory, given that rodents can exhibit two types of behaviors when entering a new setting (i.e., exploration of new settings and escaping from the bright/exposed area due to fear) (77). However, rodent responses are assessed by monitoring movement parameters when the rodent enters a new open field, which can help in determining the general pattern of locomotor activity (78), the exploratory ability (79), and the level of fear (80).

The OFT requires an open field and a video computer system. The field is a box (70 cm in width x70 cm in length x46 cm in height), wherein rodents are allowed to stay for 15 min for familiarization with the surroundings before starting the test. During the test, the rodents are placed in the center of the field and are allowed to move for 5 min. The distance traveled, the time spent in the center of the field, the level of spontaneous activity, and the number of entries into the central area are recorded. This test can be conducted either in dark or light settings (81,82) (Fig. 5).

Performance indices for the OFT include the distance traveled, the time spent moving, and the alterations in activity over time, which are integrated to determine the exploratory capacity of the animal (83). Additionally, the OFT can be used to assess the emotional state of a rodent by measuring the duration for which the animal remains stationary, the number of 'depression-like' episodes, and the escape activity. These variables are then integrated to determine the level of anxiety (84) (Fig. 5).

At present, the OFT is widely used to evaluate animal models of depressive disorders (45) and anxiety-like behavior (46). The test can also be used to assess animal models of WMI by measuring the distance traveled and the amount of time spent moving or being immobile in the central area or the periphery (47) (Table I).

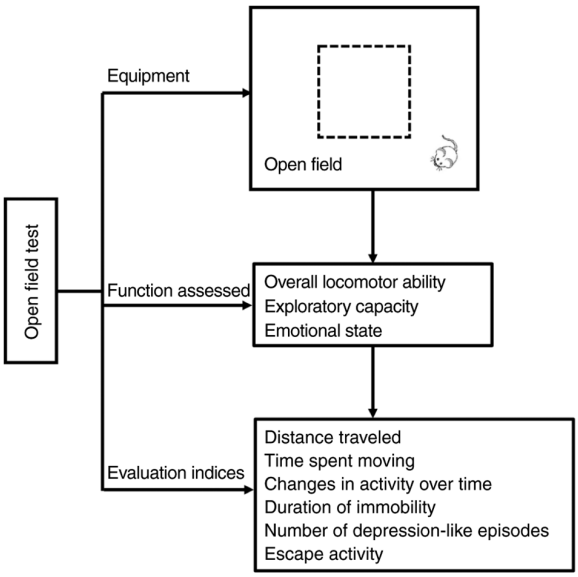

Figure 5. Illustration for open field test.

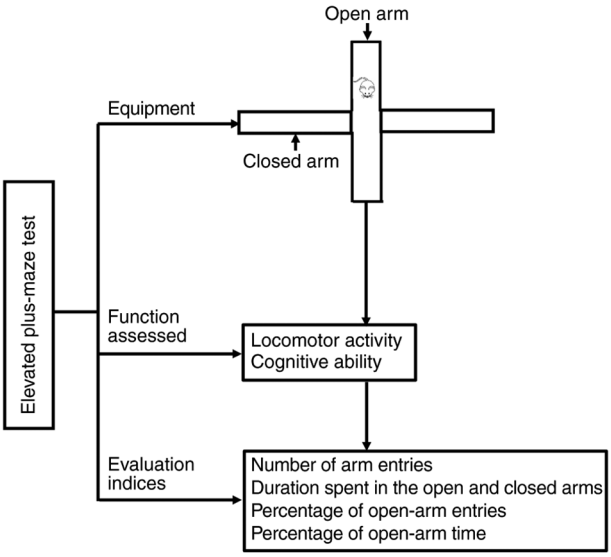

Figure 6. Illustration for elevated plus-maze test.

EPM test. Although both the EPM test and the OFT are used to assess anxiety-like behavior, the principle of the EPM test differs from that of the OFT to some degree. The EPM test was originally devised based on the natural fondness of the rodents for dark and enclosed spaces, their fear of open areas and heights, and their desire to explore unfamiliar environments (48).

The EPM apparatus comprises two open arms (40x8 cm) positioned at right angles and two closed arms of the same size that are surrounded by black walls with a height of 30 cm. Before the test, rodents are subjected to single-frequency ultrasonic stimulation for 6 min to induce anxiety-like conditions. Following stimulation, each rodent is placed in the central platform of the maze facing an open arm and is allowed to freely explore the EPM for 5 min (85,86) (Fig. 6).

Performance indices in the EPM test include the number of arm entries and the duration spent in the open and closed arms. Entry into an arm is defined as the animal placing its two front paws inside an arm. Two additional measures can be derived as indices of anxiety: The percentage of open-arm entries and the percentage of the open-arm time. The percentage of time spent is calculated as follows: (Time spent in an arm/300 sec) x 100 (48) (Fig. 6). A higher percentage of open-arm time or open-arm entries indicates a lower level of anxiety (78).

Currently, the EPM test is primarily used to assess anxiety-like behaviors and anxiolytic drug properties in rodents (78,87) (Table I).

TST. Apart from the OFT and the EPM test, dominant methods for assessment of affective disorders include the TST and FST. The TST was developed based on the innate ability of rodents to respond to an external stimulus via a set of affective alterations; it is usually used to investigate depression-like behaviors in rodents and screen the effects of psychotropic drugs (e.g., antidepressants) (88-91). Moreover, the TST has been used to investigate motor changes (i.e., motor coordination) in models of Parkinson's disease (92) and other metrics such as stress responses (93), helplessness (94), and anxiety (49).

The tail suspension apparatus mainly comprises a rectangular box (60 cm in total length x 40-55 cm in height x 15 cm in width) without external cues. During the test, rodents are

suspended by their tails in each compartment for ~5 min, and the duration of immobility is calculated (95) (Fig. 7).

The TST performance is usually assessed over two periods: An escape stage and a stationary stage. Escape activity includes movements of the hind/forelimbs, movements of the head, and the number of attempts made per minute to reach the tail by bending the body and crawling upward. Immobility activity is defined as a lack of attempts made to rescue oneself. Both escape and immobility behaviors are recorded as the typical indices of the TST performance. Measurements of body temperature, including hyperthermia assessment, are also used as an index of emotional stress (96,97) (Fig. 7).

The TST was originally developed to investigate depression-like behavior (50). Currently, the TST is extensively used to assess animal models of depression and anxiety (49), and it has recently been applied to assess behavioral performance in models of WMI (51) (Table I).

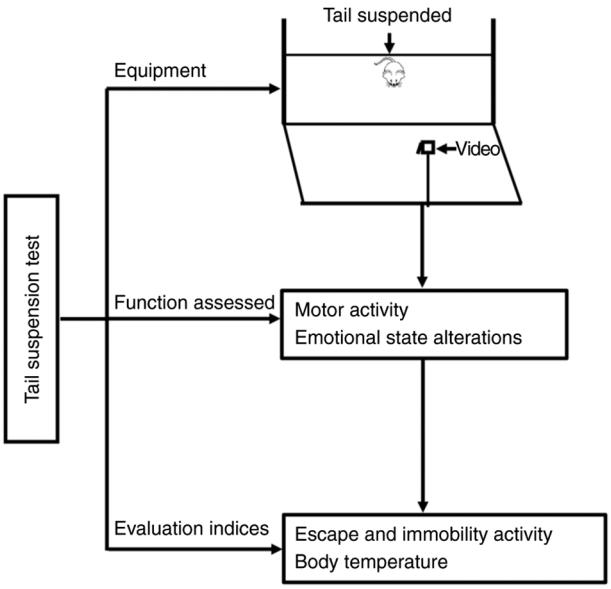

Figure 7. Illustration for tail suspension test.

FST. The FST is a dominant approach for investigating affective disorders and was originally developed based on the immobility response of rodents to external stimuli, which is considered to indicate 'behavioral despair' and a state of 'depression' (98). Researchers have demonstrated that immobility in the FST is achieved gradually through repeated failures, indicating that memory consolidation has occurred, which is associated with the role of the left dorsolateral striatum (99).

The FST apparatus comprises a small container with a visible escape platform and a video capture system, and the procedure includes two forced swimming sessions. On day 1, all the rodents are exposed to a 15-min pretest. On day 2, the rodents are placed in containers filled with water and are forced to swim for 6 min; the first 2 min represent the adaptation period (excluded from analysis), whereas the remaining 4 min are used to calculate the immobility time. Finally, behaviors (such as clawing at the edges of the container, aggressive swimming, and diving) and the number of escape attempts are recorded in the immobility condition (100) (Fig. 8).

The FST performance is typically determined based on the amount of time the animal spends in being immobile, swimming, drifting, diving, and sinking. Other measurements, such as the number of paw strokes, the swimming speed, the number of platform crossings, and uncoordinated swimming movements, are also used to evaluate locomotor ability (52,101) (Fig. 8).

Initially, this test was primarily used to assess depression-like behavior based on behavioral despair and motor behavior (52). However, the results can be influenced by changes in motor activity, thus producing false-positive results in drug screenings (102). Therefore, the original paradigm and its analysis have been modified for the screening of potential antidepressant drugs, and researchers have reached an agreement that the FST can be used in animal models of depression and anxiety (102) (Table I).

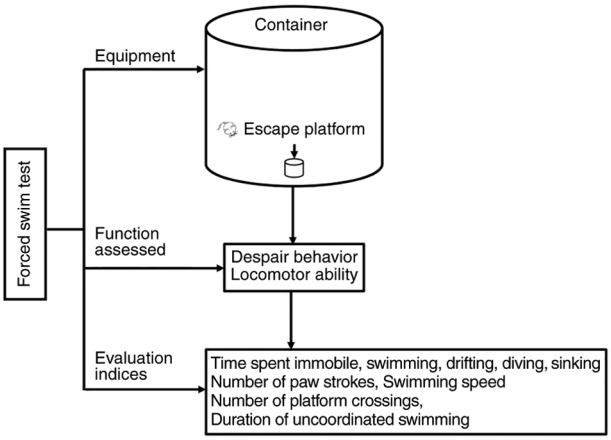

Figure 8. Illustration for forced swim test.

3. Discussion

In this review, the principles, procedures, evaluation, and applications of representative methods for behavioral assessment in rodent models of brain diseases were comprehensively analyzed. As illustrated above, all these methods were developed by taking advantage of the innate features of rodents, with each method based on different principles and performance indices. For example, the MWM test, novel object recognition test, balance beam walking test, and rotarod test are preferred for assessing brain injuries and neurodegenerative diseases, whereas the OFT, EPM test, TST, and FST are preferred for assessing affective disorders. These preferences are based on the expected alterations in cognitive function, motor coordination, and emotional states associated with the disease being modeled. For example, the MWM test is usually preferred when assessing models of WMI because the pathological changes associated with WMI occur in brain areas related to the principles of the MWM test (Fig. S1) (Table II).

Importantly, each test has both advantages and limitations. For example, the MWM test is a versatile tool that can be used to evaluate cognitive deficits associated with brain injuries and neurodegenerative diseases; however, it requires extensive setup, strict procedures, and long experimental duration

Table II. Behavioral tests used in rodent models of brain diseases.

Author, year	Rodent models	Behavioral tests	(Refs.)
Kim H *et al*, 2020	White matter injury	Morris water maze test	(23)
Chen W *et al*, 2019		Balance beam walking test	(31)
Su X *et al*, 2020		Open field test	(47)
Wang W *et al*, 2021		Tail suspension test	(51)
Tucker LB *et al*, 2018	Stroke	Morris water maze test	(24)
Bohr A *et al*, 2020		Balance beam walking test	(38)
Owfard M *et al*, 2021		Rotarod test	(44)
Zhong JY *et al*, 2017	Traumatic brain injury	Morris water maze test	(25)
Zhang R *et al*, 2012		Novel object recognition test	(29,30)
Sadegzadeh F *et al*, 2020		Rotarod test	
Park G *et al*, 2021			(43)
Schneider CB *et al*, 2017	Alzheimer's disease	Morris water maze test	(26)
Zhang R *et al*, 2012		Novel object recognition test	(29,30)
Sadegzadeh F *et al*, 2020			
Deng-Bryant *et al*, 2016	Parkinson's disease	Morris water maze test	(27)
Sun J *et al*, 2021		Balance beam walking test	(36)
Zhang R *et al*, 2012	Schizophrenia	Novel object recognition test	(29,30)
Sadegzadeh F *et al*, 2020			
Marques-Carneiro JE *et al*, 2014	Anxiety	Balance beam walking test	(37)
Lecorps B *et al*, 2016		Open field test	(46)
Shoi H *et al*, 2021		Elevated plus-maze test	(48)
Ren C *et al*, 2021		Tail suspension test	(49)
Ráez A *et al*, 2020		Forced swim test	(52)
Mitra NK *et al*, 2020	Multiple sclerosis	Balance beam walking test	(39)
Dong W *et al*, 2020		Rotarod test	(40)
Chkhartishvili E *et al*, 2011	Depressive disorder	Open field test	(45)
Castagné V *et al*, 2011		Tail suspension test	(50)
Ráez A *et al*, 2020		Forced swim test	(52)

(7 days) compared with the novel object recognition test, which is more flexible and easier to follow. Moreover, although both these tests are used to assess cognitive ability, the MWM test is considered to be more reflective of spatial learning and memory (e.g., WMI), whereas the novel object recognition test is considered to be more reflective of non-spatial memory (e.g., Alzheimer's disease). Furthermore, while the balance beam walking test is easier to set up and lower in cost than the rotarod test, it requires a longer training period (2 days). Moreover, although both these tests are used to evaluate motor coordination and balance ability, the balance beam walking test exhibits improved sensitivity for detecting motor coordination deficits compared with the rotarod test. Nonetheless, the rotarod test is more effective in evaluating endurance and disorders that affect the cerebellum. In terms of affective disorders, although both the OFT and EPM test are used to assess anxiety-like behavior, a previous study has indicated that the walls in the EPM test form visual barriers that may affect the performance results (103). Furthermore, while the OFT, TST, and FST are used for screening depression-like behavior, the OFT is more reflective of 'exploratory fear' behavior, whereas the TST is more reflective of depression induced by 'stress reactivity'. The TST is also simpler, more drug sensitive, and more reliable than the FST, particularly in response to selective serotonin reuptake inhibitors (104). Importantly, the FST cannot be used for antidepressant drug screening, given that it can be influenced by changes in motor activity that lead to false-positive results (102) (Fig. S1) (Table II).

4. Conclusion

After making a comprehensive comparison of these behavioral tests, it was found that each test could be used to evaluate more than one kind of disease animal models. However, using only a single test might not precisely reflect the characteristic of a specific disease. Therefore, at present, lack of the specific behavioral approaches for assessing specific disease animal models is a key problem that needs to be solved. Thus, developing new behavioral tests or modifying the available tests which will concisely reflect the specific animal models would be a future research direction.

In summary, our review of the preferred settings, advantages, and limitations of various behavioral assessment methods may aid researchers in selecting the optimal

strategies based on their research aims, which will in turn help in improving the reliability of their experimental results.

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Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

XS and LH contributed to the conception and design of the review and drafted the manuscript. DX and HS critically reviewed the article for important intellectual content. YQ gave important suggestions for the writing of the review. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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