Journal of Neuroscience Methods 265 (2016) 72–80

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Basic neuroscience

The utilisation of operant delayed matching and non-matching to position for probing cognitive flexibility and working memory in mouse models of Huntington's disease

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HIGHLIGHTS

- We compared delayed matching and non-matching to position (DMTP and DNMTP) tasks in two different operant apparatus, the 9-hole operant apparatus configuration and the Skinner-like operant apparatus configuration.
- We determined that the DMTP and DNMTP operant tasks produce more efficient, robust and reliable results in the Skinner-like operant apparatus configuration.
- We therefore used the Skinner-like operant apparatus configuration to test DMTP and DNMTP tasks in the Hdh^{Q111} mouse model of HD.
- We tested the DMTP and DNMTP tasks in the Hdh^{Q111} knock-in mouse model of HD which revealed significant deficits in task acquisition and reversal learning in comparison to wildtype animals.

ARTICLE INFO

Article history:
Received 22 June 2015
Received in revised form 18 August 2015
Accepted 19 August 2015
Available online 28 August 2015

Keywords:
Huntington's disease
Operant tests
9-Hole box
Reversal learning
Short-term memory
HD mice

ABSTRACT

Background: Operant behavioural testing provides a highly sensitive and automated method of exploring the behavioural deficits seen in rodent models of neurodegenerative diseases, including Huntington's disease (HD). The delayed matching to position (DMTP) and delayed non-matching to position (DNMTP) tasks probe spatial learning and working memory and when applied serially they can be used to measure reversal learning, which has been shown to be an early symptom of executive dysfunction in HD.
New method: The DMTP and DNMTP tasks were conducted in two configurations of operant apparatus; the conventional 9-hole operant apparatus, and a Skinner-like operant apparatus, to compare, contrast and optimise the DMTP and DNMTP operant protocols for use in mice. The optimised tasks were then tested in the Hdh^{Q111} mouse model of HD.
Results: Optimisation of the operant apparatus demonstrated that the mice learned the DMTP and DNMTP tasks more rapidly and effectively in the Skinner-like apparatus configuration in comparison to the conventional 9-hole apparatus configuration. When tested in the Hdh^{Q111} mouse model of HD, the DMTP and DNMTP tasks revealed significant deficits in reversal learning.
Comparison with existing method: We found that mice were capable of performing the DMTP and DNMTP tasks in both apparatus configurations, but in comparison to the 9-hole configuration, the Skinner-like configuration produced more efficient, robust and reliable results.
Conclusions: The results presented here suggest that DMTP and DNMTP tasks, incorporating a reversal learning manipulation, are valid and robust methods for probing selected cognitive deficits in mouse models of neurodegenerative diseases.

1. Introduction

Since the discovery of the genetic cause of Huntington's disease (HD) (MacDonald et al., 1993) a wide range of genetically modified animal models of the disease have been created that demonstrate good construct and face validity to HD. By far the most widely used

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http://dx.doi.org/10.1016/j.jneumeth.2015.08.022

animal as a model of HD is the genetically modified mouse, due to the highly conserved genome in relation to the human genome and the comparative ease of genetic manipulation. Understanding the nature and severity of HD disease progression in these models is central to determining the suitability and predictive validity of these animals for therapeutic trials. There are now over 20 mouse models of HD (transgenic and knock-in) that have been reviewed extensively elsewhere (Hickey and Chesselet, 2002; Menalled and Chesselet, 2002). Whilst these mouse models demonstrate a range of behavioural abnormalities, there is still a lack of sensitive, reliable and robust behavioural tasks available to probe the specific cognitive deficits observed in HD.

The large number of mouse models of HD that are now available means that there is a need to continually develop novel behavioural tasks to better understand, validate and explore the behavioural symptoms that are demonstrated in HD mouse models. The use of the rat in many previous behavioural studies means that often behavioural tests for mice are modified from those traditionally conducted and developed for the rat (Brooks and Dunnett, 2009). The delayed matching to position (DMTP) and delayed non-matching to position (DNMTP) tasks are examples of such behavioural tests. The delayed matching tasks have been used extensively in a range of species including; monkeys (Mello, 1971; Bartus and Johnson, 1976; Hudzik and Wenger, 1993; Terry et al., 1993), pigeons (Blough, 1959; Ferster, 1960; Harnett et al., 1984; Urcuioli, 1985; Picker et al., 1987) and humans (Owen et al., 1995), often for testing neurological conditions such as Alzheimer's disease, Parkinson's disease and schizophrenia (Irle et al., 1987; Sahakian et al., 1988; Elliott et al., 1998). The DMTP and DNMTP tasks were used in rats to explore the effects of lesions and associated drug treatments (Dunnett, 1985; Dunnett et al., 1989). Since the original description in the rat, operant DMTP and DNMTP testing has been used in numerous other rat studies (Dunnett et al., 1988a; Bushnell, 1990; Cole et al., 1993; Carter et al., 1995; Stephens and Cole, 1996; Yamada et al., 2005). However, the use of DMTP and DNMTP tasks in mouse studies has been comparatively limited (Beracochea and Jaffard, 1995; Estapé and Steckler, 2001) and DMTP and DNMTP protocols have yet to be extensively investigated in HD mice. In HD, reversal learning deficits are a particular feature of both the human disease (Lawrence et al., 1998, 1999) and the HD mouse (Lione et al., 1999). Using the DMTP and DNMTP tasks in sequence and serially allows us to utilise a reversal learning shift in conjunction with a working memory probe in murine models of HD.

As an increasing number of mouse models of neurological diseases, including HD, become readily available, the DMTP and DNMTP tasks (and their subsequent reversals) need to be developed and optimised for use in mice. Although maze variations of the DMTP and DNMTP tasks have been previously performed using a T-maze experimental design (Gibbs, 2002; Johnson et al., 2002; Fitz et al., 2008), this type of behavioural testing is time consuming and provides minimal amounts of data, relative to the automated mass-trials produced by operant procedures, and it is susceptible to experimenter bias. Therefore, conducting DMTP and DNMTP tasks using operant behavioural testing methods presents a fully automated, sensitive and flexible way of measuring task performance. Therefore, the aims of this study were to compare and contrast DMTP and DNMTP protocols in two different configurations of the '9-hole box' operant apparatus: a conventional configuration with central and lateralised response holes within a 9-hole array and with the reward hopper located in the opposite wall, and, a 'Skinner like' box configuration in which just two response holes were located one on either side of the central reward hopper. We then used the more efficient protocol to test the DMTP and DNMTP tasks in the Hdh^{Q111} mouse model of HD.

2. Materials and methods

2.1. Animals

Animals were maintained on a 12 h light/dark circadian schedule (0600 h lights on; 1800 h lights off), in a temperature controlled environment (21 °C ± 2 °C). Animals were housed in pairs, although sometimes had to be separated and singly housed to prevent fighting. Operant testing occurred during the light phase between 0800 h and 1100 h, five days a week. All animals were water restricted and habituated to strawberry milk (Yazoo®, Campina Ltd, Horsham, UK) in their home cages one week prior to operant testing. During operant testing, animals were maintained on a water restriction schedule of 3 h water, available daily from 1200 h to 1500 h in their home cages.

The C57BL/6J animals used in the comparison of the DMTP and DNMTP tasks in differing operant apparatus were obtained from Harlan (Bicester, Oxfordshire, UK) at 8 weeks of age. 14 C57BL/6J male animals were used in testing of the DMTP and DNMTP task in the conventional 9-hole apparatus and 15 C57BL/6J male animals were used in the testing of the DMTP and DNMTP task in the Skinner-like apparatus. Hdh^{Q111} animals were originally obtained from Jax® (Jackson Laboratories, Bar Habor, Maine) and bred in-house on a C57BL/6J background. For the testing of the DMTP and DNMTP tasks in a mouse model of HD, a total of 21 littermate animals were used, 12 $Hdh^{Q111/+}$ (6 were female and 6 were male) and 9 wildtype (5 were female and 4 were male). Animals were weaned at 3–4 weeks of age and tail tipped for genotyping (Laragen Inc., Culver City, CA, USA). CAG repeat length in $Hdh^{Q111/+}$ animals ranged from 134 to 145 repeats, with an average repeat length of 140 repeats. $Hdh^{Q111/+}$ animals began operant testing at 8 months of age. All testing was in accordance with the European Directive 2010/63/EU and the UK Animal and Scientific Procedures Act (ASPA) of 1986 and subject to local ethical review.

2.2. Apparatus

The operant apparatus used here comprised two separate operant configurations, a 9-hole operant apparatus configuration and a Skinner-like operant apparatus configuration, as shown in Fig. 1.

2.2.1. Conventional 9-hole operant box configuration

Sixteen 9-hole operant boxes (Campden Instruments, Loughborough, UK), measuring 14 cm × 13.5 cm × 13.5 cm, controlled by a BehaviourNet Controller BNC MKII operating system (Campden Instruments, Loughborough, UK) were used in this study. Each operant box constituted a sound attenuation chamber that enclosed the 9-hole box made of aluminium on all sides with a clear Perspex lid. The rear wall of each chamber was curved and contained a horizontal array of nine holes (11 mm in diameter, placed 2 mm apart and 15 mm above floor level). Each hole contained photocell infrared beams localised at the front to detect nose pokes. At the rear of each hole a white LED acted as the target visual stimulus. A peristaltic pump delivered liquid reinforcement in the form of strawberry milk (Yazoo®, Campina Ltd, Horsham, UK) to a reward magazine at the front of the box, located opposite the 9-hole array. Reward delivery to the magazine was signalled by a light located above the magazine and nose entry into the magazine was detected by an infrared beam located across the opening of the magazine. 'House lights' were also located on the side walls of the operant chamber, which illuminated to signal the end of a trial or time out intervals (TOI) within trials. Background noises were provided by an extractor fan and a computer operating system.