Behavioural Brain Research 301 (2016) 63–71

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Assessments of cognitive abilities in a mouse model of Parkinson's disease with a touch screen test

Chuljung Kwak, Chae-Seok Lim*, Bong-Kiun Kaang*

Departments of Biological Sciences & Brain and Cognitive Sciences, College of Natural Sciences, Seoul National University, Seoul 08826, Republic of Korea

HIGHLIGHTS

- Touch screen test requires low motor output for Parkinson's disease (PD) model mice to perform simple operant conditioning task.
- Touch screen test can be used to investigate mechanisms of cognitive disabilities in PD model animals that cannot be tested by conventional cognition testing tools.
- PD model mice showed impairment in location discrimination task.

ARTICLE INFO

Article history:
Received 1 September 2015
Received in revised form 2 December 2015
Accepted 11 December 2015
Available online 14 December 2015

Keywords:
Parkinson's disease
Touch screen test
Cognition test
Striatum
Location discrimination

ABSTRACT

Patients with Parkinson's disease (PD) experience both motor output deficits and cognitive disabilities. Various PD rodent models have been developed to investigate the genetic and brain circuit-related causes of PD and have contributed to the basic and clinical research and to therapeutic strategies for this disease. Most studies using PD rodent models have focused on the motor output deficits, rather than cognitive disabilities due to the lack of appropriate testing tools that do not require significant motor abilities. In this study, we assessed the cognitive disabilities of PD model mice using a touch screen test that required only little motor ability. We found that the PD model mice, which had motor deficits caused by unilateral striatal dopaminergic degeneration, successfully underwent operant conditioning with a touch screen test. Additionally, we found that the PD model mice demonstrated impaired location discrimination, but intact attention and reversal learning in the cognitive tests. Therefore, the touch screen test is useful for assessing hidden cognitive disabilities in disease model animals with decreased motor function.

1. Introduction

The main neurological feature of Parkinson's disease (PD) is dopaminergic degeneration, which has long been considered the main cause of the symptoms that distress PD patients. PD rodent models have contributed to our understanding of the pathophysiology and therapeutics of PD [1]. One of the most common methods for generating PD model mice is to destroy dopaminergic circuits genetically or pharmacologically. For example, neurotoxins, such as 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), are widely used to ablate dopaminergic neurons selectively, thereby reproducing the motor impairments that are observed in PD patients [2]. These neurotoxin-induced motor impairments can be ameliorated by pharmacological correction of the dopamine deficiency or optogenetic activation of striatal medium spiny neurons [3,4].

Many studies on the importance of the dopaminergic circuit in cognition [5] and the cognitive disabilities of PD patients [6] suggest the need for studies of such disabilities in PD rodent models. However, the investigation of cognitive disabilities in PD rodent models is limited, because most cognitive tests require normal motor function for performing the given task [7]. Therefore, care should be taken about drawing conclusions on cognitive abilities in PD rodent models, as poor performance on cognitive tasks might be due to motor impairments rather than cognitive disabilities. However, to date, no tools for testing cognition in disease model animals with motor impairments have been available.

The touch screen test was recently developed to test complex cognitive abilities in mice and rats [8]. In the touch screen test, the animals are required to perform a cognitive task in order to obtain a reward by touching a visual stimulus that is shown on a LCD monitor located in the front of the chamber. The touch screen

* Corresponding authors. Fax: +82 28849577.
E-mail addresses: cslim@snu.ac.kr (C.-S. Lim), kaang@snu.ac.kr (B.-K. Kaang).

http://dx.doi.org/10.1016/j.bbr.2015.12.016
0166-4328/

test has several advantages over conventional cognitive test tools for the testing the cognitive disabilities of PD rodent models. First, it requires relatively lower motor output [9], only ambulation in the small chamber and touching the LCD monitor in the front of the chamber. This low motor demand can reduce the possibility that poor performance in a cognitive task is due to motor impairments. Next, various types of cognition tasks can be tested with the touch screen test, and these include conventional cognition tasks [8], such as operant conditioning, delayed matched to position (DMTP), and 5-choice serial reaction time (5-CSRT) tasks, or novel complex tasks, such as paired associate learning (PAL), visual discrimination and its reversal learning, and trial-unique delayed non-matching-to-location (TUNL) tests. Because these complex tasks can also be used to test human cognition [10], the touch screen test is also useful for testing cognitive deficits in many human disease models.

In this study, we employed a touch screen test paradigm to assess cognitive disabilities in PD model mice, which were generated by unilateral injections of 6-OHDA into the dorsal striatum. We found that these mice did not show abnormal performance in a simple operant conditioning task in the touch screen test. However, they showed impairments in location discrimination, which may not be due to motor impairments, but rather to cognitive impairments. Therefore, the touch screen test can be used to test and investigate the mechanisms underlying cognitive disabilities that are concealed by motor impairments in many disease models.

2. Materials and Methods

2.1. Animals

C57BL/6N mice were purchased from Orient Bio Co. (Gyeonggi, Korea). The animals were housed in groups (3–4 mice) and maintained on a 12-h light/dark cycle as previously described [11]. Food and water were provided ad libitum except during the touch screen test. All of the animal procedures were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee of Seoul National University.

2.2. Stereotaxic 6-OHDA injections

6-OHDA (Sigma – AldrichCo. LLC, St. Louis, MO, USA) was dissolved in phosphate-buffered saline (PBS) to which ascorbic acid was added to stabilize the dissolved solution. Either 1 μL of the 6-OHDA solution (4 μg/μL) or the same volume of PBS, as a control, was injected into the right dorsal striatum of each mouse. For the stereotaxic injections of 6-OHDA, the mice were first anesthetized with an intraperitoneal injection of a ketamine and xylazine cocktail. The stereotaxic coordinates were established according to the previous studies [4] (from bregma, anterior to posterior, +0.4 mm; midline to right, 1.5 mm; dorsal to ventral, −3.0 mm).

2.3. Rotarod test

The rotarod test was performed as previously described [3,12] with a few modifications. Briefly, mice were trained for 5 consecutive days. On the first day, animals were placed on the rod that rotated at low speed (4 rpm). Every 30 s, the rotating speed was increased by 1 rpm, and the final rotating speed was 15 rpm. On the second day, mice were placed on the rod rotating at 4 rpm for 90 s, and the rotating speed was increased by 1 rpm every 30 s until it reached 20 rpm. During the 3–5 training days, falling latency was measured as the rotation speed of the rod increased linearly from 4 rpm to 40 rpm. After the 5-day training, 6-OHDA was injected. After 1 week, falling latency was measured using the same conditions as in the last 3 days of training.

2.4. Open-field test

The mice were placed in the open field for 15 min, under dim light as described in previous study with a few modifications [13]. The open field consisted of an opaque white floor and walls (40 cm × 40 cm × 40 cm). The center area was defined as a central rectangular region consisting of 20 cm × 20 cm. EthoVision XT video tracking software (Noldus Information Technology, Wageningen, The Netherlands) was used to track and analyze the thigmotaxis and moving distance of the mice.

2.5. Round chamber test

The activities of the mice in a round chamber were recorded as described in a previous study, with slight modification [4]. Briefly, the mice were placed in a small 15-cm-diameter cylinder for 10 min. The mobility, moving distance, and rotational behaviors of the mice were tracked and analyzed using EthoVision XT video tracking software.

2.6. Touch screen test

The touch screen test was performed as previously described [14]. Briefly, we used the Bussey–Saksidatouch screen chamber (Campden Instruments, Ltd., Loughborough, UK). Before testing, the animals' access to food was limited in order to increase their motivation for a reward. The weights of the mice were maintained at about 80% of their initial weight by allowing the animals' access to food for only 1–2 h/day and monitored every day throughout the touch screen test. Sweetened condensed milk was given to the mice as a reward (SeoulMilk, Seoul, Korea).

2.6.1. Operant training test

For the operant conditioning test, the mice were trained to touch a visual stimulus that was presented in 1 of 12 blanks. For the first operant conditioning test (Fig. 2), 6-OHDA was injected into the right dorsal striatum. After 1 week of recovery, the mice were habituated to the touch screen chamber for 10 min. The next day, the mice were moved to the reward collection-learning phase, during which a nose poking a reward magazine resulted in reward delivery for 40 min. On day 3, in the initial-touch phase, either nose poking or touching the visual stimulus resulted in reward delivery. On days 4–6, in the must-touch phase, the mice were required to touch the visual stimulus to earn a reward. On days 7–11, in the incorrect-punishment phase, the mice were required to not only touch the visual stimulus, but also avoid touching the blanks, to earn a reward.

For the second operant conditioning test (Fig. 2e), we used new cohorts of mice. The mice were first trained to touch the visual stimulus as in the first operant conditioning test, but without 6-OHDA injection. After completion of the operant conditioning, the mice were injected with 6-OHDA. After 1 week of recovery, the mice were tested again in the incorrect-punishment phase.

2.6.2. Visual discrimination test

6-OHDA was injected into the right striatum of animals after completion of the operant conditioning, as described above. After 1 week of recovery, we tested whether the response of the mice to a visual stimulus that was presented in 1 of 2 blanks remained intact and was the same as the responses during the operant conditioning test (Fig. 2e). During visual discrimination learning, 2 complex visual stimuli were presented on the LCD monitor. Touching one visual stimulus delivered a reward, whereas touching the other resulted in looming room light and white noise, which were wrong signals. The locations of the visual stimuli (either left or right) were randomly changed throughout the trials. When the wrong visual