Neurobehavioral Testing as Cognitive Function Evaluation tool in Experimentally Induced Neurodegeneration in Mice

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Abstract

Neurodegeneration is a complex and multifactorial process presenting one of the major issues of fundamental science and clinical medicine due to its high prevalence, multiple nosological entities, and variations in pathogenesis. Translational research contributes to the study of neurodegenerative diseases, with modeling of such pathologies being an important part of this research. Behavioral testing in various animal models of neurodegenerative diseases allows to assess the model validity and reliability, as well as to investigate the potential efficacy of pharmacotherapy and other management approaches. In this overview we present test batteries that evaluate behavior, cognitive performance, and emotional states in animals with experimentally induced neurodegeneration.

Keywords: *neurodegeneration; memory; fear conditioning; conditioned freezing; neurogenesis*

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Нейроповеденческое тестирование как инструмент оценки когнитивных функций при экспериментальной нейродегенерации у мышей

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Аннотация

Нейродегенерация — это сложный и многофакторный процесс, являющийся одной из серьёзных проблем фундаментальной науки и клинической медицины ввиду распространённости, множества нозологических форм и вариаций патогенетических механизмов. Трансляционные исследования способствуют изучению нейродегенеративных заболеваний, а немаловажной частью данного процесса является моделирование патологий. Поведенческое тестирование животных с различными моделями нейродегенеративных заболеваний позволяет оценить степень достоверности моделирования, а также рассмотреть эффективность потенциальной лекарственной терапии и других типов коррекции. В данном обзоре представлена подборка батареи тестов, применяемых для оценки поведения, когнитивных функций, эмоционального статуса у животных с экспериментальной нейродегенерацией.

Ключевые слова: *нейродегенерация; память; кондиционирование страха; условно-рефлекторное замирание; нейрогенез*

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Introduction

Studying the pathogenesis of various neurological and neurodegenerative diseases alongside with ageing processes has been a critical focus of modern neurobiology for many years. The need to improve patients' life expectancy and quality of life drives the relevance of these studies. Thus, the modeling of neurodegeneration processes and the development of related therapies represent significant challenges of modern times.

Neurodegenerative diseases include several nosological entities characterized by neuronal degeneration, which may be chronic, as in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis, Huntington's disease (HD), Lewy body dementia, and acute, as in cerebral infarction or central nervous system (CNS) trauma [1, 2]. The pathogenesis of this group of diseases is characterized by the gradual degeneration of neurons, reduced cerebral blood flow, and blood-brain barrier dysfunction, resulting in progressive behavioral and cognitive impairment. There is an urgent need for novel strategies in the recovery, management, and prevention of cognitive dysfunction. Therefore, comprehensive translational research *in vivo* is fundamental in the development of personalized therapy. Translational research allows to identify the morphological substrates and mechanisms underlying the pathogenesis of these diseases and their manifestations, and facilitates the translation of research data from preclinical studies to clinical applications.

When selecting a modeling method for a specific pathology, it is crucial to consider the validity, availability, and reproducibility of neurological symptoms and behavioral impairment that are pathognomonic of these diseases [3]. Neurobehavioral phenotyping in experimental animals allows the evaluation of various agents, therapeutic methods and approaches, as well as the associated risks, paving the way for translational approach in neurobiology [4].

Experimental mouse models of neurodegenerative diseases

Rodents have been the most extensively utilized models in experimental research, especially mice because of their genetic and physiological resemblances to humans [4–7]. According to B. Ellenbroek et al., there has been a shift in the proportion of neuroscience research using mice from about 20% in the 1970s and 1980s to around 50% in recent years [8].

Rats and mice belong to the Muridae family. Although they share many similarities, certain differences between these rodents are of critical importance for neuroscience research. Although the brains of rats and mice are anatomically identical, several significant functional dissimilarities have been identified that could impact animal behavior and research findings [8]. The larger size of the brain and spinal cord in rats offers several practical benefits for surgical procedures and targeting specific brain structures [8, 9]. Meanwhile, mice are better suited for optogenetic studies [10, 11] due to the easier penetration of light into the deeper structures of their smaller brain.

Over 95% of mouse genes have a sequence match in the human genome [12, 13], making murine models valuable surrogates for human disease studies, including the neurodegeneration research.

The lifespan of mice compared to humans is relatively short, with one human year being roughly equivalent to nine mice days [6]. To establish a precise correlation between the age of a mouse and a human, reference points for their lifespans and corresponding age ranges are used [14–16].

There are various ways to model neurodegeneration in rodents. The predominant method involves administering a neurotoxic agent directly into the rodent CNS, while the use of genetically modified animals is less common. For example, the intrahippocampal injection of amyloid-β is a traditional injection-induced model for AD [17–19]; HD models are based on quinolinic acid, PD models may be based on systemic injection of 6-hydroxydopamine (6-OHDA) [20, 21], intranigral injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or its active metabolite 1-methyl-4-phenylpyridinium. Rotenone [22] and lactacystin [23] are also used to model this disease.

Genetic aspects of neurodegeneration can be studied using knockout and transgenic mouse lines. The advantages of transgenic animal models include a more comprehensive reflection of the pathogenesis and disease progression in several genetically determined diseases. For example, studies examining prion-like properties of tau-protein in relation to Alzheimer's disease employ hTau40/ΔK280 and hTau40/ΔK280/PP transgenic mice [24, 25], as well as transgenic mice with *ApoE4* [26, 27], *PSEN-1*, and *PSEN-2* [28, 29], APP-PS1 [30], APP23 [31, 32], and various other transgenic mouse lines [33, 34]. To study PD, α, β, γ-synuclein knockout mouse lines were generated [35]. BACHD, R6/2, R6/1, and YAC 128 mouse lines were created to explore HD [36–38].

Thus, the mouse models of neurodegenerative diseases enable more accurate and reproducible study results with more practical advantages over other rodent models.

Modern methods of phenotype and cognitive function assessment in mouse models of neurodegenerative diseases

The primary focus of a mouse model-based research of neurodegeneration is the assessment of animal be-

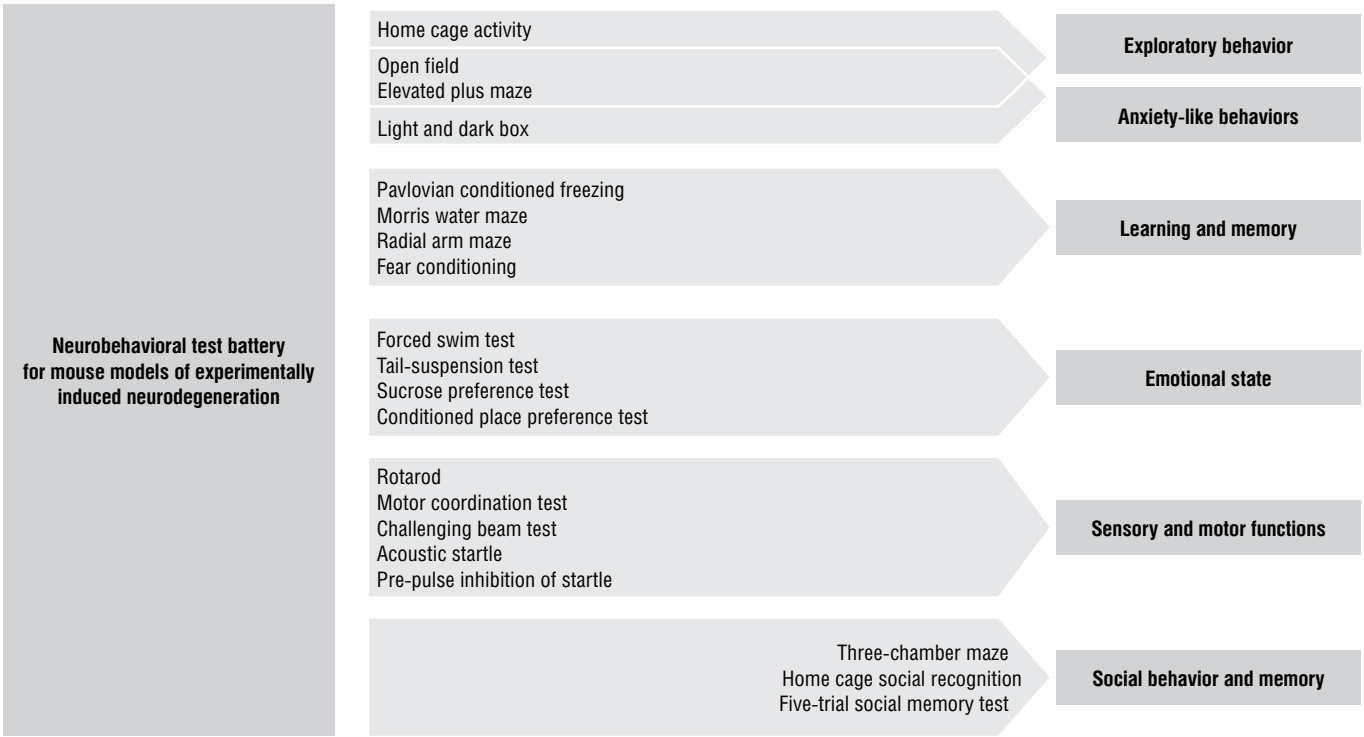

Fig. 1. A diagram of neurobehavioral testing in experimental mouse models of neurodegeneration.

havior and cognitive functions. Neuronal degradation manifests as altered behavior and memory, which can be evaluated through non-invasive methods to measure these neurodegenerative changes.

Neurobehavioral tests can be divided into several large groups based on behavioral parameter to be assessed (Fig. 1):
1) general assessment of anxiety or experimental psychiatric tests;
2) learning and memory tests;
3) assessment of emotional states;
4) sensory and motor tests;
5) exploratory behavior tests;
6) social interaction tests.

We will further provide detailed information regarding the most commonly used tests in mouse models of experimentally induced neurodegeneration.

General assessment of anxiety

In experimental modeling of neurodegeneration, it is crucial to determine whether the model matches the clinical phenotype of the specific disease. The traditional triad of primary behavioral assessment tests includes the open-field, the elevated plus maze, the light and dark box tests which can be a starting point for further research. All three tests may be used to evaluate the anxiety level, emotional behavior, and motor and exploratory activities of the animal [39]. They are simple to use with no need for expensive equipment. At the same time, they harmonize well with each other. Similar results obtained in these tests can be used to draw conclusions about the level of anxiety in the animal. At the same time, omitting one or choosing only one of the tests can result in baseline behavioral response biases.

Memory

One of the most severe clinical manifestations of neurodegeneration is the decline in cognitive functions, particularly memory [43, 44]. Given the pivotal role of memory in cognitive processes, comprehending the neural mechanisms of encoding, storing, consolidating, and reproducing information is imperative. To achieve this goal, we need to study individual neurons of the target brain structure and classify them into types based on gene expression levels, morphology, physiology, and their interactions with other neurons. It is typical to involve the entire network of neurons spread throughout the brain in performing cognitive tasks, including those associated with memory. At the same time, identifying the types of neurons localized in specific brain regions and the transmission of signals to underlying areas is essential [45, 46].

Nowadays, various subtypes of memory are known, including semantic memory, episodic memory, declarative memory, spatial memory, emotional con-

ditioning, procedural memory (skills and habits) [47]. Basically, memory is categorized into two types: declarative memory, also referred to as explicit memory, and non-declarative memory, also known as implicit memory. These types of memory are more distinguishable in humans than in animals [47, 48]. Both types of systems are independent, but they interact with each other to provide well-coordinated control over cognitive processes and behavior.

The declarative memory pertains to the recollection of personal experiences or events (episodic memory), or the factual knowledge of the world (semantic memory) [49, 50]. However, the information accumulated during our life is not limited by facts and episodes. There is also procedural non-declarative memory where information about our skills, habits, and behavior is stored making our recollections comprehensive [51].

Over the past decade, numerous studies have been conducted to identify the areas and systems of the brain responsible for various types of memory. Some studies were successful in understanding its mechanisms, but did not manage to identify memory engrams — subpopulations of neurons that bear specific memory traces. To pinpoint them, a combination of novel technologies were utilized: activation and regulation of immediate-early genes, transgenetics, optogenetics, pharmacogenetics, *in vivo* and *in vitro* cell physiology, and neurobehavioral testing [43, 52]. There are particular advances in research of classical conditioning effects regulated by the hippocampus and (or) the amigdala [48].

Studies of procedural non-declarative memory

Procedural memory, including the acquisition of a motor reflex to a sensory stimulus [45], has several specific traits. The acquisition of procedural memory traces involves two mechanisms: associative and non-associative learning. Non-associative learning refers to changes in the behavioral response to a certain stimulus over time, resulting from either habituation (a decline in response to a repeatedly presented stimulus) or sensitization (progressive amplification of a response to a repeatedly presented stimulus). Associative learning alters the behavior by establishing associations between events [53]. There are two types of associative learning: classical conditioning and instrumental conditioning [54].

Classical conditioning was first discovered and described by the Russian physiologist Ivan Pavlov at the end of the 19th century. Classical (Pavlovian) conditioning associates stimulus A causing a measurable response A with stimulus B, which normally does not cause response A. Stimulus A is an unconditioned stimulus, as a response to such a stimulus is elicited without any prior conditioning. Stimulus B is a conditioned stimulus since it requires conditioning to elicit a response. A learned response to a conditioned stimulus is a conditioned response [53, 54]. According to modern findings, this type of learning is predominantly regulated by the amigdala.

Instrumental conditioning was first discovered and studied at the beginning of the 20th century. In this learning mechanism, behavior or motor activity is associated with

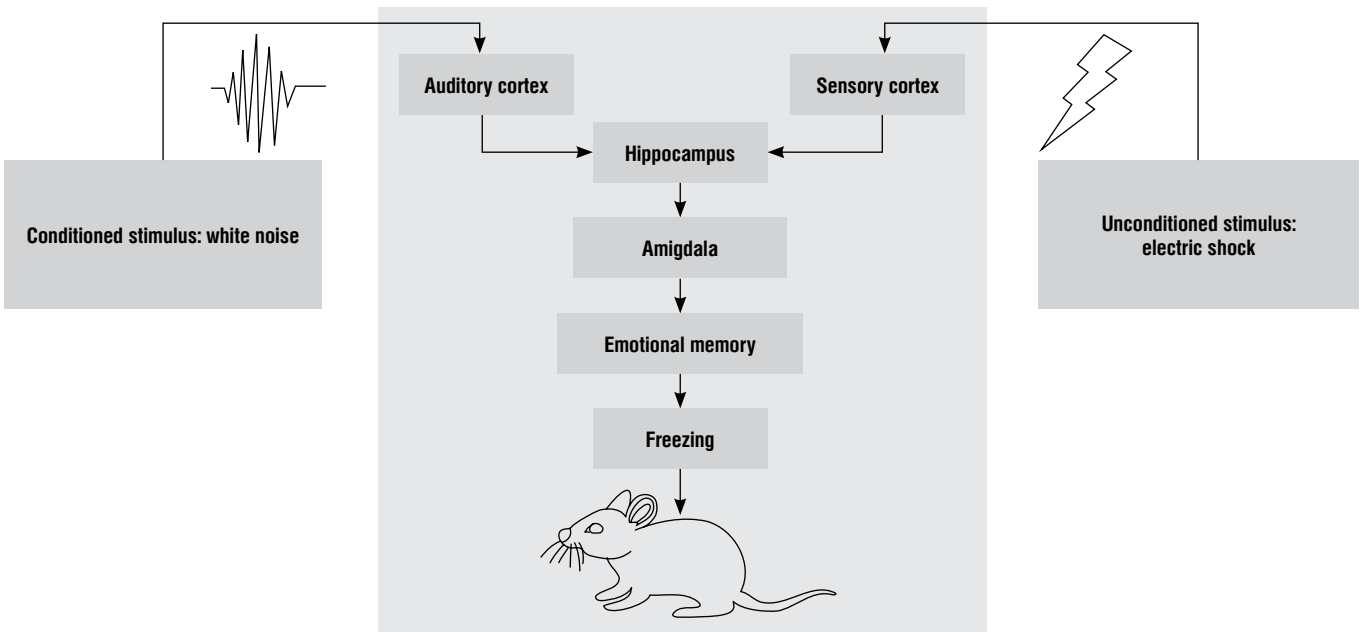

Fig. 2. The fear conditioning test to reveal the interaction between the auditory cortex, the hippocampus, and the amigdala nuclei in formation of the emotional memory.

a significant stimulus, for instance, edible reinforcement. Since motivation plays an important role in the instrumental conditioning (a well-fed animal will not be interested in performing any action for the sake of getting food), the physiology of instrumental conditioning is more intricate than that of its classical counterpart [54].

Currently, the fear conditioning test is considered to be one of the most interesting and informative (Fig. 2). It is based on classical conditioning with repeatedly presented, initially conditioned stimulus like a sound paired with an unconditioned aversive stimulus like a mild electric shock [49]. In repeated testing, the experimental animal normally starts to exhibit fear (freezing) only exposed to the sound [44]. This model can be used to study memory traces, or engrams that include the auditory cortex with memory traces of sounds; the hippocampus with memory traces associated with electric shock; the amigdala where the sound is paired with electric shock and the context [48, 50].

There is another variant of this test described in the literature: contextual fear conditioning [44, 45, 50]. We will discuss this variant below.

Assessment of declarative memory

Declarative memory consists of semantic memory and episodic memory. Learning and engram consolidation in the declarative memory system depend on the hippocampus and other brain structures located in the medial temporal lobes. In the studies of the hippocampus role in memory formation, spatial memory and contextual memory are assessed most frequently [45]. The finding that hippocampal principal neurons (place neurons) are activated when an experimental animal is placed in a specific environment allowed in vivo physiology to make a significant contribution to understanding the mechanisms of spatial memory formation and consolidation [45, 56].

The most widely used test for spatial memory assessment is the Morris water maze. The test was developed by R.G. Morris and has been used mostly in rats because mice are reluctant swimmers in their natural environment, which is why water tests are not suitable for them [8]. In the classic version of the test the animal is placed into an open circular pool that is filled with non-transparent water. The animal must swim to find a hidden platform that is submerged below the water surface and placed in a fixed location. The rodent gets no visible (proximal) cues to navigate to the platform when started from different, random locations around the perimeter of the tank, so must use hidden (distal) cues for spatial navigation [50].

The rodent placed in the maze for the first time will swim until it finds a hidden platform and climbs onto it. The rodent normally remembers the platform location very quickly and in the next tests spends less time for its search. In addition, once the animal realizes that the platform is an escape from the maze, it is much quicker to find the platform in different parts of the tank in subsequent test sessions. At the same time, in rodents with hippocampal lesions the place navigation is impaired: they either cannot understand the task or cannot remember the location of the platform [45].

Other tests to assess spatial deficits in the hippocampus include the radial arm maze test [57] and contextual fear conditioning [50]. A classic version of the radial arm maze consists of 8 arms radiating from a central platform. Some arms contain no food bait and refer to reference memory, the arms referring to working memory contain food bait at the beginning of the test. The correct response of the animal is an entry into a baited arm, a re-entry into a non-baited arm is an error. Then, the animal must move to a different arm to find a food bait, remembering the location of the bait each time, so that its working (short-term) and reference (long-term) memory can be assessed [51]. The main disadvantage of this test is its complexity: its protocols are quite time-consuming.

In the studies of the role of the hippocampus in memory formation, a term "cognitive map" can be encountered. It is a mental model of the environment's layout: presence and location of certain landmarks and entities, their relationship to each other within a certain time frame or event [45, 50].

In addition to examining spatial memory for the location of objects, the tests also study associative learning ability. Associative learning is an adaptive process of learning to anticipate events. One of the tools to study the mechanisms of associative learning is the contextual fear conditioning test. The variable used in the contextual and stimulated formation of the conditioned fear reflex is the freezing that follows the combination of an unconditioned stimulus (electric shock) with a conditioned stimulus. Freezing is a defensive response and is manifested by the absence of body movement (except breathing) for 0.75 s or longer [44, 47]. This test models one of the most commonly used hippocampal-related behavioral tasks that reflects learning and episodic memory formation in rodents and correlates with adult hippocampal neurogenesis rates.

Neurogenesis is the process by which new neurons are generated. There is evidence that hippocampal neurogenesis continues throughout life in many adult and even older mammals [44]. According to the modern outlook, neurons are generated in the subventricular zone of the olfactory bulb and in the dentate gyrus of the hippocampus [58, 59]. The hippocampus and hippocampal neurogenesis are essential for the formation of long-term cortical memory through consolidating

the episodic memory traces [58]. The process of the memory retrieval and expression is highly dependent on the hippocampus, but the role of the hippocampus diminishes over time, which may be related to the gradual transfer of memory traces to extrahippocampal areas, such as the neocortex. This process is supposed to be essential to free the hippocampus from outdated and unused information by storing memory traces in the cortex, thus making room for learning new things [60]. Also, hippocampal-cortical memory trace transfer allows to preserve memory traces because the constant integration of new neurons into existing neuronal networks would damage the structure of information acquired before [44]. However, the mechanisms, by which memory becomes completely dependent on the cortical structure and independent of the hippocampus, remain unknown [44, 58].

When hippocampal neurogenesis is physically or genetically suppressed, the period of hippocampus-dependent associative fear memory becomes longer [44, 58]. Inversely, adult neurogenesis enhanced by physical exercise shortens the period of the hippocampus dependent memory without loss of information. These observations paved the way for understanding of the mechanisms of the hippocampal-cortical complementary learning [44].

Thus, the study of various memory types provides the basis for the assessment of cognitive functions, neurogenesis, and learning processes.

Assessment of emotional states

Neurodegenerative diseases are often accompanied by emotional dysregulation when people exhibit inadequate emotions (for instance, in PD or AD patients) [61] or depression-like behavior (physiological ageing, etc.) Side effects of various anti-degenerative agents on the emotional state also have an impact on daily life.

To assess emotional states and depression-like behavior in mice, the forced swim test, the tail-suspension test, the sucrose preference test, and the conditioned place preference are widely used [62]. The first two tests are the most significant in preclinical studies of antidepressants [63], the third one allows to measure sensitivity to rewards.

The forced swim test (the Polsort test), was first introduced in 1977 to evaluate new antidepressants [64]. The method is based on the observation that a mouse, when forced to swim in a situation from which there is no escape, will, after an initial period of vigorous activity (swimming or climbing), eventually cease to move altogether making only those movements necessary to keep its head above water. This behavioral immobility was described as a state of despair in which the animal has learned that escape is impossible [64, 65]. Antidepressant agents have been shown to reduce the immobility time in the test. Reduction in passive behavior is interpreted as an antidepressant-like effect [66]. Another indicator of antidepressant effect is immobility latency, which is used to distinguish antidepressant from stimulant effects [67]. Administration of antidepressants prior to the test usually causes prolongation of the escape response. Different groups of antidepressants may have different effects on the behavior of rodents in the test.

The tail-suspension test induces similar behavior to the Porsolt test. The mouse hangs by its tail and its body hangs in the air [68–70]. The test is based on the assumption that the animal would try to escape the stressful situation. After some time, the animal stops struggling and becomes immobile. Longer immobility phases are the sign of depressive behavior [62]. The advantage of this test over the Porsolt test is that it eliminates the risk of water-induced hypothermia and allows the strength and energy of the animal's movement to be assessed [71].

The sensitivity to rewards can be assessed by a simple sucrose preference test in which animals have access to water with different concentrations of sucrose or without any additives, and the preference rate is then analyzed. This test is often used to assess the level of depression [62]. Reduced interest in the reward (water with sucrose) is a manifestation of depressive behavior.

The conditioned place preference test is used to assess reward behavior in rodents [72]. The test usually includes three stages. At the first stage the animal is allowed to get used to the apparatus to ascertain that there is no inherent preference for one side or the other. The amount of time required for each training session may vary depending on the stimulus (agent) being tested. The second stage is to develop a Pavlovian association between the agent and the chamber. The animal is confined in one of the chambers of the test box, each with a different pattern on the floor or the walls, and is given an addictive drug or a food bait. The third stage is to assess the reproducibility of the Pavlovian association: with repeated exposure to the chamber, the rodent prefers to spend more time on the drug-paired side of the chamber than on the food-paired side. Preference for the drug-paired side may be extinguished by repeated exposure to the chamber in the absence of reward.

Therefore, assessment of emotional states is important when working with animal models of neurodegenerative diseases, both in phenotyping animals and in the development and testing of new drugs.

Sensory and motor tests

Motor testing should be used when neurodegeneration is associated with impairments in motor activity and

walking [73, 74]. Such tests are essential in the studies [75] of PD that is characterized by significant motor impairment [76]. The group of motor tests includes the following classic tests:

1) Rotarod (rotating rod) test is used to screen new drugs for possible side effects on motor coordination or fatigue resistance in animals;
2) Motor coordination test, or the footprint test, or the catwalk test [77, 78];
3) Challenging beam test is a narrow "walking bridge" for mice to walk across to assess its sensorineural balance and coordination. The beam can vary in diameter to make the task more complicated [79].

It is also possible to use the open-field test where the number of floor line crossings is analyzed [39]. The motor coordination test and the challenging beam test are easy to perform and require no special equipment.

Sensory tests are also of interest, as age-related hearing loss occurs in one-third of adults older than 60 years and in 80 % of adults older than 85 [80]. Consequences of hearing loss may be substantial because it affects quality of life of the older people, results in functional decline, social isolation, loneliness, and the increase of depressive symptoms. Age-related hearing loss also correlates with cognitive dysfunction in the elderly, including long-term memory impairment [81]. Many studies have shown a positive correlation between hearing impairment and dementia [82], especially in AD patients.[83] Some studies have revealed that hearing impairment may be used as an early marker of cognitive decline [82]. The battery of sensory tests includes the acoustic startle test and the pre-pulse inhibition of startle, which are quite informative, but at the same time require special equipment, software, and animal training procedures.

Acoustic startle test allows to measure the mouse response to loud and sudden auditory stimuli. This test enables the assessment of a baseline startle response at various sound intensity levels as well as the reduced startle response to the repeatedly presented stimuli over time [84].

Pre-pulse inhibition of startle is an operational measure of sensorimotor gating. In this test the animal is first exposed to a low intensity stimulus, or pre-pulse (56–81 dB), followed by a subsequent stronger startle stimulus (120 dB). The pre-pulse is designed to reduce the startle response to the subsequent test stimulus; the more intense the stimulus, the greater the suppression of the startle response [85, 86].

Sensory and motor tests aid to assess the manifestations of neurodegenerative changes and to monitor either their progression or disease slowing and response to possible therapy.

Exploratory behavior tests

The open-field test and the elevated plus maze test may be useful in the studies of exploratory behavior [87, 88]. In the open-field test, only the first stage is significant in this context: when the animal is placed in the central zone of the experimental chamber, and variables such as ability to stay in the center or at the outer limits of the field, frequency of vertical activity, immobility or freezing, etc. are evaluated. If there is need to complicate the test and add other stages such as an inanimate or animate object in the center of the field, then the first stage of the test functions as a training prior the other stages of the test [86].

One of the methods to study exploratory behavior is video-recording of home cage activity during 12–24–48 hours and subsequent analysis of the images using specially developed software [78, 89, 90]. No training sessions are required in this case.

Social interaction tests

The progression of social behavioral disturbances, such as alienation or aggression, is often an important symptom of a neurodegenerative disease. Social behavioral studies assess levels of sociability, including social recognition [91], memory, and social interaction. Mice are social animals and exhibit complex social behavior in various patterns, types, and intensities of interactions [92].

The extended open-field test consists of 2 or 3 stages. The test begins with an empty box, at the second stage there is an inanimate object in the middle of the field, at the third stage — an animate object (an animal of the same or the opposite sex) [78]. The animal's interest in inanimate and animate objects indicates the level of sociability.

Currently, the three-chamber test is widely used to evaluate the sociability level or social preferences [85]. The rodent is placed in a three-chambered box with openings between the chambers. The testing includes three sessions when the behavior of the rodent is recorded: movements, freezing time, preferred chamber. During the first session, the animal is habituated to the test environment, then a previously unfamiliar and immobilized mouse is placed in one of the chambers, and finally a new social stimulus is added in the third chamber. There are various modifications of this test [78, 94].

The home cage social test is used to assess social interactions [95, 96], is inexpensive, and requires no additional equipment.

The five-trial social memory test is used to assess social recognition [97]. Over the course of multiple exposures, rodents become habituated to intruders and the inter-

action time to recognize a familiar animal decreases compared with the interaction time with a completely novel intruder. The intruders are selected from the rodents of the same age, sex, and weight, and it is mandatory that they have never encountered the test animal before. Two social stimuli are used to test the rodent: 4 short-term contacts are made with one intruder, and in the fifth trial another intruder is placed. The interaction time with the first, already familiar intruder would gradually decrease and the interaction time with the unfamiliar rodent would increase significantly.

Parental behavior and parental care are components of social behavior [98], but when working with neurodegeneration models, they are most often irrelevant and unused, so the above tests for assessing social memory and recognition are of the paramount importance.

Conclusion

The objective of this review was to summarize the knowledge of the modern tests for behavioral analysis in mice with experimentally induced neurodegeneration and to to assist in the selection of a test battery that will provide a comprehensive neurobehavioral phenotype of the animal. A careful approach to the selection of an experimental model and the necessary tests for a specific study allows the data obtained to be used both in fundamental research and in clinical practice.

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